National Clinical Guideline Centre

Consultation

Sepsis

Sepsis: the recognition, diagnosis and management of sepsis

NICE guideline <number>

Methods, evidence and recommendations

January 2016

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

NICE accredited

Funding
National Institute for Health and Care Excellence

Contents

Guideline Development Group members

Name	Role
Saul Faust (Chair)	Professor of Paediatric Immunology & Infectious Diseases & Director, NIHR Wellcome Trust Clinical Research Facility, University of Southampton
Richard Beale	Clinical Director of Perioperative, Critical Care & Pain Services and Consultant in Intensive Care Medicine
John Butler	Consultant in Emergency Medicine & Critical Care Medicine
Enitan Carrol	Chair in Paediatric Infection/Honorary Consultant, University of Liverpool Institute of Infection and Global Health
Simon Nadel	Adjunct Professor of Paediatric Intensive Care
Julian Newell	Corporate Matron, Patient Safety
Jenny O'Donnell	Patient member
Rachel Rowlands	Consultant in Paediatric Emergency Medicine
Mark Simmonds	Consultant in Acute and Critical Care Medicine
Alison Tavare	General Practitioner
Louella Vaughan	Senior Clinical Research Lead, Northwest London CLAHRC
James Wenman	Clinical Development Manager (Paramedic)
Catherine White	Patient member

NCGC technical team members

Name	Role
Neil Askew	Health Economist (from March 2015)
Mikaela Bartlett	Document Editor / Process Assistant (from August 2015)
Saskia Cheyne	Research Fellow (July 2014-March 2015)
Margaret Constanti	Senior Health Economist (from August 2015)
Angela Cooper	Senior Research Fellow (from April 2015)
Andreas Freitag	Research Fellow (from June 2015)
Lina Gulhane	Head of Information Science (from September 2014)
Martin Harker	Senior Health Economist (July 2014-April 2015)
Yasmina Hedhli	Project Manager (July 2014-June 2015)
Sophia Kemis-Betty	Senior Health Economist (April 2015-August 2015)
Bethany King	Document Editor / Process Assistant (August 2014-July 2015)
Norma O'Flynn	Guideline Lead and Clinical Director
Natalie Pink	Project Manager (May – July 2015)
Nancy Pursey	Senior Project Manager (from August 2015)
Silvia Rabar	Senior Research Fellow
Julie Robinson	Information Scientist (July-September 2014)
Ashwini Sreekanta	Research Fellow (from June 2015)

1 Co-optees

Name	Role
Michael Maresh	Consultant Obstetrician, St Mary's Hospital, Manchester
Ronan McMullan	Senior Lecturer & Consultant Medical Microbiologist, Queens University Belfast & Belfast HSC trust

Acknowledgements

The development of this guideline was greatly assisted by the following people:

Jill Cobb, Information Scientist, National Clinical Guideline Centre

Tamara Diaz, Project Manager, National Clinical Guideline Centre

Lefteris Floros, Health Economist, National Clinical Guideline Centre

Grace Massey, Information Scientist (Document Delivery), National Clinical Guideline Centre

Elizabeth Pearton, Information Scientist (Document Delivery), National Clinical Guideline Centre

Mark Perry, Senior Research Fellow, National Clinical Guideline Centre

Josh South, Administrator, National Clinical Guideline Centre

Thomas Strong, Information Scientist (Document Delivery), National Clinical Guideline Centre

Claire Wallnut, Information Scientist (Document Delivery), National Clinical Guideline Centre

Ruth Wong, Information Scientist (Document Delivery), National Clinical Guideline Centre

1Guideline summary

1.1 Algorithms

Figure 1: Managing adults and children and youg people 12 years and over with suspected sepsis outside of acute hospital settings

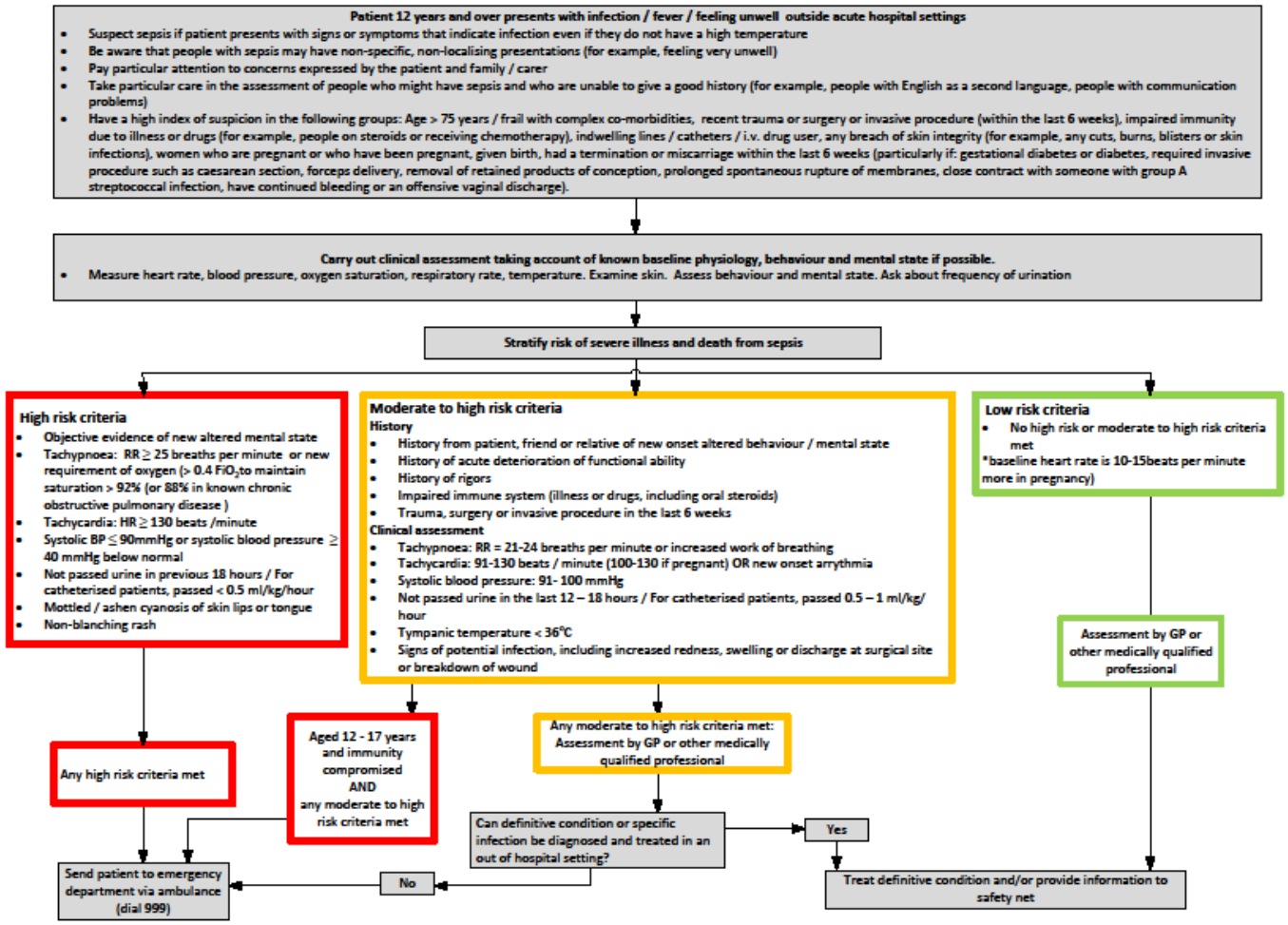


Figure 2: Managing adults and children and young people 12 years and over with suspected sepsis in acute hospital setting

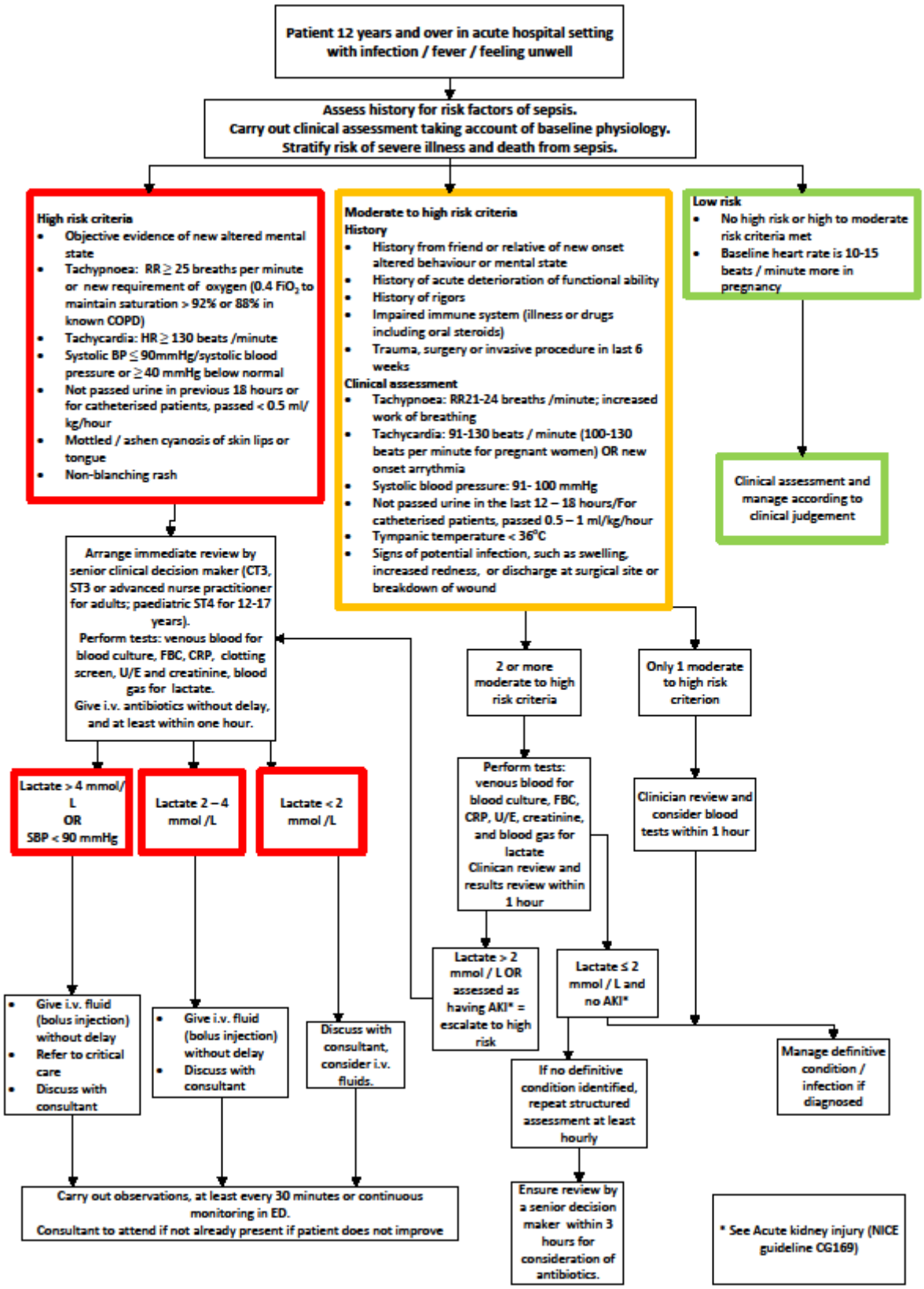


Figure 3: Managing children aged 5 -11 years with suspected sepsis outside acute hospital settings

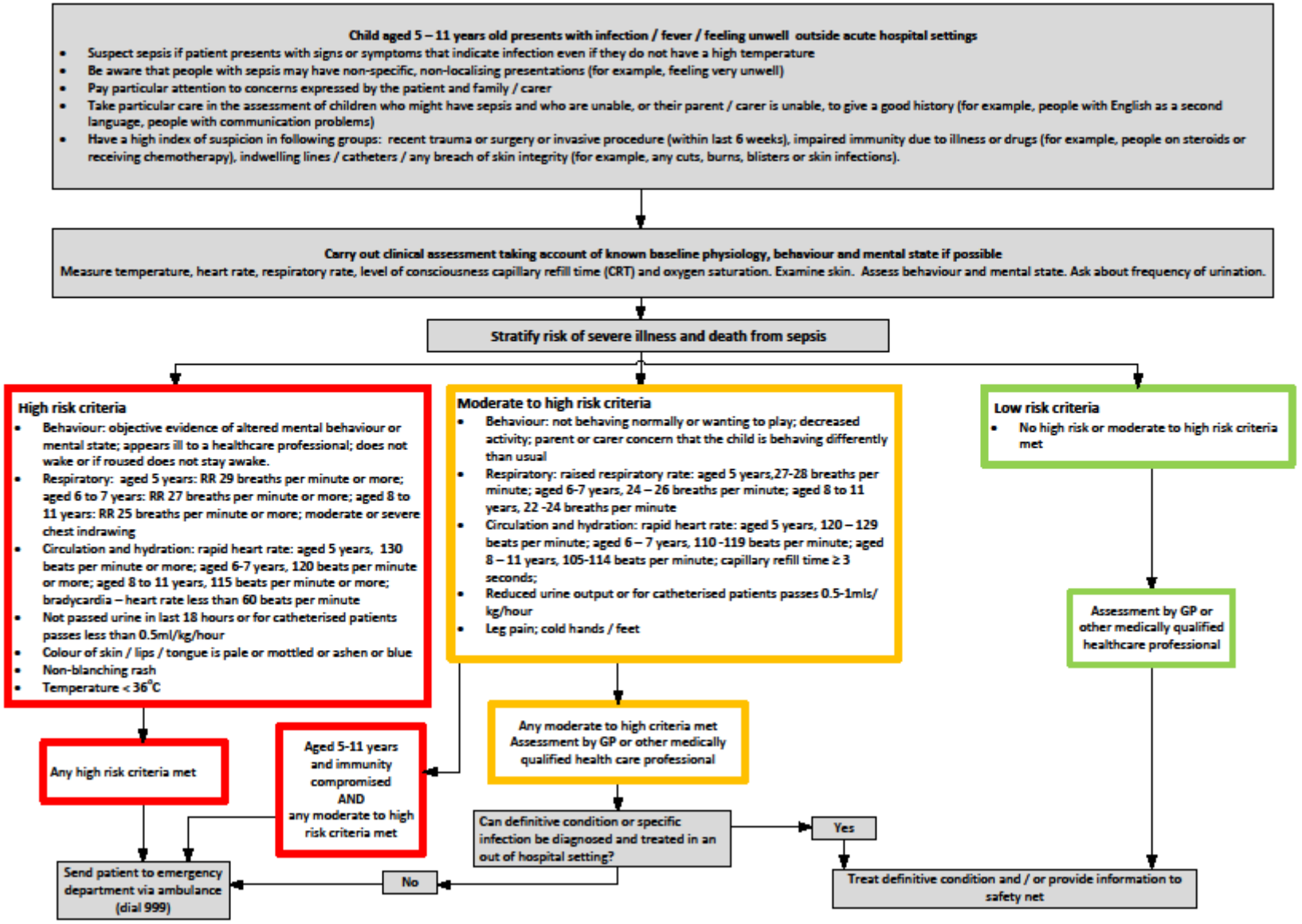


Figure 4: Managing children aged 5 -11 years with suspected sepsis in acute hospital setting

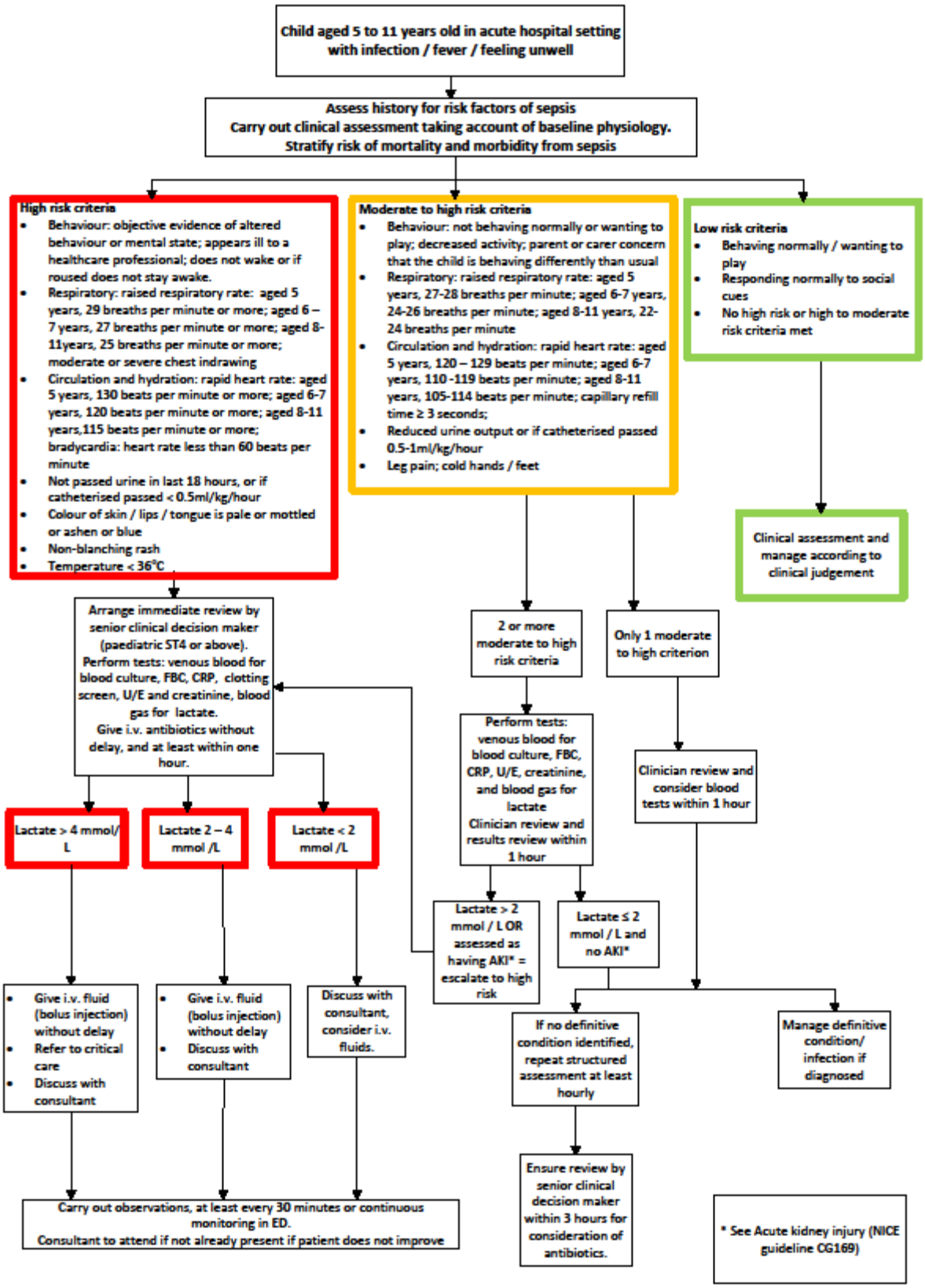


Figure 5: Managing children aged under 5 years with suspected sepsis outside acute hospital settings

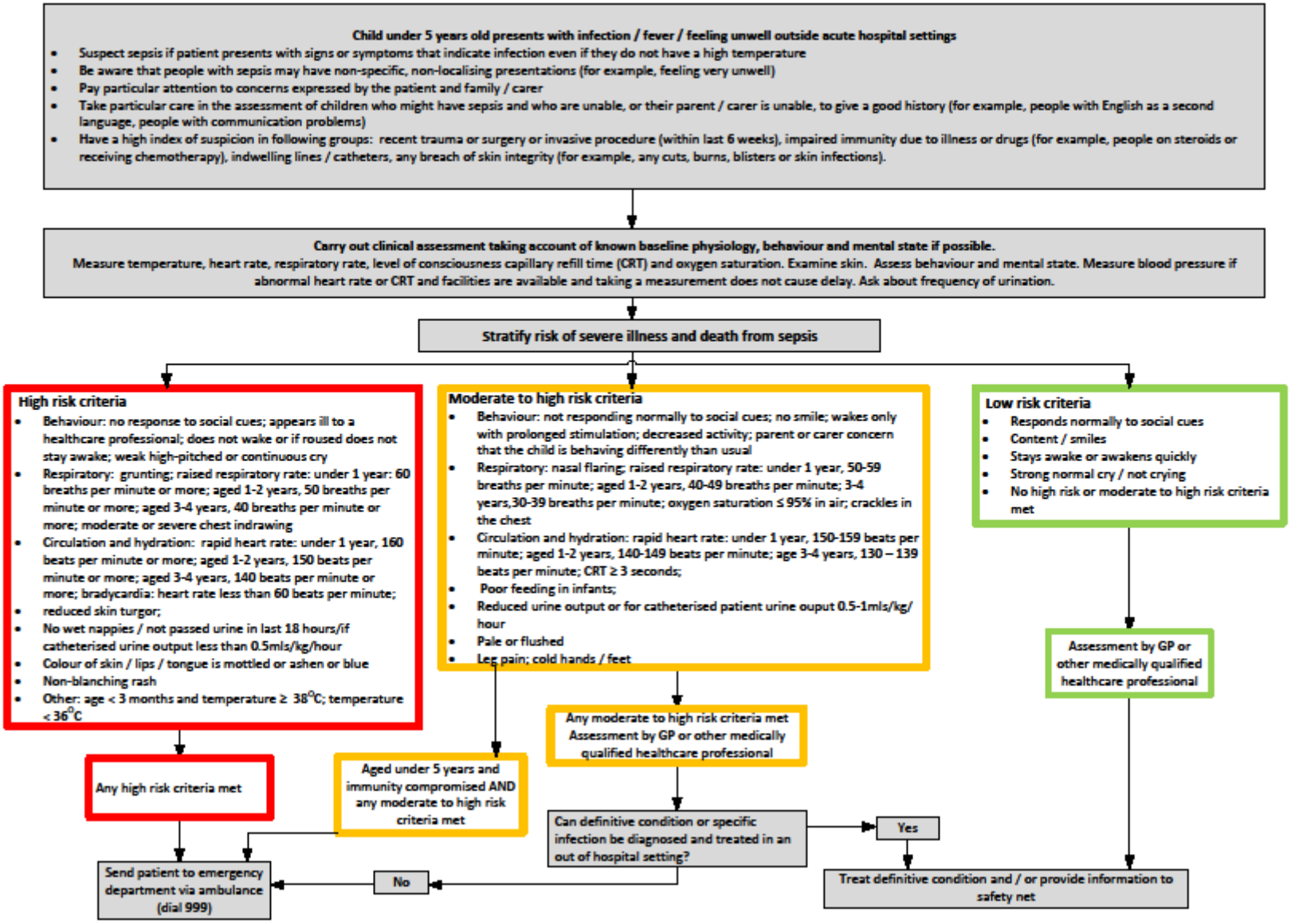
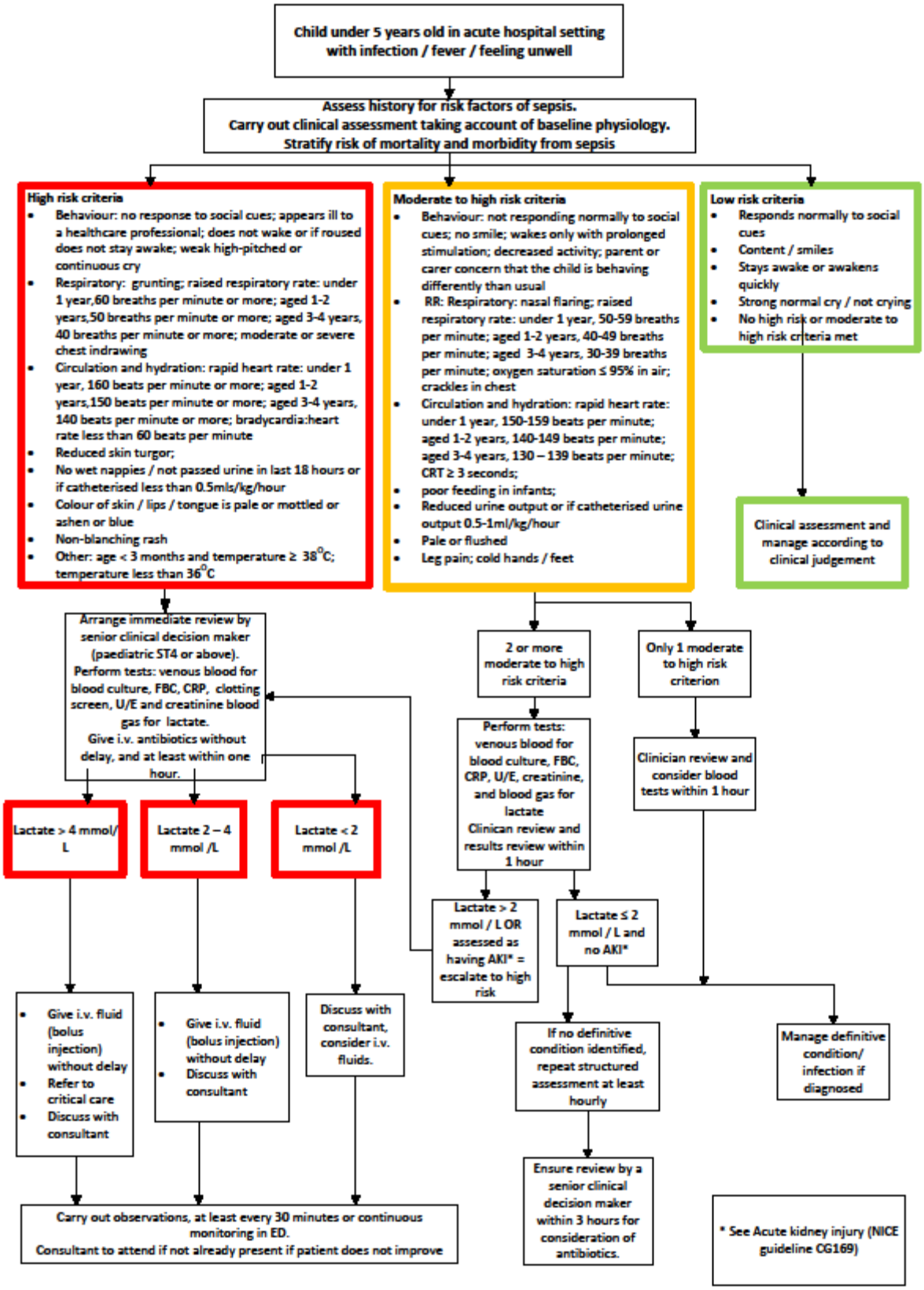


Figure 6: Managing children aged under 5 years with suspected sepsis in acute hospital setting



1.2 Full list of recommendations

Identifying sepsis and people at increased risk of sepsis

1. **Suspect sepsis if a person presents with signs or symptoms that indicate possible infection, even if they do not have a high temperature.**

2. **Take into account that people with sepsis may have non-specific, non-localised presentations, for example feeling very unwell.**

3. **Pay particular attention to concerns expressed by the person and their family or carers, for example changes from usual behaviour.**

4. **Assess people who might have sepsis with extra care if they cannot give a good history (for example, people with English as a second language or people with communication problems).**

5. **Take into account that people in the groups below are at higher risk of developing sepsis:**

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

6. **Take into account that women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the last 6 weeks, are in a high risk group for sepsis. In particular, women who:**

- **have gestational diabetes or diabetes**
- **needed invasive procedures (for example, caesarean section, forceps delivery, removal of retained products of conception)**
- **had prolonged spontaneous rupture of membranes**
- **have been in close contact with people with group A streptococcal infection**
- **have continued bleeding or an offensive vaginal discharge.**

7. **Take into account the following risk factors for early-onset neonatal infection:**

- **invasive group B streptococcal infection in a previous baby**
- **maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy**

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

[This recommendation is from Neonatal infection (NICE clinical guideline CG149).]

8. **Use a structured set of observations (see recommendations 9 and 10) when assessing people who might have sepsis. Consider using an early warning score in hospital settings.**

9. **Assess temperature, heart rate, respiratory rate, systolic blood pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis.**

10. **Assess temperature, heart rate, respiratory rate, level of consciousness, oxygen saturation and capillary refill time in children under 12 years with suspected sepsis. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]**

11. **Measure blood pressure of children under 5 years if heart rate or capillary refill time is abnormal and facilities to measure blood pressure, including correct blood pressure cuff, are available. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)].**

12. **Measure blood pressure of children aged 5 to 11 years who might have sepsis if facilities to measure blood pressure, including correct cuff, are available.**

13. **Only measure blood pressure in children under 12 years in community settings if facilities to measure blood pressure, including correct cuff, are available, and taking a measurement does not cause a delay in assessment or treatment.**

14. **Only measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.**

15. **Examine skin of people with suspected sepsis for mottled or ashen complexion, cyanosis, non-blanching rash, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection.**

16. **Ask the person, parent or carer about frequency of urination in the past 18 hours.**

17. **Use the person's history and physical examination results to grade risk of severe illness or death from sepsis using criteria based on age (see Table 76, Table 77 and Table 78)**

18. **Recognise that adults and children and young people aged 12 years and over with any of the symptoms or signs below are at high risk of severe illness or death from sepsis:**

- **objective evidence of new altered mental state**

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

19. **Recognise that adults and children and young people aged 12 years and over with any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:**

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

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

21. **Recognise that children aged 5–11 years with any of the symptoms or signs below are at high risk of severe illness or death from sepsis:**

- **has objective evidence of altered behaviour or mental state, or appears ill to a healthcare professional, or does not wake up (or if roused, does not stay awake)**
- **respiratory rate:**
  - **aged 5 years, 29 breaths per minute or more**
  - **aged 6-7 years, 27 breaths per minute or more**
  - **aged 8-11 years, 25 breaths per minute or more**
  - **or moderate or severe chest indrawing**
- **heart rate**
  - **aged 5 years, 130 beats per minute or more**
  - **aged 6–7 years, 120 beats per minute or more**

  - **aged 8-11 years, 115 beats per minute or more**
  - **or heart rate less than 60 beats per minute at any age**
- **not passed urine in last 18 hours, or for catheterised patients, passed less than 0.5ml/kg of urine per hour**
- **colour of skin, lips or tongue is pale, mottled, ashen or blue**
- **non-blanching rash**
- **has temperature less than 36°C.**

22. Recognise that children aged 5–11 years with any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- **not responding normally to social cues or decreased activity, or parent or carer concern that the child is behaving differently from usual**
- **respiratory rate:**
  - **aged 5 years, 27-28 breaths per minute**
  - **aged 6-7 years, 24-26 breaths per minute**
  - **aged 8-11 years, 22-24 breaths per minute**
- **heart rate:**
  - **aged 5 years, 120-129 beats per minute**
  - **aged 6-7 years, 110-119 beats per minute**
  - **aged 8-11 years, 105-114 beats per minute**
  - **or capillary refill time of 3 seconds or more**
- **reduced urine output, or for catheterised patients, passed 0.5-1ml/kg of urine per hour**
- **have leg pain or cold hands and feet.**

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

24. Recognise that children aged under 5 years with any of the symptoms or signs below are at high risk of severe illness or death from sepsis :

- **no response to social cues**
- **appears ill to a healthcare professional**
- **does not wake, or if roused does not stay awake**
- **weak, high-pitched or continuous cry**
- **grunting**
- **heart rate:**
  - **aged under 1 year, 160 beats per minute or more**
  - **aged 1-2 years, 150 beats per minute or more**
  - **aged 3-4 years, 140 beats per minute or more**
  - **heart rate less than 60 beats per minute at any age**
- **reduced skin turgor**
- **no wet nappies or not passed urine in past 18 hours, or for catheterised children, passed less than 0.5ml/kg of urine per hour**
- **respiratory rate:**
  - **aged under 1 year, 60 breaths per minute or more**

  - **aged 1-2 years, 50 breaths per minute or more**
  - **aged 3-4 years, 40 breaths per minute or more**
- **moderate or severe chest indrawing**
- **colour of skin, lips or tongue is pale, mottled, ashen or blue**
- **other symptoms and signs:**
  - **age under 3 months and temperature 38°C or more**
  - **non-blanching rash**
  - **temperature less than 36 °C**

  [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]

25. Recognise that children under 5 years with any of the symptoms or signs below are in a moderate to high risk of severe illness or death from sepsis:

- **not responding normally to social cues**
- **no smile**
- **wakes only with prolonged stimulation**
- **decreased activity**
- **parent or carer concern that the child is behaving differently from usual**
- **nasal flaring**
- **respiratory rate:**
  - **aged under 1 year, 50-59 breaths per minute**
  - **aged 1-2 years, 40-49 breaths per minute**
  - **aged 3-4 years, 35-39 breaths per minute**
- **oxygen saturation 95% or less in air**
- **crackles in the chest**
- **heart rate:**
  - **aged under 1 year, 150-159 beats per minute**
  - **aged 1-2 years, 140-149 beats per minute**
  - **aged 3-4 years, 130-139 beats per minute**
- **capillary refill time of 3 seconds or more**
- **poor feeding in infants**
- **reduced urine output or for catheterised patients, passed 0.5-1 ml/kg of urine per hour**
- **is pale or flushed or has pallor of skin, lips or tongue reported by parent or carer**
- **other symptoms and signs: age 3–6 months and temperature 39°C or over, leg pain, cold hands or feet.**

[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]

26. Consider children aged under 5 years who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]

Temperature

27. Do not use a person's temperature as the sole predictor of sepsis.

28. Do not rely on fever or hypothermia to rule sepsis either in or out.

29. Ask the person with suspected sepsis and their family or carers about any recent fever or rigors.

30. Take into account that some groups of people with sepsis may not develop a raised temperature. These include:

- **people who are older or very frail**
- **people having treatment for cancer**
- **people severely ill with sepsis**
- **young infants or children.**

31. Take into account that a rise in temperature can be a physiological response, for example after surgery or trauma.

Heart rate in suspected sepsis

32. Interpret the heart rate of a person with suspected sepsis in context, taking into account that:

- **baseline heart rate may be lower in young people and adults who are fit**
- **baseline heart rate in pregnancy is 10-15 beats per minute more than normal**
- **older people with an infection may not develop an increased heart rate**
- **older people may develop a new arrhythmia in response to infection rather than an increased heart rate**
- **heart rate response may be affected by medicines such as beta-blockers.**

Blood pressure in suspected sepsis

33. Interpret blood pressure in the context of a person's previous blood pressure, if known.

Confusion, mental state and cognitive state in suspected sepsis

34. Interpret a person's mental state in the context of their normal function and treat changes as being significant.

35. Be aware that changes in cognitive function may be subtle and assessment should include history from patient and family or carers.

36. Take into account that changes in cognitive function may present as changes in behaviour or irritability in both children and in adults with dementia.

37. Take into account that changes in cognitive function in older people may present as acute changes in functional abilities.

Oxygen saturation

38. Take into account that if peripheral oxygen saturation is difficult to measure in a person with suspected sepsis, this may indicate poor peripheral circulation because of shock.

Managing suspected sepsis outside acute hospital settings

39. Refer all people with suspected sepsis outside acute hospital settings for emergency medical care by the most appropriate means of transport (usually 999 ambulance) if:

- **they meet any high risk criteria (see Table 76), or**
- **they are aged under 17 years and their immunity is compromised and they have any moderate to high risk criteria.**

40. Arrange review by a GP or other doctor within 1 hour when any moderate to high risk criteria in a person with suspected sepsis are identified by a non-medical practitioner outside an acute hospital setting.

41. Assess (by a GP or other doctor) all people with suspected sepsis outside acute hospital settings with any moderate to high risk criteria for:

- **definitive diagnosis of their condition**
- **whether they can be treated safely outside hospital.**

42. If a definitive diagnosis is not reached or the person cannot be treated safely outside acute hospital setting, refer them urgently to the emergency department.

43. Arrange review by a GP or other doctor for a person with suspected sepsis but has no high or moderate to high risk criteria if they have had their first assessment by a non-medical practitioner outside an acute hospital setting.

Managing and treating sepsis in hospital

Adults and children and young people aged 12 years and over who meet 1 or more high risk criteria

44. For adults and children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker**[1]
- **carry out a venous blood test for the following:**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas to include lactate measurement**
- **give a broad-spectrum antimicrobial at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.4**

[1] A 'senior clinical decision maker'for people aged 18 years or over should be someone who is authorised to prescribe antibiotics, such as a doctor of grade CT3/ST3 or above, or an advanced nurse practitioner with antibiotic prescribing rights, depending on local arrangement. A 'senior clinical decision maker' for people aged 12-17 years is a paediatric qualified doctor of grade ST4 or above.

- **discuss with consultant.**

45. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre, or blood pressure less than 90 mmHg:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5, and**
- **refer to critical care for review of central venous access and initiation of inotropes or vasopressors and admission to critical care.**

46. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

47. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- **consider giving fluids (in line with recommendations in section 8.5).**

48. Monitor people with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients in acute hospital settings. [This recommendation is from Acute illness in adults in hospital (NICE guideline CG50)].

49. Monitor the mental state of adults and children and young people aged 12 years and over with suspected sepsis. Consider using a scale such as the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

50. Alert a consultant to attend in person if an adult, child or young person aged 12 years or over with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **systolic blood pressure persistently below 90 mmHg**
- **reduced level of consciousness despite resuscitation**
- **respiratory rate over 30 breaths per minute**
- **lactate not reduced by more than 20% within 1 hour.**

Adults and children and young people aged 12 years and over who meet 2 or more moderate to high risk criteria

51. For adults and children and young people aged 12 years and over with suspected sepsis and 2 or more moderate to high risk criteria, carry out a venous blood test for the following :

- **blood culture**
- **full blood count**
- **C reactive protein**
- **urea and electrolytes**
- **creatinine**

- **blood gas to include lactate measurement**
- **arrange for a clinician[2] to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria.**

52. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury[3], treat as high risk and follow recommendations 44-50.

53. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[3] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

54. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[3] and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition**
- **if appropriate, discharge with information (see recommendations 121 and 1222), depending on the setting.**

Adults and children and young people aged 12 years and over who meet only 1 moderate to high risk criterion

55. For adults and children and young people aged 12 years and over with suspected sepsis who meet 1 moderate to high risk criterion:

- **arrange clinician review[2] within 1 hour of meeting criterion for clinical assessment**
- **perform blood tests if indicated.**

56. For adults and children and young people aged 12 years and over with suspected sepsis who meet only 1 moderate to high risk criteria 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 121 and 122).**

57. For adults and children and young people aged 12 years and over with suspected sepsis who meet one moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[4] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker[5] within 3 hours of meeting moderate to high criterion for consideration of antibiotics.**

[2] A 'clinician' should be a medically qualified practictioner who has antibiotic prescribing rights.
[3] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)].
[4] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)

Adults and children and young people aged 12 years and over with no moderate or high risk criteria

58. Arrange clinical assessment[6] of adults and children and young people aged 12 years and over who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children aged 5-11 years who meet 1 or more high risk criteria

59. For children aged 5-11 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker[7]**
- **carry out a venous blood test for the following:**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas for glucose and lactate**
- **give people a broad-spectrum antimicrobial (see section 8.4) at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria)**
- **discuss with consultant.**

60. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate over 4 mmol:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria in line with recommendations in section 8.5) and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care.**

61. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

62. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- **consider giving fluids in line with recommendations in section 8.5.**

63. Monitor children with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is adapted from Acutely ill patients in hospital (NICE guideline CG50)].

[5] A 'clinician' should be a medically qualified practitioner who has antibiotic prescribing rights
[6] Clinical assessment should be carried out by a medically qualified practictioner with antibiotic prescribing rights
[7] A 'senior clinical decision maker' for children aged 5-11 years is a paediatric qualified doctor of grade ST4 or above

64. Monitor the mental state of children aged 5-11 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

65. Alert a consultant to attend in person if a child aged 5-11 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **reduced level of consciousness despite resuscitation**
- **heart rate or respiratory rate fulfil high risk criteria**
- **lactate remains over 2 mmol/litre after one hour.**

Children aged 5-11 years who meet 2 or more moderate to high risk criteria

66. For children aged 5-11 years with suspected sepsis and 2 or more moderate to high risk criteria:

- **carry out a venous blood test for the following :**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **blood gas for glucose and lactate**
- **arrange for a clinician to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria.**

67. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury[8], treat as high risk and follow recommendations 59-65.

68. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[8] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

69. For children aged 5-11 years with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[9] and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition, and**
- **if appropriate, discharge with information depending on setting (see recommendations 121 and 122).**

[8] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)
[9] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)

Children aged 5-11 years who meet only 1 or more moderate to high risk criteria

70. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- **arrange clinician review[10] within 1 hour of meeting 1 moderate to high risk criterion for clinical assessment and**
- **perform blood tests if indicated.**

71. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criteria 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 121 and 122)**

72. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[9] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting a moderate to high risk criterion for consideration of antibiotics.**

Children aged 5-11 years with no high risk or moderate to high risk criteria

73. Arrange clinical assessment[11] of children aged 5-11 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children aged under 5 years

Children aged under 5 years who meet 1 or more high risk criteria

74. For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker[12]**
- **carry out a venous blood test for the following :**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas for glucose and lactate**
- **give parentral antibiotics (within 1 hour of identifying that they meet any high risk criteria; see section 8.4)**
- **discuss with consultant.**

[10] A 'clinician' should be a medically qualified practictioner with antibiotic prescribing rights.
[11] This could be by a medically qualified practitioner with prescribing rights.
[12] A 'senior clinical decision maker' for children aged under 5 years is a paediatric qualified doctor of grade ST4 or above.

75. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre:

- **give fluids (in line with recommendations in section 8.5), and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care.**

76. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

77. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre, consider giving fluids in line with recommendations in section 8.5.

78. Monitor children aged under 5 years with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is adapted from Acutely ill patients in hospital (NICE guideline CG50)].

79. Monitor the mental state of children under 5 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

80. Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **reduced level of consciousness despite resuscitation**
- **heart rate or respiratory rate fulfill high risk criteria**
- **lactate over 2 mmol/litre after 1 hour.**

81. Give parenteral antibiotics to children aged under 3 months as follows:

- **infants younger than 1 month with fever**
- **all infants aged 1–3 months with fever who appear unwell**
- **infants aged 1–3 months with white blood cell count less than 5×10^9/litre or greater than 15×10^9/litre. [This recommendation is from Fever in under 5s (NICE guideline CG160)]**

Children aged under 5 years who meet 2 or more moderate to high risk criteria

82. For children aged under 5 years with suspected sepsis and 2 or more moderate to high risk criteria carry out a venous blood test for the following :

- **blood culture**
- **full blood count**
- **C reactive protein**
- **urea and electrolytes**
- **creatinine**
- **blood gas for glucose and lactate**

- **arrange for a clinician[13] to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria.**

83. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 74 to 81.

84. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criterion for consideration of antibiotics.**

85. For children aged under 5 years with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition and**
- **if appropriate, discharge with information (see recommendations 121 and 122), depending on the setting.**

Children aged under 5 years who meet only 1 moderate to high risk criterion

86. For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- **arrange clinician review within 1 hour of meeting a moderate to high risk criterion for clinical assessment and**
- **perform blood tests if indicated.**

87. For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated:

- **manage the definitive condition**
- **if appropriate, discharge with information depending on setting (see recommendations 121 and 122).**

88. For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[14] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours for consideration of antibiotics.**

[13] A clinician should be a medically qualified practictioner who has antibiotic prescribing rights
[14] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)

Children aged under 5 years with no moderate or high risk criteria

89. **Arrange clinical assessment[15] of children aged under 5 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.**

Antibiotic treatment

90. **Pre-alert secondary care (through GP or ambulance service) when any high risk criteria are met in a person with suspected sepsis outside of a hospital, and transfer them immediately.**

91. **Ensure urgent assessment mechanisms are in place to deliver antibiotics when any high risk criteria are met in secondary care (within 1 hour of meeting a high risk criterion).**

92. **Ensure GPs and ambulance services have mechanisms in place to give antibiotics in the pre-hospital setting if transfer time is likely to be more than 1 hour.**

93. **For patients in hospital who have suspected infections, take microbiological samples before prescribing an antimicrobial and review the prescription when the results are available. For people with suspected sepsis, take blood cultures before antibiotics are given. [This recommendation is adapted from Antimicrobial stewardship (NICE guideline NG15].**

94. **If meningococcal disease is specifically suspected (fever and purpuric rash) give appropriate doses of parenteral benzyl penicillin in community settings and intravenous ceftriaxone in hospital settings. [This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline 102)]**

95. **For people aged 18 years and above who need an empirical intravenous antimicrobial for a suspected infection but who have no confirmed diagnosis, use an intravenous antimicrobial from the agreed local formulary and in line with local (where available) or national guidelines. [This recommendation is adapted from Antimicrobial stewardship (NICE guideline 15)]**

96. **For people aged up to 17 years with suspected community acquired sepsis of any cause give ceftriaxone 80 mg/kg once a day with a maximum dose of 4g daily at any age. [This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE clinical guideline 102)]**

97. **For people aged up to 17 years with suspected sepsis who are already in hospital, or who are known to have previously been infected with ceftriaxone-resistant bacteria, consult local guidelines for choice of antibiotic.**

98. **For children younger than 3 months, an additional antibiotic active against listeria (for example, ampicillin or amoxicillin) should be given. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]**

[15] Clinical assessment should be carried out by medically qualified practictioner who has antibiotic prescribing rights.

99. Treat neonates presenting in hospital with suspected sepsis with intravenous benzylpenicillin and gentamicin [This recommendation is from Neonatal infection (NICE guideline CG149)]

100. Treat neonates who are more than 40 weeks postmenstrual age who present with community acquired sepsis with ceftriaxone 50 mg/kg unless already receiving an intravenous calcium infusion at the time. If 40 weeks postmenstrual age or below or receiving an intravenous calcium infusion use cefotaxime 50mg/kg.

Fluids

101. If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of 500 ml over less than 15 minutes. [This recommendation is adapted from Intravenous fluid therapy in over 16s in hospital (NICE guideline CG174)]

102. If children and young people up to 16 years need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. [This recommendation is from Intravenous fluid therapy in children (NICE guideline NG29)]

103. If neonates need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes. [This recommendation is from Intravenous fluid therapy in children and young people in hospital (NICE guideline NG29)]

104. Reassess patient after completion of the intravenous fluid bolus, and if no improvement give second bolus. If no improvement after second bolus alert consultant to attend (in line with recommendations 50, 65 and 80).

105. Use a pump or syringe if no pump is available to deliver fluids for resuscitation to people with suspected sepsis who need fluids in bolus form.

106. Do not use tetrastarch for fluid resuscitation for people with sepsis. [This recommendation is adapted from Intravenous fluid therapy in over 16s in hospital (NICE guideline CG174)].

107. Consider human albumin solution 4–5% for fluid resuscitation only in patients with sepsis with shock [This recommendation is adapted from Intravenous fluid therapy in over 16s in hospital (NICE guideline CG174)].

Using oxygen

108. Give oxygen to achieve a target saturation of 94-98% for adult patients or 88-92% for those at risk of hypercapnic respiratory failure.

109. Oxygen should be given to children with suspected sespis who have signs of shock or oxygen saturation (SpO_2) of less than 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO_2 of greater than 92%, as clinically indicated. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)].

Finding the source of infection

110. Carry out a thorough clinical examination to look for sources of infection.

111. Tailor investigations to the person's clinical history and findings on examination.

112. Consider urine analysis and chest X-ray in all people aged over 5 years with suspected sepsis.

113. Consider imaging of the abdomen and pelvis if no likely source is identified after clinical examination and initial tests.

114. Involve the adult or paediatric surgical and gynaecological teams early on if intra-abdominal or pelvic infection is suspected in case surgical treatment is needed.

115. Do not perform a lumbar puncture if any of the following contraindications are present:

- **signs suggesting raised intracranial pressure or reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)**
- **relative bradycardia and hypertension**
- **focal neurological signs**
- **abnormal posture or posturing**
- **unequal, dilated or poorly responsive pupils**
- **papilloedema**
- **abnormal 'doll's eye' movements**
- **shock**
- **extensive or spreading purpura**
- **after convulsions until stabilised**
- **coagulation abnormalities or coagulation results outside the normal range or platelet count below 100 x 10^9/litre or receiving anticoagulant therapy**
- **local superficial infection at the lumbar puncture site**
- **respiratory insufficiency in children.**

[This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline 102)]

116. Perform lumbar puncture in the following children with suspected sepsis (unless contraindicated, please see contraindications in recommendation 115):

- **infants younger than 1 month**
- **all infants aged 1–3 months who appear unwell**
- **infants aged 1–3 months with a white blood cell count less than 5 × 10^9/litre or greater than 15 × 10^9/litre.**

[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]

Information and support for people with sepsis and their families and carers

People who have sepsis, and their families and carers

117. Ensure a care team member is nominated to give information to families and carers, particularly in emergency situations such as in the emergency department. This should include:

- **an explanation that the person has sepsis, and what this means**
- **an explanation of any investigations and the management plan**
- **regular and timely updates on treatment, care and progress.**

118. Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given.

119. Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed.

120. Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis.

Information at discharge for people assessed for possible sepsis, but not diagnosed with sepsis

121. Give people who have been assessed for sepsis but have been discharged (and their family or carers, if appropriate) verbal and written information about:

- **what sepsis is, and why it was suspected**
- **what tests and investigations have been done**
- **instructions about which symptoms to monitor**
- **when to get medical attention if their illness continues.**

122. Confirm that people understand the information they have been given, and what actions they should take to get help if they need it.

Information at discharge for people at increased risk of sepsis

123. Ensure people who are at increased risk of sepsis (for example after surgery) are told before discharge about symptoms that should prompt them to get medical attention.

See Neutropenic sepsis (NICE guideline CG15) for information for people with neutropenic sepsis (recommendation 1.1.1.1).

Information at discharge for people who have had sepsis

124. Ensure people and their families and carers if appropriate have been informed that they have had sepsis.

125. Ensure discharge notifications to GPs include the diagnosis of sepsis.

126. Give people who have had sepsis (and their families and carers, when appropriate) opportunities to discuss their concerns. These may include:

- **why they developed sepsis**
- **whether they are likely to develop sepsis again**
- **if more investigations are necessary**
- **details of any community care required, for example, related to peripherally inserted central venous catheters (PICC) lines or other intravenous catheters**
- **what they should expect during recovery**
- **arrangements for follow-up, including specific critical care follow up if relevant**
- **possible short-term and long-term problems.**

127. Give people who have had sepsis and their families and carers information about national charities and support groups that provide information about sepsis and causes of sepsis.

128. Advise carers they have a legal right to have a carer's assessment of their needs, and give them information on how they can get this.

See Rehabilitation after critical Illness in adults (NICE guideline CG83) for recommendations on rehabilitation and follow up after critical illness.

See Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline CG102) for follow up of people who have had meningococcal septicaemia.

Training and education

129. Ensure all healthcare staff and professionals are given regular appropriate training in sepsis recognition. This includes:

- **ambulance clinicians**
- **allied health professionals**
- **medical students and doctors of all grades**
- **healthcare assistants**
- **midwives**
- **nurses**
- **operating department assistants**
- **receptionists in a clinical setting.**

130. Ensure all healthcare professionals are given regular, appropriate training in identifying, assessing and managing sepsis. This should include:

- **risk stratification strategies**
- **local protocols for early treatments, including antibiotics and fluids**
- **criteria for escalation to critical care.**

1.3 Research recommendations

1. **Can early warning scores, for example NEWS (national early warning scores for adults) and PEWS (paediatric early warning score), be used to improve the detection of sepsis and facilitate prompt and appropriate clinical response in pre-hospital settings and in emergency departments?**

2. **Is it possible to derive and validate a set of clinical decision rules or a predictive tool to rule out sepsis which can be applied to patients presenting to hospital; with suspected sepsis?**

3. **What is the clinical and cost effectiveness of procalcitonin (PCT) point-of-care tests at initial triage for diagnosis of serious infection and the initiation of appropriate antibiotic therapy?**

4. **A UK sepsis registry should be established to collect clinical and epidemiological data to provide information to support clinical audit to inform the research agenda.**

5. **What effect will the NICE sepsis guideline have on patient care processes and outcomes in the UK over the next 5 years?**

2 Introduction

Sepsis is a clinical syndrome caused by the body's immune and coagulation systems being switched on by an infection. Sepsis with shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement, and organ dysfunction or failure. Sepsis is an important cause of death in people of all ages. Both a UK Parliamentary and Health Service Ombudsman enquiry (2013) and UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2015) have recently highlighted sepsis as being a leading cause of avoidable death that kills more people than breast, bowel and prostate cancer combined.

Clinicians and healthcare professionals of all kinds, at all levels of seniority and in all clinical settings often find sepsis difficult to diagnose with certainly. Although people with sepsis may have a history of infection, fever is not present in all cases. The signs and symptoms of sepsis are usually very non-specific and can be missed if clinicians do not think "could this be sepsis?"

Detailed guidelines exist for the management of sepsis in adult and paediatric intensive care units, and by intensive care clinicians called to other settings. To reduce avoidable deaths, people with sepsis need to be recognised early and treatment initiated. This guideline aims to ensure healthcare systems in all clinical settings consider sepsis as an immediate life-threatening condition that should be recognised and treated as an emergency. The guideline outlines the immediate actions required for those with suspicion of sepsis and who are at highest risk of morbidity and mortality from sepsis. It provides a framework for risk assessment, treatment and follow-up or "safety-netting" of people not requiring immediate resuscitation.

The terminology around sepsis is changing with new international consensus definitions imminent. Terminology when the guideline was being developed included terms SIRS (systematic inflammatory response syndrome), severe sepsis and septic shock. The recommendations do not use the terms SIRS or severe sepsis but use the term 'suspected sepsis' or 'sepsis' throughout and recommend actions according to clinical parameters.

This guideline aims to consider the clinical evidence to help healthcare professionals and the public recognise when and in whom to suspect sepsis, how to identify the source of infection, what should be part of the clinical risk assessment including the evidence for the use of existing scoring tools and blood tests, initial fluid management and the timing of the escalation of care and senior staff involvement, and early disease monitoring and information and support for patient and their relatives or carers. Particular emphasis has been placed on early sepsis recognition and the initial treatments prior to escalation of care or moving onto a more specific clinical pathway.

In formulating these guidelines the Guideline Development Group and NICE have recognised relevant overlap with other specific NICE and Royal College guidance, in particular the care of acutely ill patients in hospital (CG50), the assessment and initial management of fever in under 5s (CG160), bacterial meningitis and meningogoccal septicaemia (CG102), neutropenic sepsis (CG151), antibiotics for prevention and treatment of neonatal infection (CG149), pneumonia in adults (CG191) and the Royal College of Obstetricians and Gynaecologists Sepsis in and following pregnancy guidelines (64a and 64b).

The guideline attempted to provide information on the cost effectiveness of the recommendations. However, detailed information on the underlying incidence of sepsis in the community and in hospital is lacking despite widely quoted estimates, and this question remains a key research priority for the NHS.

The guideline uses the best available evidence to enable all people presenting with sepsis across the country, whether in the community or in hospital, to receive the best care, improving their chance of survival without long term consequences of their infection. Use of the guideline will address many of the recommendations outlined by the National Confidential Enquiry into Patient Outcome and Death

(NCEPOD 2015) , including how to formulate an early recognition protocol for the identification and management of people with sepsis, which vital signs can inform the recognition of sepsis and the actions that should arise from differences to normal values, and who should be involved in the escalation of care.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- the 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NCGC to produce the guideline.

The Department of Health has asked NICE: 'to produce a guideline on Sepsis: the recognition, diagnosis and management of severe sepsis'.

13.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals, lay members and researchers developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Saul Faust in accordance with guidance from NICE.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

3.3.1 What this guideline covers

This guideline includes all populations. There are a number of different NICE guidelines that may cover aspects of recognition and management of sepsis in subgroups of the population. This guideline cross-refers to existing guidance that makes specific recomemndations about sepsis when appropriate. For further details please refer to the scope in Appendix A and the review questions in Section 4.2.

3.3.2 What this guideline does not cover

No groups have been excluded.

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE guidelines:

- Antimicrobial stewardship. NICE clinical guideline NG15 (2015).
- Pneumonia. NICE clinical guideline CG191 (2014).
- Acute kidney injury. NICE clinical guideline CG169 (2013).
- Critical illness rehabilitation. NICE clinical guideline CG83 (2013).
- Intravenous fluid therapy in adults in hospital. NICE clinical guideline CG174 (2013).
- Fever in under 5s. NICE clinical guideline CG160 (2013).
- Patient experience in adult NHS services. NICE clinical guideline CG138 (2012).
- Antibiotics for early-onset neonatal infection. NICE clinical guideline CG149 (2012).
- Infection control. NICE clinical guideline CG139 (2012).
- Neutropenic sepsis. NICE clinical guideline CG151 (2012).
- Diabetic foot problems - inpatient management. NICE clinical guideline CG119 (2011).

- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline CG102 (2010).
- Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline CG108 (2010).
- Venous thromboembolism - reducing the risk. NICE clinical guideline CG92 (2010).
- Diarrhoea and vomiting in children under 5. NICE clinical guideline CG84 (2009).
- Induction of labour. NICE clinical guideline CG70 (2008).
- Intrapartum care. NICE clinical guideline CG55 (2008) (update due for publication October 2014).
- Surgical site infection. NICE clinical guideline CG74 (2008).
- Acutely ill patients in hospital. NICE clinical guideline CG50 (2007).
- Urinary tract infection in children. NICE clinical guideline CG54 (2007).
- Nutrition support in adults. NICE clinical guideline CG32 (2006).
- Postnatal care. NICE clinical guideline CG37 (2006).

Related NICE guidance currently in development:

- Intravenous fluids therapy in children. NICE clinical guideline. Publication expected December 2015.
- Acute medical emergency guideline. NICE clinical guideline. Publication date to be confirmed.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2012 and 2014 versions.[233,235]

4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 18 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions, except for source of infection, early goal-directed therapy (EGDT) and central venous (CV) access. The recommendations for source of infection and CV access are based on discussions, consensus and expert opinion of the GDG and were also informed by other review questions. The rationale for these decisions is explained in more detail in relevant chapters. The review on EGDT only includes a recent systematic review on three large multi-centre RCTs, the ProMISe, ARISE, and ProCESS trials. This systematic review was considered to adequately address the EDGT review question.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
Blood tests	Diagnostic	In people with suspected sepsis how accurate are blood tests to identify whether sepsis is present?	Detecting sepsis and severe sepsis
Signs and Symptoms	Diagnostic	In people with suspected sepsis how accurate are physiological signs and symptoms to identify whether sepsis is present?	Detecting sepsis and severe sepsis
Monitoring	Prognostic and diagnostic	In people with sepsis or severe sepsis, what is the clinical and cost effectiveness of scoring systems, and specified blood markers (lactate clearance) in monitoring response to treatment?	Critical outcomes: • mortality • clinical resolution • health-related quality of life • critical care admission. Important: • treatment failure • appropriate or inappropriate use of antibiotics • duration of

Chapter	Type of review	Review questions	Outcomes
			treatment • hospital re-admission • length of hospital stay • complications.
Escalation of care	Intervention	When is the most appropriate time for care of people with sepsis to be directed to (a) a senior healthcare professional, and (b) critical care providers?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported. Less important: • adverse events.
Central venous access	Intervention	When is the most appropriate time for care of people with sepsis for venous access and arterial lines?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported. Less important: • adverse events.
Inotropic agents	Intervention	What is the most clinical and cost effective inotropic agent and vasopressor for early management of	Critical: • 28-day mortality

Chapter	Type of review	Review questions	Outcomes
		people with severe sepsis? What are the most clinically and cost effective timings of inotropic agents and vasopressors in patients with sepsis?	• health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported. Less important: • adverse events.
Source of infection	Diagnostic	What is the clinical test accuracy of the following tests to identify the source of infection? a) Blood culture b) Lumbar puncture c) Chest X-ray and other imaging	Diagnostic accuracy outcomes for identifying the source of infection
Information and support	Qualitative	What information, education and support would be useful for: a) People assessed for possible sepsis, but discharged from medical care b) People at high risk of sepsis c) People who have sepsis or severe sepsis, families and carers d) People who survived episodes of severe sepsis	• patient satisfaction, including understanding • reduction in time to diagnosis.
Intravenous fluids	Intervention	What is the most clinical and cost effective immediate/bolus IV fluid for resuscitation of patients with sepsis? What is the clinical and cost effectiveness of different volumes/dosages of immediate/bolus IV fluid resuscitation in patients with sepsis? What is the most clinically and cost effective rate of administration of immediate/bolus IV fluids in patients with sepsis?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported

Chapter	Type of review	Review questions	Outcomes
			• time to shock reversal. Less important: • adverse events.
Bicarbonates	Intervention	Is acid-base balance (that is, the use of bicarbonate) clinically and cost effective in people with sepsis?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported • time to shock reversal. Less important: • adverse events.
Oxygen	Intervention	Is the use of supplemental oxygen clinically and cost effective in patients with sepsis?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported • time to shock reversal. Less important:

Chapter	Type of review	Review questions	Outcomes
			• adverse events.
Education and training	Quantitative and qualitative	What education and training programmes improve early recognition, diagnosis and management of sepsis and severe sepsis?	• identifying patients who need intervention • what the research study did and achieved • are monitored data correctly evaluated/is the research robust? • time from presentation to diagnosis/how quickly sepsis was identified • antibiotics within one hour.
Scoring tools	Prognostic and diagnostic	What is the most accurate and cost effective assessment tool to identify patients with sepsis?	If thresholds are established/pre-defined: • relative risk (RR) or hazard ratios (HR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher or lower risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • Sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Antimicrobials	Intervention	What are the most clinically and cost effective timings of IV or IM empiric antimicrobial treatments	Critical:

Chapter	Type of review	Review questions	Outcomes
		in patients with (a) septic shock, (b) severe sepsis without shock or (c) sepsis? What is the most clinically and cost effective IV or IM empiric antimicrobial treatment in patients with sepsis?	• 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported • adverse events.
Early goal-directed therapy	Intervention	What is the clinical and cost effectiveness of implementing early goal-directed therapy?	Critical: • 28-day mortality • health-related quality of life • admission to critical care as a proxy for progression to severe sepsis. Important: • duration of hospital stay • duration of critical care stay • number of organs supported • time to shock reversal • adverse events •
Creatinine	Diagnostic	In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis?	Reference standards for worsening sepsis: • all-cause mortality • hospitalisation • ICU admission • length of stay.
DIC	Prognostic	In people with suspected sepsis what is the extent to	Reference

Chapter	Type of review	Review questions	Outcomes
	(poor clinical outcomes in people with sepsis)	which disseminated intravascular coagulation (DIC) affects clinical outcomes?	standards for worsening sepsis: • all-cause mortality • hospitalisation • ICU admission • length of stay.
Lactate	Diagnostic	In people with suspected sepsis how accurate is lactate to identify worsening sepsis?	Reference standards for worsening sepsis: • all-cause mortality • hospitalisation • ICU admission • length of stay.

14.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual.[235] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject specific databases were used for one question: CINAHL and PsycINFO for information support. All searches were updated on 9 October 2015. No papers added to the databases after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- NHS Evidence Search (www.evidence.nhs.uk)
- TRIP database (https://www.tripdatabase.com/)
- Sepsis Alliance (http://www.sepsisalliance.org/)
- The UK Sepsis Trust (http://sepsistrust.org/)
- Center for Sepsis Control & Care (http://www.cscc.uniklinikum-jena.de/cscc/en/CSCC-p-7.html)

4.2.2Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to sepsis and bacterial meningitis populations in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. The Health Economic Evaluation Database (HEED) ceased production in 2014 with access ceasing in January 2015. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2012, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. All searches were updated on 9 October 2015. No papers added to the databases after this date were considered.

4.3 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 2:

- potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual.[235]
- key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix H).
- summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
    - randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews)
    - observational studies: data were presented as a range of values in GRADE profiles
    - prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors
    - diagnostic studies: for reviews of diagnostic tests, diagnostic RCTs were the first line approach and, as with intervention reviews, evidence summaries were generated. If no evidence was found from diagnostic RCTs, diagnostic accuracy studies were reviewed. Coupled sensitivity and specificity values were summarised in forest plots. Accuracy measures were meta-analysed and reported as pooled results where appropriate. Where meta-analysis was performed, coupled sensitivity and specificity values were also presented on summary Receiver Operating Characteristic (sROC) plots along with the results of the meta-analysis (the summary sensitivity and specificity point and 95% confidence region) and the summary curve. Where evidence was not meta-analysed, because studies differed in population or outcome, then no alternative pooling strategies were carried out, on the basis that such pooling would have little meaning. Results from single studies were presented.
    - qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Figure 2: Step-by-step process of review of evidence in the guideline

1

4.3.1 Inclusion and exclusion criteria

3 The inclusion and exclusion of studies was based on the review protocols, which can be found in
4 Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in
5 Appendix L. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

6 The guideline population was defined to be adults, children (including neonates) and young people at
7 risk of developing sepsis. For some review questions, the review population also included people
8 with definite sepsis, severe sepsis or septic shock. The review on information and support also
9 included families and carers of people who had sepsis or severe sepsis, and people who had survived
10 episodes of severe sepsis. For the review on education and training, the review population was
11 defined as all healthcare professionals involved in the diagnosis, management and monitoring of
12 sepsis.

13 The subgroups considered included children, adults, pregnant women, people at higher risk of
14 infection, and different settings of care delivery. For some review questions, the evidence was
15 grouped by predefined subgroup analysis based on severity of illness.

16 Randomised trials, non-randomised trials, and observational studies (including diagnostic or
17 prognostic studies) were included in the evidence reviews as appropriate.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C.

4.3.12 Methods of combining clinical studies

4.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as mortality, critical care admission and adverse events.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as health-related quality of life, length of stay in ICU or hospital, and the number of organs supported, were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Where reported, time-to-event data was presented as a hazard ratio.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions, diagnosis and prognosis were expected to be different according to severity of illness.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I squared of 50-74% representing serious inconsistency and an I squared of >75% representing very serious inconsistency). Where considerable heterogeneity was present (I squared value of more than 50%), we carried out predefined subgroup analyses for children, adults, pregnant women, people at higher risk of developing sepsis, and different settings of care delivery.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no subgroup analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect. If sub-grouping successfully explained heterogeneity then each of the sub-groups was presented as a separate outcome (such as, mortality in people <30 and mortality in people > 30) and a fixed effect model was used.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was

reported as 'p≤0.001', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook[1] 'Missing standard deviations' were applied as the last resort.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

4.3.12.2 Data synthesis for prognostic factor reviews

A variety of prognostic effect measures were extracted from papers, depending on the type of outcome.

For binary outcomes, odds ratios, risk ratios or hazard ratios (with their 95% confidence intervals) for the independent effect of each prognostic factor on the outcome were extracted. Beta coefficients for dichotomous outcomes were normally converted to an OR by taking the anti-natural logarithm of the beta coefficient (as Beta coefficient = ln OR).

For continuous outcomes the Beta coefficients (or standardised beta coefficients) with their 95% confidence intervals for the independent effect of each prognostic factor were extracted.

RCTs, pooled analyses of patient level data, and prospective or retrospective cohort studies were included. Case-control studies were excluded because of their high risk of recall bias. All non-RCT studies were required to have considered **all** key confounders previously identified by the GDG at the protocol stage for that outcome. Studies not considering these key confounders were excluded. For a confounder to be regarded as having been adequately considered, it would have to have been included in the multivariable analysis (although in a step-wise model it would not necessarily have to be present in the final model) or would have to have been shown to be matched across risk factor or outcome groups at baseline.

If more than one study covered the same combination of population, risk factor and outcome then meta-analysis was used to pool results. Meta-analysis was carried out using the generic inverse variance function on Review Manager using fixed effects. Heterogeneity was assessed using the same criteria as for intervention studies, with an I^2 of 50-74% representing serious inconsistency and an I^2 of >75% representing very serious inconsistency. If serious or very serious heterogeneity existed, then sub-grouping strategies were based on pre-specified sub-grouping criteria as for interventional reviews. If sub-grouping failed to explain heterogeneity, then the random effects model was used. If sub-grouping successfully explained heterogeneity then each of the sub-groups was presented as a separate outcome (such as, mortality in people <30 and mortality in people > 30) and a fixed effect model was used.

Where evidence was not meta-analysed, because studies differed in population, outcome or risk factors, then no alternative pooling strategies were carried out, on the basis that such pooling would have little meaning. Results from single studies were presented.

4.3.12.3 Data synthesis for diagnostic test accuracy reviews

Data and outcomes

For the reviews of diagnostic tests, the first line approach was to use diagnostic RCTs. For outcomes and data synthesis of diagnostic RCTs, a similar approach to intervention reviews was used.

For reviews of diagnostic accuracy studies, the diagnostic test accuracy measures used in the analysis were: area under curve (AUC) for the ROC curve (as reported by the individual studies for each index test), sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio. For most diagnostic review questions, index tests were either not available or not reported by the included studies.

The likelihood ratio (LR) combines information about the sensitivity and specificity. It explains how much a positive or negative result changes the likelihood that a patient would have the disease. It can be calculated as follows: likelihood ratio of a positive test result (LR+) = sensitivity divided by [1-specificity].

The GDG did not predefine a clinically relevant threshold as it was the aim of the reviews to determine any such thresholds. Studies reported multiple thresholds, many of which were clinically relevant depending on the situation (for example, the severity of presentation: bacteraemia, sepsis, severe sepsis or septic shock), or the position of the test within the patient pathway. Therefore, any study regardless of the threshold was considered.

Taking into account that a threshold was not pre-determined, and currently there is not a gold standard for the diagnosis of sepsis, the GDG pragmatically decided that it was not necessary to calculate the likelihood ratios from sensitivity and specificity data, and likelihood ratios were extracted only if reported by the paper.

For decision making, emphasis was placed on the sensitivity and specificity of the test at a particular threshold to distinguish between people with and without sepsis. Whether a more sensitive or a more specific test is desirable depends on the outcome of false positive cases and false negative cases. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a specificity of 97% will only incorrectly diagnose 3% of people who don't have the condition as positive.

The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without sepsis and, in practice, it varies amongst studies. Diagnostic parameters considered for this guideline are:

- 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, polymorphs
- biochemical tests: urea, electrolytes (sodium, potassium), renal or liver function, creatinine, haematocrit
- clotting screen: prothrombin time PT/INR, aPTT/APTR, TT and fibrinogen
- C-reactive protein (CRP)
- creatinine
- DIC
- assessment tools.

A ROC plot shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity) and the AUC gives an overall measure of accuracy of the test across a range of thresholds. Individual studies presenting ROC curves show the accuracy of a single test in a single population. It compares test accuracy over different thresholds for positivity and often reports the AUC as an overall measure of the performance of the test. A summary ROC (sROC) graph functions in a similar way to a ROC plot, apart from that each data point in the sROC graph comes from a different study,

not a different threshold, and so the AUC gives an overall measure of accuracy of the test across the range of studies, rather than a range of thresholds. The sROC is applied to pooled data from multiple studies and diagnostic thresholds are similar for each study, so threshold effect does not influence the shape of the curve. The curve is shaped solely by the results across the studies. The AUC can be calculated for the sROC and, as the diagnostic test is constant throughout the studies, the AUC reflects overall performance of that test. The perfect test, with a sensitivity and specificity of 100%, will have an AUC of one. The sROC AUC can be used to compare accuracy of different diagnostic tests.

The review question on the accuracy of tests to identify the source of infection (blood culture, lumbar puncture, chest X-ray or other imaging techniques) was based on discussions by the GDG. No literature search and data analyses were performed.

Data synthesis

For the reviews of diagnostic accuracy, the following measures were used:

- **the coupled sensitivity and specificity values at a given threshold:**
  Coupled forest plots of sensitivity and specificity with their 95% CIs across studies were produced for each test (and for each clinically relevant threshold), using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study where possible, or else were derived from raw data or calculated from the set of test accuracy statistics.

  Data were meta-analysed when data were available from 3 or more studies (given data were reported at the same threshold or within a defined range of similar thresholds). To do this, data were entered into a bivariate model using WinBUGS. If the model did not converge due to heterogeneity, the pooled estimate was not presented. A diagnostic meta-analysis was not conducted because the included population and the patient outcomes in the included studies were too different from each other. Where meta-analysis was performed, in addition to the forest plots, the coupled sensitivity and specificity values were also presented on sROC plots for visual information along with the results of the meta-analysis (the summary sensitivity and specificity point and 95% confidence region) and the summary curve. To do this, bivariate WinBUGS model outputs were entered into RevMan5.

  Pooled sensitivity and specificity values were reported in the clinical evidence profile tables (or, if meta-analysis was not performed, results from single studies were presented). For comparison of multiple index tests (or between different thresholds for the same test), the sensitivity and specificity values were compared between tests.

4.3.2.4 Data synthesis for qualitative study reviews

Where possible a meta-synthesis was conducted to combine qualitative study results. This guideline includes two qualitative review questions; one on information, education and support considered to be useful by people who are at risk of developing sepsis, have sepsis or have survived episodes of sepsis, and one on the availability of education training programmes for healthcare professionals to recognise, diagnose and manage sepsis. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had identified this theme. A frequently identified theme may indicate an important issue for the review, but frequency of theme is not the only indicator of importance. Study type and population in qualitative research can differ widely meaning that themes that may only be identified by one or a few studies can provide important new information. Therefore for the purpose of the qualitative review in this guideline the categorisation of themes was exhaustive, that is all themes

were accounted for in the synthesis. The GDG could then draw conclusions on the relative merits of each of the themes and how they may help in forming recommendations.

4.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. For example, the review question on escalation of care did not include any RCTs as randomly assigning people with sepsis to either be referred to a senior healthcare professional or remain under the care of staff with less experience would be highly unethical. The same applies to the review question on timing of antimicrobial treatment: randomly assigning people with sepsis to a delayed intervention would be unethical. The reviews on inotropic agents or vasopressors also included observational studies as the GDG agreed that the evidence presented by those studies could help inform recommendations.

For reviews of diagnostic tests, diagnostic RCTs were considered the first line approach, in which patients are randomised to one diagnostic test or another followed by treatment, and patient outcomes are assessed. If no evidence was identified from diagnostic RCTs, diagnostic accuracy was reviewed using prospective and retrospective cohort studies in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design. Two-gate study designs (sometimes referred to as case-control) were excluded. These are cross-sectional studies which compare the results of the index test in patients with an already established diagnosis of the target condition, with healthy controls. This study design is unrepresentative of practice and is unlikely to contain the full spectrum of health and disease over which the test would be used. Studies of this design may lead to the selective inclusion of cases with more advanced disease and over estimations of sensitivity. The inclusion of healthy controls is likely to lead to over-estimations of specificity.

For prognostic reviews, RCTs, pooled analysis of patient level data, and retrospective cohort or prospective cohort studies were included. Case-control studies were excluded because of their high risk of recall bias.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Interventional studies

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary

measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 4.3.4.1.5 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Table 2: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.4.1.1 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was to be carried out several times and there

was a consistently wrong answer, the results would be inaccurate. The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The main domains of risks of bias are listed in Table 5. Risk of bias was assessed in two stages. First, an overall risk of bias is obtained for each study and outcome by summarising across all domains of bias. Then, the all-domain risk of bias per study is summarised across all the studies for that outcome taking into account the weighting of studies in the meta-analysis.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes Recruitment bias in cluster-randomised trials

4.3.4.1.2 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, indirectness was assessed in a 2-stage process. First, indirectness was assessed for each study and outcome. Then, it was summarised across all studies taking into account the weighting of studies in the meta-analysis.

4.3.4.1.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as prespecified in the protocols (Appendix C).

When heterogeneity existed (chi-squared $p<0.1$, I^2 inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation could be found (for example, duration of

intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I^2 and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention was associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

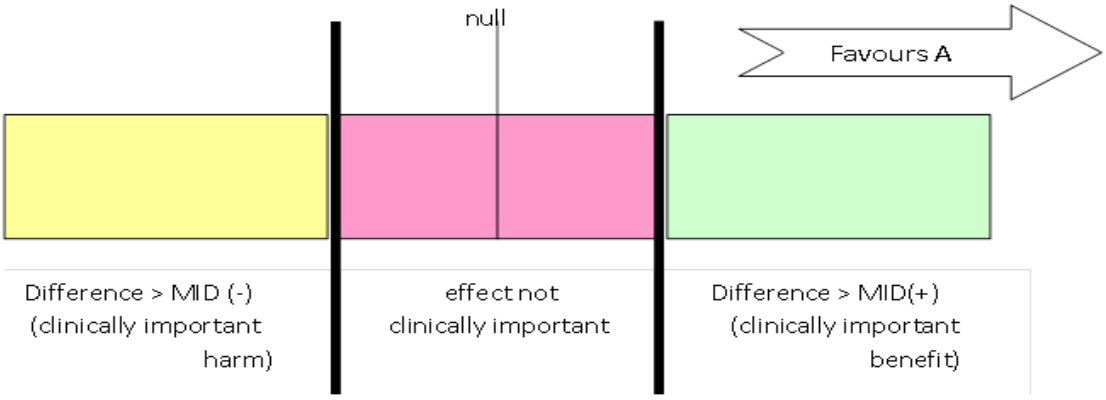
4.3.4.1.4 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate was relevant to decision-making, considering each outcome in isolation. Figure 3 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 3: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: for binary outcomes, a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. For continuous outcomes with an SD unit of 1, the default values are + 0.5 SD and - 0.5 SD. These default MIDs were used for all the outcomes in the interventions evidence reviews.

4.3.4.1.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. a quality rating was assigned, based on the study design. RCTs started as High, observational studies as Low, and uncontrolled case series as Low or Very low
2. the rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively
3. the downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively
4. the reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality elements are discussed further in the following sections 4.3.4.1.1 to 4.3.4.1.4.

4.3.4.2 Diagnostic studies

4.3.4.2.1 Risk of bias and indirectness

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist was used (see Appendix H in the NICE guidelines manual 2014[244]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains:

- patient selection
- index test
- reference standard
- flow and timing.

Optional domain, multiple test accuracy was applicable when a single study examined more than 1 diagnostic test (head-to-head comparison between 2 or more index tests reported within the same study). This optional domain contained 3 questions relating to risk of bias:

- did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients?
- were index tests conducted within a short time interval?
- were index test results unaffected when undertaken together on the same patient?

4.3.4.2.2 Inconsistency

Inconsistency was assessed as for intervention studies.

4.3.4.2.3 Imprecision

Imprecision was assessed according to the range of point estimates or, if only one study contributed to the evidence in collaboration with the GDG.

4.3.4.2.4 Grading the quality of evidence

Quality rating started at High for prospective and retrospective cross sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by one increment to a minimum grade of Very low, as explained for interventional studies.

4.3.4.3 Prognostic studies

A modified GRADE methodology was used for prognostic studies, considering risk of bias, indirectness, inconsistency and imprecision.

4.3.4.3.1 Risk of bias

The quality of evidence for prognostic studies was evaluated according to the criteria given in Table 6.

Table 6: Description of risk of bias quality elements for prospective studies

Domain	Risk of bias for prognostic risk factor studies	Response and score
Selection bias	Was there a lack of reported attempts made to achieve some group comparability between the risk factor and non-risk factor groups? (ignore if 2 or more risk factors considered)	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Was there a lack of consideration of any of the key confounders, or was this unclear? *If the study can show that a particular confounder was not at risk of causing bias (for example by being well-matched at baseline between groups) then this confounder does not have to have been adjusted for in a multivariate analysis*	Exclude
	Was there a lack of consideration of non-key plausible confounders, or was this unclear? *If the study can show that a particular confounder was not at risk of causing bias (for example by being well-matched at baseline between groups) then this confounder does not have to have been adjusted for in a multivariate analysis*	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	If the outcome is categorical: were there <10 events per variable included in the multivariable analysis? If the outcome is continuous: were there <10 people	Consider if this was moderate, high or very high risk of bias if answer was 'yes' to either

Domain	Risk of bias for prognostic risk factor studies	Response and score
	per variable included in the multivariable analysis?	
	Was it very clear that one group was more likely to have had more outcomes occurring at baseline than another group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
Detection bias	Was there a lack of assessor blinding AND the outcome was not completely objective?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Were the risk factors measured in a way that would systematically favour either group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Were the outcomes measured in a way that would systematically favour either group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	If there were multiple raters, was there lack of adjustment for systematic inter-rater measurement errors, OR was inter-rater reliability unreported?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Was there an excessively short follow up, such that there was not enough time for outcomes to occur?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
Attrition bias	Was there >10% group differential attrition (for reasons related to outcome) and there was no appropriate imputation? (if one risk factor) or Was there >10% overall attrition(for reasons related to outcome) and there was no appropriate imputation? (if > 1 risk factor).	Consider if this was moderate, high or very high risk of bias if answer was 'yes'. Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	For each domain make a judgement of risk of bias (for example very high if there are two moderate boxes and a high box) **Sum these domain risks to form an overall rating of risk of bias (for example no risk, serious risk or very serious risk)**	

The risk of bias rating was assigned per study for each combination of risk factor/outcome. When studies were pooled the overall risk of bias for all studies covering a specific risk factor/outcome was determined by a weighted mean of the ratings across the studies (with no risk = 0; serious risk = -1 and very serious risk = -2). The weighting depended on the weighting used in the meta-analysis, as in intervention reviews. Where a meta-analysis had not been conducted a simple average was used.

4.3.4.3.2 Indirectness

Indirectness was assessed as for intervention studies.

4.3.4.3.3 Inconsistency

Inconsistency was assessed as for intervention studies.

4.3.4.3.4 Imprecision

Imprecision was assessed as for intervention studies.

4.3.4.3.5 Grading the quality of evidence

Quality rating started at High for prospective and retrospective cross sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by one increment to a minimum grade of Very low, as explained for interventional studies.

4.3.4.4 Qualitative studies

For qualitative studies, quality was assessed using the checklist for qualitative studies (Appendix H in the NICE guidelines manual 2014[244]). The quality rating (Low, High, Unclear) was derived by assessing the risk of bias across 6 domains:

- theoretical approach
- study design
- data collection
- validity
- analysis
- ethics.

4.3.5 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.6 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements encompass the following key features of the evidence:

- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence.

4.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[233] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.

4.4.1 Literature review

The health economist:

- identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained
- reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details)
- critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual[233,235]
- extracted key information about the studies' methods and results into evidence tables (included in Appendix I)
- generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see Table 7 below and the economic evaluation checklist (Appendix G of the NICE guidelines manual 2012[235]) and the health economics review protocol in Appendix C.

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

4.4.11.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[235] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[250]

Table 7: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness • partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness • not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness • potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness • very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of the NICE guidelines manual (2012)[235]

4.4.2 Undertaking new health economic analysis

No new health economic analysis was undertaken for this guideline due to feasibility.

The GDG originally identified the timing of antimicrobial treatment as the highest priority area for original economic modelling. This question was originally intended to determine the cost effectiveness of early empirical antibiotic use compared to the use of targeted antibiotics following diagnosis. This question changed following agreement of the protocol and examined the timing of empirical antibiotics. The clinical evidence for this question indicates that early empirical antimicrobials (given <1 hour) result in lower mortality than delayed use. The GDG were confident that any resource implications, and therefore costs, would be offset by the benefits in terms of reduced mortality. As a result the GDG agreed that the cost-effectiveness could be deduced without the need to model. Thus, this area was no longer a priority of economic modelling.

An additional lower priority of a pathway approach (the impact of identifying and treating people with sepsis) was also considered. However a pathway approach was considered unfeasible due to the large number of unkowns in the epidemiology of sepsis.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[234] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention costs less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[234]

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I
- summaries of clinical and economic evidence and quality (as presented in Chapters 5-16)
- forest plots (Appendix K).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 4.5.1 below).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- the actions health professionals need to take
- the information readers need to know
- the strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- the involvement of patients (and their carers if needed) in decisions on treatment and care
- consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in the NICE guidelines manual[235]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Suspicion of sepsis and identifying people at increased risk

The aim of early medical care is to recognise people who have or who are developing a systemic response to infection that may be life-threatening. People with sepsis may present in any clinical setting. A suspicion of sepsis is required to enable prompt recognition and treatment. While anyone can develop sepsis and vigilance is therefore required in all clinical encounters, there are people whose risk is increased because of personal characteristics or because of concurrent medical conditions or medicines they may be taking. The recommendations in this chapter were developed by the guideline group to alert healthcare professionals to the possibility of sepsis and to highlight particular groups who may be at risk.

5.1 Recommendations and links to evidence

No specific evidence review was carried out to inform these recommendations. They are informed by what is known about the pathophysiology and epidemiology of sepsis. The recommendations were reached by consensusand draw on existing guidance and expertise co-opted to the GDG.

Recommendations	**1. Suspect sepsis if a person presents with signs or symptoms that indicate possible infection, even if they do not have a high temperature.** **2. Take into account that people with sepsis may have non-specific, non-localised presentations, for example feeling very unwell.** **3. Pay particular attention to concerns expressed by the person and their family or carers, for example changes from usual behaviour.** **4. Assess people who might have sepsis with extra care if they cannot give a good history (for example, people with English as a second language or people with communication problems).** **5. Take into account that people in the groups below are at higher risk of developing sepsis:** • **the very young (under 1 year) and older people (over 75 years) or very frail people** • **people who have impaired immune systems because of illness or drugs, including** – **people being treated for cancer with chemotherapy** – **people who have impaired immune function (for example, people with diabetes, people who have had a splenectomy, or people with sickle cell disease)** – **people taking long-term steroids** – **people taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis** • **people who have had surgery, or other invasive procedures, in the past**

	6 weeks • **people with any breach of skin integrity (for example, cuts, burns, blisters or skin infections)** • **people who misuse drugs intravenously** • **people with indwelling lines or catheters.** **6. Take into account that women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the last 6 weeks, are in a high risk group for sepsis. In particular, women who:** • **have gestational diabetes or diabetes** • **needed invasive procedures (for example, caesarean section, forceps delivery, removal of retained products of conception)** • **had prolonged spontaneous rupture of membranes** • **have been in close contact with people with group A streptococcal infection** • **have continued bleeding or an offensive vaginal discharge.** **7. Take into account the following risk factors for early-onset neonatal infection:** • **invasive group B streptococcal infection in a previous baby** • **maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy** • **prelabour rupture of membranes** • **preterm birth following spontaneous labour (before 37 weeks' gestation)** • **suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth** • **intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis** • **parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth (this does not refer to intrapartum antibiotic prophylaxis)** • **suspected or confirmed infection in another baby in the case of a multiple pregnancy.** **[This recommendation is from Neonatal infection (NICE guideline CG149).]**
Relative values of different outcomes	Not applicable
Trade-off between clinical benefits and harms	Early recognition of sepsis increases the possibility that the patient will receive appropriate and timely treatment and this provides the best chance of reducing morbidity and mortality. An individual patient is unlikely to come to harm if sepsis is suspected and they have a thorough assessment. The GDG considered that the overwhelming benefit if sepsis is diagnosed early outweighed any harm or inconvenience to the patient.

Economic considerations	The assessment of a person's signs and symptoms will take place during a consultation with a healthcare professional, possibly a GP or in an emergency department or on a hospital ward. The length of this consultation will not vary significantly dependant on which signs are assessed and what use is made of these findings. It can be assumed that all consultations will be of standard length, and that equipment for measuring vital signs is available. Therefore cost is not a significant factor when looking at each individual consultation. The GDG considered there are some specific groups who will be of higher risk of sepsis due to compromised immunity, and being part of these groups should be a risk factor considered during a thorough assessment. This may increase the number of people who require a thorough assessment or who require a face to face assessment based on a factor in their history. Although this may lead to a lower threshold of suspecting sepsis, the consequences of missing sepsis and benefit of early identification are likely to outweigh either longer term spend in consultation with people from these groups or any further investigation or referral.
Quality of evidence	Not applicable
Other considerations	The recommendations were developed by the GDG using informal consensus. The GDG considered that one of the most important issues in recognition and management of sepsis is that the healthcare professional considers sepsis as a possible diagnosis. One of the difficulties for healthcare professionals and for patients is that people with sepsis may present with non-specific symptoms which are difficult to articulate and to assess. People with sepsis may not develop usual responses to infection so may not have symptoms such as fever. Any symptoms may be subtle and history from the patient, their friend or relative of a change in behaviour or mental state should be taken seriously. Particular care should be taken with people who have difficulty expressing themselves such as people with communication problems or people with English as a second language. While anyone can develop sepsis, factors that either affect immunity or situations where infective organisms are easily introduced to the body will increase the risk of sepsis. Very young children and older people may have reduced immunity as may people who are being treated for cancer or are taking drugs that may impair their immune function. Diagnosis can also be more difficult in these groups because of how they respond to infection. Immune function may also be impaired for other reasons such as people with diabetes, people who have undergone splenectomy, and people with sickle cell disease. The GDG considered that all those who have had an invasive procedure should be considered at risk of sepsis for up to six weeks post the procedure. People with indwelling lines and catheters and people with breach of skin are at increased risk of more invasive infection as their skin barrier is already breached. The GDG made recommendations for women who may have sepsis associated with pregnancy. Their recommendations were informed by RCOG 'Green Top' Guidelines Bacterial Sepsis in Pregnancy (Green top guideline 64a) and Bacterial Sepsis following Pregnancy (Green top Guideline 64b) and by a co-opted expert. Women who are pregnant or have been pregnant should be considered to be at risk of sepsis. Women who are having a miscarriage, or who have had a miscarriage or who have elected to terminate a pregnancy are also in this group but may be more easily overlooked. Women whose immunity may be reduced for other reasons such as diabetes are at additional risk. Procedures such as removal of retained products of conception risk the introduction of bacteria from the lower genital tract to blood stream. Caesarean section is the most common invasive procedure in later pregnancy but some women will need other procedures such as instrumental delivery. Both mother and baby are at risk of sepsis if there is prolonged rupture of membranes. Group A streptococcus can cause severe infection and can be spread

	from one person to another. A pregnant woman's reduced immunity means she is more at risk close contacts such as family members have had group A streptococcal infections. Continued heavy bleeding or offensive vaginal discharge are potential indicators of genital tract infection which increase the risk of sepsis. The GDG recognised that other NICE guidance makes recommendations on early neonatal infection. For completeness they included the recommendation on risk factors from NICE guideline CG149Antibiotics for early-onset neonatal infection:antibiotics for the prevention and treatment of early-onset neonatal infections they considered these are relevant and should be included for ease of access.

6 Assessment and stratification of risk

This chapter describes the evidence reviews and GDG decision-making for assessment and stratification of risk of morbidity and mortality from sepsis. The reviews were used to develop recommendations on what parameters should be assessed, some specific considerations given to those parameters and which parameters the guideline group judged to indicate low, moderate to high or high risk for morbidity and mortality from sepsis.

The chapter starts with a review of the evidence for scoring systems in section 6.1. This is followed by an evidence review and recommendations for symptoms and signs in section 6.2.

The parameters for low, moderate to high and high risk for severe illness or death from sepsis are also presented in table format for ease of reference and these are in section 6.3.

16.1 Scoring systems

6.1.1 Introduction

The GDG were aware of many scoring systems that might or are used in different settings. If there was good quality evidence for a specific score, the variables in the score would dictate the parameters required in clinical assessment. The evidence review for scores therefore preceded the review for value of individual symptoms and signs. Because of the number of potential scores the GDG reviewed a list of scores and prioritised those for inclusion on the basis of which were considered to be most likely to be helpful. This included review for their ease of use in different clinical settings according to the nature of the parameters in the score. The evidence search was therefore targeted to find and assess scores according to where they might be of value. The scores are listed below by setting.

Potential scores for primary and community care

STSS (Simple Triage Scoring System, **Table 8**), REMS (Rapid Emergency Medicine Score, **Table 9**) or modified-REMS, MEWS (Modified Early Warning score, **Table 10**), and NEWS (National Early Warning score, **Table 11**) are easy to use tools, that only require simple physiological measures such as heart rate, blood pressure, respiratory rate, oxygen saturation, mental status and urine output. These variables can easily be measured in primary care (see Section 6.1.1.1).

Potential scores for Emergency department

SOFA (Sequential Organ Failure Assessment, **Table 13**), MEDS (Mortality in Emergency Department, Sepsis, **Table 14**), CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years and older, **Table 15**), PIRO (Predisposition, infection, response, and organ dysfunction, **Table 16**), and Sepsis trust UK Toolkit (**Table 17**) in addition to simple physiological measures, also require a blood test to determine for example platelet, bilirubin, urea, glucose and white blood cell count. For this reason, these tests cannot be used in primary care setting, but could easily be used in the emergency department (see Section 6.1.1.2). The MTS (Manchester Triage System, **Table 18**) is an algorithm to be used in the emergency department to classify patients according to urgency category, and can be used for adults and children.

Potential scores for Critical care

APACHE II (Acute Physiology and Chronic Health Evaluation, **Table 19**) and SAPS II (Simplified Acute Physiology Score, **Table 20**) are more complicated scores to calculate, as they require for example the measurement of arterial oxygenation, therefore they are used in critical care settings (see Section 6.1.1.3).

Potential scores for Pregnant and post-partum women

SOS (Sepsis in Obstetrics Score, **Table 21**) is a tool specific for pregnant and post-partum women (see Section 6.1.1.4)

Potential scores for use in Paediatric settings

PEWS (Paediatric Early Warning Score, **Table 22**) and POPS (Paediatric Observation Priority Score, **Table 23**) are tools specific for paediatric setting; they do not require a blood test, therefore can be used in the paediatric emergency department (see Section 6.1.1.5).

6.1.11 Scoring systems that could be used in primary care setting

Table 8: STSS (Simple Triage Scoring System) [range: 0-5]

Variable	Rule points
Respiratory rate > 30 breaths per minute	1
Shock index >1 (HR>BP)	1
Low oxygen saturation	1
Altered mental status	1
Age of 65 to 74 years	1
Age of at least 75 years	1

Table 9: REMS (Rapid Emergency Medicine Score) [range: 0-26] and mREMS (modified REMS)

	0	1	2	3	4	5	6
Age (years)	<45		45–54	55–64		66–74	>74
Heart rate (beats/min)	70–109		110–139 or 40–54	140–179 or 40–54	>179 or <39		
Respiratory rate (breaths/min)	12–24	25–34 or 10–11	6–9	35–49	>49 or <5		
mean arterial pressure, MAP (mmHg)	70–109		110–129 or 50–69	130–159	>159 or <49		
Peripheral O2 saturation (%)	>90	86–89		75–85	>75		
GCS	>13	11–13	8–10	5–7	<5		
Modified-REMS (mREMS): GCS is replaced with confusion:							
Modified altered mental status (AMS) (yes/no)?	No	Yes					

Table 10: MEWS (Modified Early Warning score)

It was originally developed to allow early identification of critically ill patients on general wards; it was not specifically designed to identify the presence of sepsis.

	3	2	1	0	1	2	3
Respiratory rate		≤8		9-14	15-20	21-29	>29
Temperature		≤35	35.1-36	36.1-39	38.1-38.5	≥38.6	
Systolic BP	≤70	71-80	81-100	101-199		≥200	
Pulse		≤40	41-50	51-100	101-110	111-129	>129
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive
Urine output (ml/kg/h)	Nil	<0.5					

Table 11: NEWS (National Early Warning score) [0-20]

	3	2	1	0	1	2	3
Respiratory rate	≤8		9-11	12-20		21.24	≥25

	3	2	1	0	1	2	3
Temperature	≤35		35.1-36	36.1-38	38.1-39	≥39.1	
Systolic BP	≤90	91-100	101-110	111-219			≥220
Pulse	≤40		41-50	51-90	91-110	111-130	≥131
Conscious level				A			V, P, U
Oxygen saturation	≤91	92-93	94-95	≥96			
Supplemental oxygen		Yes		No			

1 **Table 12: ViEWS (VitalPAC Early Warning Score) [0-20]**

ViEWS score	3	2	1	0	1	2	3
Pulse (bpm)	< 40		41 – 50	51 – 90 Unrecordable because patient refused, equipment unavailable, other reason	91 – 110	111 – 130	> 131 Unrecordable due to patient condition
Temp. (ºC)	< 35		35.1 – 36	36.1 – 38 Unrecordable because patient refused, equipment unavailable, other reason	38.1 – 39	> 39.1	Unrecordable due to patient condition
BP Systolic (mm Hg)	< 90	91 – 100	101 – 110	111 – 219 Unrecordable because patient refused, equipment unavailable, other reason			> 220 Unrecordable due to patient condition
Resp. Rate (bpm)	< 8		9 – 11	12 – 20 Unrecordable because patient refused, equipment unavailable, other reason		21 – 24	> 25 Unrecordable due to patient condition
AVPU				Alert			*Voice Pain Unresponsive
SaO_2	< 91	92 – 93	94 – 95	> 96 Unrecordable because patient refused, equipment unavailable, other reason			Unrecordable due to patient condition
Inspired O_2				Air		** Any supplemental O_2	

2 ** If AVPU is V or C due to patient sedation, the score is 0 rather than 3.*
3 *** Note that "Any supplemental O2" applies to any supplementary oxygen the patient is receiving. It does NOT apply to*
4 *patients who are on 'masks' through which only Air is being supplied*

(Air delivery possible through Tracheostomy, BiPAP or CPAP for example)

6.1.1.2 Scoring systems that could be used in the emergency department

Table 13: SOFA (Sequential Organ Failure Assessment) [range: 0-24]

The SOFA is a morbidity severity score and mortality estimation tool developed from a large sample of ICU patients throughout the world. The SOFA score is made of 6 variables, each representing an organ system. Each organ system is assigned a point value from 0 (normal) to 4 (high degree of dysfunction/failure).

	0	1	2	3	4
Respiratory (PaO2/FiO2, mmHg)	>400	≤400	≤300	≤200	≤100
Coagulation (Platelets x103/µl)	>150	≤150	≤100	≤50	≤20
Liver (Bilirubin, Mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)	Dop>5, epi≤0.1, or norepi≤0.1	Dop>15, epi>0.1, or norepi>0.1
Central nervous system (Glasgow Coma Score Scale)	15	13-14	10-12	6-9	<6
Renal (Creatinine, mg/dl, or urine output, ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

Table 14: MEDS (Mortality in Emergency Department, Sepsis) [Range: 0-27]

MEDS is a risk-stratification tool predict 1-month mortality in ED patients with suspected infection

Factor	Score	Comment
Terminal illness	6	Rapidly fatal illness such as metastatic cancer with perceived 30-day mortality
Age >65 years	3	
Tachypnea or hypoxia	3	RR > 20 breaths/min, requiring O2 by mask, O2 saturation < 90%
Shock	3	SBP < 90 after appropriate IVF bolus
Thrombocytopenia (Platelet count)	3	<150,000 cells/mm3
Bandemia*	3	>5%
Nursing home resident	2	
Lower respiratory tract infection	2	
Altered mental status	2	By history or examination

**Bandemia refers to an excess of band cells (immature white blood cells) released by the bone marrow into the blood.*

Table 15: CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years and older) [0-5]

Variable	Points
Confusion	1
Urea > 7 mmol/L (>19.6 mg/dL)	1
Respiratory rate > 30 breaths/min	1
Hypotension (SBP < 90 or DBP < 60 mmHg)	1
Age ≥ 65	1

Table 16: PIRO (Predisposition, infection, response, and organ dysfunction)

	0	1	2	3	4
Predisposition					
Age (years)	<65	65 to 80	>80		
COPD		Yes			
Liver disease			Yes		
Nursing home resident			Yes		
Malignancy		Without metastases	With metastases		
Infection:					
Skin/soft tissue infection	Yes				
Any other infection			Yes		
Pneumonia					Yes
Response					
Respiratory rate (bpm)				>20	
Bands		>5%			
Heart rate (bpm)			>120		
Organ dysfunction					
SBP (mmHg)	>90		70 to 90		<70
BUN (blood urea nitrogen) (mmol/l)			>7.1		
Respiratory failure/hypoxemia				Yes	
Lactate (mmol/l)				>4.0	
Platelet count ($\times 10^9$/l)			<150		

Table 17: Sepsis trust UK Toolkit

Temperature	>38.3 or <36
Respiratory rate (per minute)	>20
Heart rate (per minute)	>90
Consciousness level	Reduced conscious level/ Acute confusion
Glucose (mmol/L)	>7.7 (unless DM)
Systolic B.P. (mmHg)	<90
Lactate(mmol/L)	>2

Temperature	>38.3 or <36
WBC	WBC>12 or <4 x 10^9/L
Respiratory rate (per minute)	>25
Oxygen saturation (%)	<91
Responsiveness	Responds only to voice or pain/ unresponsive
Purpuric Rash	Yes

Table 18: MTS (Manchester Triage System)

The system is an algorithm based on flowcharts and consists of 52 flowchart diagrams (49 suitable for children) that are specific for the patient's presenting problem. The flowcharts show six key discriminators (life threat, pain, haemorrhage, acuteness of onset, level of consciousness, and temperature) as well as specific discriminators relevant to the presenting problem. Selection of a discriminator indicates one of the five urgency categories, with a maximum waiting time ("immediate" 0 minutes, "very urgent" 10 minutes, "urgent" 60 minutes, "standard" 120 minutes, and "non-urgent" 240 minutes). The presence of key discriminators in different flowcharts will lead to the same level of urgency. Pain is scored on a scale from 0-10 and could assign patients to a higher urgency level.

6.11.3 Scoring systems that could be used in critical care setting

Table 19: APACHE II (Acute Physiology and Chronic Health Evaluation) [Range: 0-71]

APACHE II was designed to measure the severity of disease for adult patients admitted to intensive care units

	+4	-3	-2	-1	0	+1	-2	+3	-4
Temperature	≥41	39-40.9	-	38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129	-	70-109	-	50-69		≤49
Heart Rate	≥180	140-179	110-139	-	70-109	-	55-69	40-54	≤39
Respiratory Rate	≥50	35-49	-	25-34	12-24	10-11	6-9	-	≤5
Oxygenation (F1O2 > 0.5 record oA-aO2 F1O2 < 0.5 record PaO2	≥500	350-499	200-349	-	<200 PaO2>70	61-70	-	55-60	≤55
pH	≥7.7	7.6-7.69	-	7.5-7.59	7.33-7.49	-	7.25-7.32	7.15-7.24	≤7.15
Serum Sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149	-	120-129	111-119	≤110
Serum Potassium (mmol/L)	≥7	6.6-6.9	-	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	-	≤2.5
Creatinine	-	-	-	-	-	-	-	-	-

	+4	-3	-2	-1	0	+1	-2	+3	-4
Hematocrit	≥60	-	50-59.9	46-49.9	30-45.9	-	20-29.9	-	≤20
White Cell Count	≥40	-	20-39.9	15-19.9	3-14.9	-	1-2.9	-	0.1
15-GCS	-	-	-	-	-	-	-	-	-

1 **Table 20: SAPS II (Simplified Acute Physiology Score)**

Score	26	13	12	11	9	7	6	5	4	3	2	0	1	2	3	4	6	7	8	9	10	12	16	16	17	18
Age, y												<40						40-59				60-69	70-74	75-79		≥80
Heart rate, beats/min				<40							40-69	70-119				120-159		≥160								
Systolic BP, mm Hg		<70						70-99				100-199		≥200												
Body temperature, °C												<39			≥39											
Only if ventilated or continuous pulmonary artery pressure Pao2, mm Hg/Fio2				<100	100-199		≥200																			
PaO2, kPa/Fio2 <13.3 13.3-26.5				<13.3	13.3-26.5		≥26.6																			
Urinary output, L/d				<0.500					0.500-0.999			≥1.000														
Serum urea level, mmol/L (g/L) or serum urea nitrogen level, mg/dL												<10.0 (<0.60) <28					10.0-29.9 (60.-1.79) 28-				≥30.0 (≥1.80) ≥84					

Score	26	13	12	11	9	7	6	5	4	3	2	0	1	2	3	4	6	7	8	9	10	12	16	16	17	18
																	83									
WBC count (103/cu mm)			<1.0									1.0-19.9			≥20											
Serum potassium, mmol/d										<3.0		3.0-4.9			≥5.0											
Serum sodium level, mmol/L								<125				125-144	≥145													
Serum bicarbonate level, mEq/L							<15			15-19		≥20														
Bilirubin level, µ /L (mg/dL)												<68.4 (<4.0)				68-4-102.5 (4.0-5.9)				≥102 (≥6.0)						
Glasgow Coma Score	<6	6-8				9-10		11-13				14-15														
Chronic diseases																				Metastatic cancer	Hematologic malignancy				AIDS	
Type of admission												Scheduled surgical					Medical		Unscheduled surgical							

1

6.1.11.4 Scoring systems specific for pregnant and postpartum women

Table 21: SOS (Sepsis in Obstetrics Score)

Variable	High abnormal range				Normal	Low abnormal range			
Score	**+4**	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Temperature	>40.9	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<30
Systolic blood pressure (mmHg)					>90		70-90		<70
Heart rate (beats per minute)	>179	150-179	130-149	120-129	≤119				
Respiratory rate (breaths per minute)	>49	35-49		25-34	12-24	10-11	6-9		≤5
SpO2 (%)					≥92	90-91		85-89	<85
White blood cell count (/microL)	>39.9		25-39.9	17-24.9	5.7-16.9	3-5.6	1-2.9		<1
% Immature Neutrophils		≥10		<10					
Lactic Acid (mmol/L)		≥4		<4					

6.1.11.5 Scoring systems for paediatric setting

Table 22: PEWS (Paediatric Early Warning Score)

	0	1	2	3
Behaviour	Playing/appropriate	Sleeping	Irritable	- Lethargic/ confused or - reduced response to pain
Cardiovascular	- Pink or - capillary refill 1-2 seconds	- Pale or dusky or - capillary refill 3 seconds	- Grey or cyanotic or - capillary refill 4	- Grey or cyanotic and mottled, or - capillary refill 5 seconds or

	0	1	2	3
			seconds or -tachycardia of 20 above normal rate	above or -tachycardia of 30 above normal rate or -bradycardia
Respiratory	Within normal parameters, no retractions	- >10above normal parameters or - using accessory muscles or - 30+ %FiO2 or 3+ litres/min	- >20above normal parameters or - retractions or - 40+ %FiO2 or 6+ litres/min	- ≥5 below normal parameters with retractions or grunting or - 50+ %FiO2 or 8+ litres/min

1

2 **Table 23: POPS (Paediatric Observation Priority Score)**

Age	Score	2	1	0	1	2
Any	O2 saturation (%)	<90	90-94	>95	90-94	<90
Any	Breathing	Stridor	Audible grunt or wheeze	No distress	Mild or moderate recession	Severe recession
Any	AVPU (alert, voice, pain, unresponsive)	Pain	Voice	Alert	Voice	Pain
Any	Gut feeling	High level concern	Low level concern	Well	Low level concern	High level concern
Any	Other	Oncology patient	Patient on long term steroids or diabetic		Ex-prem or any syndromic condition	Congenital heart disease
0-1	Pulse	<90	90-109	110-160	161-180	>180
0-1	Respiratory Rate	<25	25-29	30-40	41-50	>50
0-1	Temperature	<35	35-35.9	36-37.5	37.6-39	>39
1-2	Pulse	<90	90-99	100-150	151-170	>170
1-2	Respiratory Rate	<20	20-24	25-35	36-50	>50
1-2	Temperature	<35	35-35.9	36-38.4	38.5-40	>40
2-5	Pulse	<80	80-94	95-140	141-160	>160
2-5	Respiratory Rate	<20	20-24	25-30	31-40	>40
2-5	Temperature	<35	35-35.9	36-38.4	38.5-40	>40
5-12	Pulse	<70	70-79	80-120	121-150	>150
5-12	Respiratory Rate	<15	15-19	20-25	26-40	>40
5-12	Temperature	<35	35-35.9	36-38.4	38.5-40	>40

6.1.2 Review question: What is the most accurate and cost-effective assessment tool to identify patients with sepsis?

For full details see review protocol in Appendix C.

Table 24: Characteristics of review question

Population	All populations, including the following subgroups: • Adults • Children • People at higher risk of infection • Pregnant women and recently pregnant women
Reference standard or target condition/patient outcomes	Patient outcomes: • mortality • hospital admission • health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). • escalation of care • unplanned critical care admission • composite unexpected patient death/cardiac arrest/admission to critical care Critical care outcomes were excluded Other outcomes: • test practicality.
Index test(s)/comparator(s)	Scoring systems, for example: PEWS, MEWS, NEWS, early warning scores, triage scoring, MTS (Manchester triage), emergency severity index, POP score, CURB65, APACHE, SOFA, PIRO Only tools used in ED or ward are included (exclude critical care context)
Reference standard(s)	N/A
Statistical measures	If thresholds are established/pre-defined: • relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher or lower risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Study design	• Systematic reviews (SRs), RCTs and non-RCTs comparative study including any of the above severity tools. • External validation studies.

6.1.3 Clinical evidence

Forty-three studies were included in the review. The quality of the evidence was evaluated using the QUADAS-2 checklist for diagnostic accuracy studies. Evidence from these are summarised in the

clinical summary table (**Table 25**) and in the clinical evidence summary tables (section 6.1.3.1). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix L.

For each scoring system, we found the following number of studies:

Tool	Number of studies
APACHE II (Acute physiology and chronic health evaluation)	21[22,34,35,45,60,61,63,65,67,68,133,136,153,154,172,175,187,219,227,331,336]
CURB-65 (Confusion, urea nitrogen, respiratory rate, blood pressure, 65 years and older)	4[23,75,136,144]
MEDS (Mortality in emergency department, sepsis)	16[60,66,68,70,75,135,136,144,157,196,280,292,295,307,321,339,340]
MEWS (Modified early warning score)	6[7,70,92,118,321,334]
MOEWS (modified obstetric early warning scoring)	1[92]
MTS (Manchester triage system)	2[72,317]
NEWS (National early warning score)	1[74]
PEWS (Paediatric early warning score)	1[6]
PIRO (Predisposition, infection, response, and organ dysfunction)	5[61,67,68,80,196]
POPS (Paediatric observation priority score)	0
REMS (Rapid emergency medicine score) and mREMS (Modified-REMS: GCS is replaced with confusion)	4[7,75,136,144]
SAPS II/ SAPS III (Simplified acute physiology score)	2[153,170]
Sepsis UK Toolkit	0
SOFA (Sequential organ failure assessment)	5[4,123,170,172,196]
SOS (Sepsis in obstetrics score)	1[7]
SSS (Sepsis severity score)	1[251]
STSS (Simple triage scoring system)	2[4,306]
ViEWS (VitalPAC early warning score)	2[153,270]

1 **Table 25: Summary of studies included in the review (in alphabetical order)**

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
Adeniji 2011A[4] Retrospective cohort	To compare STSS performance versus SOFA in predicting ICU admission and mechanical ventilation	Patients admitted to hospital with H1N1 (n=62)	STSS SOFA	-	Unclear (in hospital stay)	AUC for ICU admission STSS: 88 (78-98) SOFA: 77 (65-89) AUC for requirement for mechanical ventilation STSS: 91 (83-99) SOFA: 87 (72-100)
Akre 2010[6] Retrospective cohort	To evaluate the sensitivity or PEWS for a group of patients who had documented RRT (Rapid Response Team) or code blue event.	RRT calls and blue events on medical surgical units excluding ICU and ICU step-down units. (n=186)	PEWS	-	Unclear	patients having a critical score within 24 hours before the event Sens: 85.8
Albright 2014[7] Retrospective cohort	To design an emergency department sepsis scoring system for ICU admission in pregnant and postpartum women.	N=850 women with suspected SIRS or sepsis.	SOS REMS MEWS	-	Unclear (in hospital stay)	ICU admission: SOS AUC 97 Sens 88.9 Spec 99.2 PPV 16.7 NPV 99.9 REMS Sens 77.8 Spec 93.3 PPV 11.1

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						NPV 99.7 MEWS Sens 100 Spec 77.6 PPV 4.6 NPV 100
Band 2011[22] Secondary analysis of prospectively collected registry data.	To evaluate arrival at ED to time to initiation of antibiotics, IVF and in-hospital mortality in patients with sepsis and septic shock.	N=963 severe sepsis patients who presented at the ED and were admitted to hospital.	APACHE II	-	Unclear (in hospital stay)	Hospital mortality RR= 1.05 (1.03-1.07) (multivariable analysis)
Bohnen 1988[34] Retrospective cohort	To evaluate the usefulness of APACHE II in the prediction of mortality	Patients hospitalised for generalised peritonitis or abdominal abscess (n=100)	APACHE II	Age, use of steroids, generalised peritonitis vs abscess	Unclear (in hospital stay)	APACHE II score and use of steroids are factors independently associated with mortality
Bohnen 1994[35] Retrospective cohort	To determine the effect of steroids in patients with abdominal infections, and the relationship between APACHE II and mortality	Patients with abdominal infections treated with percutaneous or surgical drainage (n=297)	APACHE II	-	Unclear (in hospital stay)	APACHE II score and use of steroids are factors independently associated with mortality
Buck 2012[45] Prospective cohort	To determine the predictive clinical ability of the clinical tools to predict	Consecutive patients who underwent surgical treatment for peptic ulcer perforation	APACHE II	-	30 days	APACHE II ≥ 12 **30-day mortality** PPV 24 NPV 97

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
	adverse outcome in peptic ulcer perforation.	(n=117) Scores taken preoperatively.				RR = 31.6 (1.8-542.2) **Septic shock** PPV 35 NPV 94 RR = 10.0 (1.4-69.4) **ICU admission** PPV 49 NPV 75 RR = 2.7 (0.8-9.5)
Chen 2006[60] Retrospective cohort	To determine the efficacy of MEDS in stratify patients in ED with severe sepsis	Patients presented to the ED with severe sepsis	MEDS APACHE II	-	28 days	AUC: MEDS 74.5 APACHE II 62.4
Chen 2009[65] Prospective cohort	To determine the prognostic importance of BNP in sepsis patient.	n=327 participants with sepsis	APACHE II	Plasma serum brain natriuretic peptide (BNP)	28 days	28-day mortality Cut-off value: 21.5 Sens 35 Spec88 PPV 63 NPV 69 AUC 0.664 OR = 3.9 (2.2-6.9)
Chen 2013A[67] Prospective cohort	To create a PIRO system for patients with community acquired sepsis (CAS) presenting to the ED and assess its prognostic and stratification	n=1691 ED patients with community acquired sepsis (CAS) (n=831 derivation cohort; n=860 validation cohort)	PIRO APACHE II	-	28 days	AUC to predict 28-day mortality: PIRO derivation cohort 83.3 APACHE II derivation cohort 68.3 PIRO validation cohort 81.3 APACHE II validation cohort 71.9 PIRO cut-off 14.5, derivation cohort

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
	capabilities					Sens 73.5 Spec 76.0 PPV 40.5 NPV 92.8 PIRO cut-off 15.5, validation cohort Sens 72.3 Spec 78.1 PPV 40.7 NPV 93
Chen 2013D[66] Prospective cohort	N=837 consecutive SIRS patients AM compared to PCT and MEDs	N=837 consecutive SIRS patients	MEDS	Adrenomedullin (AM) Procalcitoin (PCT)	In-hospital	In-hospital mortality OR=1.127, p=0
Chen 2014A[68] Retrospective cohort	To determine PIRO's predictive ability of MOD (Multiple Organ Dysfunction), ICU admission and 28 day mortality, compared to MEDS and APACHE II.	Consecutive septic patients admitted to ED. (n=276)	APACHE II MEDS PIRO	-	28 days	Admission to ICU: PIRO: AUC=88.9 (85.5-92.3), OR=1.758 (1.559-1.982) MEDS: AUC=77.4 (73.1-81.7) , OR=0.980 (0.919-1.044) APACHE II: AUC=78.9 (75.0-82.9) , OR=1.046 (1.002-1.092) MOD: PIRO: AUC=81.7 (78.5-84.9) , OR=1.343 (1.241-1.454) MEDS: AUC=75.8 (72.1-79.6) , OR=1.043 (99.2-1.097) APACHE II: AUC=76.4 (72.7-80.1) , OR=1.067 (1.032-1.104)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						28-day mortality: PIRO: AUC=74.4 (70.1-78.6) , OR=1.119 (1.043-1.200) MEDS: AUC=73.6 (69.3-77.9) , OR=1.067 (1.015-1.122) APACHE II: AUC=74.2 (70.0-78.4) , OR=1.078 (1.043-1.114)
Cildir 2013[70] Prospective cohort	To investigate the value of MEWS and mMEDS in the prediction of 28-day mortality in patients presenting to the ED who were diagnosed with sepsis.	ED patients with community-acquired sepsis Sepsis (n=64) severe sepsis (n=166)	MEWS mMEDS	-	28 days	**28-day mortality** MEWS>6 Sens 43.24 Spec 75 PPV 45.1 NPV 73.6 AUC 60.8 MEWS≤5, patients with sepsis (n=64): Sens 87.5 Spec 30.4 PPV 15.2 NPV 94.4 AUC 57.4 MEWS>6, patients with severe sepsis (n=166): Sens 48.5

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						Spec 67.0 PPV 49.2 NPV 66.3 AUC 59.6 mMEDS>10 Sens 90.54 Spec 55.1 PPV 48.9 NPV 92.5 AUC 77.2 mMEDS>9, patients with sepsis (n=64): Sens 87.5 Spec 80.4 PPV 38.9 NPV 97.8 AUC 83.4 mMEDS >12, patients with severe sepsis (n=166): Sens 68.2 Spec 65.0 PPV 56.2 NPV 75.6 AUC 71.2
Cooke 1999[72]	To determine	All patients admitted	MTS	-	1 month	Of the 91 patients admitted to

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
Retrospective cohort	whether the MTS can reliably detect those ED patients subsequently needing admission to critical care areas.	from ED to critical care. (n=91)				critical care: • 67% were correctly triaged (applying the MTS retrospectively) • 20% the guidelines were not followed • 7% potentially under-triaged using MTS • 5% inadequate information to retrospectively triage • 1% not requiring critical care
Corfield 2014[74] Retrospective cohort	To determine, in patients with sepsis, whether a single NEWS on ED arrival is a predictor of in-hospital death within 30 days, or ICU admission within 2 days.	Patients presented to ED with a suspicion or confirmation of infection within 2 days of attendance. (n=2003)	NEWS	-	Unclear (in hospital stay)	Admission to ICU within 2 days AUC: 67 (61-72) 30 days in-hospital mortality AUC: 70 (67-74)
Crowe 2010[75] Secondary analysis of prospectively collected data.	To determine the predictive ability of REMS, MEDS and CURB 65 for mortality in patients with sepsis.	Emergency department diagnosis.	REMS MEDS CURB65	-	In-hospital	In-hospital mortality AUC: MEDS: 0.74 (0.67-0.81) mREMS: 0.62 (0.54-0.69) CURB-65: 0.59 (0.51-0.67)
de Groot 2012[80] Prospective cohort	To compare PIRO to clinical judgement and sepsis category.	N=323 High risk cohort with severe sepsis and septic shock. N=485 Low risk cohort	PIRO MEDS	-	28 days	28 day mortality AUC PIRO: 0.81 (0.72-0.91) MEDS: 0.79 (0.71-0.87) In-hospital mortality AUC

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
		with suspected infection.				MEDS (high risk): 0.69 (0.63-0.76) MED (low risk): 0.70 (0.70-0.86) PIRO (high risk): 0.68 (0.61-0.74) PIRO (low risk): 0.83 (0.75-0.91)
Edwards 2015[92] Retrospective cohort	To compare the predictive power of published MOEWS for the development of severe sepsis in women with chorioamnionitis	N=364 women with chorioamnionitis	6 different MOEWS MEWS	-	Unclear	MOEWS A Sens 100 (47.8-100) Spec 29 (24.3-34) PPV 1.92 (0.63-4.43) PPN 100 (69.5-100) AUC 65 (62-67) MOEWS B Sens 100 (47.8-100) Spec 3.9 (2.15-6.46) PPV 1.43 (0.47-3.3) PPN 100 (76.8-100) AUC 52 (51-53) MOEWS C Sens 100 (47.8-100) Spec 3.6 (1.94-6.11) PPV 1.42 (0.46-3.29) PPN 100 (75.3-100) AUC 52 (51-53) MOEWS D Sens 60 (14.7-94.7) Spec 84.4 (80.2-88) PPV 5.08 (1.06-14.1) PPN 99.3 (97.7-99.9) AUC 72 (48-96)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						MOEWS E Sens 40 (5.27-85.3) Spec 96.9 (94.6-98.5) PPV 15.4 (1.92-54.4) PPN 99.1 (97.5-99.8) AUC 68 (44-92) MOEWS F Sens 40 (5.27-85.3) Spec 90.8 (87.3-93.6) PPV 5.71 (0.70-19.2) PPN 99.1 (97.4-99.8) AUC 65 (41-89) MEWS Sens 100 (47.8-100) Spec 90.4 (87.7-91.8) PPV 5.15 (1.69-11.6) PPN 100 (99.5-100) AUC 95 (94-96)
Gardner-Thorpe 2006[118] Prospective cohort	To establish the value of MEWS in surgical in-patients	Emergency and elective patients admitted under the colorectal team (surgical in-patient) (n=334)	MEWS	-	Unclear (in hospital stay)	Admission to ITU or HDU MEWS ≥3 Sens 88 Spec 68 MEWS ≥4 Sens 75 Spec 83 MEWS ≥5 Sens 38 Spec 89

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						MEWS ≥6 Sens 19 Spec 93 MEWS ≥7 Sens 6 Spec 94
Giannazzo 2006[123] Retrospective cohort	Prevalence and mortality of patients with severe sepsis in ED.	N=90 patients in ED with clinical suspicion of infection and 2 or more SIRS criteria and elevated lactate level (>4mmol/l) or systolic blood pressure <90mmHg	SOFA	Age >80 years, COPD, ARF, DIC, SO2, serum lactate, NNPV	28 days	Stepwise forward regression model adjusted for age >80 years, COPD, ARF, DIC, SO2, serum lactate, NNPV. Adverse outcome at 24 hours: SOFA >7 OR 15.86 (1.40-179.32), p=0.026 Adverse outcome at 28 days: SOFA >7 NS, p=0.157
Hamilton 2007[133] Retrospective cohort	To evaluate the impact of APACHE II and anti-microbial resistance over mortality	Patients with positive culture and complete APACHE II data (n=91)	APACHE II	Resistance to fluoroquinolones, African-American race	Unclear (in hospital stay)	Median APACHE II score (95% CI) Deceased subjects 21 (13-27) Survivors 11 (10-13) 1 day before specimen was obtained Deceased subjects 21 (11-25) Survivors 12 (10-12) 2 days before specimen was obtained Deceased subjects 19.5 (11.2-28.7) Survivors 11 (9-12)
Hermans 2012[135] Retrospective	To validate the MEDS score as a predictor of 28-day mortality in ED patients with	Adults who fulfilled the clinical criteria for sepsis, severe sepsis or septic shock	MEDS	C reactive protein (CRP) and lactate	28 days	28-day mortality AUC 81 (73-88)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
cohort	sepsis in the Netherlands, and to compare its performance to C reactive protein (CRP) and lactate.	(n=331)				
Hilderink 2015[136] Retrospective cohort	To evaluate the prognostic accuracy of MEDS, REMS, APACHE II and CURB-65 for 28-day mortality.	Adults who fulfilled the clinical criteria for sepsis, severe sepsis or septic shock (n=600)	MEDS CURB-65 APACHE II REMS	-	28 days	AUC for in-hospital mortality: MEDS: 82 (77-86) CURB-65: 82 (77-87) CURB-65: 77 (69-85) APACHE II:76 (68-84) REMS: 78 (72-83) AUC for total mortality: MEDS: 82 (78-87) CURB-65: 78 (73-83) CURB-65: 72 (63-80) APACHE II: 71 (64-79) REMS: 74 (69-80)
Howell 2007[144] Prospective cohort	To validate MEDS, mREMS and CURB-65 in patients with suspected infection	Adults presenting to the ED with suspected infection (n=2132)	MEDS REMS (modified) CURB-65	-	28 days	AUC for 28-day mortality CURB-65: 78.8 (74.4-83.3) mREMS: 80.2 (75.2-85.2) MEDS: 84.9 (81.2-88.7)
Jo 2013[153] Retrospective cohort	To assess whether the addition of lactate improve mortality prediction of ViEWS alone.	Critically ill patients transferred to ICU from ED (65.6% had sepsis) (n=151)	ViEWS ViEWS-L (with Lactate) APACHE II SAPS II SAPS III	Lactate	28 days	AUC for in hospital mortality ViEWS 74.2 (72.9-87.5) ViEWS-L (with Lactate) 80.2 (72.9-87.5) APACHE II 68.9 (57.7-74.7) SAPS II 79.8 (72.6-87.2)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						SAPS III 80.3 (72.9-87.8) AUC for 28-day mortality ViEWS 73.2 (65.0-81.4) ViEWS-L (with Lactate) (80.3-73.1-87.6) APACHE II 67.1 (58.3-76.0) SAPS II 78.2 (70.5-85.9) SAPS III 79.0 (71.2-86.8)
Johnston 2005[154] Secondary analysis of prospectively collected data.	To evaluate predictors of mortality in septic patients.	N=826 patients with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional organ system.	APACHE II	Multivariate analysis adjusted for age, APACHE II acute physiology score, APACHE II chronic health points, patient types, primary focus of infection, time in hospital before diagnosis, white blood cell count, serum pH, platelet count, prothromin time.	In-hospital	In-hospital mortality APACHE II acute physiology score APACHE II 1-15: OR = 1 APACHE II 16-19: OR = 0.99 (0.61-1.62) APACHE II 20-25: OR = 1.35 (0.84-2.16) APACHE II ≥26: OR = 2.31 (1.39-3.83)
Kofoed 2008[170] Prospective cohort	To evaluate prognostic value of SAPS II and SOFA to predict mortality	Patients admitted to the ED or infectious disease services with 2 SIRS criteria (n=151)	SAPS II SOFA	None	30 and 180 days	30-day mortality SAPS II >22.5 Sens 100 Spec 68 AUC 89 (80-98) SOFA >4.5

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						Sens 44 Spec 95 AUC 80 (65-94) 180-day mortality SAPS II >22.5 Sens 100 Spec 73 AUC 91 (56-96) SOFA >1.5 Sens 74 Spec 61 AUC 75 (64-86)
Komatsu 2006[172] Retrospective cohort	To evaluate the predictive value for mortality of APACHE II, SOFA, MPI, MOF	Patient who underwent emergency surgery for colorectal perforation (n=26)	APACHE II SOFA MPI MOF	-	In hospital (until death or discharge from surgical ward. Mean: 42 (2-150) days)	Overall mortality: 26.9% APACHE II ≥19: survivors: 0 (0%); non-survivors: 6 (85.7%) APACHE II <19 survivors: 19 (100%); non-survivors: 1 (14.3%) SOFA ≥8 survivors: 3 (15.9%); non-survivors: 7 (100%) SOFA <8 survivors: 16 (84.1%); non-survivors: 0 (0%) MPI ≥30 survivors: 4 (21.1%); non-survivors: 6 (85.7%) MPI <30 survivors: 15 (78.9%); non-survivors: 1 (14.3%) MOF ≥7 survivors: 3 (15.9%); non-survivors: 7 (100%) MOF <7 survivors: 16 (84.1%); non-survivors: 0 (0%)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
Kumar 1995[175] Prospective cohort	To assess which factors significantly affect prognosis in patients with intra-abdominal sepsis	Patients with proven intra-abdominal sepsis (n=86)	APACHE II	Duration of illness Source of infection	Unclear (in hospital stay)	APACHE I: 0-5: mortality 5.6% APACHE I: 6-10: mortality 6.7% APACHE I: 11-15: mortality 45% APACHE I: 16-20: mortality 91.7% APACHE I: 21-25: mortality 100% APACHE I: 26-30: mortality 100%
Levison 1991[187] Retrospective cohort	Predictive ability of APACHE II in the 24 hours prior to intra-abdominal abscess.	N=91 Intra-abdominal abscess after surgery	APACHE II	-	Unclear (in hospital stay)	Mortality: APACHE II score <15: 1 patient APACHE II score 15-19: 4 patients APACHE II score ≥20: 85% (number of patients not stated) APACHE II score 20-24 (operating room): 7/10 patients APACHE II score 20-24 (percutaneous): 7/7 patients APACHE II score ≥25: All patients (number of patients not stated)
Macdonald 2014[196] Subgroup analysis of data gathered in the Critical Illness and Shock Study (CISS)[15]	To compare PIRO, SOFA and MEDS to predict mortality in ED patients with sepsis/severe sepsis/septic shock	N=240	PIRO MEDS SOFA	-	30-day	AUC (to predict 30-day mortality) PIRO 86 (80-92) MEDS 81 (74-88) SOFA 78 (71-85)
Moscovitz 1994[219] Prospective	To determine the predictive value of IL6 and TNF-alpha in bacteraemia,	Patients admitted to ED with bacteraemia and one of the following: temperature >38°C or	APACHE II	Age, and plasma levels of IL6 and TNF	Unclear (in hospital stay)	21 patients used the ICU within 72h of admission. Mean APACHDE II score 12.1±8.2 at

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
cohort	morbidity, and mortality	<36.5°C, mean arterial pressure <70 mm Hg, leukocytes >12500, pH <7.28, or physical findings indicating a focal infection (n=100)				entry.
Mylotte 2001[227] Retrospective cohort	To determine predictors of 30 day mortality in patients with community-acquired bacteraemia (CAB).	Patients ≥18 years with CAB retrospectively identified from blood cultures. (n=174)	APACHE III	Underlying disease, age, initial combination antibiotic treatment, intravenous catheter source of CAB, S aureus bacteremia and E coli bacteremia.	30 days	30 day mortality: APACHE III >35 on admission OR 5.6 (2.6-13.1) p=<.001
Osborn 2014[251] Retrospective cohort	To develop a Sepsis Severity Score the estimate the probability of hospital mortality among subjects in the Surviving Sepsis Campaign database	Patients with severe sepsis or septic shock. (n=23,428)	SSS	-	Unclear (in hospital stay)	In-hospital mortality AUC : 73.6 (development cohort); AUC 74.8 (validation cohort)
Prytherch 2010[270] Prospective cohort	To develop a validated, paper-based, aggregate weighted track and trigger system (AWTTS) that could	n=198,755 patient with completed, acute medical admissions	ViEWS	-	Unclear (in hospital stay)	In-hospital mortality within 24 hours of the observation AUC 88.8 (88.0-89.5)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
	serve as a template for a national early warning score (EWS) for the detection of patient deterioration					
Sankoff 2008[280] Prospective cohort	To externally validate MEDS to predict 28-day mortality	Adults (≥18 years), who have met criteria for SIRS, have been admitted to the hospital from the ED.	MEDS	-	28 days	28-day mortality AUC 88 (83-92)
Shapiro 2003[295] Prospective cohort	Derivation and internal validation of MEDS (to predict 28-day mortality)	Patients admitted to ED with suspected infection (n=3179)	MEDS	-	28 days	AUC (derivation dataset): 82 AUC (validation dataset): 76
Shapiro 2007[292] Prospective cohort	To determine MEDS performance in predicting mortality at 1 year	Patients admitted to ED with suspected infection (n=3102)	MEDS	Charlson index, sex, age	1 year	1-year mortality: Low risk (5-7 points): HR 2.2 (1.7-2.9) Moderate risk (8-12 points): HR 3.5 (2.7-4.6) High risk (13-15 points): 6.7 (4.9-9.3) Very high risk (>15 points): HR 10.5 (7.2-15.4)
Talmor 2007[306] Retrospective cohort	To derive and both internally and externally validate a simple triage risk-stratification tool that predicts the primary outcome of mortality, in addition	Patients admitted to ED with suspected infection (n=5133) Cohort 1: patients with suspected infection admitted to the hospital and discharged	STSS	-	In hospital	In-hospital mortality Cohort 1: AUC 80 Cohort 2: AUC76 Cohort 3: AUC 73 Intensive care admission Cohort 1: AUC 70 Cohort 2: AUC72

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
	to the need for mechanical ventilation and treatment in an ICU, in patients presenting to the ED with infection	from the ED Cohort 2: ED patients with suspected infection and admitted to hospital Cohort 3: patients admitted to hospital from the ED with a principle diagnosis of an infectious pathogenesis				Cohort 3: AUC 70 Use of mechanical ventilation Cohort 1: AUC 69 Cohort 2: AUC73 Cohort 3: AUC 68
ter Avest 2013[307] Retrospective cohort	To evaluate which patient characteristics in uncomplicated sepsis patients are related to outcome.	N=70 ED patients with uncomplicated sepsis	MEDS	-	Unclear	Abbrev. MEDS score, survivors 4.8±2.9, non-survivors=7.2±3.4, p=0.03
van Veen 2008[317] Prospective cohort	To validate use of the Manchester triage system in paediatric emergency care.	Children in ED (n=16,735)	MTS	-	Unclear	**Agreement with reference standard – urgency according to the MTS compared with the predefined reference standard for five urgency levels.** Overall: Sens 63 (59-66) Spec 79 (79-80) LR+ 3.0 (2.8-3.2) for a high urgency result LR- 3.0 (2.8-3.2) for a low urgency result <u>0-2 months:</u>

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
						Sens 50 (42-58) Spec 79 (76-82) LR+ 2.4 (1.9-2.9) LR- 0.63 (0.54-0.74) <u>3-11 months:</u> Sens 65 (56-73) Spec 69 (67-72) LR+ 2.1 (1.9-2.5) LR- 0.50 (0.39-0.63) <u>1-3 years:</u> Sens 67 (61-73) Spec 75 (74-77) LR+ 2.7 (2.5-3.0) LR- 0.43 (0.36-0.52) <u>4-7 years:</u> Sens 66 (55-76) Spec 81 (80-83) LR+ 3.6 (3.0-4.2) LR- 0.41 (0.31-0.56) <u>8-16 years:</u> Sens 64 (53-73) Spec 88 (87-89) LR+ 5.4 (4.5-6.5) LR- 0.41 (0.31-0.54)

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
Vorwerk 2009[321] Retrospective cohort	To determine the efficacy of the abbreviated MEDS score (without neutrophil bands), and MEWS in predicting 28-day mortality in adult ED patients with sepsis.	Patients admitted to ED with sepsis (n=307)	abbreviated MEDS MEWS	-	28 days	Ab-MEDS AUC 82 (78-87) Ab-MEDS ≥5 Sens 98.6 (92.5-99.9) Spec 26.5 (21.0-32.6) Ab-MEDS>12 Sens 31.9 (21.4-44.0) Spec 26.5 (21.0-32.6) MEWS AUC 72 (67-77) MEWS ≥5 Sens 31.9 (21.4-44.0) Spec 93.2 (89.2-96.1)
Yilmazlar 2007[331] Retrospective cohort	To determine the prognostic factors for mortality in patients with necrotizing soft tissue infections (NSTI)	Patients admitted to general surgery with NSTI (n=67)	APACHE II	Age, sex, time between initiation of symptoms and admission to the clinic, presence of systemic coexisting disease, origin of infection, dissemination of NSTI, method of therapy	Unclear	Overall mortality rate: 49%. ROC analysis revealed a threshold APACHE II score for mortality of 13 (Note: AUC not reported). Univariate regression identified 3 factors that significantly affected patient survival: age, APACHE II score, and NSTI dissemination. Multivariate analysis determined that only APACHE II score ≥13 and NSTI dissemination were significant risk factors affecting mortality.
Yoo 2015A[334] Retrospective cohort	To evaluate whether the combination of MEWS and lactate improves the ability	In Patients with severe sepsis/septic shock screened or contacted by medical alert team	MEWS MEWS + lactate	Lactate	28 days	Prediction of ICU admission: MEWS ≥5.5 AUC 81.6

Study	Objective	Population/Setting	Score(s)	Additional prognostic factors	Time of follow up	Results
	of MEWS to identify sepsis/septic shock patients who should be transferred to ICU. Also to assess the ability of MEWS and lactate to predict 28-day mortality.					Sens: 81.6 Spec: 66.1 Prediction of 28-day mortality: MEWS (Multivariable analysis) OR 1.387 (1.090-1.766)
Yzerman 1996[336] Prospective cohort	To evaluate the predictive value of APACHE II in predicting complications and mortality	Patients with hospital-acquired bacteraemia (S. aureus) (n=99)	APACHE II	Age, sex, underlying disease, focus of infection, therapy	In hospital stay	Overall mortality rate: 18%. In the multivariate analysis the ΔAPACHE II score was the only independent factor for mortality.
Zhao 2013[340] Prospective cohort	To evaluate MEDS, PCT, IL-6 and CRP predictive severity and 28 day mortality ability.	N=501 adult ED patients with sepsis	MEDS	Logistic regression adjusted for PCT, IL-6, CRP and age	28 days	Severity of sepsis OR 1.356 (1.267-1.450) p=<.001 28-day mortality OR 1.265 (1.189-1.347) p=<.001
Zhao 2015[339] Prospective cohort	To investigate the prognostic performance of MEDS in predicting in-hospital mortality	n=468 adults in ED (179 with sepsis, 209 with severe sepsis, 80 with septic shock)	MEDS	-	Unclear (in hospital)	MEDS > 12.5 AUC 76.7 (72.1-81.4) Sens 78.5 Spec 59.9 PPV 46.5 NPV 86.2 LR+ 1.96 LR- 0.36 OR 5.44 (3.45 – 8.58)

1

6.1.3.1 Clinical evidence summary tables

Table 26: APACHE II

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
APACHE II to predict in-hospital mortality in patients with severe sepsis	1[22]	RR= 1.05 (1.03-1.07)	No serious imprecision	VERY LOW
APACHE II ≥ 12 to predict 30-day mortality in peptic ulcer perforation	1[45]	PPV 24 NPV 97	NA	VERY LOW
APACHE II ≥ 12 to predict 30-day mortality in peptic ulcer perforation	1[45]	RR = 31.6 (1.8-542.2)	No serious imprecision	VERY LOW
APACHE II ≥ 12 to predict septic shock in peptic ulcer perforation	1[45]	PPV 35 NPV 94	NA	VERY LOW
APACHE II ≥ 12 to predict septic shock in peptic ulcer perforation	1[45]	RR = 10.0 (1.4-69.4)	No serious imprecision	VERY LOW
APACHE II ≥ 12 to predict ICU admission in peptic ulcer perforation	1[45]	PPV 49 NPV 75	NA	VERY LOW
APACHE II ≥ 12 to predict ICU admission in peptic ulcer perforation	1[45]	RR = 2.7 (0.8-9.5)	Serious	VERY LOW
APACHE II to stratify patients in ED with severe sepsis	1[60]	AUC 62.4	NA	VERY LOW
APACHE II (cut-off value: 21.5) to predict 28-day mortality in septic patients	1[65]	Sens 35 Spec 88 PPV 63 NPV 69	NA	VERY LOW
APACHE II (cut-off value: 21.5) to predict 28-day mortality in septic patients	1[65]	AUC 0.664	NA	VERY LOW
APACHE II (cut-off value: 21.5) to predict 28-day mortality in septic patients	1[65]	OR = 3.9 (2.2-6.9)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
APACHE II to stratify patients in ED with sepsis	1[67]	AUC 68.3 (derivation cohort) AUC 71.9 (validation cohort)	NA	VERY LOW
APACHE II to predict admission to ICU	1[68]	OR 1.046 (1.002-1.092)	No serious imprecision	VERY LOW
APACHE II to predict admission to ICU	1[68]	AUC 78.9 (75.0-82.9)	No serious imprecision	VERY LOW
APACHE II to predict MOD (Multiple Organ Dysfunction)	1[68]	OR 1.067 (1.032-1.104)	No serious imprecision	VERY LOW
APACHE II to predict MOD (Multiple Organ Dysfunction)	1[68]	AUC 76.4 (72.7-80.1)	No serious imprecision	VERY LOW
APACHE II to predict 28-day mortality	1[68]	OR 1.078 (1.043-1.114)	No serious imprecision	VERY LOW
APACHE II to predict 28-day mortality	1[68]	AUC 74.2 (70.0-78.4)	No serious imprecision	VERY LOW
APACHE II to predict in-hospital mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 76 (68-84)	No serious imprecision	VERY LOW
APACHE II to predict total mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 71 (64-79)	No serious imprecision	VERY LOW
APACHE II to predict in-hospital mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 68.9 (57.7-74.7)	No serious imprecision	VERY LOW
APACHE II to predict 28-day mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 67.1 (58.3-76.0)	No serious imprecision	VERY LOW
APACHE II to predict in-hospital mortality in patients with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional	1[154]	APACHE II 1-15: OR = 1	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
organ				
APACHE II to predict in-hospital mortality in patients with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional organ	1[154]	APACHE II 16-19: OR = 0.99 (0.61-1.62)	Serious	VERY LOW
APACHE II to predict in-hospital mortality in patients with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional organ	1[154]	APACHE II 20-25: OR = 1.35 (0.84-2.16)	No serious imprecision	VERY LOW
APACHE II to predict in-hospital mortality in patients with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional organ	1[154]	APACHE II ≥26: OR = 2.31 (1.39-3.83)	No serious imprecision	VERY LOW
APACHE III >35 on admission to predict 30-day mortality in patients with community-acquired bacteraemia	[227]	OR 5.6 (2.6-13.1)	No serious imprecision	VERY LOW

Table 27: CURB-65

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CURB-65 to predict in-hospital mortality in patients with sepsis	1[75]	AUC 0.59 (0.51-0.67)	No serious imprecision	VERY LOW
CURB-65 to predict in-hospital mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 82 (77-87)	No serious imprecision	VERY LOW
CURB-65 to predict total mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 78 (73-83)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CURB-65 to predict 28-day mortality in patients with suspected infection	1[144]	AUC 78.8 (74.4-83.3)	No serious imprecision	VERY LOW

Table 28: MEDS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
MEDS to stratify patients in ED with severe sepsis	1[60]	AUC 74.5	NA	VERY LOW
MEDS to predict in-hospital mortality in patients with SISR/sepsis	1[66]	OR=1.127	NA	VERY LOW
MEDS to predict admission to ICU	1[68]	OR 0.980 (0.919-1.044)	Serious	VERY LOW
MEDS to predict admission to ICU	1[68]	AUC 77.4 (73.1-81.7)	No serious imprecision	VERY LOW
MEDS to predict MOD (Multiple Organ Dysfunction)	1[68]	OR 1.067 (1.032-1.104)	No serious imprecision	VERY LOW
MEDS to predict MOD (Multiple Organ Dysfunction)	1[68]	AUC 1.043 (99.2-1.097)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality	1[68]	OR 1.067 (1.015-1.122)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality	1[68]	AUC 73.6 (69.3-77.9)	No serious imprecision	VERY LOW
mMEDS>10 for predicting 28-day mortality in ED patients with community-acquired sepsis (sepsis or severe sepsis)	1[70]	Sens 90.54 Spec 55.1 PPV 48.9 NPV 92.5	NA	VERY LOW
mMEDS>10 for predicting 28-day mortality in ED patients with community-acquired sepsis (sepsis or severe sepsis)	1[70]	AUC 77.2	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
mMEDS>9 for predicting 28-day mortality in ED patients with sepsis	1[70]	Sens 87.5 Spec 80.4 PPV 38.9 NPV 97.8	NA	VERY LOW
mMEDS>9 for predicting 28-day mortality in ED patients with sepsis	1[70]	AUC 83.4	NA	VERY LOW
mMEDS >12 for predicting 28-day mortality in ED patients with severe sepsis	1[70]	Sens 68.2 Spec 65.0 PPV 56.2 NPV 75.6	NA	VERY LOW
mMEDS >12 for predicting 28-day mortality in ED patients with severe sepsis	1[70]	AUC 71.2	NA	VERY LOW
MEDS to predict in-hospital mortality in patients with sepsis	1[75]	AUC 74 (67-81)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality in patients with suspected infections/severe sepsis/septic shock	1[80]	AUC 79 (71-87)	No serious imprecision	VERY LOW
MEDS to predict in hospital mortality in patients with severe sepsis/septic shock	1[80]	AUC 69 (63-76)	No serious imprecision	VERY LOW
MEDS to predict in hospital mortality I patients with suspected infections	1[80]	AUC 70 (70-86)	No serious imprecision	VERY LOW
MEDS to predict of 28-day mortality in ED patients with sepsis	1[135]	AUC 81 (73-88)	No serious imprecision	VERY LOW
MEDS to predict in-hospital mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 82 (77-86)	No serious imprecision	VERY LOW
MEDS to predict total mortality in	1[136]	AUC 82 (78-87)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
adults with sepsis, severe sepsis, or septic shock			imprecision	
MEDS to predict 28-day mortality in patients with suspected infection	1[144]	AUC 84.9 (81.2-88.7)	No serious imprecision	VERY LOW
MEDS to predict mortality in ED patients with sepsis/severe sepsis/septic shock	1[196]	AUC 81 (74-88)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality in patients with SIRS	1[280]	AUC 88 (83-92)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality in patients with suspected infection	1[295]	AUC 82 (derivation dataset) AUC 76 (validation dataset)	NA	VERY LOW
MEDS to predict 1-year mortality in patients with suspected infection, low risk (5-7 points)	1[292]	HR 2.2 (1.7-2.9)	No serious imprecision	VERY LOW
MEDS to predict 1-year mortality in patients with suspected infection, moderate risk (8-12 points)	1[292]	HR 3.5 (2.7-4.6)	No serious imprecision	VERY LOW
MEDS to predict 1-year mortality in patients with suspected infection, very high risk (>15 points)	1[292]	HR 10.5 (7.2-15.4)	No serious imprecision	VERY LOW
Abbreviated MEDS (without neutrophil bands)for predicting 28-day mortality in adult ED patients with sepsis	1[321]	AUC 82 (78-87)	No serious imprecision	VERY LOW
Abbreviated MEDS≥5 (without neutrophil bands)for predicting 28-day mortality in adult ED patients with sepsis	1[321]	Sens 98.6 (92.5-99.9) Spec 26.5 (21.0-32.6)	NA	VERY LOW
Abbreviated MEDS>12 (without neutrophil bands)for predicting 28-day mortality in adult ED patients with	1[321]	Sens 31.9 (21.4-44.0) Spec 26.5 (21.0-32.6)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
sepsis				
MEDS to predict severity of sepsis in ED patients with sepsis	1[340]	OR 1.356 (1.267-1.450)	No serious imprecision	VERY LOW
MEDS to predict 28-day mortality in ED patients with sepsis	1[340]	OR 1.265 (1.189-1.347)	No serious imprecision	VERY LOW
MEDS>12.5 to predict in-hospital mortality in ED patients with sepsis/severe sepsis/septic shock	1[339]	OR 5.44 (3.45 – 8.58)	No serious imprecision	VERY LOW
MEDS>12.5 to predict in-hospital mortality in ED patients with sepsis/severe sepsis/septic shock	1[339]	Sens 78.5 Spec 59.9 PPV 46.5 NPV 86.2 LR+ 1.96 LR- 0.36	NA	VERY LOW
MEDS>12.5 to predict in-hospital mortality in ED patients with sepsis/severe sepsis/septic shock	1[339]	AUC 76.7 (72.1-81.4)	No serious imprecision	VERY LOW

Table 29: MEWS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
MEWS for predicting ICU admission	1[7]	Sens 100 Spec 77.6 PPV 4.6 NPV 100	NA	VERY LOW
MEWS>6 for predicting 28-day mortality in ED patients with community-acquired sepsis (sepsis or severe sepsis)	1[70]	Sens 43.24 Spec 75 PPV 45.1 NPV 73.6	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
MEWS>6 for predicting 28-day mortality in ED patients with community-acquired sepsis (sepsis or severe sepsis)	1[70]	AUC 60.8	NA	VERY LOW
MEWS≤5 for predicting 28-day mortality in ED patients with sepsis	1[70]	Sens 87.5 Spec 30.4 PPV 15.2 NPV 94.4	NA	VERY LOW
MEWS≤5 for predicting 28-day mortality in ED patients with sepsis	1[70]	AUC 57.4	NA	VERY LOW
MEWS>6 for predicting 28-day mortality in ED patients with severe sepsis	1[70]	Sens 48.5 Spec 67.0 PPV 49.2 NPV 66.3	NA	VERY LOW
MEWS>6 for predicting 28-day mortality in ED patients with severe sepsis	1[70]	AUC 59.6	NA	VERY LOW
MEWS for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 100 (47.8-100) Spec 90.4 (87.7-91.8) PPV 5.15 (1.69-11.6) PPN 100 (99.5-100)	NA	VERY LOW
MEWS for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	AUC 95 (94-96)	No serious imprecision	VERY LOW
MEWS≥3 for predicting Admission to ITU or HDU in surgical in-patients	1[118]	Sens 88 Spec 68	NA	VERY LOW
MEWS≥4 for predicting Admission to ITU or HDU in surgical in-patients	1[118]	Sens 75 Spec 83	NA	VERY LOW
MEWS≥5 for predicting Admission to	1[118]	Sens 38	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
ITU or HDU in surgical in-patients		Spec 89		
MEWS≥6 for predicting Admission to ITU or HDU in surgical in-patients	1[118]	Sens 19 Spec 93	NA	VERY LOW
MEWS≥7 for predicting Admission to ITU or HDU in surgical in-patients	1[118]	Sens 6 Spec 94	NA	VERY LOW
MEWS (without neutrophil bands)for predicting 28-day mortality in adult ED patients with sepsis	1[321]	AUC 72 (67-77)	No serious imprecision	VERY LOW
MEWS≥5 (without neutrophil bands)for predicting 28-day mortality in adult ED patients with sepsis	1[321]	Sens 31.9 (21.4-44.0) Spec 93.2 (89.2-96.1)	NA	VERY LOW
MEWS ≥5.5 for predicting ICU admission in patients with severe sepsis/septic shock	1[334]	Sens: 81.6 Spec: 66.1	NA	VERY LOW
MEWS for predicting ICU admission in patients with severe sepsis/septic shock	1[334]	AUC 81.6	NA	VERY LOW
MEWS for predicting 28-day mortality in patients with severe sepsis/septic shock	1[334]	OR 1.387 (1.090-1.766)	No serious imprecision	VERY LOW

Table 30: MOEWS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
MOEWS A for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 100 (47.8-100) Spec 29 (24.3-34) PPV 1.92 (0.63-4.43) PPN 100 (69.5-100)	NA	VERY LOW
MOEWS A for predicting the	1[92]	AUC 65 (62-67)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
development of severe sepsis in women with chorioamnionitis			imprecision	
MOEWS B for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 100 (47.8-100) Spec 3.9 (2.15-6.46) PPV 1.43 (0.47-3.3) PPN 100 (76.8-100)	NA	VERY LOW
MOEWS B for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	AUC 52 (51-53)	No serious imprecision	VERY LOW
MOEWS C for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 100 (47.8-100) Spec 3.6 (1.94-6.11) PPV 1.42 (0.46-3.29) PPN 100 (75.3-100)	NA	VERY LOW
MOEWS C for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	AUC 52 (51-53)	No serious imprecision	VERY LOW
MOEWS D for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 60 (14.7-94.7) Spec 84.4 (80.2-88) PPV 5.08 (1.06-14.1) PPN 99.3 (97.7-99.9)	NA	VERY LOW
MOEWS D for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	AUC 72 (48-96)	Serious	VERY LOW
MOEWS E for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 40 (5.27-85.3) Spec 96.9 (94.6-98.5) PPV 15.4 (1.92-54.4) PPN 99.1 (97.5-99.8)	NA	VERY LOW
MOEWS E for predicting the development of severe sepsis in	1[92]	AUC 68 (44-92)	Serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
women with chorioamnionitis				
MOEWS F for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	Sens 40 (5.27-85.3) Spec 90.8 (87.3-93.6) PPV 5.71 (0.70-19.2) PPN 99.1 (97.4-99.8)	NA	VERY LOW
MOEWS F for predicting the development of severe sepsis in women with chorioamnionitis	1[92]	AUC 65 (41-89)	Serious	VERY LOW

Table 31: MTS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
MTS for predicting ICU admission in ED patients	1[72]	Of the 91 patients admitted to critical care: • 67% were correctly triaged (applying the MTS retrospectively) • 20% the guidelines were not followed • 7% potentially under-triaged using MTS • 5% inadequate information to retrospectively triage • 1% not requiring critical care	NA	VERY LOW
MTS to establish level of urgency in children presenting to ED	1[317]	Sens 63 (59-66) Spec 79 (79-80) LR+ 3.0 (2.8-3.2) for a high urgency result LR- 3.0 (2.8-3.2) for a low urgency result	NA	VERY LOW
MTS to establish level of urgency in children (0-2 months) presenting to ED	1[317]	Sens 50 (42-58) Spec 79 (76-82) LR+ 2.4 (1.9-2.9) LR- 0.63 (0.54-0.74)	NA	VERY LOW
MTS to establish level of urgency in	1[317]	Sens 65 (56-73)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
children (3-11 months) presenting to ED		Spec 69 (67-72) LR+ 2.1 (1.9-2.5) LR- 0.50 (0.39-0.63)		
MTS to establish level of urgency in children (1-3 years) presenting to ED	1[317]	Sens67 (61-73) Spec 75 (74-77) LR+ 2.7 (2.5-3.0) LR- 0.43 (0.36-0.52)	NA	VERY LOW
MTS to establish level of urgency in children (4-7 years) presenting to ED	1[317]	Sens 66 (55-76) Spec 81 (80-83) LR+ 3.6 (3.0-4.2) LR- 0.41 (0.31-0.56)	NA	VERY LOW
MTS to establish level of urgency in children (8-16 years) presenting to ED	1[317]	Sens 64 (53-73) Spec 88 (87-89) LR+ 5.4 (4.5-6.5) LR- 0.41 (0.31-0.54)	NA	VERY LOW

Table 32: NEWS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
NEWS on ED arrival for predicting ICU admission within 2 days	1[74]	AUC 67 (61-72)	No serious imprecision	VERY LOW
NEWS on ED arrival for predicting 30 days in-hospital mortality	1[74]	AUC 70 (67-74)	No serious imprecision	VERY LOW

1 **Table 33: PEWS**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
PEWS for predicting RRT (Rapid Response Team) or code blue even	1[6]	Sens: 85.8	NA	VERY LOW

2 **Table 34: PIRO**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
PIRO to stratify patients in ED with sepsis	1[67]	AUC 83.3 (derivation cohort) AUC 81.3 (validation cohort)	NA	VERY LOW
PIRO (cut off 14.5, derivation cohort) to stratify patients in ED with sepsis	1[67]	Sens 73.5 Spec 76.0 PPV 40.5 NPV 92.8	NA	VERY LOW
PIRO (cut off 15.5, validation cohort) to stratify patients in ED with sepsis	1[67]	Sens 72.3 Spec 78.1 PPV 40.7 NPV 93	NA	VERY LOW
PIRO to predict admission to ICU	1[68]	OR 1.758 (1.559-1.982)	No serious imprecision	VERY LOW
PIRO to predict admission to ICU	1[68]	AUC 88.9 (85.5-92.3)	No serious imprecision	VERY LOW
PIRO to predict MOD (Multiple Organ Dysfunction)	1[68]	OR 1.343 (1.241-1.454)	No serious imprecision	VERY LOW
PIRO to predict MOD (Multiple Organ Dysfunction)	1[68]	AUC 81.7 (78.5-84.9)	No serious imprecision	VERY LOW
PIRO to predict 28-day mortality	1[68]	OR 1.119 (1.043-1.200)	No serious imprecision	VERY LOW
PIRO to predict 28-day mortality	1[68]	AUC 74.4 (70.1-78.6)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
PIRO to predict 28-day mortality in patients with suspected infections/severe sepsis/septic shock	1[80]	AUC 81 (72-91)	No serious imprecision	VERY LOW
PIRO to predict in hospital mortality in patients with severe sepsis/septic shock	1[80]	AUC 68 (61-74)	No serious imprecision	VERY LOW
PIRO to predict in hospital mortality I patients with suspected infections	1[80]	AUC 83 (75-91)	No serious imprecision	VERY LOW
PIRO to predict mortality in ED patients with sepsis/severe sepsis/septic shock	1[196]	AUC 86 (80-92)	No serious imprecision	VERY LOW

1 **Table 35: REMS**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
REMS for predicting ICU admission	1[7]	Sens 77.8 Spec 93.3 PPV 11.1 NPV 99.7	NA	VERY LOW
mREMS to predict in-hospital mortality in patients with sepsis	1[75]	AUC 62 (54-69)	No serious imprecision	VERY LOW
REMS to predict in-hospital mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 78 (72-83)	No serious imprecision	VERY LOW
REMS to predict total mortality in adults with sepsis, severe sepsis, or septic shock	1[136]	AUC 74 (69-80)	No serious imprecision	VERY LOW
mREMS to predict 28-day mortality in patients with suspected infection	1[144]	AUC 80.2 (75.2-85.2)	No serious imprecision	VERY LOW

Table 36: SAPS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
SAPS II to predict in-hospital mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 79.8 (72.6-87.2)	No serious imprecision	VERY LOW
SAPS II to predict 28-day mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 78.2 (70.5-85.9)	No serious imprecision	VERY LOW
SAPS III to predict in-hospital mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 80.3 (72.9-87.8)	No serious imprecision	VERY LOW
SAPS III to predict 28-day mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 79.0 (71.2-86.8)	No serious imprecision	VERY LOW
SAPS II >22.5 to predict 30-day mortality in patients with 2 SIRS criteria	1[170]	Sens 100 Spec 68	NA	VERY LOW
SAPS II >22.5 to predict 30-day mortality in patients with 2 SIRS criteria	1[170]	AUC 89 (80-98)	No serious imprecision	VERY LOW
SAPS II >22.5 to predict 180-day mortality in patients with 2 SIRS criteria	1[170]	Sens 100 Spec 73	NA	VERY LOW
SAPS II >22.5 to predict 180-day mortality in patients with 2 SIRS criteria	1[170]	AUC 91 (56-96)	No serious imprecision	VERY LOW

Table 37: SSS

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
SSS to estimate the probability of hospital mortality among subjects in the Surviving Sepsis Campaign database	1[251]	AUC : 73.6 (development cohort) AUC 74.8 (validation cohort)	NA	VERY LOW

1 **Table 38: STSS**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
STSS for predicting ICU admission	1[4]	AUC 88 (78-98)	No serious imprecision	VERY LOW
STSS for predicting requirement for mechanical ventilation	1[4]	AUC 91 (83-99)	No serious imprecision	VERY LOW
STSS for predicting in-hospital mortality in patients with suspected infection admitted to the hospital and discharged from the ED	1[306]	AUC 80	NA	VERY LOW
STSS for predicting in-hospital mortality in ED patients with suspected infection and admitted to hospital	1[306]	AUC 76	NA	VERY LOW
STSS for predicting in-hospital mortality in patients admitted to hospital from the ED with a principle diagnosis of an infectious pathogenesis	1[306]	AUC 73	NA	VERY LOW
STSS for predicting ICU admission in patients with suspected infection admitted to the hospital and discharged from the ED	1[306]	AUC 70	NA	VERY LOW
STSS for predicting ICU admission in ED patients with suspected infection and admitted to hospital	1[306]	AUC 72	NA	VERY LOW
STSS for predicting ICU admission in patients admitted to hospital from the ED with a principle diagnosis of an infectious pathogenesis	1[306]	AUC 70	NA	VERY LOW
STSS for predicting the use of mechanical ventilation in patients with	1[306]	AUC 69	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
suspected infection admitted to the hospital and discharged from the ED				
STSS for predicting the use of mechanical ventilation in ED patients with suspected infection and admitted to hospital	1[306]	AUC 73	NA	VERY LOW
STSS for predicting the use of mechanical ventilation in patients admitted to hospital from the ED with a principle diagnosis of an infectious pathogenesis	1[306]	AUC 68	NA	VERY LOW

1 **Table 39: SOFA**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
SOFA for predicting ICU admission	1[4]	AUC77 (65-89)	No serious imprecision	VERY LOW
SOFA for predicting requirement for mechanical ventilation	1[4]	AUC 87 (72-100)	No serious imprecision	VERY LOW
SOFA >7 to predict adverse outcome at 24 hours	1[123]	OR 15.86 (1.40-179.32)	No serious imprecision	VERY LOW
SOFA >4.5 to predict 30-day mortality in patients with 2 SIRS criteria	1[170]	Sens 44 Spec 95	NA	VERY LOW
SOFA >4.5 to predict 30-day mortality in patients with 2 SIRS criteria	1[170]	AUC 80 (65-94)	No serious imprecision	VERY LOW
SOFA >1.5 to predict 180-day mortality in patients with 2 SIRS criteria	1[170]	Sens 74 Spec 61	NA	VERY LOW
SOFA >1.5 to predict 180-day mortality in patients with 2 SIRS criteria	1[170]	AUC 75 (64-86)	No serious imprecision	VERY LOW
SOFA to predict mortality in ED	1[196]	AUC 78 (71-85)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
patients with sepsis/severe sepsis/septic shock			imprecision	

1 **Table 40: SOS**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
SOS for predicting ICU admission	1[7]	Sens 88.9 Spec 99.2 PPV 16.7 NPV 99.9	NA	VERY LOW
SOS for predicting ICU admission	1[7]	AUC 97	NA	VERY LOW

2 **Table 41: ViEWS**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
ViEWS to predict in-hospital mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 74.2 (72.9-87.5)	No serious imprecision	VERY LOW
ViEWS to predict 28-day mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 73.2 (65.0-81.4)	No serious imprecision	VERY LOW
ViEWS-L (with lactate) to predict in-hospital mortality in critically ill patients transferred to ICU from ED	1[153]	AUC 80.2 (72.9-87.5)	No serious imprecision	VERY LOW
ViEWS-L (with lactate) to predict 28-day mortality in critically ill patients transferred to ICU from ED	1[153]	AUC (80.3-73.1-87.6)	No serious imprecision	VERY LOW
ViEWS to predict 24-hour hospital	1[270]	AUC 88.8 (88.0-89.5)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
mortality			imprecision	

6.1.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix C.

Economic considerations

The following table is presented as an overview of which information is needed for each of the tools, and hence how complicated and how expensive it may be to carry them out.

Table 42: Summary of scoring systems and ease of use

Scoring tool	Required tests	Potential Settings
STSS (Simple Triage Scoring System)	Measure vital signs, O_2, Observations	Primary care ED
REMS (Rapid Emergency Medicine Score)	Measure vital signs, O_2, Observations	Primary care ED
MEWS (Modified Early Warning Score)	Measure vital signs, urine output, observations	Primary care ED
NEWS National Early Warning Score	Measure vital signs, O_2, Observations	Primary care ED
SOFA	Blood tests, measure vital signs, observations	ED
MEDS (Mortality in Emergency Department, Sepsis)	Blood tests, measure vital signs, observations, history	ED
CURB-65 (Confusion, urea nitrogen, respiratory rate, BP, 65 years and older)	Blood test, measure vital signs, observations	ED
PIRO (Predisposition, infection, response, organ dysfunction)	Blood tests (incl lactate), measure vital signs, history	ED
Sepsis Trust UK toolkit	Blood tests (incl lactate), measure vital signs, O_2, observations	ED
APACHE II (Acute Physiology and Chronic Health Evaluation)	Arterial blood gas, blood tests, measure vital signs, observations	Critical care only
SAPS II (Simplified Acute Physiology Score)	Arterial blood gas, blood tests, measure vital signs, urine output, Observations, history	Critical care only
SOS (Sepsis in Obstetrics Score)	Blood tests, measure vital signs, O_2, observations	Hospital (ED or obstetrics)
PEWS (Paediatric Early Warning Score)	Observations	Primary care Hospital (ED or paediatrics)
POPS (Paediatric Observation Priority Score)	Measure vital signs, O_2, observations, history	Primary care Hospital (ED or paediatrics)

Vital signs include some or all of blood pressure, pulse rate, breathing rate and temperature
'Observations' indicated an assessment of level of consciousness (alertness or confusion or Glasgow coma score) for most tools, but also includes purpuric rash in the case of Sepsis Trust UK toolkit and behaviour for the paediatric tools

6.1.5 Evidence statements

Clinical

There was significant variability amongst the included studies relating to (1) the included population, (2) the patient outcomes, and (3) the statistical measures that were reported and analysed. It was not possible to meta-analyse any of the results because studies with comparable populations reported different patient outcomes or analysed statistical measures in different ways.

Taking into account these inconsistencies, overall there was a trend in the evidence suggesting that any scoring system is helpful to assess prognosis and diagnosis of a patient.

Economic

No relevant economic evaluations were identified.

6.1.6 Recommendations and links to evidence

Recommendations	**8. Use a structured set of observations (see recommendations 9 and 10) when assessing people who might have sepsis. Consider using an early warning score in hospital settings.**
Relative values of different outcomes	Critical patients outcomes were: mortality hospital admission, health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36),escalation of care, unplanned critical care admission, composite unexpected patient death/cardiac arrest/admission to critical care The GDG also considered the test practicality. The statistical measures considered were: if thresholds are established/pre-defined: relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes specified for those in higher or lower risk groups; area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).
Trade-off between clinical benefits and harms	The main harm that may come to patients is both over diagnosis of suspected sepsis and lack of identification of suspected sepsis. The first group of patients will be subject to investigations and treatments they might not need and the latter group may not get appropriate treatment. The evidence showed that using the use of a scoring system does help in identification of people with poor outcomes however, it was not possible, based on the evidence alone, to establish either thresholds for individual systems or which scoring system would lead to the greatest benefit. The GDG used their experience and opinion in judging test practicality. The feasibility of using a score varies according to the variables, including the score and the setting in which the score may be used. The simpler assessments can be carried out using standard physiological measurements with the use of basic equipment. While more complex scores might only be used in hospital settings; it is possible that simpler scores could work as well in these settings.
Economic considerations	No published economic evaluations were identified for this question. As scoring tools are used to formulate a diagnosis, the costs of carrying out the assessment need to be considered alongside the subsequent management costs of

	those identified as having possible sepsis (both the true positives who do have sepsis and the false positives who do not have sepsis), the costs of managing those identified as not having sepsis (including false negatives), and the health outcomes in all cases. The costs of using the tools will depend on the measures included within it, the person carrying out the test and the length of time the test takes. Some tools include only measurement of vital signs, such as blood pressure and temperature, and simple assessment of alertness or consciousness, which can be conducted quickly and at any level of the health service. The cost of these assessments will be the cost of the consultation time, which will vary depending on the seniority of the staff involved. There is likely to be little difference in the cost of using the different tools suitable for primary care. Other tools require blood samples to be taken and tested. The cost of carrying out standard blood tests is low, and will have less of an effect on the suitability of the test than the necessity to have access to a laboratory that can process blood tests rapidly – for which reason these tests may only be appropriate to use in a hospital setting. However, the cost-effectiveness of using a tool is also highly influenced by its accuracy (sensitivity and specificity) in predicting who has sepsis or is developing sepsis. Tools with low specificity will produce many false positives – these people will receive further investigations and may be kept in hospital for some time while they are monitored, despite not having sepsis. This would have a large economic impact without any clinical benefit. However, tools with low sensitivity will produce many false negatives – these people will be told they are not at risk of sepsis and sent home, despite being at need of treatment. They will most likely be identified later when their sepsis has progressed further. They will, therefore, have worse clinical outcomes, and it is also likely to cost more to treat them. Therefore, in general tools with both high sensitivity and high specificity are more cost effective as they are picking up the appropriate people to be treated, and excluding those that correctly require no treatment. The GDG agreed that the tools are similar to each other and the evidence was not sufficient to recommend one tool over another although standardisation of a tool across the country would be useful. Training would be required to correctly implement the tool, as current practice varies locally. The GDG agreed it was more important that a structured assessment is taking place with or without a tool in order to record the key information from various parameters (such as vital signs and observations – rather than on individual parameters alone) which can inform the clinician as to the status of the patient. This recommendation is unlikely to have a cost impact.
Quality of evidence	The recommendation was based on review of scoring tools and GDG expert opinion and consensus. The GDG acknowledged the limited quality of the included studies. Most of the studies were retrospective (database) and single centre studies, which lowers the quality of the studies. Overall, the quality of evidence was very low. The most common outcome reported was AUC. Based on the AUC alone, the scoring systems appear to be moderately predictive; however, the GDG recognised that discrimination data based on the AUC alone are not an adequate way of establishing whether one scoring system performs better than another for a number of reasons, for example, the AUC was based on the ranks of the predicted probabilities and compared these ranks in people with and without the disease; but the ROC curve did

	not use the actual predicted probabilities; therefore it was not very sensitive to differences in probabilities between scoring systems. In addition, studies included in the review contained individuals of different age ranges, different baseline values, and the sample sizes were small (the majority of the studies included a cohort of less than 1000 people) which may have affected the AUC. Results on the sensitivity and specificity of the scoring systems at selected thresholds were also not sufficient to conclude whether one tool performs better than another. To demonstrate the reproducibility and generalisability of a prediction model, external validation studies are preferred to demonstrate satisfactory performance of the prediction model on patients from a different population than those used to derive the model (preferably carried out by independent investigators), and in different settings. Whilst prospective studies are desirable, retrospective data can be used to evaluate the generalisability of the model. Some validation studies were found for most of the tools (between 1 and 17), except for the Manchester Triage System (MTS) and Paediatric Observation Priority Score (POPS). About half of the studies also reported a head-to-head comparison between two or more tools in the same cohort. The studies' results did not show that any tool performs better than another; therefore, a conclusion on which tool is the best could not be reached.
Other considerations	The GDG agreed that it is important that all patients with sepsis are diagnosed as quickly as possible and that treatment should be started promptly. The group noted that most of the tools considered are very similar to each other and that there was some evidence for most scores. The GDG noted that having different tools in different hospitals and trusts means different care for patients, with implications for the training of doctors and nurses who have to be re-trained and adapt to a new system every time they change hospital. The GDG considered that there were issues about the potential use of most of the tools and that undue emphasis on tools can also be misleading. MEWS and NEWS The group was aware that Modified Early Warning score (MEWS) is used in ward monitoring. However, early warning systems have been modified by different units and hospitals so that multiple versions of scores are used and none of these adapted scores have been validated. The GDG discussed the practicality of measuring oxygen saturation in primary care and agreed that while this was possible, it was not routine for all practices. The MEWS tool has only has 2 optionsfor assessment of urine output: Nil or <0.5 ml/kg/hour, but the GDG agreed that a proxy for this would be to ask the patient whether they have recently passed urine. The GDG concluded that the MEWS and National Early Warning score (NEWS) could be implementable in primary care. They noted that the main difference is that MEWS includes urine output but not oxygen saturation and NEWS includes oxygen saturation but not urine output., There is however a lack of validation studies in primary care and emergency care settings and studies would need to assess the practicality of using the scores in these settings. The GDG were concerned that in the case of sepsis patients who are already ill will be identified, but patients who are in the process of deteriorating could be missed. PIRO Both PIRO (Predisposition, infection, response, and organ dysfunction) and MEDs (Mortality in Emergency Department Sepsis) include the measurement of bands, which is not generally done in the UK. The GDG also noted that these tools include risk factors that might not be helpful to detect sepsis, such as nursing home residents and terminal illness. Sepsis trust UK toolkits There is no published evidence on the validation of the Sepsis trust UK toolkits. The Sepsis Trust UK Toolkits use SIRS criteria and include assessment and an algorithm for management including sepsis bundles.

	. Manchester Triage score The Manchester Triage Score is not tied to physiology, it is symptom led and is only used in A&E to determine the urgency of intervention and maximum waiting time in A&E for all patients, not those specifically with a suspicion of infection/sepsis. The GDG considered that it would be important to recommend the use of one tool or strategy for all settings if possible. While this guideline is interested in recognition and assessment of sepsis, an early warning score needs to be appropriate for use for all unwell patients and not just those with sepsis. The NICE guideline for Acutely ill patients in hospital (CG50) suggested a track and trigger system should be used but was unable to recommend a particular score. This review was not able to inform the appropriate score further and the GDG agreed that without strong evidence it would be inappropriate to make a recommendation for people with suspected sepsis only. The GDG considered that the most important aspect of using a tool is likely to be that it ensures an assessment is made of several important parameters rather than the assessment being made on one or two parameters. The severity of illness might not be appreciated without these measurements. This approach is more important than the use of a score. The GDG were also aware of the common use of scores in hospital settings. The recommendation is therefore for a structured assessment which should include the parameters listed in recommendations 9 and 10. These are the parameters included in NICE guideline for Acutely ill patients in hospital (CG50) for assessment of acutely ill adults and in the Fever in under 5s guideline (CG160) with some adaptations recommended according to setting. The use of a tool may be appropriate in hospital settings where tools are likely to be used for monitoring Research recommendations The GDG considered that the area with least evidence is primary and community care and emergency settings and that use of a score could potentially improve recognition of unwell patients and improve communication across primary and community care and hospital settings. They therefore developed a research recommendation in this area (see 6.1.6.1).

6.1.6.1 Research recommendation

1. **Can early warning scores, for example NEWS (national early warning scores for adults) and PEWS (paediatric early warning score), be used to improve the detection of sepsis and facilitate prompt and appropriate clinical response in pre-hospital settings and in emergency departments?**

16.2 Signs and symptoms

6.2.1 Introduction

Early identification of sepsis requires attention to symptoms and signs. In the absence of well validated scores to identify people the value of individual signs and symptoms is important. While these will not be adequate to make a diagnosis they might ensure that appropriate clinical assessment and review takes place.

6.2.2 Review question: In people with suspected sepsis how accurate are physiological signs and symptoms to identify whether sepsis is present?

For full details see review protocol in Appendix C.

Table 43: Characteristics of review question

Population	All people with suspected (or under investigation for) sepsis, including the following groups: • Adults • Young people aged 12-18 years • Children including infants and neonates (pre- term neonates excluded) • People aged over 70 years • People at higher risk of infection • Pregnant women and recently pregnant women • Immunocompromised people.
Index tests: sign(s) or symptom(s)	1. heart rate 2. respiratory rate 3. systolic blood pressure, pulse pressure, mean arterial pressure 4. level of consciousness 5. altered mental state: (possible descriptors - delirium, hypoactive, for children- no response to social cues, does not wake or if roused does not stay awake) 6. low oxygen saturation 7. fever (includinghistory of fever) 8. hypothermia 9. reduced urine output 10. appearing ill to a healthcare professional/or relative 11. history of falls 12. rigor 13. skin rash 14. pain, including pleuritic pain, limb pain 15. diarrhoea/ watery diarrhoea/ vomiting 16. abdominal pain/vaginal discharge 17. shock/hypoperfusion (prolonged capillary refill time, cold hands and feet , reduced skin turgor, pale/mottled/ashen/blue skin, lips or tongue) 18. altered breathing (for example, nasal flaring, grunting, chest indrawing) 19. weak, high-pitched or continuous cry 20. bulging fontanelle
Reference standards	• Blood culture proven infection • American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of SIRS, sepsis, severe sepsis or septic shock • Other composite definitions of sepsis based on clinical biochemistry tests and signs and symptoms

	• All-cause mortality at 28 days (or nearest time point) • Onset of organ failure
Statistical measures	Sensitivity Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio: univariate analyses only included if no multivariate analyses reported
Key confounders for studies reporting odds ratios	No pre-specified confounders
Study design	Cross-sectional studies Prospective and retrospective cohorts Systematic reviews of the above

6.2.3 Clinical evidence

A search was conducted for cross-sectional studies, cohort studies (including both retrospective and prospective analyses) and systematic reviews that assessed the diagnostic test accuracy of a sign(s) or symptom(s) to identify whether sepsis is present in people under investigation. No systematic reviews were identified.

Fourty-four studies were included in the review. Fifteen studies are in children[8,9,12,36,40,42,43,51,89,140,141,176,183,239,248] and 29 were in adults[5,19,24,28,41,48,59,62,64,87,90,104,125,131,169,173,177,181,182,185,192,208,224,262,264,288,302,310,325]. Evidence from these is summarised in Table 44 for children Table 45 for adults.

The aim of this review was to evaluate a number of signs and symptoms for the identification of people with sepsis. The standard approach for this type of review is to use diagnostic test accuracy studies reporting data such as sensitivity (ability of the test to identify those with the target condition) and specificity (ability of the test to identify those who do not have the target condition). Accuracy of a given test is measured against a reference standard, defined as providing the true measure. Ideally both index and reference standard should be measured at the same time. Sepsis is essentially a syndrome and there is no consensus about what constitutes the reference standard for sepsis. In the studies identified various reference standards were used such as blood culture proven infection, ICD-9 codes for sepsis or SIRS, and American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of SIRS, sepsis, severe sepsis or septic shock.

Some of the identified studies used clinical outcome data to examine the usefulness of a sign or symptom. The presence or absence of a sign or symptom was assessed at time of presentation, and the clinical outcomes were determined at a later time point. The GDG were aware that there was limited evidence available using the diagnostic accuracy study-design approach. Therefore these studies reporting ORs of clinical outcomes were considered relevant because ORs provide an overall assessment of the strength of association, in this review the association of a sign or symptom with all-cause mortality or organ failure. If diagnostic accuracy statistics were reported in a study, then ORs were not included in evidence report. This is because diagnostic accuracy data take into account the misclassification of individuals i.e. false-positive and false-negative classifications, and the GDG were most interested in identifying a symptom that could would not miss cases, but equally would not rule in non-affected individuals (thereby giving unwarranted antibiotic therapy). Hence for this

review both sensitivity and specificity were considered to be of equal importance when the protocol was written.

No evidence was was identified for the following signs or symptoms; pulse pressure, mean arterial pressure, level of consciousness, hypothermia, reduced urine output, appearing ill to a healthcare professional/or relative, history of falls, rigor, skin rash, pleuritic pain, limb pain, diarrhoea, vomiting, abdominal pain, vaginal discharge for pregnant or recently pregnant women, shock, hypoperfusion, altered breathing, weak breathing, high-pitched or continuous cry and bulging fontanelle.

The signs and symptom results are detailed in the following sections:

- Temperature: section 6.2.3.2.1
- Heart rate: section 6.2.3.2.2
- Blood pressure: section 6.2.3.2.3
- Respiratory rate: section 6.2.3.2.4
- Altered mental state: section 6.2.3.2.5
- Level of consciousness: section 6.2.3.2.6
- Oxygen saturation: section 6.2.3.2.7.

See also the study selection flow chart in Appendix E, clinical evidence tables in Appendix H, exclusion list in Appendix L, and forest plots in Appendix K.

The quality of the evidence was evaluated using the QUADAS-2 checklist for diagnostic accuracy studies. It was not possible to conduct meta-analysis of the diagnostic accuracy data nor the ORs because of heterogeneity in the study settings and in the cut-off values of the sign or sypmtom, in addition to the lack of a reference standard. Univariate odds ratio results were only reported in the review if no multivariate results were given in the included studies.

6.2.3.7.1 Summary of included studies

Table 44: Summary of studies included in the review, children

Study	Index test	Population	Target condition / reference test	Comments
Ammann 2003[8]	Fever	n=111 (285 episodes) patients <18 years	Serious bacterial infection	Retrospective design Population only those children at low risk of Serious bacterial infection with fever after chemotherapy-induced neutropenia
Ammann 2004[10]	Temperature History of temperature	n=364 <17years diagnosed with malignancy screened for fever or neutropenia	Bacteraemia	Retrospective design.
Angel 1994[12]	Temperature (>38°C or >39°C)	n=200 children (orthopaedic	Infectious complications	Retrospective design; sepsis

Study	Index test	Population	Target condition / reference test	Comments
		operation or intervention)		diagnosis not confirmed by blood test; low incidence of infections (<2%).
Bonadio 1994[36]	Body temperature	n=356 consecutive febrile infants 8-12 weeks who received outpatient sepsis assessment	Serious bacterial infection	
Bonsu 2007[40]	Temperature (also: leucocyte in urine, age, peripheral blood leucocyte, peripheral bands)	n=3765 febrile infants	Invasive sepsis	Retrospective design
Brent 2011[43]	Temperature-pulse centiles Age specific temperature-pulse centiles	n=1360 First study at ED: 3 months – 10 years presenting to ED with suspected infection. Second study, large national case control on meningococcal. Review of data from Office for National Statistics.	Serious bacterial infection, meningococcal sepsis	Note that two studies with different populations analysed.
Brent 2011A [42]	Consciousness level Temperature Tachycardia Capillary refill time Hypotension Tachypnoea Rash	n=1951 children with suspected serious bacterial infection	Serious bacterial infection	Single centre
Castellanos 2002[51]	Refractory hypotension GCS Oliguria Systolic blood pressure Heart rate (beats/min) Respiratory rate (breaths/min) Rectal temperature (C)	n=192 in development sample from 4 PICUs (Jan 1 1983 – June 30 1995) n=158 in validation sample form 10 PICUs (Jan 1 1996 – Dec 31 1998) Aged 1 month – 14 years with confirmed or presumed diagnosis of meningococcal septic shock.	Death	Retrospective design
Duke 1997A[89]	Mean arterial pressure	n=31 children in ICU with sepsis or severe sepsis	Sepsis-related mortality	lack of standardisation of therapy.
Hofer 2012[141]	Temperature, HR	Neonates hospitalised	Culture-proven	Retrospective design

Study	Index test	Population	Target condition / reference test	Comments
		within the first 24h of life	Early onset Sepsis	
Hofer 2012A[140]	Temperature (temperature symptoms: fever (rectal temperature >38.5°C); hypothermia (rectal temperature <36°C); temperature instability (increase or decrease of rectal temperature of >1.5°C within 3 h)	Newborns (first 72 h of life) n=851 N =127 with temperature symptoms (15%): 8% fever; 8% hypothermia; 6% temperature instability n=209 (25%)had diagnosis of clinical EOS	Diagnosis of culture-proven EOS/pneumonia	Retrospective design analysis of medical reports, case histories and electronic patient filing system
Kupperman 1998[176]	Temperature	n=6680 3-36 months of age, temperature ≥39C and no apparent focal infection.	Occult pneumococcal bacteraemia.	
Lee 1998A[183]	Temperature	n=11911 patients 3-36 months old, at risk of occult bacteraemia	Serious bacterial infection	
Nijman 2013[239]	Temperature (˚C) Tachypnoea Tachycardia Oxygen saturation Capillary refill time CRP	n=1750 children presenting with fever at ED	Serious bacterial infection	
Ohlin 2010[248]	Blood pressure/skin colour Bradycardia Tachypnea	n=401 consecutive newborn infants <28 days of suspected sepsis admitted to NICU	Positive blood culture	

1

2

3 **Table 45: Summary of studies included in the review, adults**

Study	Index tests	Population	Target condition / reference test	Comments
Ahn 2012[5]	Respiratory rate, duration of fever prior to admission, pulse rate, body temperature	n=249 (285 episodes) adults with febrile neutropenia after chemotherapy	Bacteraemia.	Population only adults after chemotherapy who visited Emergency Department
Baez 2013A[19]	Mean arterial pressure, heart rate, respiratory rate	n=63 Adults (≥18 years) admitted to hospital through ED with the	In-hospital mortality	Retrospective design

Study	Index tests	Population	Target condition / reference test	Comments
		diagnosis of SIRS, sepsis, severe sepsis, or septic shock		
Bates 1990[24]	Temperature	n=1516 blood culture episodes	Bacteraemia	Single centre.
Benchekroune 2008[28]	SAP and DAP	n=68 Adults in ICU with septic shock	In-hospital mortality	
Boulain 2014[41]	Low ScvO2; initial body temperature; initial arterial partial pressure to predict 28-day mortality	n=363 adults with severe sepsis or septic shock	Mortality	
Carbonell 2004 [48]	Hypotension Respiratory failure	n=200 patients with acute renal failure.	Mortality	Single centre.
Chassagne 1996[59]	Fever, fever spike, tachycardia, altered mental status	n=258 elderly patients (over 65 years) with suspected bacteraemia included in study.	Bacteraemia	Single centre. Population on elderly (>65 years).
Chen 2008[64]	Heart rate variability. SDNN: mean, standard deviation of NN (consecutive normal-to-normal intervals) nHFP: normalised high-frequency power	n=132 Consecutive adults visiting the ED who met the criteria for sepsis	In-hospital mortality	Small sample size.
Chen 2014[62]	Temperature (>38°C or <36°C), HR>90 beats/min Also: Leptin, WBS and Platelets	n=331 (sepsis n=128; non-sepsis = 203) Adults in ICU	Sepsis	Retrospective design
Deulofeu 1998[87]	Absence of fever; Barthel index <60 (functional status)	n=242 Consecutive adults (≥15 years) with bacteraemia	Bacteraemia-related mortality	Prediction of bacteraemia-related mortality. Unclear how many patients had sepsis
Dunser 2009A[90]	MAP, SAP	n=274 Adults in ICU with sepsis	28-day mortality	Retrospective design; lack of standardisation of therapy.
Fontanarosa 1992[104]	Altered mental status	n=750 >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn. Jan 1 1988 – Dec 31 1988.	Bacteraemia	Retrospective design.
Glickman	Temperatire, heart	n=472 adults in ED	Septic shock	Sepsis progression

Study	Index tests	Population	Target condition / reference test	Comments
2010[125]	rate, respiratory rate	with sepsis		and patient outcomes are probably influenced by treatment.
Ha 2011[131]	Hypotension Body temperature (≥39°C)	n=802 patients (993 episodes) of low-risk febrile neutropenia	Bacteraemia	Population after anti-cancer chemotherapy. Retrospective.
Koch 2015[169]	Central oxygen saturation (ScvO2) Mean arterial blood pressure (MAP)	n=50 adults with sepsis, severe sepsis or septic shock	Mortality	
Kreuzer 1992[173]	Temperature (also: leucocyte count, cardiac index, left ventricular stroke work index, APACHE II)	n=110 adults undergoing cardiac surgery	Sepsis	
Kushimoto 2013[177]	Hypothermia (T≤36.6°C)	n=624 Adults in ICU with severe sepsis with or without septic shock	28-day mortality	Method by which core temperature was taken was not standardises; influence of treatment.
Lavrentieva 2007[181]	Temperature (also: PCT, CRP, Neutrophils, WBC)	n=43 adults in ICU with severe burn injury	Sepsis	
Lee 2012A[182]	Temperature (multivariable) Heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure (univariable)	n=396 Febrile adults who entered ED.	Bacteraemia	Single centre.
Leibovici 2007[185]	Excessive tachycardia (heart rate/temperature ratio >2.71 bpm/°C Stupor or coma Dyspnoea Diastolic blood pressure (continuous variable, increment of 10 mmHg)	n=3382 Adults with sepsis	30-day mortality	Retrospective design.
Lindvig 2014[192]	Temperature	n=11988 adults (>15years) presenting at medical emergency department	Bacteraemia	Single centre.
Martin 2010[208]	Delirium	n=14,262 adults undergoing isolated CAGB surgery.	Sepsis	Retrospective design. Low percentage of patients developed sepsis.
Murray 2007[224]	Temperature	n=222 patients with	Bloodstream	Retrospective design.

Study	Index tests	Population	Target condition / reference test	Comments
		burns	infection.	Population: burn patients only.
Pfitzenmeyer 1995[262]	Fever ≥38.5°C; Confusion	n=438 older patients (n=558 episodes of suspected bacteraemia)	Bacteraemia	Single centre. The decision to obtain blood culture was made individually, without reference to a particular standardised criteria.
Poutsiaka 2009[264]	Maximal HR; minimal SBP; maximal temperature	n=384 Immunosuppressed adults with severe sepsis	28-day mortality	Retrospective design.
Seigel 2012[288]	Abnormal temperature (hypothermia or fever)	n=3563 consecutive patients admitted to tertiary care centre via ED, ≥18 years, who had blood cultures taken within 3 hours of admission. 289	Bacteraemia	
Slotman 1997[302]	MAP ≤ 70mmHg; GCS≤11	n=59 adults with severe sepsis	Onset of organ failure	Retrospective design. 34% of patients received continuous IV sedation, which may have decreased GCS variation pharmacologically. Patients received either placebo or IL-1ra.
Theerawit 2011[310]	HR>130 beats/min; RR>24 breaths/min; GCS≤7	n=183 adults with septic shock	30-day mortality	Retrospective design. Single database.
Weinkove 2015[326]	Early peak temperature	n=118,067 adults (>16 years) with sepsis	Mortality	Retrospective design, single database

1

2

3

6.2.3.12 Clinical evidence summary tables

6.2.3.2.1 Temperature

Table 46: Clinical evidence summary: Temperature, children

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Temperature for predicting EOS/pneumonia in term new-borns >37 weeks	1[140]	Sensitivity: 40 (16-68) Specificity: 93 (88-96) PPV: 30 (12-54) NPV: 95 (91-98)	VERY LOW
Temperature ≥39 °C (and no apparent focal infection) for predicting occult pneumococcal bacteraemia (adjusted OR) in children 3-36 months of age	1[176]	Adjusted OR: 1.77 (1.21 to 2.58)	VERY LOW
Temperature (AUC) for predicting 30-day mortality (adjusted OR) in children aged 3-36 months old, at risk of occult bacteraemia	1[183]	AUC: 0.62(0.03)	VERY LOW
Temperature 40.4 °C compared to temperature 39.0 °C-39.4 °C for predicting 30-day mortality (adjusted OR) in children aged 3-36 months old, at risk of occult bacteraemia	1[183]	OR:1.90 (1.13-3.21)	VERY LOW
Temperature 40.5 °C-40.9 °C compared to temperature 39.0 °C-39.4 °C for predicting 30-day mortality (adjusted OR) in children aged 3-36 months old, at risk of occult bacteraemia	1[183]	OR:2.6 (1.5-4.5)	VERY LOW
Temperature 41.0 °C-42.0 °C compared to temperature 39.0 °C-39.4 °C for predicting 30-	1[183]	OR: 3.7 (1.9-7.3)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
day mortality (adjusted OR) in children aged 3-36 months old, at risk of occult bacteraemia			
Temperature >38 °C for predicting post-operative infectious complications (sensitivity, specificity, PPV and NPV) in children	1[12]	Sensitivity: 67 Specificity: 26 PPV: 2 NPV: 98	VERY LOW
Temperature >39 °C for predicting post-operative infectious complications (sensitivity, specificity, PPV and NPV) in children	1[12]	Sensitivity: 33 Specificity: 91 PPV: 6 NPV: 99	VERY LOW
Temperature <40 or >40 °C for predicting serious bacterial infection (sensitivity, specificity, PPV and NPV) febrile infants 8-12 weeks who received outpatient sepsis assessment	1[36]	Sensitivity: 21 Specificity: 96 PPV: 35 NPV: 93	VERY LOW
Temperature ≥38 °C for predicting invasive sepsis (AUC) in febrile infants	1[40]	AUC: 0.52	VERY LOW
Age-specific temperature-pulse centiles above 97th centile for predicting significant bacterial infections (sensitivity, specificity, PPV and NPV) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Sensitivity: 13.7 (5.7-26.3) Specificity: 89.4 (87.5-91.1) PPV: 5.3 (2.2-10.6) NPV: 96.0 (94.6-97.1)	VERY LOW
Age-specific temperature-pulse centiles above 90th centile for predicting significant bacterial infections (sensitivity, specificity, PPV and NPV)	1[43]	Sensitivity: 21.6 (11.3-35.3) Specificity: 80.0 (77.6-82.3) PPV: 4.5 (2.3-7.9)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
in 3 months – 10 year olds presenting to ED with suspected infection		NPV: 95.9 (94.5-97.1)	
Age-specific temperature-pulse centiles above 75th centile for predicting significant bacterial infections (sensitivity, specificity, PPV and NPV) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Sensitivity: 43.1 (29.3-57.8) Specificity: 61.7 (58.8-64.5) PPV: 4.7 (2.9-7.0) NPV: 96.2 (94.5-97.4)	VERY LOW
Age-specific temperature-pulse centiles above 50th centile for predicting significant bacterial infections (sensitivity, specificity, PPV and NPV) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Sensitivity: 74.5 (60.4-85.7) Specificity: 36.2 (33.4-39.0) PPV: 4.8 (3.4-6.6) NPV: 97.0 (95.0-98.4)	VERY LOW
Age-specific temperature-pulse centiles 97th centile for predicting significant bacterial infections (unadjusted OR) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Unadjusted OR: 1.84 (0.72-4.71)	VERY LOW
Age-specific temperature-pulse centiles 90th-97th centile for predicting significant bacterial infections (unadjusted OR) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Unadjusted OR: 1.19 (0.38-3.73)	VERY LOW
Age-specific temperature-pulse centiles 75th-90th centile for predicting significant bacterial infections (unadjusted OR) in 3 months – 10 year olds presenting to ED with suspected infection	1[43]	Unadjusted OR: 1.67 (0.73-3.79)	VERY LOW
Age-specific temperature-pulse centiles 50th-	1[43]	Unadjusted OR: 1.75 (0.83-3.69)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
75th centile for predicting significant bacterial infections (unadjusted OR) in 3 months – 10 year olds presenting to ED with suspected infection			
Age-specific temperature-pulse centiles above 97th centile for predicting significant bacterial infections large national case control on meningococcal.	1[43]	Sensitivity: 1.84 (0.72-4.71)	VERY LOW
Age-specific temperature-pulse centiles 90th-97th centile for predicting significant bacterial infections large national case control on meningococcal.	1[43]	Sensitivity: 1.19 (0.38-3.73)	VERY LOW
Age-specific temperature-pulse centiles 75th-90th centile for predicting significant bacterial infections large national case control on meningococcal.	1[43]	Sensitivity: 1.67 (0.73-3.79)	VERY LOW
Age-specific temperature-pulse centiles above 50th-75th centile for predicting significant bacterial infections large national case control on meningococcal.	1[43]	Sensitivity: 1.75 (0.83-3.69)	VERY LOW
Temperature <36 °C to predict bacteraemia neonates in hospital	1[141]	Sensitivity: 10 (2-27) Specificity: 92 (81-98) PPV: 43 (10-82) NPV: 64 (52-75)	VERY LOW
Temperature >38.5 °C to predict bacteraemia neonates in hospital	1[141]	Sensitivity: 10 (2-27) Specificity: 94 (84-99) PPV: 50 (12-88)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		NPV: 64 (532-75)	
Temperature ≥39.8 °C to predict SBI in children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection	1[8]	OR: 1.27 (0.58-2.89)	VERY LOW
At least 3 past episodes of fever or neutropenia to predict bacteraemia <17years diagnosed with malignancy screened for fever or neutropenia	1[10]	OR: 3.2 (1.5-7.1)	VERY LOW
At least 2 past episodes of fever or neutropenia with SBI to predict bacteraemia <17years diagnosed with malignancy screened for fever or neutropenia	1[10]	OR: 1.9 (1.1-3.2)	VERY LOW
At least 2 past episodes of fever or neutropenia with SBI to predict bacteraemia <17years diagnosed with malignancy screened for fever or neutropenia	1[10]	OR: 2.0 (1.1-3.2)	VERY LOW
At least 2 past episodes of fever or neutropenia with bacteraemia to predict bacteraemia <17 years diagnosed with malignancy screened for fever or neutropenia	1[10]	OR: 3.0 (1.2-7.3)	VERY LOW
Temperature (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with fever at ED	1[239]	OR: 0.98 (0.75-1.26)	VERY LOW

1

2 **Table 47: Clinical evidence summary: temperature, adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Initial body temperature (for each 1 °C increase) to predict 28-day mortality	1[41]	OR: 0.78 (0.62-0.98)	VERY LOW
T>38 °C or <36 °C to predict sepsis in ICU patients	1[62]	OR: 3.187 (1.655-6.139)	VERY LOW
T>38 °C or <36 °C to predict sepsis in ICU patients	1[62]	AUC: 0.898	VERY LOW
Fever to predict bacteraemia >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 1.21 (0.56-2.61)	VERY LOW
<36.1 to predict bacteraemia >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 1.80 (0.65-5.01)	VERY LOW
36.1-37.2 to predict bacteraemia >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 0.45 (0.21-0.94)	VERY LOW
37.2-38.3 to predict bacteraemia >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 1.11 (0.63-1.97)	VERY LOW
38.3-39.4 to predict bacteraemia >65	1[104]	OR=1.31 (0.69-2.47)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn.			
>39.4 to predict bacteraemia >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn.	1[104]	OR: 1.37 (0.49-3.84)	VERY LOW
Hyperthermia to predict progression to septic shock in adults in ED with sepsis or severe sepsis (but no septic shock)	1[125]	Multivariable: OR: 1.34 (1.06-1.68)	VERY LOW
Temperature ≥39.9 °C	1[182]	OR: 2.68 (1.03-6.94)	VERY LOW
Fever ≥38.5 °C to predict bacteraemia in older patients with suspected bacteraemia.	1[262]	Sensitivity: 87.0 Specificity: 27.0 PPV: 9.7 RR: 2.46	VERY LOW
Early peak temperature <36.5 °C to predict mortality in adults with non-neutropenic sepsis	1[326]	OR: 1.57 (1.47-1.67)	VERY LOW
Early peak temperature 36.5-37.4 °C to predict mortality in adults with non-neutropenic sepsis	1[326]	OR: 1	VERY LOW
Early peak temperature 37.5-39.4 °C to predict mortality in adults with non-neutropenic sepsis	1[326]	OR: 0.85 (0.81-0.88)	VERY LOW
Early peak temperature >39.4 °C to predict mortality in adults with non-	1[326]	OR: 0.83 (0.74-0.91)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
neutropenic sepsis			
Early peak temperature <36.5 °C to predict mortality in adults with neutropenic sepsis	1[326]	OR: 1.92 (1.34-2.75)	VERY LOW
Early peak temperature 36.5-37.4 °C to predict mortality in adults with neutropenic sepsis	1[326]	OR: 1	VERY LOW
Early peak temperature 37.5-39.4 °C to predict mortality in adults with neutropenic sepsis	1[326]	OR: 0.91 (0.74-1.11)	VERY LOW
Early peak temperature >39.4 °C to predict mortality in adults with neutropenic sepsis	1[326]	OR: 1.21 (0.92-1.59)	VERY LOW
T>38 °C to predict bacteraemia in adults (>15years) presenting at medical emergency department	1[192]	Sensitivity: 64.3 (59.3-69.1) Specificity: 80.8 (80.0-81.6) PPV: 11.5 (10.2-13.0) NPV: 98.3 (98.0-98.6)	VERY LOW
Fever to predict bacteraemia in elderly patients (over 65 years) with suspected bacteraemia	1[59]	Sensitivity: 80 Specificity: 45	VERY LOW
Fever spike to predict bacteraemia in elderly patients (over 65 years) with suspected bacteraemia	1[59]	Sensitivity: 61 Specificity: 50	VERY LOW
Temperature >39.0 °C in adults	1[173]	Sensitivity: 44	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
undergoing cardiac surgery to predict septic complications		Specificity: 89 PPV: 41 NPV: 90	
Temperature to predict sepsis in adults with severe burn injury	1[181]	AUC: 0.281 (SE 0.172)	VERY LOW
Abnormal temperature (hypothermia or fever) in patients admitted to tertiary care centre via ED, who had blood cultures taken within 3 hours of admission	1[288]	Sensitivity: 67	VERY LOW

1

2

3 **Table 48: Clinical evidence summary: Temperature (hypothermia), adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
T≤36.6 °C in adults in ICU with severe	1[177]	OR: 1.952 (1.253-3.040)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
sepsis to predict 28-day mortality			
T≤36.6 °C in adults in ICU with severe sepsis and septic shock to predict 28-day mortality	1[177]	OR: 2.778 (1.555-4.965)	VERY LOW
Absence of fever to predict bacteraemia-related mortality in adults in a community hospital with a positive blood culture	1[87]	OR: 5.2 (1.05-26)	VERY LOW

1

2

3 **Table 49: Clinical evidence summary: temperature, adults, immunocompromised subgroup**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Temperate ≥39 °C to predict bacteraemia in low-risk febrile neutropenia	1[131]	OR: 1.86 (1.12-3.11)	VERY LOW
Maximal temperature to predict 28-day mortality in immunosuppressed adults with	1[264]	OR: 1.02 (1.01-1.02)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
severe sepsis			

6.2.3.2.2 Heart rate

Table 50: Clinical evidence summary: heart rate, children

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Tachycardia >180/min or bradycardia <100/min predicting culture-proven EOS in term neonates hospitalised within the first 24 hours of life	1[141]	Sensitivity: 27 (12-46) Specificity: 81 (67-90) PPV: 44 (22-69) NPV: 66 (53-77)	VERY LOW
Age-specific pulse centiles above 97th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	Sensitivity: 2.0 (0.04-10.4) Specificity: 97.7 (96.7-98.5) PPV: 3.6 (0.1-18.3) NPV: 95.8 (94.5-96.9)	VERY LOW
Age-specific pulse centiles above 97th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	OR: 1.51 (0.19-12.0)	VERY LOW
Age-specific pulse centiles above 90th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	Sensitivity: 21.6 (11.3-35.3) Specificity: 90.8 (89.0-92.4) PPV: 9.2 (4.7-15.9) NPV: 96.4 (95.1-97.4)	VERY LOW
Age-specific pulse centiles above 75th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED	1[43]	Sensitivity: 45.1 (31.1-59.7) Specificity: 75.7 (73.1-78.1) PPV: 7.2 (4.6-10.7)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
with suspected infection		NPV: 96.9 (95.6-97.9)	
Age-specific pulse centiles above 50th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	Sensitivity: 72.5 (58.3-84.1) Specificity: 48.6 (45.7-51.5) PPV: 5.8 (4.1-7.9) NPV: 97.6 (96.0-98.7)	VERY LOW
Age-specific pulse centiles >90th-97th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	OR: 5.04 (2.14-11.9)	VERY LOW
Age-specific pulse centiles 75th-90th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	OR: 2.62 (1.19-5.79)	VERY LOW
Age-specific pulse centiles 50th-75th centile for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	OR: 1.85 (0.87-3.93)	VERY LOW
Tachycardia for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	Sensitivity: 66.7 (52.1-79.2) Specificity: 59.2 (56.3-62.0) PPV: 6.6 (4.6-9.1) NPV: 97.6 (96.2-98.6)	VERY LOW
Tachycardia for significant bacterial infections in children aged 3 months – 10 years presenting to ED with suspected infection	1[43]	OR: 2.90 (1.60-5.26)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
>90th centile for predicting meningococcal sepsis in children	1[43]	Sensitivity: 27.8 (22.8-33.2)	VERY LOW
>75th centile for predicting meningococcal sepsis in children	1[43]	Sensitivity: 49.2 (43.4-55.0)	VERY LOW
>50th centile for predicting meningococcal sepsis in children	1[43]	Sensitivity: 73.9 (68.5-78.8)	VERY LOW
<50th centile for predicting meningococcal sepsis in children	1[43]	Sensitivity: 26.1 (21.2-31.5)	VERY LOW
Tachycardia for predicting meningococcal sepsis in children	1[43]	Sensitivity: 68.9 (63.3-74.1)	VERY LOW
Tachycardia (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with fever at ED	1[239]	OR: 0.98 (0.62-1.56)	VERY LOW

Table 51: Clinical evidence summary: heart rate, adults

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
HR>90 to predict ICU admission in adults with SIRS or sepsis	1[19]	OR: 1.30 (0.48-3.53)	VERY LOW
HR>90 to predict in hospital mortality adults with SIRS or sepsis	1[19]	OR: 1.44 (0.36-5.71)	VERY LOW
SDNN to predict in-hospital mortality in adults with sepsis	1[64]	OR: 0.719 (0.537-0.962)	VERY LOW
SDNN to predict in-hospital mortality in adults with sepsis	1[64]	AUC: 0.700 (0.487-0.914)	VERY LOW
nHFP to predict in-hospital mortality in adults with sepsis	1[64]	OR: 1.064 (1.009-1.122)	VERY LOW
nHFP to predict in-hospital mortality in adults with sepsis	1[64]	AUC: 0.739 (0.549-0.930)	VERY LOW
HR>90 beats/min to predict sepsis in adults in ICU	1[62]	OR: 1.063 (1.036-1.092)	VERY LOW
Tachycardia (>125 beats/min) to predict bacteremia in adult patients with community-acquired pneumonia	1[96]	OR: 1.90 (1.20-3.02)	VERY LOW
HR predicting progression to septic shock in adults in ED with sepsis	1[125]	OR: 1.01 (1.00-1.02)	VERY LOW
HR predicting bacteraemia in febrile adults who entered ED	1[182]	OR: 1.44 (0.80-2.60)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Excessive tachycardia (heart rate/temperature ratio >2.71 bpm/°C to predict 30-day mortality	1[185]	OR: 1.54 (1.10-2.17)	VERY LOW
HR>130 beats/min to predict mortality in adults with septic shock, in univariable analysis	1[310]	OR: 3.679 (1.853-7.302)	VERY LOW
HR>130 beats/min to predict mortality in adults with septic shock, in multivariable analysi	1[310]	OR: 4.377 (1.338-14.321)	VERY LOW
Tachycardia to predict bacteraemia in elderly patients (over 65 years) with suspected bacteraemia	1[59]	Sensitivity: 28 Specificity: 77	VERY LOW

1

2

3 **Table 52: Clinical evidence summary: heart rate, adults, immunocompromised subgroup**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Maximal HR to predict 28-day mortality in immunosuppressed adults with severe sepsis	1[264]	OR: 1.02 (1.01-1.02)	VERY LOW

1

1

6.2.3.2.3 Blood pressure

3 **Table 53: Clinical evidence summary: blood pressure, children**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
MAP at 24h to predict mortality in children in ICU with sepsis or severe sepsis	1[89]	AUC: 0.80	VERY LOW
Refractory hypotension predicting death in patients in meningococcal septic shock in development sample from 4 PICU. Aged 1 month – 14 years	1[51]	OR: 3.30 (2.44-4.47)	VERY LOW
Blood pressure/skin colour to predict death in newborn infants <28 days of suspected sepsis admitted to NICU	1[248]	OR: 2.45 (1.31-4.59)	VERY LOW
Bradycardia to predict death in newborn infants <28 days of suspected sepsis admitted to NICU	1[248]	OR: 1.19 (0.50-2.85)	VERY LOW
Tachypnea to predict death in newborn infants <28 days of suspected sepsis admitted to NICU	1[248]	OR: 2.00 (1.02-3.92)	VERY LOW

4

1 **Table 54: Clinical evidence summary: blood pressure, adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
MAP<65 to predict ICU admission in adults with SIRS or sepsis	1[19]	OR: 1.47 (0.53-4.11)	VERY LOW
MAP<65 to predict in hospital mortality in adults with SIRS or sepsis	1[19]	OR: 1.68 (0.61-4.61)	VERY LOW
SAP (100 mm Hg) to predict Day 2 in hospital mortality in adults in ICU with septic shock	1[28]	OR: 5.0 (1.5-17.6)	VERY LOW
DAP (50 mm Hg) to predict Day 2 in hospital mortality in adults in ICU with septic shock	1[28]	OR: 7.6 (2.0-29.3)	VERY LOW
SAP (100 mm Hg) to predict Day 3 in hospital mortality in adults in ICU with septic shock	1[28]	OR: 6.5 (1.9-22.2)	VERY LOW
DAP (50 mm Hg) to predict Day 3 in hospital mortality in adults in ICU with septic shock	1[28]	OR: 33.0 (4.1-167.0)	VERY LOW
Hypotension predicting mortality in septic patients with acute renal failure	1[48]	OR: 1.36 (1.02-1.83)	VERY LOW
MAP at baseline to predict mortality in adults in ICU with sepsis, severe sepsis or septic shock	1[169]	AUC=0.748 (0.610-0.886)	VERY LOW
Systolic blood pressure <90 in febrile adults who entered ED	1[182]	OR: 3.59 (1.71-7.54)	VERY LOW
Diastolic blood pressure <60 to predict bacteraemia in febrile adults who entered ED	1[182]	OR: 2.47 (1.33-4.59)	VERY LOW
Diastolic blood pressure (continuous variable, increment of 10 mmHg) to predict 30-day mortality in adults with sepsis	1[185]	OR:0.67 (0.62-0.74)	VERY LOW
HTI of ABP drops <95 mmHg SAP to predict 28-day mortality in adults with sepsis	1[90]	AUC: 0.743	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		Sensitivity: 93.4 Specificity: 29 PPV: 77.4 NPV: 62.9	
HTI of ABP drops <65 mmHg SAP to predict 28-day mortality in adults with sepsis	1[90]	AUC: 0.731 Sensitivity: 94.4 Specificity: 26.3 PPV: 77 NPV: 64.5	VERY LOW
HTI of ABP drops <75 mmHg MAP to predict 28-day mortality in adults with sepsis	1[90]	AUC: 0.775 Sensitivity: 93.4 Specificity: 42.1 PPV: 80.7 NPV: 71.1	VERY LOW
HTI of ABP drops <45 mmHg MAP to predict 28-day mortality in adults with sepsis	1[90]	AUC: 0.751 Sensitivity: 94.4 Specificity: 29 PPV: 77.5 NPV: 66.7	VERY LOW
Systolic hypotension (<90 mm Hg) to predict bacteraemia in adult patients with community-acquired pneumonia	1[96]	OR: 1.75 (1.07-3.02)	VERY LOW
Blood pressure - <100mm Hg >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 3.20 (1.28-8.11)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
(univariable analysis)			
MAP ≤ 70mmHg to predict onset of organ failure at 24h in adults with severe sepsis	1[302]	Sensitivity: 100 Specificity: 71	VERY LOW
MAP ≤ 70mmHg to predict onset of organ failure at 48h in adults with severe sepsis	1[302]	Sensitivity: 92 Specificity: 100	VERY LOW
MAP ≤ 70mmHg to predict onset of organ failure at 72h in adults with severe sepsis	1[302]	Sensitivity: 100 Specificity: 0	VERY LOW

1

2 **Table 55: Clinical evidence summary: blood pressure, adults, immunocompromised**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Hypotension to predict bacteraemia in low-risk febrile neutropenia	1[131]	OR: 6.19 (2.22-17.28)	VERY LOW
Minimal SBP to predict 28-day mortality in immunosuppressed adults with severe sepsis	1[264]	OR: 0.84 (0.77-0.93)	VERY LOW

1

6.2.3.2.4 Respiratory rate

3 **Table 56: Clinical evidence summary: respiratory rate, children**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Tachypnoea (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with fever at ED	1[239]	OR: 0.90 (0.48-1.69)	VERY LOW

4

5 **Table 57: Clinical evidence summary: respiratory rate, adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Respiratory rate >20 to predict ICU admission in adults with SIRS or sepsis	1[19]	OR: 4.81 (1.16-21.01)	VERY LOW
RR>20 to predict in hospital mortality in adults with SIRS or sepsis	1[19]	OR: 2.87 (0.79-10.25)	VERY LOW
Respiratory failure predicting mortality in septic patients, with acute renal failure	1[48]	OR:1.53 (1.14-2.05)	VERY LOW
Respirations >20/minute to predict bacteraemia in adults>65 years presenting to	1[104]	OR: 0.65 (0.37-1.13)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
ED and hospitalised for suspicion of infection, who had a blood culture drawn			
Respiratory rate max 0-4hr, cut-off 20/min, in adults admitted from the ED, who had at least 1 blood culture taken on admission	1[124]	Sensitivity: 0.79 (0.73-0.84) Specificity: 0.40 (0.29-0.52)	VERY LOW
Respiratory rate max 0-4hr, cut-off 20/min, in adults admitted from the ED, who had at least 1 blood culture taken on admission	1[124]	OR: 2.45 (1.36-4.41)	VERY LOW
Respiratory rate max 0-4hr, cut-off 17/min, in adults admitted from the ED, who had at least 1 blood culture taken on admission	1[124]	Sensitivity: 0.89 (0.84-0.92), Specificity: 0.23 (0.15-0.35)	VERY LOW
Respiratory rate max 0-4hr, cut-off 17/min, in adults admitted from the ED, who had at least 1 blood culture taken on admission	1[124]	OR: 2.35 (1.17-4.75)	VERY LOW
Respiratory rate to predict progression to septic shock in adults in ED with sepsis	1[125]	OR:1.01 (0.98-1.05)	VERY LOW
Respiratory rate >20 breaths/min to predict bacteraemia in febrile adults who entered ED	1[182]	OR: 1.60 (0.90-2.86)	VERY LOW
Dyspnoea to predict 30-day mortality in adults with sepsis	1[185]	OR: 1.83 (1.32-2.53)	VERY LOW
Respiratory rate >24 breaths/min to predict mortality in adults with septic shock (univariableanalysis)	1[310]	OR: 2.488 (1.262-4.904)	VERY LOW
Respiratory rate >24 breaths/min to predict mortality in adults with septic shock	1[310]	OR: 0.636 (0.194-2.087)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
(multivariable analysis)			

1

2 **Table 58: Clinical evidence summary: respiratory rate, adults, immunocompromised**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Respiratory rate ≥24/min adults with febrile neutropenia after chemotherapy	1[5]	OR:4.1 (1.20-13.63)	VERY LOW

6.2.3.2.5 Altered mental state

Table 59: Clinical evidence summary: altered mental state, adults

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Delirium to predict sepsis in adults undergoing isolated CAGB surgery	1[208]	OR: 2.32 (1.59-3.39)	VERY LOW
Altered mental status to predict bacteraemia in elderly patients (over 65 years) with suspected bacteraemia	1[59]	Sensitivity: 12 Specificity: 93	VERY LOW
Altered mental status to predict bacteraemia in adults >65 years presenting to ED and hospitalised for suspicion of infection who had a blood culture drawn	1[104]	OR: 2.88(1.52-5.50)	VERY LOW
Confusion to predict bacteraemia in older patients with suspected bacteraemia	1[262]	Sensitivity: 30.4 Specificity: 79.3 PPV: 11.4 RR: 1.68	VERY LOW

6.2.3.2.6 Level of consciousness

Table 60: Clinical evidence summary: level of consciousness, children

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
GCS predicting death in patients in meningococcal septic shock in development sample from 4 PICU. Aged 1 month – 14 years	1[51]	OR: 3.15 (2.41-4.12)	VERY LOW

Table 61: Clinical evidence summary: level of consciousness, adults

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Stupor or coma to predict 30-day mortality in adults with sepsis	1[185]	OR: 1.27 (1.01-1.60)	VERY LOW
GCS≤7 to predict mortality in univariable analysis in adults with septic shock	1[310]	OR: 8.044 (3.460-18.69)	VERY LOW
GCS≤7 to predict mortality in multivariable analysis in adults with septic shock	1[310]	OR: 3.476 (1.072-11.270)	VERY LOW
CGS ≤11 to predict onset of organ failure at 24h in adults with severe sepsis	1[302]	Sensitivity: 60 Specificity: 100	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
CGS ≤11 to predict onset of organ failure at 48h in adults with severe sepsis	1[302]	Sensitivity: 75 Specificity: 75	VERY LOW
CGS ≤11 to predict onset of organ failure at 72h in adults with severe sepsis	1[302]	Sensitivity: 79 Specificity: 100	VERY LOW

1

6.2.3.22.7 Oxygen saturation

3 **Table 62: Clinical evidence summary: oxygen saturation, adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Each 1% increase in initial $ScvO_2$ to predict 28-day mortality	1[41]	OR: 0.96 (0.93-0.99)	VERY LOW
Initial $ScvO_2$ <70% to predict 28-day mortality	1[41]	OR: 3.60 (1.76-7.36)	VERY LOW
Initial $ScvO_2$ <75% to predict 28-day mortality	1[41]	OR: 2.15 (1.16-3.98)	VERY LOW
$ScvO_2$ at baseline to predict mortality in adults in ICU with sepsis, severe sepsis or septic shock	1[169]	AUC: 0.683 (0.535-0.832)	VERY LOW
Oxygen saturation <94% (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with	1[239]	OR: 0.04 (0.00-19.22)	VERY LOW

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
fever at ED			

1

6.2.3.2.8 Urine output

3 **Table 63: Clinical evidence summary: urine output, children**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Oliguria predicting death in patients in meningococcal septic shock in development sample from 4 PICU, children aged 1 month – 14 years	1[51]	OR: 5.04 (2.44-10.38)	VERY LOW

1

6.2.3.2.9 Diarrhoea

3 **Table 64: Clinical evidence summary: diarrhoea, adults**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Diarrhoea to predict bacteraemia in patients >65 years presenting to ED and hospitalised for suspicion of infection, who had a blood culture drawn	1[104]	OR: 1.47 (0.83-2.62)	VERY LOW

4

6.2.3.2.10 Capillary refill time

6 **Table 65: Clinical evidence summary: capillary refill time, children**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Capillary refill time >3 sec (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with fever at ED	1[239]	OR:1.35 (0.53-3.42)	VERY LOW

1

6.2.3.2.11 Ill appearance

3 **Table 66: Clinical evidence summary: ill appearance, children**

Index test	Number of studies	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Ill appearance (multivariable analysis) to predict SBI other than pneumonia in children 1 month – 15 years presenting with fever at ED	1[239]	OR:1.31 (0.84-2.05)	VERY LOW

4

6.2.14 Heart rate and respiratory rate ranges in children

The GDG wished to provide guidance on use of heart rate and respiratory rate in assessment of people with sepsis. Heart rate and respiratory rate vary by age so recommendations across a large age range need to take this into account. The GDG discussed the available information on normal ranges for heart rate and respiratory rate in children of different ages, including neonates. The GDG recognised the most commonly used scale in the UK is from the Advanced Paediatric Life Support (APLS)[26], which was also used in the Fever in under 5s(CG160)[232].

In discussing normal heart and respiratory rates, the GDG also considered the findings of a systematic review, Fleming 2011,[103] and of a retrospective cross-sectional study, O'Leary 2015,[244] as summarised in the paragraphs below.

6.2.14.1 Data from the Advanced Paediatric Life Support (APLS) guideline[26]

The three tables below report normal ranges, stratified by age groups, and abnormal ranges for children with fever and with asthma. The fever in under 5s guideline (CG160)[232] also adopted **Table 68** in defining their amber' and 'red' categories for children under 5 years with fever of unknown origin.

Table 67: Normal ranges of heart rate and respiratory rate according to Advanced Paediatric Life Support (APLS)[26]

Age range (years)	heart rate	respiratory rate
Neonate (<1)	110 – 160	30 – 40
1 – 2	100 – 150	25 – 35
3 – 5	95 – 140	25 – 30
6 – 12	80 – 120	20 – 25
>12	60 – 100	15 – 20

For children under 5 years of age, with fever of unknown origin, the APLS guideline classifies children in 'amber' and' red' categories as follows:

Table 68: Abnormal ranges of heart rate and respiratory rate according to APLS[26], for children <5 years with fever of unknown origin.

	Amber	Red
Respiratory rate (<1y)	≥50	>60/min (any age)
Respiratory rate (>1y)	≥40	
Heart rate (<1y)	>160	-
Heart rate (1-2y)	>150	-
Heart rate (2-5y)	>140	-

The APLS guideline[26] also reports abnormal respiratory rate and heart rate for children (up to 18 years) with asthma (management of acute wheezing):

Table 69: Abnormal ranges of heart rate and respiratory rate according to APLS[26], for children (up to 18 years) with asthma

	Severe	Life-threatening
Respiratory rate (<5y)	>40	Poor respiratory effort
Respiratory rate (>5y)	≥25	
Heart rate (<5y)	>140	Silent chest

	Severe	Life-threatening
Heart rate (>5y)	>125	

The APLS guideline does not provide abnormal heart or respiratory rates for children over 5 years without asthma.

6.2.4.2 Data from the Fleming 2011[103] paper

The Fleming 2011[103] paper is a systematic review of normal heart and respiratory rates in children. This review contained data on heart rate in children from 59 studies that included 143,346 children, and data on respiratory rate from 20 studies that included 3,881 children. Based on centile charts, the Fleming 2011 proposed the following normal cut offs for respiratory and hear rates (Table 70 and Table 71).

Fleming 2011[103] showed that there are inconsistencies between existing reference ranges and ranges of normal heart rate reported in observational studies. The authors demonstrated that this potentially leads to the misclassification of children as having either normal or abnormal heart rates, and that the use of updated centile heart rate charts could improve the specificity by up to 20%. However, the authors concluded that further research was needed before their centile charts could be adopted in practice.

Table 70: Proposed respiratory rate cut-offs (breaths/minutes) according to the Fleming study[103]

Age range	1st centile	10th centile	25th centile	Median	75th centile	90th centile	99th centile
0 – 3 m	25	34	40	43	52	57	66
3 – 6 m	24	33	38	41	49	55	64
6 – 9 m	23	31	36	39	47	52	61
9 – 12 m	22	30	35	37	45	50	58
12 – 18 m	21	28	32	35	42	46	53
18 – 24 m	19	25	29	31	36	40	46
2 – 3 y	18	22	25	28	31	34	38
3 – 4 y	17	21	23	25	27	29	33
4 – 6 y	17	20	21	23	25	27	29
6 – 8 y	16	18	20	21	23	24	27
8 – 12 y	14	16	18	19	21	22	25
12 – 15 y	12	15	16	18	19	21	23
15 – 18 y	11	13	15	16	18	19	22

Age ranges given in years (y) and months (m)

Table 71: Proposed heart rate cut-offs (beats/minutes) according to the Fleming study[103]

Age range	1st centile	10th centile	25th centile	Median	75th centile	90th centile	99th centile
Birth	90	107	116	127	138	148	164
0 – 3 m	107	123	133	143	154	164	181
3 – 6 m	104	120	129	140	150	159	175
6 – 9 m	98	114	123	134	143	152	168
9 – 12 m	93	109	118	128	137	145	161
12 – 18 m	88	103	112	123	132	140	156
18 – 24 m	82	98	106	116	126	135	149

Age range	1st centile	10th centile	25th centile	Median	75th centile	90th centile	99th centile
2 – 3 y	76	92	100	110	119	128	142
3 – 4 y	70	86	94	104	113	123	136
4 – 6 y	65	81	89	98	108	117	131
6 – 8 y	59	74	82	91	101	111	123
8 – 12 y	52	67	75	84	93	103	115
12 – 15 y	47	62	69	78	87	96	108
15 – 18 y	43	58	65	73	83	92	104

Age ranges given in years (y) and months (m). "Birth" refers to the immediate neonatal period.

Fleming 2011[103] also reported existing reference ranges for respiratory rate (Table 72) and heart rate (Table 73)

Table 72: Respiratory rate (breaths/minute)

Age range (years)	APLS/ PHPLS	PALS	EPLS	PHTLS	ATLS	WHO+
Neonate	30 – 40	30 – 60	30 – 40	30 – 50*	<60	
0 – 1	30 – 40	30 – 60	30 – 40	20 – 30*	<60	<50+
1 – 2	25 – 35	24 – 40	26 – 34	20 – 30	<40	<40
2 – 3	25 – 30	24 – 40	24 – 30	20 – 30	<40	<40
3 – 4	25 – 30	24 – 40	24 – 30	20 – 30	<35	<40
4 – 5	25 – 30	22 – 34	24 – 30	20 – 30	<35	<40
5 – 6	20 – 25	22 – 34	20 – 24	20 – 30	<35	
6 – 12	20 – 25	18 – 30	20 – 24	(12 – 20) – 30	<30	
12 – 13	15 – 20	18 – 30	12 – 20	(12 – 20) – 30	<30	
13 – 18	15 – 20	12 – 16	12 – 20	12 – 20^	<30	

**PHTLS provides separate ranges for neonates up to six weeks, and for infants between seven weeks and one year of age.*
^ PHTLS does not provide ranges for adolescents over 16 years of age.
+WHO only provides ranges for children between two months and five years of age.

Table 73: Heart rate (beats/minute)

Age range (years)	APLS/ PHPLS	PALS*	EPLS*	PHTLS	ATLS
Neonate	110 – 160	85 – 205^	85 – 205^	120 – 160+	<160
0 – 1	110 – 160	100 – 190^	100 – 180^	80 – 140+	<160
1 – 2	100 – 150	100 – 190	100 – 180	80 – 130	<150
2 – 3	95 – 140	60 – 140	60 – 140	80 – 120	<150
3 – 5	95 – 140	60 – 140	60 – 140	80 – 120	<140
5 – 6	80 – 120	60 – 140	60 – 140	80 – 120	<140
6 – 10	80 – 120	60 – 140	60 – 140	(60 – 80) – 100	<120
10 – 12	80 – 120	60 – 100	60 – 100	(60 – 80) – 100	<120
12 – 13	60 – 100	60 – 100	60 – 100	(60 – 80) – 100	<100
13 – 18	60 – 100	60 – 100	60 – 100	60 – 100~	<100

**PALS and EPLS provide multiple ranges – ranges for awake children are tabulated*
^ PALS and EPLS provide separate ranges for infants up to three months, and for those between three months and two years of age.
+PHTLS provides separate ranges for infants up to six weeks, and for those between seven weeks and one year of
~PHTLS. TLS does not provide ranges for adolescents over 16 years of age.

6.2.4.3 Data from the O'Leary 2015[244] paper

The O'Leary 2015[244] paper is a retrospective, cross-sectional study of 111,696 infants and children presenting to the ED of a children's hospital in Australia. The children were aged 0-15 years and were assigned to the lowest priority according to the local triage system (no respiratory or haemodyamic compromise, be alert, have no or minimal pain, and no risk factors for serious illness or injury). The study developed centile charts using quantile regression analysis.

The study also reported the comparison of normal ranges cut-offs for heart rate (Table 74) and respiratory rate (Table 75) of their findings with Fleming 2011[103] and Bonafide 2013[37] studies. (The Bonafide 2013 is a cross-sectional study from the electronic records of 14,014 children on general medical and surgical wards at two tertiary-care children's hospitals in the USA)

Table 74: A comparison of derived centiles for heart rate from this study and the work of Fleming and Bonafide (from O'Leary 2015[244])

Centile	1st			5th			10th			25th			50th		
Comparison		F	B		F	B		F	B		F	B		F	B
0-<3 months	109	107	103	119	N/A	113	123	123	119	132	133	N/A	142	143	140
3-<6 months	100	104	98	113	N/A	108	118	120	114	124	129	N/A	135	140	135
6-<9 months	100	98	94	110	N/A	104	115	114	110	121	123	N/A	131	134	131
10-<12 months	98	93	91	105	N/A	101	111	109	107	119	118	N/A	127	128	128
12-<18 months	94	88	87	101	N/A	97	107	103	103	116	112	N/A	124	123	124
18-<24 months	90	82	82	99	N/A	92	103	98	98	112	106	N/A	120	116	120
2-<3 y	85	76	77	96	N/A	87	99	92	93	107	100	N/A	117	110	115
3-<4 y	80	70	71	89	N/A	82	94	86	88	102	94	N/A	111	104	111
4-<6 y	74	65	66	82	N/A	77	88	81	83	96	89	N/A	105	98	106
6-<8 y	69	59	61	78	N/A	71	81	74	77	90	82	N/A	100	91	100
8-<12 y	64	52	56	72	N/A	66	77	67	72	84	75	N/A	94	84	94
12-<15 y	59	47	51	64	N/A	61	69	62	66	77	69	N/A	86	78	87
15-<16 y	56	43	48	62	N/A	57	66	58	62	74	65	N/A	83	73	82

Table 74 continued

Centile	75th			90th			95th			99th		
Comparison		F	B		F	B		F	B		F	B
0-<3 months	154	154	N/A	165	164	164	171	N/A	171	181	181	186
3-<6 months	145	150	N/A	155	159	159	161	N/A	167	174	175	182
6-<9 months	141	143	N/A	151	152	156	159	N/A	163	172	168	178
10-<12 months	139	137	N/A	150	145	153	160	N/A	160	174	161	176
12-<18 months	136	132	N/A	149	140	149	159	N/A	157	176	156	173

Centile	75th			90th			95th			99th		
18-<24 months	132	126	N/A	145	135	146	154	N/A	154	172	149	170
2-<3y	126	119	N/A	138	128	142	146	N/A	150	162	142	167
3-<4 y	121	113	N/A	131	123	138	138	N/A	146	152	136	164
4-<6 y	117	108	N/A	126	117	134	133	N/A	142	146	131	161
6-<8 y	111	101	N/A	122	111	128	128	N/A	137	141	123	155
8-<12 y	104	93	N/A	116	103	120	122	N/A	129	135	115	147
12-<15 y	97	87	N/A	106	96	112	113	N/A	121	127	108	138
15-<16 y *	94	83	N/A	103	92	107	111	N/A	115	122	104	132

*F=Fleming data; B=Bonafide data; * Fleming and Bonafide age range 15- <18 years*

Table 75: A comparison of derived centiles for respiratory rate from this study and the work of Fleming and Bonafide (from O'Leary 2015[244])

Centile	1st			5th			10th			25th			50th		
Comparison		F	B		F	B		F	B		F	B		F	B
0-<3 months	20	25	22	25	N/A	27	27	34	30	30	40	N/A	35	43	41
3-<6 months	20	24	21	23	N/A	25	25	33	28	27	38	N/A	31	41	38
6-<9 months	20	23	20	22	N/A	23	24	31	26	26	36	N/A	29	39	35
10-<12 months	20	22	19	21	N/A	22	23	30	24	25	35	N/A	28	37	33
12-<18 months	20	21	18	20	N/A	21	22	28	23	24	32	N/A	26	35	31
18-<24 months	19	19	16	20	N/A	20	21	25	21	23	29	N/A	25	31	29
2-<3y	18	18	16	20	N/A	18	20	22	20	22	25	N/A	24	28	27
3-<4 y	18	17	15	20	N/A	18	20	21	19	21	23	N/A	24	25	25
4-<6 y	18	17	14	19	N/A	17	20	20	18	20	21	N/A	23	23	24
6-<8 y	17	16	13	18	N/A	16	20	18	17	20	20	N/A	22	21	23
8-<12 y	16	14	13	18	N/A	15	18	16	16	20	18	N/A	20	19	21
12-<15y	14	12	11	16	N/A	13	16	15	15	18	16	N/A	20	18	19
15-<16y *	13	11	11	16	N/A	13	16	13	14	18	15	N/A	20	16	18

Table 75 continued

Centile	75th			90th			95th			99th		
Comparison		F	B		F	B		F	B		F	B
0-<3 months	40	52	N/A	47	57	62	51	N/A	62	60	66	76
3-<6 months	36	49	N/A	42	55	58	46	N/A	58	55	64	71
6-<9 months	33	47	N/A	38	52	54	42	N/A	54	51	61	67
10-<12 months	31	45	N/A	36	50	51	39	N/A	51	46	58	63
12-<18 months	29	42	N/A	33	46	48	36	N/A	48	42	53	60
18-<24 months	28	36	N/A	31	40	45	34	N/A	45	40	46	57
2-<3 y	27	31	N/A	30	34	42	32	N/A	42	38	38	54

Centile	75th			90th			95th			99th		
3-<4 y	25	27	N/A	28	29	40	30	N/A	40	34	33	52
4-<6 y	24	25	N/A	27	27	37	28	N/A	37	32	29	50
6-<8 y	24	23	N/A	26	24	35	28	N/A	35	31	27	46
8-<12 y	23	21	N/A	24	22	31	26	N/A	31	29	25	41
12-<15 y	22	19	N/A	24	21	28	24	N/A	28	28	23	35
15-<16 y *	20	18	N/A	23	19	26	24	N/A	26	28	22	32

*F=Fleming data; B=Bonafide data; * Fleming and Bonafide age range 15- <18 years*

The authors reported that with regards respiratory rate, the data between O'Leary 2015 and Fleming 2011 are clinically different. When compared with the Bonafide study, the 50th centiles are similar, suggesting that the derived 50th centiles are valid for hospital setting.

The authors concluded that it is difficult to explain the differences found between Fleming's community data and the hospital-derived data, and further studies are required to investigate this.

The GDG noted that comparing data from APLS guidleine[26], Fleming 2011[103] and O'Leary 2015[244] studies highlights that there is still controversy on what represents a normal respiratory and heart rate in infants and children of different ages.

6.12.5 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix C.

6.12.6 Evidence statements

Clinical

The evidence in the included studies was of very low quality. There is significant variability amongst the 16 included studies for children and the 38 for adults relating to (1) the included population, (2) the patient outcomes, and (3) the statistical measures that were reported and analysed. It was not possible to meta-analyse any of the results because studies with comparable populations reported different patient outcomes or analysed statistical measures in different ways. Taking into account these inconsistencies, overall there is a trend in the evidence suggesting that any of the following (alone or in combination) is cause for concern for the patient: elevated temperature, heart rate or respiratory rate; hypothermia; hypotension; altered mental state; low oxygen saturation; low urine output.

Economic

No relevant economic evaluations were identified.

6.12.7 Recommendations and link to evidence

6.12.7.1 Signs and symptoms

Recommendations	9. Assess temperature, heart rate, respiratory rate, systolic blood

	pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis. **10. Assess temperature, heart rate, respiratory rate, level of consciousness, oxygen saturation and capillary refill time in children under 12 years with suspected sepsis. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]** **11. Measure blood pressure of children under 5 years if heart rate or capillary refill time is abnormal and facilities to measure blood pressure, including correct blood pressure cuff, are available. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)].** **12. Measure blood pressure of children aged 5 to 11 years who might have sepsis if facilities to measure blood pressure, including correct cuff, are available.** **13. Only measure blood pressure in children under 12 years in community settings if facilities to measure blood pressure, including correct cuff, are available and taking a measurement does not cause a delay in assessment or treatment.** **14. Only measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.** **15. Examine skin of people with suspected sepsis for mottled or ashen complexion, cyanosis, non-blanching rash, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection.** **16. Ask the person, parent or carer about frequency of urination in the past 18 hours.** **17. Use the person's history and physical examination results to grade risk of severe illness or death from sepsis using criteria based on age (see Table 76, Table 77 and Table 78).** **18. Recognise that adults and children and young people aged 12 years and over with any of the symptoms or signs below are at high risk of severe illness or death from sepsis :** • **objective evidence of new altered mental state** • **respiratory rate of 25 breaths per minute or above, or new need for 40% oxygen to maintain oxygen saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)** • **heart rate of 130 beats per minute or above** • **systolic blood pressure of 90 mmHg or less, or systolic blood pressure more than 40 mmHg below normal**

- **not passed urine in previous 18 hours (for catheterised patients, passed less than 0.5 ml/kg/hour)**
- **mottled or ashen complexion, with cyanosis of the skin, lips or tongue**
- **non-blanching rash of the skin, lips or tongue.**

19. **Recognise that adults and children and young people aged 12 years and over with any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:**

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

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

21. **Recognise that children aged 5–11 years with any of the symptoms or signs below are at high risk of severe illness or death from sepsis:**

- **has objective evidence of altered behaviour or mental state, or appears ill to a healthcare professional, or does not wake up (or if roused, does not stay awake)**
- **respiratory rate:**
  - **aged 5 years, 29 breaths per minute or more**
  - **aged 6-7 years, 27 breaths per minute or more**
  - **aged 8-11 years, 25 breaths per minute or more**
  - **or moderate or severe chest indrawing**
- **heart rate:**
  - **aged 5 years, 130 beats per minute or more**
  - **aged 6-7 years, 120 beats per minute or more**
  - **aged 8-11 years, 115 breaths per minute or more**
  - **or heart rate less than 60 beats per minute**

- **not passed urine in last 18 hours, or for catheterised patients, passed less than 0.5ml/kg of urine per hour**
- **colour of skin, lips, or tongue is pale, mottled, ashen or blue**
- **non-blanching rash**
- **has temperature less than 36°C.**

22. Recognise that children aged 5–11 years with any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- **not responding normally to social cues or decreased activity, or parent or carer concern that the child is behaving differently from usual**
- **respiratory rate:**
  - **aged 5 years, 27-28 breaths per minute**
  - **aged 6-7 years, 24-26 breaths per minute**
  - **aged 8-11 years, 22-24 breaths per minute**
- **heart rate:**
  - **aged 5 years, 120-129 beats per minute**
  - **aged 6-7 years, 110-119 beats per minute**
  - **aged 8-11 years, 105-114 beats per minute**
  - **or capillary refill time of 3 seconds or over**
- **reduced urine output, or for catheterised patients, passed 0.5-1 ml/kg of urine per hour**
- **have leg pain or cold hands or feet.**

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

24. Recognise that children aged under 5 years with any one of the symptoms or signs below are at high risk of severe illness or death from sepsis:

- **no response to social cues**
- **appears ill to a healthcare professional**
- **does not wake, or if roused does not stay awake**
- **weak, high-pitched or continuous cry**
- **grunting**
- **heart rate:**
  - **aged under 1 year, 160 beats per minute or more**
  - **aged 1-2 years, 150 beats per minute or more**
  - **aged 3-4 years, 140 beats per minute or more**
  - **heart rate less than 60 beats per minute at any age**
- **reduced skin turgor**
- **no wet nappies or not passed urine in past 18 hours, or for catheterised children, passed less than 0.5 ml/kg of urine per hour**
- **respiratory rate:**

	– **aged under 1 year, 60 breaths per minute or more** – **aged 1-2 years, 50 breaths per minute or more** – **aged 3-4 years, 40 breaths per minute or more** • **moderate or severe chest indrawing** • **colour of skin, lips or tongue is pale, mottled, ashen or blue** • **other symptoms and signs:** – **age under 3 months and temperature 38°C or more** – **non-blanching rash** – **temperature less than 36°C** **[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]** **25. Recognise that children under 5 years with any of the symptoms or signs below are in a moderate to high risk of severe illness or death from sepsis:** • **not responding normally to social cues** • **no smile** • **wakes only with prolonged stimulation** • **decreased activity** • **parent or carer concern that the child is behaving differently from usual** • **nasal flaring** • **respiratory rate:** – **aged under 1 year, 50-59 breaths per minute** – **aged 1-2 years, 40-49 breaths per minute** – **aged 3-4 years, 35-39 breaths per minute** • **oxygen saturation 95% or less in air** • **crackles in the chest** • **heart rate:** – **aged under 1 year, 150-159 beats per minute** – **aged 1-2 years, 140-149 beats per minute** – **aged 3-4 years, 130-139 beats per minute** • **capillary refill time of 3 seconds or more** • **poor feeding in infants** • **reduced urine output or for catheterised patients, passed 0.5-1 ml/kg of urine per hour** • **is pale or flushed or has pallor of skin, lips or tongue reported by parent or carer** • **other symptoms and signs: age 3–6 months and temperature 39°C or over, leg pain, cold hands or feet** **[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]** **26. Consider children aged under 5 years who do not meet any high or moderate to high risk criteria to be at low risk of severe illness**

	or death from sepsis. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)] **Temperature** **27. Do not use a person's temperature as the sole predictor of sepsis.** **28. Do not rely on fever or hypothermia to rule sepsis either in or out.** **29. Ask the person with suspected sepsis and their family or carers about any recent fever or rigors.** **30. Take into account that some groups of people with sepsis may not develop a raised temperature. These include:** • **people who are older or very frail** • **people having treatment for cancer** • **people severely ill with sepsis** • **young infants or children.** **31. Take into account that a rise in temperature can be a physiological response, for example after surgery or trauma.** **Heart rate in suspected sepsis** **32. Interpret the heart rate of a person with suspected sepsis in context, taking into account that:** • **baseline heart rate may be lower in young people and adults who are fit** • **baseline heart rate in pregnancy is 10-15 beats per minute more than normal** • **older people with an infection may not develop an increased heart rate** • **older people may develop a new arrhythmia in response to infection rather than an increased heart rate** • **heart rate response may be affected by medicines such as beta-blockers.** **Blood pressure in suspected sepsis** **33. Interpret blood pressure in the context of a person's previous blood pressure, if known.** **Confusion, mental state and cognitive state in suspected sepsis** **34. Interpret a person's mental state in the context of their normal function and treat changes as being significant.** **35. Be aware that changes in cognitive function may be subtle and assessment should include history from patient and family or**

	carers. **36. Take into account that changes in cognitive function may present as changes in behaviour or irritability in both children and in adults with dementia.** **37. Take into account that changes in cognitive function in older people may present as acute changes in functional abilities.** **Oxygen saturation** **38. Take into account that if peripheral oxygen saturation is difficult to measure in a person with suspected sepsis, this may indicate poor peripheral circulation because of shock.**
Relative values of different outcomes	Diagnostic test accuracy studies were used in this review where accuracy of a given sign or symptom was measured against a reference standard, and sensitivity, specificity, positive predictive value, negative predictive value, ROC curve and area under the curve were reported where available. The GDG were aware that there was limited evidence available using the diagnostic accuracy study-design approach and therefore studies were included that assessed the association of a sign or symptom with all-cause mortality or organ failure, and ORs were reported. If diagnostic accuracy statistics were reported in a study, then ORs were not included in evidence report. Diagnostic accuracy for sign or symptom determination of sepsis, rather than ORs for association, were the outcomes prioritised for this review. Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with sepsis would have serious implications, including death. Specificity was important because the misclassification of an individual without sepsis would result in inappropriate administration of antibiotics. When there was no diagnostic accuracy data for a sign or symptom and ORs for association were considered, the outcomes of all-cause mortality and organ failure were regarded as critical.
Trade-off between clinical benefits and harms	The main harm that may come to patients is both over diagnosis of suspected sepsis and lack of identification of suspected sepsis. The first group of patients will be subject to investigations and treatments they might not need and the latter group may not get appropriate treatment. The evidence suggested an association between signs and symptoms and sepsis; however, the included studies were so heterogeneous in terms of included population, settings, thresholds and methods of analysis, that it was not possible to ascertain precisely if which signs and symptoms, and at what thresholds, could lead to an over- or under-diagnosis of sepsis.
Economic considerations	No health economic evidence was identified for this question. The assessment of a person's signs and symptoms will take place during a consultation with a healthcare professional, most likely a GP or in an emergency department but assessment may also take place on a hospital ward. The length of this consultation will not vary significantly dependant on which signs are assessed and what use is made of these findings. It can be assumed that all consultations will be of standard length, and that equipment for measuring vital signs is available. Therefore cost is not a significant factor when looking at each individual consultation. However, the decision rules for using signs and symptoms as predictive of sepsis is a major economic issue – indeed the most significant economic issue in

	this guideline – as this will determine the number of people who for example are referred from primary care to hospital or who may be given antibiotics If a very broad combination of symptoms are agreed to suggest sepsis, that is the GDG chooses high sensitivity but low specificity criteria (few false negatives but many false positives) then a large number of people will be sent to hospital to undergo consultations, blood tests or other assessments and treatments. This will increase costs greatly, with little clinical benefit for those individuals without sepsis (it is likely that many individuals may receive an alternative diagnosis during this process for the condition that they in fact do have, which may assist them in managing that condition to some extent, while they may also benefit from peace of mind). There is a danger of over-cautiousness and unnecessary use of resources with this approach. If a very narrow combination of symptoms are agreed to suggest sepsis, that is the GDG chooses low sensitivity but high specificity criteria (few false positives but some false negatives) then we will avoid many of the unnecessary referrals in the first scenario, but at the cost of missing and not referring to hospital some people who do in fact have sepsis. Not only is this a health risk to these individuals; but identifying them and initiating treatment late may also lead to higher overall costs for treating them such as longer ICU admission. The risk in this second option could potentially be partly mitigated by very good information provision. If people with a low but possible chance of early sepsis are given very clear instructions (for example, to go directly to hospital if their symptoms worsen), then the number of people missed by this approach would be reduced. However this is not the subject of this question. The clinical evidence was generally of very low quality and could not be meta-analysed. Although individual studies did show a link between symptoms and sepsis, it was not clear what combinations of symptoms predict sepsis. Therefore the GDG could not tell exactly where the line should be drawn on either clinical or economic grounds between referral to hospital being appropriate or not, or whether further intervention should be triggered if the patient is already in hospital. Any strategy will lead to some individuals with sepsis being missed and some people without sepsis being referred for further assessment. Any strategy will have to include safety nets to catch people wrongly discharged or not referred to hospital if their condition later worsens. The GDG agreed that symptoms should be considered together and not in isolation, and decisions also based on further test results if in hospital, and on review by a senior clinician if at moderate risk and out of hospital.
Quality of evidence	Overall, the quality of evidence was very low. In many studies the description of selection of patients was limited, it was unclear if selection was random or consecutive. The majority of studies had small numbers of patients, and the studies were unlikely to be sufficiently powered to and the studies were unlikely to be sufficiently powered to take into account measurement variability and the subjective nature of assessment of signs and symptoms. The majority of the studies did not provide sufficient information on the timing of assessment of the sign or symptom and the determination the diagnosis using the reference standard. The very low quality and lack of consistency of the evidence meant that the GDG could not rely on evidence review to make recommendations but used the evidence as a starting point for development of recommendations. There was significant variability amongst the included studies. The data could not be meta-analysed which contributed to the the GDG lack of confidence in the evidence. • The inclusion criteria varied amongst the studies and were ill-defined. Some of this was inevitable as definitions of sepsis and severe sepsis have changed over time but in other cases terms such as bacteraemia were used when it was clear that the population were severely ill. • The settings in which the symptoms were assessed were not clear for example hospitalised patients on a general ward or ICU, or patients

	presenting to the ED. • For each sign or symptom, there was inconsistency on how the threshold was defined or what the abnormal value was. • The reference standard varied amongst the included studies. In addition the studies used differing definitions for sepsis, severe sepsis, progression to septic shock), pneumonia, bacteraemia, serious bacterial infection and occult pneumococcal bacteraemia.
Other considerations	The GDG concurred that none of the signs and symptoms alone is sufficient to make a diagnosis of sepsis, or to predict patien outcome. While the available evidence was of very low quality the GDG also recognised that sepsis can be overwhelming and of rapid onset with few early clinical signs. The evidence suggests that all the signs and symptoms listed in this review are risk factors for sepsis. The review did suggest some thresholds and highlight the importance of mental state, respiratory rate and blood pressure for suspicion of more severe illness. However, the thresholds reported by the studies, for any sign or symptom, were inconsistent with each other; therefore the GDG established the thresholds used in the recommendations by consensus, also taking into account other published NICE guidelines. The GDG were also aware of the use to which they wished to put the symptoms and signs. In line with the review of treatments, they wished to highlight the people who required treatment quickly but did not want to promote overuse of resources such as anitbiotics. The thresholds for moderate to high, and high risk were decided from this perspective. The GDG emphasised that sepsis is difficult to diagnose and the clinical situation can change rapidly. They agreed therefore to structure their recommendations around likely risk of severe illness and death from sepsis and agreed categories of high risk, high to moderate risk and low risk. They considered it important that the middle category be labelled high to moderate as people in this category are at potentially significant risk. **Temperature** Fever as an isolated factor may be risk factor for sepsis, however some studies showed that a high proportion of sepsis patients did not have a temperature, therefore lack of fever did not rule out infection/sepsis. In addition, hypothermia was also a risk factor for sepsis. It is clearly important to ask for a history of fever or rigors as a patient may not have a temperature or rigors when seen. The GDG agreed not to include a raised temperature in risk stratification for adults, children and young people of 5 years and over. Very high temperature is unusual in children, and therefore it is often indicative of bacterial infection. The GDG therefore reviewed and discussed the evidence and recommendations in the Fever in under 5s guideline (CG160).243 and agreed to include the recommendations from that guideline that a temperature of 38^0C or more is a high risk criterion in very young children (up to 3 months)s and that a temperature of 39^0C or more is a moderate to high risk criterion in very young children (3-6 months). There are a number of groups who are less likely to develop a raised temperature with sepsis. This includes he elderly, infants and young children, people receiving treatments for cancer and those severely unwell with sepsis. The GDG considered it important to include a recommendation that a raised temperature may also be a physiological response to events such as trauma or surgery. The GDG also discussed the importance of measuring temperature accurately, and at regular intervals and not to rely on a single measure. Recommendations on how to measure temperature in children are included in Fever in under 5s(NICE guideline CG160).[243]

Heart rate

The evidence suggested that tachycardia is a risk factor for serious infections and sepsis, and also for ICU admission and mortality. The evidence was insufficient to determine clear cut-offs for the different risk categories, and this decision was taken by the GDG using the evidence presented, consensus and expert opinion. Heart rates in adults over 120bpm appeared to be increased with poorer outcomes. The GDG agreed a HR of 130bpm for high risk criteria and HR between 90 and 129 for moderate to high risk criteria for adults.

The GDG recognised that heart rate needs to be considered in the context of the individual. For example, a young healthy patient may have a very low heart rate at baseline, may develop an arrhythmia rather than increased heart rate People with suspected sepsis may also be taking medicines that may effect their heart rate response such as beta-blockers.

The GDG were informed by a co-opted expert that heart rate in pregnancy is about 10-15 beats per minute greater during pregnancy than in non-pregnant state. The GDG agreed to add this information to the recommendations on risk categorisation. The GDG agreed that a heart rate of 100-129 beats per minute was appropriate as a high to moderate risk criteria for woman who are pregnant. Although this may overdiagnose suspected sepsis this categorisation will not result in women receving antibiotics but will ensure adequate clinical assessment. It was agreed that the same heart rate as for adults, of 130beats per minute, or more was appropriate for high risk categorisation for pregnant women.

Respiratory rate

The evidence suggested that increased respiratory rate is associated with poor patient's outcomes and diagnosis of infection. Pneumonia is a common cause of sepsis and is likely to be accompanied by a raised respiratory rate. Respiratory rates of >24 breaths per minute were consistently associated with worse outcomes. The GDG agree a respiratory rate of over 25 for the high risk category for adults and 21-24 for moderate to high levels.

The GDG noted that in practice, respiratory rate may not be measured frequently or adequately enough. The GDG considered that the recommendation to perform a structured assessment would result in respiratory rate not being ignored.

Heart rate and respiratory rate parameters in children less than 12 years

The purpose of providing specific heart rate and respiratory rate levels is to inform risk of morbidity and mortality from sepsis and therefore actions required for treatment. The GDG aimed to be consistent with the Fever in under 5s guideline (CG160) where possible as they recognised that these guidelines are useful when children with fever are being assessed and that there is overlap with the populations included in these guidelines. Children with suspected sepsis however are a subset of children who present with fever, and some will not have fever as part of their presentation. The studies in the evidence review showed a tendency to include a higher proportion of children with severe disease in higher heart rate centile categories. For children under 12 years the GDG used the systematic review by Fleming 2011,[103] and agreed to use the 99th centile to specify high risk criteria, and 90th to 98th centile for high to moderate risk criteria for heart rate in each age group. The GDG recognised that these differed from the APLS criteria but considered that the Fleming 2011,[103] systematic review provided more up to date information.

There was insufficient evidence to inform respiratory rates in children so for children under 12 years the GDG used the systematic review by Fleming 2011,[110] and agreed to use the 99th centile of observed vlauesto specify high risk criteria, and

90th to 98th centile for high to moderate risk criteria for heart rate in each age group.

The GDG used consensus to agree that a heart rate of 60 beats per minute was indicative of bradycardia when used as a high risk criteria in children under 12 years.

The NICE Fever in under 5s guideline (CG160)[232] includes specific respiratory symptoms such as grunting, nasal flaring, chest crackles and chest indrawing in their risk stratification for children with fever under 5 years. The GDG reviewed the evidence and recommendations in the Fever in under 5s guideline for these and agreed they were applicable to the children under 5 in this guideline, that the evidence was unlikely to have changed and to therefore include these parameters in this guideline without an additional search for evidence.

Blood pressure

The evidence suggested that extreme values of blood pressure are a cause of clinical concern however, the evidence was not sufficient to determine a threshold, and the decision on cut-off values was taken by the GDG by consensus and expert opinion.

The GDG agreed that a systolic blood pressure less than 90 mm Hg in adults is generally cause of concern, however the baseline blood pressure needs to be taken into account for the individual patient: a drop of 40 mm Hg or more from baseline could be a more precise predictor of infection or sepsis. The GDG included a recommendation that blood pressure should be interpreted in the context of a person's previous blood pressure if this is known.

The GDG noted that the evidence often refers to mean arterial pressure; however, this is not generally used outside acute hospital settings. The GDG noted that there is is little evidence of for normal blood pressure levels in children less than 12 years. While they considered measurement of blood pressure in children to be good practice when at all possible, it was recognised that this is usually difficult in primary caresome settings such as primary care because of lack of equipment in particular appropriate cuff size. It can also be difficult in other settings when a child is moving or unco-operative. The GDG wished to encourage blood pressure measurement for children when possible but wished to emphasise that this should not delay assessment or treatment.

The GDG reviewed the evidence and recommendation adapted recommendation in Fever in under 5s (CG160) guideline to measure blood pressure if a child under 5 has increased heart rate or increased CRT. [232] The GDG agreed to include this recommendation but added emphasis on appropriate cuff size for clarity.

The GDG were informed by the co-opted expert that there is a small drop in pre-pregnancy values for systolic blood pressure which is probably present in early pregnancy. Diastolic blood pressure drops further than systolic blood pressure but both are likely to have returned to normal values by late pregnancy. Since the majority of sepsis in obstetrics is around the time of delivery or post–partum the GDG were advised and agreed that normal adult levels should be used for women who are pregnant or post-partum. Women who are pregnant are likely to be younger and healthy and have low baseline values of systolic and diastolic blood pressure.

Capillary refill time (CRT)

CRT is included in the traffic light system developed for children under 5 in Fever in under 5s guideline (CG160)[232] CRT is also included as a sign in the Meningitis (bacterial) and menigococcal septicaemia in under 16s guideline (CG102). The GDG reviewed the evidence and recommendations in those guidelines and considered it applicable to those less than 16 years who might have sepsis which would children with meningococcal septicaemia. The GDG were not aware of any change in the

evidence and a separate search of the evidence was not performed for this guideline. CRT was considered a useful bedside tool when assessing children. CRT> 3 was included as a high to moderate risk criteria for children under 12 years. Reduced perfusion may also be indicated by a complaint of cold hands and feet or pain in legs by children and the GDG included these as symptoms to indicate high to moderate risk in children with suspected sepsis.

Level of consciousness and altered mental state

The evidence suggested that a low score on the GCS is a risk factor for mortality in patients with infection, sepsis or septic shock. A low score on GCS is consistent with objective evidence of altered consciousness and this was considered by the GDG to be a high risk criterion when assessing risk. The GDG agreed that consciousness/ altered mental state needs to be considered in context of normal function; a change in cognitive function might be observed through different behaviour, or irritability in children and agitation in the elderly. The history from the patient and from relatives or carers is important both in understanding the patient's normal mental state and function and in order to establish whether the patient's behaviour is different from usual. Changes may be subtle and not clear to those who have not known the patient previously. It is also important to pay particular attention to confusion in the elderly, A change in mental state in the elderly as it might go undetected unless the importance of a change in functional state is appreciated.

The GDG considered scoring systems like GCS and AVPU can be useful tools to assess level of consciousness and altered mental state. They may be use in hospital settings where they are already used for monitoring purposes. The GDG did not wish to recommend that such scores should be used. The changes in mental state may be quite subtle and might be better explored in clinical history and assessment.

The GDG reviewed the evidence and recommendations for children under 5 in the Fever in under 5s guideline (CG160). That guideline makes recommendations for assessment of behaviour such as reponse to social cues, waking easily and type of cry. No evidence was found in the review for this guideline to change those recommendations and the GDG agreed to use the same wording for the under 5 age group. The GDG used consensus for the wording to include for the 5-11 such as wanting to play.

Oxygen saturation

The evidence was insufficient to establish that low oxygen saturation is a risk factor for sepsis; The GDG acknowledged that low oxygen saturation can be due to confounding factors, for example pneumonia.

The GDG noted that oxygen saturation is an important parameter to keep monitored, to see whether the patient is improving or a change in treatment is needed, and it also helps with prognosis.

The GDG discussed that measuring oxygen saturation in primary care is not always possible, and it can cause delay in hospital admission. On the other hand, it is important to measure oxygen saturation in secondary care, where there are adequate tools to measure it. The GDG noted that peripheral oxygen saturation may be difficult to assess because the patient has reduced peripheral perfusion and that diffuclty in assessing oxygen saturation should cause the clinican to at least consider the cause for this.

In the absence of other evidence the GDG agreed to use the British Thoracic Society[243] guidelines (BTS) to inform their recommendations on oxygen level. These are that a normal or near normal oxygen saturation should be the aim for acutely ill people. The GDG agreed that the inability to achieve the levels recommended by the BTS despite adequate oxygen delivery is an indication of severe illness and should be included as a high risk criterion.

Reduced urine output

The evidence suggested that oliguria is associated with an increased risk of mortality in children with sepsis. The evidence however was not sufficient to determine a threshold, and the decision on cut-off values, for different categories of patients, was taken by the GDG by consensus and expert opinion. The GDG agreed that lack of urine output could be assessed from history and while it might be caused by dehydration it could be associated with renal dysfunction and a clear history should be taken seriously.

The GDG considered that a time period of 18 hours was sufficient time over which to make this assessment. Assessment in children may require asking about wet nappies and in older people wetness of incontinence pads may be relevant. Some people, particularly those in hospital, may have their urine output measured or they may be catheterised. The NICE guideline on Acute Kidney Injury (CG 169) specifies a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people to detect acute kidney injury. The GDG agreed an output of 0.5ml to 1ml/kg/hour for indicative of reduced urine output and should be considered a high to moderate risk criterion.

Examination of skin

Appearing ill to a health professional is included as a non –specific indicator of illness in the Meningitis and meningococcal septicaemia guideline (CG102) and as an indicator of high risk in Fever in under 5s guideline (CG160). The GDG reviewed the evidence and recommendations in those guidelines and agreed that the evidence review was unlikely to have changed and was relevant to children with sepsis. They therefore included this criterion as a marker of high risk for severe illness or death from sepsis. Appearing ill to a healthcare professional is likely to be a result of a global assessment from an experienced clinician. This is likely to include skin colour in a shocked patient which is described as ashen or mottled. Patients may also be cyanosed. The GDG agreed that these descriptive terms should be included. Non-blanching rashes of skin are classically associated with meningococcal disease but the GDG noted that rash can also be associated with other causes of sepsis.

Examination of the skin should also be performed to find possible causes of infection such as infected cuts and bits.

6.3 Stratifying risk

6.3.1 Introduction

The risk stratification tables present the recommendations about symptoms and signs in an alternative way which the GDG considered would be useful as easy reference for healthcare professionals in clinical situations. The GDG were aware that a similar table was presented in the Fever in under 5's guideline and their experience was that this was useful for easy reference and was helpful in implementation of the guideline.

The tables are presented by age group - children under 5 years, children 5-12 years, and young people and adults over 12 years. These age groups were decided by GDG consensus taking into account the NICE Fever in under 5s guideline which makes recommendations for children under 5 only.

6.3.2 Risk stratification tables

Table 76: Risk stratification tool for adults and children and young people aged 12 years and over with suspected sepsis

	High risk criteria	Moderate to high risk criteria	Low risk criteria
History	Objective evidence of new altered mental state	History from patient, friend or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability History of rigors Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks	Normal behaviour
Respiratory	Raised respiratory rate: 25 breaths per minute or more New requirement of oxygen (more than40% FiO_2) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)	Raised respiratory rate: 21–24 breaths per minute or increased work of breathing	No high risk or moderate to high risk criteria met
Blood pressure	Systolic blood pressure less than 90 mmHg or systolic blood pressure	Systolic blood pressure 91–100 mmHg	No high risk or moderate to high risk criteria met

	High risk criteria	Moderate to high risk criteria	Low risk criteria
	more than 40 mmHg below normal		
Circulation and hydration	Raised heart rate: more than 130 beats per minute Not passed urine in previous 18 hours. For catheterised patients, passed <0.5 ml/kg of urine per hour	Raised heart rate: 91–130 beats per minute (for pregnant women 100 - 130 beats per minute) or new onset arrhythmia Not passed urine in the last 12–18 hours For catheterised patients, passed 0.5–1 ml/kg of urine per hour	No high risk or moderate to high risk criteria met * typical heart rate in pregnancy is 10 -15 beats per minute more than normal
Temperature	-	Tympanic temperature less than36°C	-
Skin	Mottled or ashen, with cyanosis of skin, lips or tongue Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound	No non-blanching rash

1

2 **Table 77: Risk stratification tool for children aged 5-11 years with suspected sepsis**

	High risk criteria	Moderate to high risk criteria	Low risk criteria
Behaviour	Objective evidence of altered behaviour or mental state Appears ill to a healthcare professional Does not wake or if roused does not stay awake	Not behaving normally or wanting to play Decreased activity Parent or carer concern that the child is behaving differently than usual	Behaving normally, wanting to play Responds normally to social cues
Respiratory	Raised respiratory rate: Aged 5 years, 29 breaths per minute or more Aged 6-7 years, 27 breaths per minute or more Aged 8-11 years, 25 breaths per minute or more Moderate or severe chest indrawing	Rasiedrespiratory rate: Aged 5 years, 27-28 breats per minute Aged 6-7 years, 24-26 breaths per minute Aged 8-11 years, 22 - 24 breaths per minute	No high risk or moderate to high risk criteria met
Circulation and hydration	Rapid heart rate: Aged 5 years, 130 beats per minute or more Aged 6-7 years, 120 beats per minute or more Aged 8-11 years, 115 breaths per minute or more Heart rate less than 60 beats per minute	Rapid heart rate: Aged 5 years, 120-129 beats per minute Aged 6-7 years, 110-119 beats per minute Aged 8-11 years, 105-114 beats per minute Capillary refill time (CRT) of 3 seconds or	No high risk or moderate to high risk criteria met

	High risk criteria	Moderate to high risk criteria	Low risk criteria
	Not passed urine in last 18 hours For catheterised patients, passed less than 0.5 ml/kg of urine per hour	more Reduced urine output For cateterised patients, passed 0.5-1lmk/kg of urine per hour	
Skin	Colour of skin/lips/tongue is pale ormottled orashen orblue Non-blanching rash		
Other	Temperature less than 36°C	Leg pain Cold hands / feet	No high or high to moderate risk criteria met

1

2

3

4 **Table 78: Risk stratification tool for children aged under 5 years old**

5 This table is adapted from Fever in under 5s (NICE guideline CG160).

6

	High risk criteria	Moderate to high risk criteria	Low risk criteria
Behaviour	No response to social cues Appears ill to a healthcare professional Does not wake, or if roused does not stay awake Weak high-pitched or continuous cry	Not responding normally to social cues No smile Wakes only with prolonged stimulation Decreased activity Parent or carer concern that child is behaving differently than usual	Responds normally to social cues Content/smiles Stays awake or awakens quickly Strong normal cry/not crying
Respiratory	Grunting Raised respiratory rate: Under 1 year, 60 breaths per minute or more Aged 1-2 years, 50 breaths per minute or more Aged 3-4 years, 40 breaths per minute Moderate or severe chest indrawing	Nasal flaring Raised respiratory rate:: Aged under 1 year, 50-59 breaths per minutee Aged 1-2 years, 40-49 breaths per minute Aged 3-4 years, 35-39 breaths per minute Oxygen saturationof less than 95% in air Crackles in the chest	No high risk or moderate to high risk criteria met
Circulation and	Rapid heart rate:	Rapid heart rate:	No hig risk or moderate

	High risk criteria	Moderate to high risk criteria	Low risk criteria
hydration	Aged under 1 year, 160 beats per minute or more Aged 1-2 years, 150 beats per minute or more Aged 3-4 years, 140 beats per minute or more Heart rate less than 60 beats per minute Reduced skin turgor No wet nappies/not passed urine in past 18 hours	Aged under 1 year,150-159 beats per minute Aged 1-2 years,140-149 beats per minute Aged 3-4 years, 130-139 beats per minute Capilary refill time of 3 seconds or more Poor feeding in infants Reduced urine output For catheterised patients, passed 0.5-1 ml/kg of urine per hour	to high risk criteria met
Skin	Colour of lips/skin/tongue is mottled or ashen or blue Non-blanching rash	Pale /pallor/flushed Pallor reported by carer	Normal colour
Other	Age under 3 months and temperature 38°C or more Temperature less than 36°C	Age 3–6 months and temperature 39°C or moreLeg pain Cold hands / feet	No high risk or high to moderate risk criteria met

1

2

7 Managing sepsis outside acute hospital settings

7.1 Introduction

Sepsis can be life-threatening. The interventions required to improve outcomes in sepsis are primarily delivered in hospital settings. The GDG developed a risk stratification strategy using the evidence on symptoms and signs and the evidence on interventions. People who may have sepsis and who present outside of an acute hospital setting require assessment and referral to hospital if necessary. The recommendations in this section cover the actions required according to the symptoms or signs presented.

These recommendations are summarised in the pathways in section **Error! Reference source not ound.**.

7.2 Recommendations and links to evidence

Recommendations	**39. Refer all people with suspected sepsis outside acute hospital settings for emergency medical care by the most appropriate means of transport (usually 999 ambulance) if:** • **they meet any high risk criteria (see Table 76), or** • **they are aged under 17 years and their immunity is compromised and they have any moderate to high risk criteria.** **40. Arrange review with a GP or other doctor within 1 hour when any moderate to high risk criteria in a person with suspected sepsis are identified by a non-medical practitioner outside an acute hospital setting.** **41. Assess (by a GP or other doctor) all people with suspected sepsis outside acute hospital settings with any moderate to high risk criteria for:** • **definitive diagnosis of their condition** • **whether they can be treated safely outside hospital.** **42. If a definitive diagnosis is not reached or the person cannot be treated safely outside acute hospital setting, refer them urgently to the emergency department.** **43. Arrange review by a GP or other doctor for a person with suspected sepsis but has no high or moderate to high risk criteria if they have had their first assessment by a non-medical practitioner outside an acute hospital setting.**
Relative values of different outcomes	No specific review was conducted for these recommendations.
Trade-off between clinical benefits and	Sepsis with organ dysfuntion has a high mortality. Management requires antibiotics and fluids and potentially other supportive care. This must be delivered in a timely fashion and in many circumstances requires specialist and potentially critical care

harms	input. This care requires access to acute hospital facilities. Providing this care for those patients at most risk improves their chance of survival. The likely benefit outways any potential harm from transfer to hospital. Inappropriate referral to acute hospital services for people at low risk and who can be managed in the community may lead to iatrogenic harm. Assesment by appropriately qualified healthcare personnel is important in making decisions about the balance between benefit and harm for individual patients.
Economic considerations	The assessment of a person's signs and symptoms to indicate level of risk will take place during a consultation with a healthcare professional, most likely a GP or paramedic outside of hospital. The length of this consultation will not vary significantly dependant on which signs are assessed and what use is made of these findings. It can be assumed that all consultations will be of standard length, and that equipment for measuring vital signs is available. Therefore cost is not a significant factor when looking at each individual consultation. However, the decision rules for using signs and symptoms as diagnostic of sepsis is a major economic issue – indeed the most significant economic issue in this guideline – as this will determine the number of people who are referred from primary care to hospital or who may be given antibiotics If a very broad combination of symptoms are agreed to suggest sepsis, that is the GDG chooses high sensitivity but low specificity criteria (few false negatives but many false positives) then a large number of people will be sent to hospital to undergo consultations, blood tests or other assessments and treatments. This will increase costs greatly, with little clinical benefit for those individuals without sepsis (it is likely that many individuals may receive an alternative diagnosis during this process for the condition that they in fact do have, which may assist them in managing that condition to some extent, while they may also benefit from peace of mind). There is a danger of over-cautiousness and unnecessary use of resources with this approach. If a very narrow combination of symptoms are agreed to suggest sepsis, that is the GDG chooses low sensitivity but high specificity criteria (few false positives but some false negatives) then we will avoid many of the unnecessary referrals in the first scenario, but at the cost of missing and not referring to hospital some people who do in fact have sepsis. Not only is this a health risk to these individuals; but identifying them and initiating treatment late may also lead to higher overall costs for treating them such as longer ICU admission. The danger in this second option could potentially be partly mitigated by very good information provision. If people with a low but possible chance of early sepsis are given very clear instructions (for example, to go directly to hospital if their symptoms worsen), then the number of people missed by this approach would be reduced. However this is not the subject of this question. We cannot tell exactly where the line should be drawn on either clinical or economic grounds between referral to hospital being appropriate or not. Any strategy will lead to some individuals with sepsis being missed and some people without sepsis being referred for further assessment. Any strategy will have to include safety nets to catch people not referred to hospital if their condition later worsens. The GDG agreed that symptoms should be considered together and not in isolation, and decisions also based on review by a senior clinician if at moderate risk and out of hospital. Although this may incur the cost of the GP assessment, this will enable the GP to make an informed decision, using also the risk criteria, about whether someone needs to go to hospital or can be diagnosed and treated out of hospital. The use of ambulance resources (via 999 call) to take people to hospital if they are considered at high risk of sepsis is also a resource that would incur cost as well as opportunity cost. The GDG opinion overall was that sepsis is a condition associated with high mortality where patients can deteriorate quickly, and the consequences of not taking immediate action based on the symptoms indicating high risk would outweigh the resources used. The GDG decision on the classification of the risk groups associated with the risk of sepsis and mortality are based on clinical evidence and GDG

	consensus.
Quality of evidence	No specific studies were reviewed for these recommendations
Other considerations	The recommendations were informed by the evidence reviews on symptoms and signs, the evidence for interventions and the clinical experience of the GDG. In particular GDG knowledge of the organisation of health services informed these recommendations. The evidence on symptoms and signs resulted in a stratification of people suspected of sepsis by risk of mortality and morbidity from sepsis. The ongoing suspicion of sepsis is an important part of the pathway as experienced professionals may consider alternative diagnoses when they clinically assess a patient. People with a continuing suspicion of sepsis and any high risk criteria should be referred to acute hospital setting usually by 999 ambulances. The GDG considered that any young people who may be immunocompromised with any moderate to high risk criteria should be treated as high risk. The GDG agreed that people in the moderate to high risk groups do not need to be sent to a hospital if a definitive condition can be diagnosed and they can be safely treated outside an acute hospital setting. These patients do require face to face assessment by either a GP or other medical professional if their first assessment has not been by a medically qualified practitioner. People with suspected sepsis and no moderate to high or high risk criteria should be assessed by a GP if their initial presentation has been to a non-medical practitioner such as a pharmacist. The actions recommended here for children less than 5 differ from those in the Fever in under 5s guideline (CG160).[232] Children with suspected sepsis are a subset of children who present with fever, and some will not have fever as part of their presentation. The children identified in this guideline include those with suspected meningococcal septicaemia where immediate transfer to hospital is required if high risk criteria are present as recommended in NICE guideline for Meningitis and meningococcal septicaemia.(CG102). The GDG agreed that this was also appropriate for children with suspected sepsis from any cause.

8 Managing and treating sepsis in acute hospital settings

8.1 Introduction

The medical management of people who are suspected of having sepsis is a medical emergency where assessment and institution of treatment needs to take place as soon as possible. A number of actions need to take place at the same time. The recommendations on managing people with sepsis in acute hospital settings are organised around stratification of risk. Each recommendation includes a number of actions. Each action is supported by a different evidence review.

The primary actions are involvement of appropriate clinical staff, the performance of blood tests and giving of antibiotics. According to results of blood tests such as lactate further treatments such as IV fluids, referral to critical care and consultant input may be required.

This chapter is therefore organised as follows: the recommendations are first listed in section 8.1 and the evidence reviews informing the recommendations are then reported. The sections relevant to individual tasks are as follows:

- blood tests: Section 8.3
- use of antimicrobial agents: Section 8.4
- intravenous fluid administration: Section 8.5
- escalation of care: Section 8.6

For ease of reference we have includedthe main recommendations informed by each evidence review in the individual sections.

The recommendations for recognition and management of sepsis, particularly in acute hospital settings, set out a series of actions required for people with suspected sepsis. Research recommendations to provide robust epidemiological data on sepsis and an evaluation of changes assocated with sepsis are outlined in section 8.6.7 and Appendix N.

8.2 Recommendations

Adults and children and young people aged 12 years and over who meet 1 or more high risk criteria

44. For adults and children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker[p]**
- **carry out a venous blood test for the following:**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**

p A 'senior clinical decision maker' for people aged 18 years or over should be someone who is authorised to prescribe antibiotics, such as a doctor of grade CT3/ST3 or above, or an advanced nurse practitioner with antibiotic prescribing rights, depending on local arrangements. A 'senior clinical decision maker' for people aged 12-17 years is a paediatric qualified doctor of grade ST4 or above.

- **creatinine**
- **clotting screen**
- **blood gas to include lactate measurement**

- **give a broad-spectrum antimicrobial at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.4**
- **discuss with consultant.**

45. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre, or blood pressure less than 90 mmHg:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5 and**
- **refer to critical care for review of central venous access and initiation of inotropes or vasopressors and admission to critical care.**

46. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

47. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- **consider giving fluids (in line with recommendations in section 8.5).**

48. Monitor people with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients in acute hospital settings. [This recommendation is from Acute illness in adults in hospital (NICE guideline CG50)].

49. Monitor the mental state of adults and children and young people aged 12 years and over with suspected sepsis. Consider using a scale such as the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

50. Alert a consultant to attend in person if an adult, child or young person aged 12 years or over with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **systolic blood pressure persistently below 90 mmHg**
- **reduced level of consciousness despite resuscitation**
- **respiratory rate over 30 breaths per minute**
- **lactate not reduced by more than 20% within 1 hour.**

Adults and children and young people aged 12 years and over who meet 2 or more moderate to high risk criteria

51. For adults and children and young people aged 12 years and over with suspected sepsis and 2 or more moderate to high risk criteria, carry out a venous blood test for the following :

- **blood culture**
- **full blood count**
- **C reactive protein**
- **urea and electrolytes**
- **creatinine**
- **blood gas to include lactate measurement**
- **arrange for a clinician[q] to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria**

52. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury[r], treat as high risk and follow recommendations 44-50.

53. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[q] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

54. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[q] and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition**
- **if appropriate, discharge with information (see recommendations 121 and 122), depending on the setting.**

Adults and children and young people aged 12 years and over who meet only 1 moderate to high risk criterion

55. For adults and children and young people aged 12 years and over with suspected sepsis who meet 1 moderate to high risk criterion:

- **arrange clinician review[p] within 1 hour of meeting criterion for clinical assessment**
- **perform blood tests if indicated.**

56. For adults and children and young people aged 12 years or over with suspected sepsis who meet only 1 moderate to high risk criteria and in whom a definitive condition can be identified and treated:

- **manage the definitive condition**

[q] A 'clinician' should be a medically qualified practitioner who has antibiotic prescribing rights

r For definition of acute kidney injury, see Acute kidney injury (NICE guideline 169)

- **if appropriate, discharge with information depending on setting (see recommendations 121 and 122).**

57. For adults and children and young people aged 12 years and over with suspected sepsis who meet one moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[s] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker[t] within 3 hours of meeting moderate to high criterion for consideration of antibiotics.**

Adults and children and young people aged 12 years and over with no moderate or high risk criteria

58. Arrange clinical assessment[u] of adults and children and young people aged 12 years and over who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children aged 5-11 years who meet 1 or more high risk criteria

59. For children aged 5-11 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker[v]**
- **carry out a venous blood test for the following:**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas for glucose and lactate**
- **give people a broad-spectrum antimicrobial (see section 8.4) at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria)**
- **discuss with consultant.**

60. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate over 4 mmol:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria in line with recommendations in section 8.5) and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care.**

61. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

[s] For definition of acute kidney injury, see Acute kidney injury (NICE guideline 169)].

t A 'clinician' should be a medically qualified practitioner who has antibiotic prescribing rights

[u] Clinical assessment should be carried out by a medically qulaified practitioner who has antibiotic prescribing rights

v A 'senior clinical decision maker' for children aged 5-11 years old is a paediatric qualified doctor of grade ST4 or above.

62. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- **consider giving fluids in line with recommendations in section 8.5.**

63. Monitor children with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is adapted from Acutely ill patients in hospital (NICE guideline CG50)].

64. Monitor the mental state of children aged 5-11 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unesponsive' scale.

65. Alert a consultant to attend in person if a child aged 5-11 years with suspected sepsis and any high risk criteria fails to repond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by:

- **reduced level of consciousness despite resuscitation**
- **heart rate or respiratory rate fulfil high risk criteria**
- **lactate remains over 2 mmol/litre after one hour.**

Children aged 5-11 years who meet 2 or more moderate to high risk criteria

66. For children aged 5-11 years with suspected sepsis and 2 or more moderate to high risk criteria:

- **carry out a venous blood test for the following :**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **blood gas for glucose and lactate**
- **arrange for a clinician to review the person's condition and test results within 1 hour of meeting moderate to high risk criteria.**

67. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury[w], treat as high risk and follow recommendations 59-65.

68. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[v] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

w For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)

69. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[x] and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition, and**
- **if appropriate, discharge with information depending on setting (see recommendations 121 and 122).**

Children aged 5-11 years who meet only 1 or more moderate to high risk criteria

70. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- **arrange clinician review[y] within 1 hour of meeting 1 moderate to high risk criterion for clinical assessment and**
- **perform blood tests if indicated.**

71. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criteria 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 121 and 122).**

72. For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[i] and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting a moderate to high risk criterion for consideration of antibiotics.**

Children aged 5-11 years with no high risk or moderate to high risk criteria

73. Arrange clinical assessment[z] of children aged 5-11 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children aged under 5 years

Children aged under 5 years who meet 1 or more high risk criteria

74. For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker[aa]**
- **carry out a venous blood test for the following :**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**

x For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)

[y] A 'clinician' should be a medically qualified practitioner with antibiotic prescibing rights

[z] This could be by a medically qualified practitioner with prescribing rights.

aa A 'senior clinical decision maker' for children aged under 5 years is a paediatric qualified doctor of grade ST4 or above.

  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas for glucose and lactate**

- **give parentral antibiotics (within 1 hour of identifying that they meet any high risk criteria; see section 8.4)**
- **discuss with consultant.**

75. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre:

- **give fluids (in line with recommendations in section 8.5), and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care.**

76. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

77. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre, consider giving fluids in line with recommendations in section 8.5.

78. Monitor children aged under 5 years with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is adapted from Acutely ill patients in hospital (NICE guideline CG50)].

79. Monitor the mental state of children under 5 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

80. Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **reduced level of consciousness despite resuscitation**
- **heart rate or respiratory rate fulfil high risk criteria**
- **lactate over 2 mmol/litre after 1 hour.**

81. Give parenteral antibiotics to children aged under 3 months as follows:

- **infants younger than 1 month with fever**
- **all infants aged 1–3 months with fever who appear unwell**
- **infants aged 1–3 months with white blood cell count less than 5×10^9/litre or greater than 15×10^9/litre. [This recommendation is from Fever in under 5s (NICE guideline CG160)][232]**

Children aged under 5 years who meet 2 or more moderate to high risk criteria

82. For children aged under 5 years with suspected sepsis and 2 or more moderate to high risk criteria carry out a venous blood test for the following:

- **blood culture**
- **full blood count**
- **C reactive protein**
- **urea and electrolytes**
- **creatinine**
- **blood gas for glucose and lactate**
- **arrange for a clinician[bb] to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria.**

83. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 74 to 81.

84. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

85. For children aged under 5 years with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:

- **manage the definitive condition and**
- **if appropriate, discharge with information (see recommendations 121 and 122) depending on the setting.**

Children aged under 5 years who meet only 1 moderate to high risk criterion

86. For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- **arrange clinician review within 1 hour of meeting a moderate to high risk criterion for clinical assessment, and**
- **perform blood tests if indicated.**

87. For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated:

- **manage the definitive condition**
- **if appropriate, discharge with information depending on setting (see recommendations 121 and 122).**

[bb] A 'clinician' should be a medically qulaified practitioner who has antibiotic prescribing rights

88. **For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[cc] and in whom a definitive condition cannot be identified:**

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours for consideration of antibiotics.**

Children aged under 5 years with no moderate or high risk criteria

89. **Arrange clinical assessment[dd] of children aged under 5 years who have suspected sepsis and no high risk or moderate to high risk criterion and manage according to clinical judgement.**

8.3 Blood tests for diagnosis

8.3.1 Introduction

The aim of the blood test review was to determine which blood tests were most accurate in identifying patients with sepsis. The most appropriate approach when assessing diagnostic accuracy is to use diagnostic accuracy data, for example sensitivity, specificity and area under the curve (AUC). Accuracy of a given test is measured against a reference ('gold') standard, and the reference standard is defined as providing the true measure at point of testing (base line testing).

However no reference standard is available for the diagnosis of sepsis because sepsis is essentially a syndrome, an array of signs and symptoms as a consequence of systemic infection. Despite the lack of a reference standard and the use of different terms for sepsis in different studies the GDG considered that diagnostic accuracy data could inform recommendations. The GDG were aware that healthcare professionals do use measures of inflammation such as CRP when assessing patients and did use normal tests to rule out significant illness and that it was important to review this. In addition the GDG decided that it would be of value to explore the prognostic ability of these blood tests to predict clinical outcomes as these would also inform their use.

The initial search retrieved a large number of studies and the evidence review in section 8.3.2 reports on these. No test was found to be sufficiently accurate for the 'rule' in of sepsis (sensitivity) or the 'rule' out of sepsis of sepsis (specificity). A comparison of the search findings with the results of the searches in more specific but overlapping NICE guidance such as Feverish Illness in Children guideline, indicated that a search targeted at specific infections would yield a similarly large but different set of studies. No other guidance however had found convincing evidence for these tests. The GDG therefore chose not to expand the initial diagnostic search further but to look specifically for evidence of the prognostic value of lactate, renal function and disseminated intravascular coagulation. The GDG were aware that these are used as discriminating factors in clinical practice and wished to explore whether they predict poor outcomes in people with sepsis.

The additional evidence reviews for prognostic value of lactate, creatinine and disseminated intravascular coagulation are in sections 8.3.9, 8.3.15 and 1.1.18.3.21 respectively.

One of the blood tests recommended is blood cultures prior to antibiotic use. This is discussed in section 8.4 on anti-microbial use and chapter 14 on finding the cause of infection.

[cc] For definition of acute kidney injury, see Acute kidney injury (NICE guideline CG169)
[dd] Clinical assessment should be carried out by a medically qualified practitioner who has antibiotic prescribing rights

8.3.2 Review question: In people with suspected sepsis how accurate are blood tests to identify whether sepsis is present??

For full details see review protocol in Appendix C.

Table 79: Characteristics of review question

Population	All people with suspected (or under investigation for) sepsis/severe sepsis
Index tests	All of the following, alone or in combination: • 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 standards	• 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 • Clinical outcome of all-cause mortality at 28 days (or nearest time point)
Statistical measures	Sensitivity Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio: univariate analyses only included if no multivariate analyses reported
Key confounders for studies reporting odds ratios	No pre-specified confounders
Study design	• RCTs • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies (if there is no other evidence)

8.3.3 Clinical evidence

A search was conducted for RCTs, cross-sectional studies, cohort studies (including both retrospective and prospective analyses), case series that assessed the diagnostic test accuracy of test of blood tests to identify whether the sepsis is present in people under investigation. No RCTs were identified. Case-control studies were not included because we found cross-sectional and cohort studies.

A search was conducted for RCTs, cross-sectional studies, cohort studies, case series (including both retrospective and prospective analyses) that assessed the diagnostic test accuracy of test of blood tests to identify whether the sepsis is present in people under investigation. No RCTs were identified.

Case-control studies were not included because we found cross-sectional and cohort studies. The search retrieved a large number of studies and the evidence review in Section 8.3.3 reports on these. No test was found to be sufficiently accurate for the 'rule' in of sepsis (sensitivity) or the 'rule' out of sepsis of sepsis (specificity). A comparison of the search findings with the results of the searches in more specific but overlapping NICE guidance such as Fever in under 5s[232] guideline, indicated that a search targeted at specific infections would yield a similarly large but different set of studies. No other guidance however had found convincing evidence for these tests. The GDG therefore chose not to expand the initial blood test diagnostic search further, but to look specifically for evidence of lactate, renal function and disseminated intravascular coagulation (DIC) for the early identification of people likely to experience worsening sepsis. The GDG were aware that these are used as discriminating factors in clinical practice and wished to explore whether they predict poor outcomes in people with sepsis. Evidence for blood lactate, serum creatinine and DIC are detailed in Sections 8.3.11, 8.3.16, 8.3.22, respectively.

One hundred and seven studies were included in the initial blood test review; 62 in adults[1-3,17,27,30,33,52-54,56-58,69,77,82,106,111,122,128,130,132,137,139,150,152,164,165,167,171,186,195,198,206,215-217,221,224,230,245,246,253,256,260,261,265,266,268,289,291,298,299,303,305,313,314,316,318,320,329,333] and 45 in children or neonates.[11,20,29,38,39,44,78,85,91,95,98,102,105,107,112,121,126,127,134,143,145-147,166,178,200,203-205,228,229,241,249,257,269,271,274,276,285,290,296,301,308,311,337]

The aim of the review was to utilise the diagnostic test accuracy studies to evaluate the accuracy of the blood tests in diagnosing sepsis. There is no consensus about what constitutes the reference standard for sepsis. In the studies identified various reference standards were used to identify the cases and non-cases. Some studies used a composite of a number of available tests, for example the American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of SIRS, sepsis, severe sepsis and septic shock, while other studies used blood culture-proven infection .

Given the lack of a universal reference standard, some studies used all-cause mortality follow-up data.[77,128,139,165,167,230,245,246,261,291,298] All the studies identified used in-hospital or up to 28-day mortality, with the exception of one study which measured mortality at 180 days.[167] Studies using a clinical outcome and follow-up may be viewed as prognostic studies in that they are measuring the accuracy with which a risk factor is able to predict a future event, rather than the accuracy with which it is able to determine current status. The standard definition of a risk factor is a variable that contributes to disease progression. This review concerns the use of blood test in the diagnosis of sepsis, and all-cause mortality may be viewed as a reference standard for the identification of people with sepsis. Therefore the GDG considered that studies could provide a guide to clinical decision making.

In summary, the objective of the review was to be comprehensive because the lack of a universal reference standard, hence the inclusion of both diagnostic studies that evaluated blood tests at point of care against a reference standard, and the inclusion of studies that evaluated blood tests at point and the outcome of all-cause mortality at 28 days (or nearest time point).

The majority of the studies compared one blood test to another. A few studies examined combinations of blood tests.[128,139,167,206,224] The included studies had differing cut-off points (thresholds for diagnosis), and differing presentation settings (for example ED, ICU). It was not possible to conduct meta-analysis of diagnostic nor ORs data because of the heterogeneity in these study variables, in addition to lack of a reference standard.

The quality of the evidence was evaluated using the QUADAS-2 checklist for diagnostic accuracy studies.

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

Evidence from the included studies in adults is summarised in **Table 80** and the evidence for children is summarised in **Table 81** . See also the study selection flow chart in Appendix B, sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in Appendix D, study evidence tables in Appendix E and exclusion list in Appendix G.

8.3.3.1 Summary of included studies, adults

Table 80: Summary of studies included in the review, adults

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
Aalto 2004[1]	CRP CRP ≥125 mg/l	n=92 patients with suspected systemic infections. ED Finland	Bloodstream infection	CRP ≥125 mg/l Sensitivity: 85 (55-98) Specificity: 81 (71-89) PPV 42 (23-63) NPV 97 (89-100) AUC 85 (63-96)	Observational design, small sample size, single centre. Indirectness: prediction of bloodstream infection. Risk of bias: very high.
Adams 2005[2]	CRP (CRP >10 mg/l defined as elevated)	n=1214 ED patients Australia	Bacteraemia	Sensitivity: 94 (86-98) Specificity: 18 (16-20) PPV 7 (6-9) NPV 98 (94-99)	Retrospective design, possible selection bias (convenience sample). Indirectness: none. Risk of bias: very high.
Adamzik 2012[3]	CRP Thrombin time Fibrinogen Platelets	n=130 Postoperative patients admitted to ICU Germany	Sepsis	**AUC** CRP: 51.3 (41.2-61.4) Thrombin time: 59.3 (45.6-66.9) Fibrinogen: 56.3 (45.6-66.7) Platelets: 73.6 (64.9-82.3)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Aube 1992[17]	Creatinine >20 mg/l Prothrombin time <60%	n=331 Patients who had both blood cultures within 6 hours of suspected	Septic shock	Creatinine >20 mg/l: OR=4.31 (2.15-8.65) Prothrombin time <60%: OR=5.33 (2.65-19.7)	Retrospective design, possible selection bias (convenience sample). Indirectness: none.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
		infection. France			Risk of bias: very high.
Bell 2003[27]	CRP	n=123 hospitalised patients from whom blood cultures were drawn for sepsis Australia	Bacteraemia	AUC: 0.53 (SE: 0.06)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Biller 2014[30]	CRP	n=116 Consecutive intensive care patients with a diagnosis of infection. ICU Austria.	Survival after infection	**CRP** AUC: 0.407	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Bogar 2006[33]	LAR (Leucocyte anti-sedimentation rate)	n=39 critically ill patients, ICU Hungary	Bacteraemia	AUC: 80 (64-95)	Observational design, small sample size, single centre. Indirectness: prediction of bacteraemia. Risk of bias: very high.
Castelli 2004[54]	CRP CRP cut off 128 mg/l	n=150 Medico-surgical patients in ICU Italy	Sepsis/ severe sepsis	CRP cut off 128 mg/l AUC: 75.5 (64.0-86.0) Sensitivity: 67 Specificity: 82 PPV 51	Observational design, small sample size. Indirectness: none Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				NPV 90	
Castelli 2006[52]	CRP CRP cut off 128 mg/l	n=255 Medico-surgical patients in ICU Italy	Sepsis, severe sepsis, and septic shock	CRP cut off 128 mg/l AUC: 74 (67-81) Sensitivity: 61 Specificity: 87 PPV 66 NPV 87	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Castelli 2009[53]	CRP	n=94 trauma patients in ICU Italy	Sepsis	AUC: 48.9	Observational design, small sample size. Indirectness: indirect (trauma patients who survived ≥24 hours) Risk of bias: very high.
Caterino 2004[56]	WBC (<4.3 or >11.4 cells/mm^3)	n=108 ED patients USA	Bacteraemia	AUC: 50 (30-70) Sensitivity: 57 (31-83) Specificity: 66 (48-88) PPV 44 (22-67) NPV 81 (67-94)	Observational design, possible selection bias (convenience sample), small sample size. Indirectness: none. Risk of bias: very high.
Cavallazzi 2010[57]	Immature neutrophils (band): **Band >10%** WBC	n= 145 critically ill patients in ICU USA	Infection	**Band >10%** Sensitivity: 43 (28-59) Specificity: 92 (28-59) AUC: 74 (64-83) **WBC >12 x10^9/l**	Observational design, small sample size, critically ill patients. Indirectness: prediction of infection, not sepsis. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	WBC >12 x10^9/l **WBC <4 x10^9/l** **Band >10% and WBC >12 x10^9/l**			Sensitivity: 52 (36-68) Specificity: 59 (49-69) **WBC <4 x10^9/l** Sensitivity: 10 (3-23) Specificity: 96 (90-99) **Band >10% and WBC >12 x10^9/l** Sensitivity: 26 (14-42) Specificity: 97 (92-99)	
Chase 2012[58]	Neutrophils (>80%) Platelets (<150) WBC (<4 or >12) Lactate (>4)	n=3310 ED USA	Bacteraemia	Univariable model to predict bacteraemia (defined as a positive blood culture): Lactate >4: p≤0.001 WBC <4 or >12 p = 0.435 Multivariable model to predict bacteraemia (defined as a positive blood culture), adjusted for: suspected endocarditis, suspected line infection, bandemia, suspected urinary source, platelets <150, vasopressor in ED, neutrophils >80%, indwelling catheter, abnormal temperature, respiratory failure: Neutrophils >80%: B coefficient=0.56, OR=1.76 (1.40-2.21), p=<.0001 Platelets <150: B coefficient=0.66, OR=1.94 (1.50-2.52), p=<.0001	Observational design, small sample size, single centre. Indirect: predicting bacteraemia (defined as a positive blood culture) not sepsis. Risk of bias: very high
Cheval 2000[69]	CRP	n=60 patients with shock	Sepsis	**CRP>100 mg/ml to predict the infectious origin**	Observational design, small

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
		ICU France		**of any shock** Sensitivity: 93±10 Specificity: 40±18 **CRP to predict sepsis in patients with shock** AUC: 85.4 (66.9-95.7)	sample size, single centre. Indirectness: none Risk of bias: very high.
Dahaba 2006[77]	CRP	n=69 post-op patients with severe sepsis ICU Austria	28-day mortality related to severe sepsis	AUC: 61	Observational design, small sample size, post-op patients. Indirectness: prediction of 28-mortality from severe infection. Risk of bias: very high.
de Kruif 2010[82]	CRP (sensitivity cut off: 9 mg/l) Leukocyte count Thrombocyte count	n=211 adults with fever, ED The Netherlands	Bacterial infection	**CRP** OR multiv. Analysis 1.008 (1.001-1.014) AUC: 76 (67-85) Sens:(cut off: 9 mg/l) 99 Sepc 15 PPV 71 NPV 83 **Leukocyte count** OR multiv. Analysis 1.125 (0.997-1.295)	Observational design, small sample size. Indirectness: prediction of bacterial infection, not sepsis. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				Thrombocyte count OR multiv. Analysis 0.996 (0.990-1.003)	
Freund 2012[106]	**Sepsis: Lactate** (mmol/l) Threshold = 1.4 **Severe sepsis: Lactate** (mmol/l) Threshold = 2.0 **Septic shock: Lactate** (mmol/l) Threshold = 2.60 WBC count > 12,000/mm	n=not stated ED patients with suspected infection France	Sepsis Severe sepsis Sepsis shock	Multivariable analysis, backward logistic regression, only adjusting for those found significant at univariable analysis. **Sepsis** (multivariable analysis, including PCT≥0.25 ng/ml, temperature >38C or <36C, WBC count > 12,000/mm^3): **WBC** count > 12,000/mm^3: OR=1.83 (1.17-2.86) **Severe sepsis** (multivariable analysis including PCT≥0.25 ng/ml, lactate>2 mmol/l) **Lactate**>2 mmol/l: OR=10.88 (6.51-18.19) **Sepsis shock** (multivariable analysis including PCT≥0.25ng/ml, lactate>2mmol/l, SAP<90mm Hg, SpO2<90%) **Lactate**>2mmol/l: OR=6.36 (1.87-21.62) **Sepsis: Lactate** (mmol/l) Threshold = 1.4 AUC: 56.5 (50.8-61.6) P=0.02 **Severe sepsis: Lactate** (mmol/l)	Observational design, sample size not stated, population includes some immunocompromised patients, single centre. Multivariable analysis only adjusted for those confounders significant at univariable (unclear what was analysed at univariable). Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				Threshold = 2.0 AUC: 79.2 (73.6-83.8) P=<0.001 **Septic shock: Lactate** (mmol/l) Threshold = 2.60 AUC: 84.0 (71.9-91.2) P=<0.001	
Gaini 2006A[111]	CRP **cut offs: 38 mg/l, 50 mg/l, 100 mg/l** WBC Neutrophil	n=173 hospital patients with suspected infection Denmark	Infection Sepsis/ severe sepsis	**CRP to diagnose sepsis/ severe sepsis:** AUC: 84 (75-92) **cut off: 38 mg/l** Sensitivity: 79.7 Specificity: 57.9 PPV 88.1 NPV 42.3 **cut off: 50 mg/l** Sensitivity: 71.6 Specificity: 63.2 PPV 88.3 NPV 36.4 **cut off: 100 mg/l** Sensitivity: 63.5 Specificity: 94.7 PPV 97.9	Observational design, small sample size, elderly patients with a burden of comorbidity. The physician scoring the infection status was blinded to all biochemical laboratory results. Indirectness: none Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				NPV 40.0 **WBC to diagnose sepsis/severe sepsis** AUC: 66.71 **Neutrophil to diagnose sepsis/severe sepsis** AUC: 65.83	
Geppert 2003[122]	CRP	n=66 in Patients with cardiogenic shock Austria. Cardiovascular ICU	Sepsis	AUC: 83 (73-94)	Retrospective design, small sample size, population with cardiogenic or septic shock. Indirectness: none. Risk of bias: very high.
Green 2011[128]	Lactate (cut-off ≥4 mmol/dl) CRP (cut-off 10 mg/dl)	n=1143 ED patients with suspected infection USA	Sepsis	**Multivariable analysis adjusted for patient demographics and co-morbidities:** CRP >10.0 mg/dl and lactate ≥4.0 mmol/l: OR 12.34 (6.81-22.34). CRP >10.0 mg/dl and lactate <4.0 mmol/l: OR 1.91 (1.22-2.98). CRP ≤10.0 mg/dl and lactate ≥4.0 mmol/l: OR 1.38 (0.58-3.24). CRP ≤10.0 mg/dl and lactate <4.0 mmol/l: OR 1.00 (reference).	Retrospective design. Indirectness: none. Risk of bias: very high.
Ha 2011[130]	CRP (Ratio of follow-up CRP level to the initial CRP level (CRP	n=87 Hospital (cirrhotic patients with bacteraemia)	Bacteraemia	OR 19.12 (1.32-276.86), p=0.043.	Retrospective design, possible selection bias (convenience sample). Indirectness: none.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	ratio ≥0.7 defined as elevated))	Korea			Risk of bias: very high.
Hambach 2002[132]	CRP **CRP>5 mg/l, >50 mg/l, >100mg/l, >150 mg/l**	n=214 clinical events, in a cohort of 61 immunocompromised patients Hospital Germany	Infections (bacterial and fungal)	AUC: 0.76 (0.69-0.93) **CRP>5 mg/l** Sens: 100 Spec: 4 PPV: 40 NPV: 100 **CRP>50 mg/l** Sens: 94 Spec: 41 PPV: 51 NPV: 91 **CRP>100 mg/l** Sensitivity: 83 Specificity: 61 PPV: 58 NPV: 85 **CRP>150 mg/l** Sensitivity: 68 Specificity: 74 PPV: 63 NPV: 78	Observational design, small sample size Indirectness: prediction of infections, not sepsis. Risk of bias: very high.
Hillas 2010[137]	CRP	n=45 patients with	Severe	**CRP>15.2 ng/ml, Day 1**	Observational design, small

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	CRP>15.2 ng/ml (Day 1), CRP>15.75 ng/ml (Day 7)	suspected VAP (ventilator-associated pneumonia) ICU Greece	sepsis	Sensitivity: 86.4 Specificity: 65.2 PPV 70.4 NPV 83.3 AUC: 79.4 (66.4-92.5) **CRP>15.75 ng/ml, Day 7** Sensitivity: 93.8 Specificity: 73.9 PPV 71.4 NPV 94.4 AUC: 78.3 (62.6-93.9)	sample size, single centre, patients with suspected VAP Indirectness: none. Risk of bias: very high.
Hoeboer 2012[139]	Bloodstream infection Day 0-2: CRP (cut-off 196 mg/l) Lactate (cut-off 1.5 mmol/l) WBC (cut-off 20.3 x 10^9/l) Septic shock Day 0-7: **CRP** (cut-off 208 mg/l)	n=101 adults with fever in ICU The Netherlands	Bloodstream infection Day 0-2 Septic shock Day 0-7 Mortality Day 0-28	Bloodstream infection Day 0-2, prediction by peak values of biomarkers **CRP, mg/l** (cut-off 196 mg/l) AUC: 74 Sensitivity: 92 Specificity: 60 PPV 23 NPV 98 **Lactate, mmol/l** (cut-off 1.5 mmol/l) AUC: 75 Sensitivity: 83 Specificity: 61	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	Mortality Day 0-28: **Lactate** (cut-off 1.7 mmol/l)			PPV 23 NPV 96 **WBC, x 10^9/l** (cut-off 20.3) AUC: 70 Sensitivity: 58 Specificity: 84 PPV 33 NPV 94 Septic shock Day 0-7, prediction by peak values of biomarkers **CRP, mg/l** (cut-off 208 mg/l) AUC: 75 Sensitivity: 71 Specificity: 78 PPV 62 NPV 84 Mortality Day 0-28, prediction by peak values of biomarkers **Lactate, mmol/l** (cut-off 1.7 mmol/l) AUC: 71 Sensitivity: 60 Specificity: 75	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				PPV 44 NPV 85	
Jansen 2009A[150]	Lactate (hyperlactatemia ≥2.5 mmol/l)	n=394 ICU The Netherlands	28-day mortality	28-day survival all sepsis patients AUC: At ICU admission: 0.52 AUC: 12 hours after admission: 0.62 AUC: 24 hours after admission: 0.68	Observational design, small sample size Indirectness: none. Risk of bias: very high.
Jekarl 2013[152]	CRP **CRP (mg/l),** cut-off=55 WBC **WBC(x10^9/l),** cut-off=11.0	n=177 patients diagnosed with SIRS in the ED. South Korea`	Sepsis and septic shock/ severe sepsis	**CRP (mg/l),** cut-off=55 AUC: 72.5 Sensitivity: 81.2 (54.4-96.0) Specificity: =59.2 (51.0-66.7) PPV 16.5 (6.99-25.9) NPV 96.9 (93.1-100) **WBC(x10^9/l),** cut-off=11.0: AUC: 53.6 Sensitivity: 62.5 (35.4-84.8) Specificity: 57.1 (49.1-64.9) PPV 12.6 (4.17-21.1) NPV 93.8 (88.5-99.1)	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.
Kim 2011[164]	CRP Cut-off > 10 mg/dl)	n=286 ED (patients with febrile neutropenia) Korea	Bacteraemia	AUC: (CRP) 0.655 (0.548-0.761) Sensitivity (CRP> 10 mg/dl) 57.6 Specificity 67.3 OR (multivariable analysis)	Retrospective design, small sample size, heterogeneity of the cancer population. Indirectness: diagnosis of bacteraemia, not sepsis.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				CRP >10 mg/dl 0.8 (0.34-2.1)	Risk of bias: very high.
Kim 2014A[165]	DNI (delta neutrophil index) CRP **Prediction of sepsis/septic shock** **CRP (cut-off 6.84 mg/l)** **DNI (cut-off >12.3%)** **Prediction of mortality** **CRP (cut-off 8.88 mg/l)** **DNI (cut-off >12.8%)**	N=128 Adults. Setting unclear (possible ED/hospital). Korea	Prediction of sepsis/septic shock Prediction of mortality	**Prediction of sepsis/septic shock** **CRP (cut-off 6.84 mg/l)** AUC: 81.9 Sensitivity: 87.5 Specificity: 63.5 PPV 50.9 NPV 92.2 **DNI (cut-off >12.3%)** AUC: 93.2 Sensitivity: 88.6 Specificity: 90.3 PPV 77.5 NPV 95.5 **Prediction of mortality** **CRP (cut-off 8.88 mg/l)** AUC: 72.3 Sensitivity: 85.7 Specificity: 66.7 PPV 29.3 NPV 96.7 **DNI (cut-off >12.8%)** AUC: 80.0 Sensitivity: 75.0	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				Specificity: 81.3 PPV 37.5 NPV 95.6	
Kim 2015B[167]	CRP/Albumin (cut-off >5.09 mg/dl) CRP alone (cut-off >67.5 mg/dl)	N=670 Adults. ED Korea	Prediction of 180-day mortality	**CRP/albumin ratio at admission (cut-off >5.09 mg/dl)** AUC: 0.6211 (0.5053-0.6166) Sensitivity: 61.08 (54.06-68.11) Specificity: 61.05 (56.67-65.44) PPV 37.92 (32.41-43.43) NPV 80.11 (76.00-84.22) **CRP alone** (cut-off >67.5 mg/dl) AUC: 0.5620 (0.5053-0.6166) Sensitivity: 84.86 (79.70-90.03) Specificity: 30.95 (26.79-35.10) PPV 32.37 (28.21-36.53) NPV 84.00 (78.56-89.43) CRP/albumin at admission HR=1.06 (1.03-1.10) (multivariable analysis) Lactate at admission HR=1.10 (1.05-1.14) (multivariable analysis)	Observational retrospective design Indirectness: none. Risk of bias: very high.
Kofoed 2007[171]	CRP **(cut off: 60**	n=151 hospital patients	Bacterial	**CRP (cut off: 60 mg/l)**	Observational design, small

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	mg/l) Neutrophil count **(cut off: 7.5x10^9 cells/l)**	with SIRS Denmark	infection	AUC: 81 (73-86) Sensitivity: 86 (78-93) Specificity: 60 (46-73) PPV 79 NPV 73 **Neutrophil count (cut off: 7.5x10^9 cells/l)** AUC: 74 (66-81) Sensitivity: 74 (64-82) Specificity: 64 (50-76) PPV 82 NPV 57	sample size. Indirectness: prediction of bacterial infection (not sepsis). Risk of bias: very high
Leth 2013[186]	Leukocyte count Leukocyte count≥4.0x10^9/l or ≤12.0x10^9/l compared to Leukocyte count<4.0x10^9/l or >12.0x10^9/l CRP Leukocyte count≥4.0x10^9/l or ≤12.0x10^9/l	n=828 patients who had blood cultures taken at admission Hospital Denmark	Bloodstream infection	Analysis adjusted for body temperature, leucocyte count, C-reactive protein. Leukocyte count≥4.0x10^9/l or ≤12.0x10^9/l compared to Leukocyte count<4.0x10^9/l or >12.0x10^9/l: OR=1.07 (0.63-1.80) CRP >8mg/l compared to CRP <8mg/l: OR=6.06 (0.82-44.6) Neutrophils≥2.0x10^9/l or ≤7.0x10^9/l compared to Neutrophils<2.0x10^9/l or >7.0x10^9/l:	Observational design, small sample size, single centre. Indirect: predicting bloodstream infection, in all patients with a blood sample taken, not those who were suspected of sepsis or SIRS. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	compared to Leukocyte count<4.0x10^9/l or >12.0x10^9/l Neutrophils Neutrophils≥2.0x10^9 /l or ≤7.0x10^9/l compared to Neutrophils<2.0x10^9 /l or >7.0x10^9/l			OR=0.88 (0.36-2.13)	
Luzzani 2003[195]	CRP	n=70 ICU (medico-surgical) Italy	Infection	AUC: 58.0 (48.8-67.2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Magrini 2014[198]	CRP WBC	n=513 patients presenting to the ED with signs/symptoms of local infection or sepsis Italy	Sepsis	**AUC (diagnosis of sepsis)**: WBC 53 CRP 72 CRP+WBC 71	Retrospective design, small sample size, single centre. Indirectness: none. Risk of bias: very high.
Mare 2015[206]	Immature neutrophils – band cells: **cut-off 8.5%** Total WBC counts, platelet numbers (**<150 x 10^9/l**	N=156 Adults with SIRS ICU UK	Detection of definite sepsis, possible sepsis, non-infectious	Results: **Definite sepsis** **% Band cells (cut-off 8.5%)** AUC 80: (72 – 88) Sensitivity: 84.3	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	(thrombocytopenia), CRP values **(cut-off >5 µg/l)**		(N-I) SIRS, no SIRS	Specificity: 71.4	
Meynaar 2011[215]	CRP (cut off: 50 mg/l)	n=761 patients in ICU The Netherlands	Sepsis	CRP (cut off: 50 mg/l) AUC: 75 (63-86) Sensitivity: 88 Specificity: 23 PPV 45 NPV 71	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Mokart 2005[216]	CRP (cut off: 93 mg/ml)	n=50 patients undergoing elective major surgical procedures. ICU France	Sepsis (septic complication during the first 5 postoperative days)	CRP (cut off: 93 mg/ml) AUC: 66.4 (49.3-83.5) Sensitivity: 63 Specificity: 72 PPV 53 NPV 79	Observational design, small sample size, single centre, postop patients. Indirectness: none. Risk of bias: very high.
Moreira 2010[217]	CRP (cut off: 11 ng/ml)	n=110 febrile patients Hospital (ED, ward or ICU) Spain	Sepsis	CRP (cut off: 11 ng/ml) AUC: 79 (64-89) Sensitivity: 87.1 (69.2-95.8) Specificity: 78.4 (61.3-89.6) PPV 77.1 NPV 87.9	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.
Muller 2010[221]	CRP (>20 mg/l, >50 mg/l, >100 mg/l,	n=925 patients with CAP	Bacteraemia	**CRP**	Observational design.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	>200 mg/l) Blood urea nitrogen (>11mM) WBC (WBC≤5 or ≥20 x10^9/l)	Hospital Switzerland		AUC: (CRP) 67 (59-74) Sensitivity: (CRP >20 mg/l) 96 Specificity: (CRP >20 mg/l) 9 Sensitivity: (CRP >50 mg/l) 89 Specificity: (CRP >50 mg/l) 18 Sensitivity: (CRP >100 mg/l) 81 Specificity: (CRP >100 mg/l) 33 Sensitivity: (CRP >200 mg/l) 61 Specificity: (CRP >200 mg/l) 64 **Blood urea nitrogen** AUC: (Blood urea nitrogen) 64 (57-71) Sensitivity: (Blood urea nitrogen >11mM) 32 Specificity: (Blood urea nitrogen >11mM) 78 **WBC** AUC: (WBC) 58 (50-65) Sensitivity: (WBC≤5 or ≥20 x10^9/l) 22 Sepc (WBC≤5 or ≥20 x10^9/l) 84	Indirectness: prediction of bacteraemia, not sepsis. Risk of bias: high.
Murray 2007[224]	WBC + neutrophil percentage	n=223 patients with burns ICU USA	Bloodstream infection	AUC: 62.4 (56.9-67.9)	Retrospective design, small sample size, single centre. Burn patients only Indirect: bloodstream infection prediction not sepsis. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
Nakamura 2009[230]	CRP (**>3.5 mg/dl)**	n=116 patients with fever suspected of having bacteraemia. Japan	Bacteraemia 21-day mortality	**CRP>3.5 mg/dl** **Bacteraemia** Sensitivity: 75.0 Specificity: 40.4 PPV 60.8 NPV 56.8 OR = 2.03 (0.93-446) **21 day mortality** Sensitivity: 10.7 Specificity: 92.7 PPV 72.7 NPV 36.2 OR = 1.51 (0.38-6.00)	Observational design, small sample size, single centre. Indirect: predicting clinical bacteraemia and 21 day mortality in those with suspected bacteraemia, not sepsis. Risk of bias: very high.
Oberhoffer 1999A[245]	CRP (**>198 mg/l)** Leucocytes (**>15000/µl)**	n=242 critically ill patients. ICU Germany	Mortality	**CRP >198 mg/l** Sensitivity: 66 Specificity: 80 PPV 51 NPV 83 AUC: 81.1 **Leucocytes >15000/µl** Sensitivity: 36 Specificity: 80	Observational design, small sample size, single centre. Indirectness: prediction of mortality. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				PPV 31 NPV 83 AUC: 62.0	
O'Connor 2004[246]	CRP	n=62 Patients with traumatic brain injury or subarachnoid haemorrhage ICU Australia	Mortality	CRP for prediction of mortality **AUC** Day 0: 31 Mean all days (0-7): 68 Peak CRP value: 63 **Sensitivity** Day 0: 17 Mean all days (0-7): 50 Peak CRP value: 33	Observational design, small sample size. Indirectness: select population (patients with neurotrauma or subarachnoid haemorrhage and 80% with either SIRS or sepsis) Risk of bias: very high.
Pancer 2011[253]	CRP (cut off: 52 mg/l)	n=168 Patients with SIRS USA	Sepsis	AUC: 77.7 (56.9-80.0) Sensitivity: 75 (63-84.7) Specificity: 54.9 (49.2-69.1)	Retrospective design, small sample size, single-centre Indirectness: none. Risk of bias: very high.
Patterson 2012[256]	Haemoglobin (≤100 g/l) WCC (White Cell Count) (<4 or >20 ($x10^9$/l))	n=200 ED diagnosis of non-hospital acquired pneumonia. Australia.	Bacteraemia	**OR – unvariable analysis** Haemoglobin ≤100 g/l: OR=0.71 (0.09-5.7) WCC <4 or >20 ($x10^9$/l): OR=0.61 (0.3-7.17)	Retrospective design, small sample size Indirectness: prediction of bacteraemia. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
Pettilä 2002[260]	CRP Antithrombin III WBC	n=61 patients with SIRS ICU Finland	Sepsis	AUC: for CRP Day 1: 38.6 (23.0-54.3) Day 2: 53.3 (39.6-71.0) AUC: for Antithrombin III Day 1: 59.8 (24.4-76.0) Day 2: 62.8 (45.0-80.5) AUC: for WBC Day 1: 55.1 (39.7-70.6) Day 2: 66.1 (52.2-79.9)	Observational design, small sample size Indirectness: none. Risk of bias: very high.
Pettila 2002A[261]	WBC CRP Platelets Thromboplastin time (P-TT)	n=108 consecutive critically ill patients with suspected sepsis. ICU. Finland	In-hospital mortality	**AUC** CRP: 60, SE=0.06 (Calculated 95%CI: 48-72) WBC: 53, SE=0.06 (Calculated 95%CI: 41-65) Platelets: 69, SE=0.05 (Calculated 95%CI: 59-79) P-TT: 63, SE=0.06 (Calculated 95%CI: 51-75)	Observational design, small sample size, single centre. Indirect: predicting in-hospital mortality in critically ill patients with suspected sepsis. Risk of bias: very high.
Povoa 1998[265]	CRP (cut-off 50 mg/l)	n=23; (n=306 patient-days) ICU Portugal	Sepsis	Sensitivity: 98.5 Specificity: 75	Observational design, small sample size. Indirectness: none. Risk of bias: very high
Povoa 2005A[266]	CRP cut-off 8.7mg/dL	n=260 critically ill patients	Infection	CRP (cut-off 8.7mg/dL) Sens: 93.4	Observational design, small sample size, single centre

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
		ICU Portugal		Spec: 86.1 PPV: 93.4 NPV: 86	Indirect: predicting infection in critically ill patients. Risk of bias: very high.
Povoa 2006[268]	CRP (maximum daily variation; increase >4.1 mg/dl) WBC (maximum daily variation)	n=181 ICU Portugal	Infection (ICU-acquired)	**CRP (maximum daily variation):** AUC: 86.0 (75.2-93.3) **CRP increase >4.1 mg/dl** Sensitivity 92.1 Specificity 71.4 **WBC (maximum daily variation):** AUC: 66.8 (54.1-77.9)	Observational design, small sample size. Indirectness: prediction of ICU-acquired infections Risk of bias: very high.
Shaaban 2010[289]	CRP (≥70mg/l) Eosinophil cell count (≤50 cells/mm^3)	n=68 patients admitted to the ICU USA	Infection	CRP Cutoff value ≥70mg/l Sensitivity: 94 Specificity: 84 PPV 83 NPV 94 Eosinophil cell count Cutoff value ≤50 cells/mm^3 Sensitivity: 81 Specificity: 65 PPV 66 NPV 80	Observational design, small sample, single centre. Indirect: predicting infection. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
Shapiro 2010[291]	Lactate (POC: point of care, and laboratory)	n=699 ED patients with suspected infections. USA	In-hospital mortality	AUC, POC lactate:72 AUC, laboratory lactate: 70	Observational design, small sample size, convenience sample, criteria for suspected infections not rigorously defined. Indirectness: prediction of in-hospital mortality in patients with suspected infections. Risk of bias: very high
Shorr 2008[298]	Protein C (%) Protein S (%) Anti-thrombin III (%) Photothrombin time (seconds) D-dimer (µg/ml	n=4065 patients with known or suspected infection (data from PROWESS and ENHANCE trials). Multiple countries	28-day mortality	Protein C (%) AUC: 58.9 OR=2.12 (1.55-2.89) Protein S (%) AUC: 57.7 OR=1.91 (1.38-2.64) Anti-thrombin III (%) AUC: 60.1 OR=2.32 (1.70-3.18) Photothrombin time (seconds) AUC: 57.4 OR=1.89 (1.38-2.58)	Post hoc analysis. Indirectness: none Risk of bias: high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				D-dimer (µg/ml) AUC: 55.1 OR=1.51 (1.11-2.05)	
Sierra 2004[299]	CRP (≥8 mg/dl)	n=200 Critically ill patients in ICU Spain	Sepsis	CRP ≥8 mg/dl Sensitivity: 94.3 Specificity: 87.3 PPV 90.4 NPV 92.3 AUC: 94 (89-98)	Observational design, small sample size, accurate times of SIRS onset and data collection were not recorded. Indirectness: about half of all SIRS patients had diagnosis of trauma. Risk of bias: very high.
Stucker 2005[303]	CRP (**≥3 mg/ml)**) WBC (**≤4000 or ≥12000 /mm^3)**	n=218 Elderly patients in hospital Switzerland	Infection	**CRP (≥3 mg/ml)** AUC: 63 Sensitivity: 92 Specificity: 36 PPV 30 NPV 94 OR (multivariable analysis) 3.4 (1.1-10.6) **WBC (≤4000 or ≥12000 /mm^3)** Sensitivity: 30 Specificity: 89 PPV 45	Observational design, small sample size, elderly population. Indirectness: prediction of infections. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				NPV 81 OR (univariable analysis) 3.5 (1.6-7.7)	
Svaldi 2001[305]	WBC (<10^9/l; >10^9/l)	n=73 immunocompromised patients Hospital Italy	Sepsis, including severe sepsis and septic shock	WBC (<10^9/l) Sensitivity: 63 Specificity: 60 WBC (>10^9/litre) Sensitivity: 94 Specificity: 60	Observational design, small sample size, single centre, immune-compromises population. Indirectness: none. Risk of bias: very high.
Tsalik 2012[313]	CRP (**40 mg/dl; 100 mg/dl; 200 mg/dl)**	n=336 ED patients with suspected sepsis USA	Infection Sepsis	**CRP to predict Septicaemia:** AUC: 67 **cut off 40 mg/dl** Sensitivity: 82.3 Specificity: 38.7 PPV 26.5 NPV 89.0 **cut off 100 mg/dl** Sensitivity: 60.1 Specificity: 65.6 PPV 32.0 NPV 85.9 **cut off 200 mg/dl** Sensitivity: 30.7 Specificity: 88.1	Retrospective analysis, small sample size. Indirectness: none Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				PPV 41.0 NPV 82.5	
Tsangaris 2009[314]	CRP **(cut off 100 mg/dl)** WBC **(cut off: 12000x10^9/µ)**	n=50 Critically ill patients in ICU Greece	Infection	**WBC (cut off: 12000x10^9/µ)** Sensitivity: 66 Specificity: 45 PPV 76 NPV 72 AUC: 68 (49-81) **CRP (cut off 100 mg/dl)** Sensitivity: 59 Specificity: 57 PPV 62 NPV 54 AUC: 65 (46-78)	Observational design, small sample size, single centre. Indirectness: prediction of infection. Risk of bias: very high.
Uusitalo-Sepplala 2011[316]	CRP	n=539 patients with suspected infection. ED. Finland	Sepsis Severe sepsis	Severe sepsis: Multivariable logistic regression included: continuous medication for cardiovascular disease, continuous systemic cortisone treatment (daily dose >10mg oral prednisolone), continuous acetylsalicylic acid medication, antimicrobial treatment 1 week previously, viral infection, inflammation focus documented, log_PCT, log_IL-6. Log_CRP: OR=1.02 (0.75-1.37)	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
				Sepsis: CRP OR=1.33 (1.10-1.61) (multivariable logistic regression, unclear variables) CRP AUC: 70 (65-74)	
Vassiliou 2014[318]	CRP	n=89 Critically ill patients in ICU Greece	Sepsis, including severe sepsis and septic shock	AUC: 53.9 (43.0-64.5)	Observational design, small sample size, does not take into account sepsis severity (sepsis, severe sepsis, septic shock). Indirectness: none. Risk of bias: very high
von Lilienfeld-Toal 2004[320]	CRP	n=31 Patients with haematological malignancies after chemotherapy. Germany	Bacteraemia	AUC: 64	Observational design, small sample size. Indirectness: prediction of bacteraemia. Risk of bias: very high.
Wyllie 2005[329]	CRP LC (lymphocyte count) NP (neutrophil count	n=6234 ED UK	Bacteraemia	**AUC** CRP+LC+NP 78 LC+NP 75 CRP 72 LC 70 NP 66	Retrospective design, single centre. Indirectness: prediction of bacteraemia. Risk of bias: very high.
Yonemori 2001[333]	CRP **Threshold 30.8 mg/l (to predict**	n=97 patients who received chemotherapy for	Documented infections Bacteraemia	**CRP to predict documented infections**: AUC: 61	Retrospective design, small sample size. Indirectness: prediction of

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of evidence
	documented infections) **Threshold 68.6 mg/l (to predict bacteraemia)**	haematological malignancies and developed neutropenia Japan	(positive blood culture)	**Threshold 30.8 mg/l:** Sensitivity: 71 Specificity: 50 PPV 27 NPV 88 **CRP to predict bacteraemia (positive blood culture)**: AUC: 55 **Threshold 68.6 mg/l**: Sensitivity: 46 Specificity: 73 PPV 20 NPV 91	bacteraemia and infections (not specific sepsis). Risk of bias: very high.

1
2

8.3.4 Summary of included studies, children and neonates

Table 81: Summary of included studies in the review, children and neonates

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Andreola 2007[11]	CRP WBC ANC	N=408 Children under 3 years with fever of unknown source. ED Italy	Serious bacterial infection	AUC CRP 85 (81-88) WBC 71 (66-75) ANC 74 (70-78) Optimal statistical cutoff for detecting serious bacterial infection CRP>32 ng/ml Sensitivity: 84.0 spec 75.5 WBC>10,470/mm^3 Sensitivity: 84.9 Specificity: 47.4 ANC>6450/mm^3 Sensitivity: 81.8	Observational design. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 62.3 Multivariable analysis- included body temperature, Yale observation score, CRP values, PCT values, WBC and ANC. CRP OR 1.02 (1.01-1.03) p<0.001 Sensitivity, specificity, positive and CRP>20ng/ml Sensitivity: 88.3 (80.0-94.0) Specificity: 60.8 (55.2-66.3) CRP>40ng/ml Sensitivity: 71.3 (61.0-80.1) Specificity: 81.2 (76.4-85.4) CRP>80ng/ml Sensitivity: 46.0 (36.4-57.4) Specificity: 94.6 (91.5-96.8)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC>15,000/mm^3 Sensitivity: 51.6 (41.0-62.1) Specificity: 75.5 (70.3-80.2) ANC>10,000/mm^3 Sensitivity: 38.3 (28.5-48.9) Specificity: 67.8 (62.4-73.0)	
Baez 2011[20]	CRP, NPV*, platelets, fibrinogen, glucose	N=103 Children undergoing major surgery ICU Spain	Post-operative sepsis	CRP +10 (24 hours) Sensitivity: 84 Specificity: 74 +10 (48 hours) Sensitivity: 90 Specificity: 70 +11 (24 hours) Sensitivity: 92 Specificity: 61	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				+11 (48 hours) Sensitivity: 87 Specificity: 89 +15 (48 hours) Sensitivity: 88 Specificity: 72 +20 (48 hours) Sensitivity: 88 Specificity: 76 **Platelets** 20% increase in 24 hours Sensitivity: 93 Specificity: 39 20% increase in 48 hours Sensitivity: 95 Specificity: 19	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Fibrinogen 20% increase in 24 hours Sensitivity: 71 Specificity: 63 20% increase in 48 hours Sensitivity: 76 Specificity: 64 **Glucose** 20% increase in 24 hours Sensitivity: 93 Specificity: 53 20% increase in 48 hours Sensitivity: 90 Specificity: 63	
Bilavsky 2009[29]	CRP, WBC count	N=892 Febrile infants aged ≤3 months	Diagnosis of serious bacterial infection	Variables significantly associated with serious bacterial infection in a multivariable logistic regression:	Observational design. Indirectness: none. Risk of bias: High.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		Hospital. Israel		WBC (k/µl) OR 1.1 (1.06-1.15) CRP (mg/dl) OR 1.21 (1.13-1.29) P value <0.001 WBC >15,000/µl Sensitivity: 48 (38.6-57.6) Specificity: 84.1 (81.4-86.5) WBC >20,000/µl Sensitivity: 21.6 (14.7-30.5) Specificity: 95.2 (93.5-96.5) WBC>15,000 or <5,000/µl Sensitivity: 50 (40.5-59.5) Specificity: 78.1 (75-80.8) WBC>20,000 or <400K/µl Sensitivity: 21.6 (14.7-30.5)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 92.1 (90-93.8) CRP>8 mg/dl Sensitivity: 23.5 (16.4-32.6) Specificity: 98.2 (97.1-98.9) CRP>4 mg/dl Sensitivity: 44.1 (34.9-53.8) Specificity: 92.2 (90.1-93.8) CRP>2 mg/dl Sensitivity: 55.9 (46.2-65.1) Specificity: 82.2 (79.3-84.7)	
Bonsu 2003[38]	Peripheral WBC count	N=3810 Febrile infants 0-89 days old. ED USA	Diagnosis of bacteraemia	WBC≥5,000s/mm^3 Sensitivity: 79 (63-90) Specificity: 5 (4-6) WBC≥10,000s/mm^3 Sensitivity: 61 (43-76) Specificity: 42 (40-44)	Retrospective design. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC≥15,000s/mm^3 Sensitivity: 45 (29-62) Specificity: 78 (76-79) WBC≥20,000s/mm^3 Sensitivity: 24 (11-40) Specificity: 93 (92-94) WBC≥25,000s/mm^3 Sensitivity: 13 (4-28) Specificity: 98 (97-99) WBC≥30,000s/mm^3 Sensitivity: 5 (1-2) Specificity: 99 (99-100) WBC≥15,000 or <5,000/ mm^3 Sensitivity: 66 (49-80) Specificity: 72 (71-74) WBC≥20,000 or <5,000/ mm^3 Sensitivity: 45 (29-62) Specificity: 88 (87-89)	
Bonsu 2004[39]	Peripheral WBC count ANC	N=5885 Infants 3-89 days old.	Diagnosis of bacteraemia	Peripheral WBC count (Cells/mm^3) Values are shown as % (N)	Retrospective design. Indirectness: none.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		ED USA	SBI (acute bacterial meningitis and bacteraemia)	Bacteraemia WBC <5000 PPV 1.2 (3/244) NPV 99.1 (5588/5641) Sensitivity: 6 (3) WBC ≥15,000 PPV 2.0 (27/1358) NPV 99.4 (4502/4527) Sensitivity: 52 (27) WBC ≥20,000 PPV 3.0 (12/406) NPV 99.3 (5421/5479) Sensitivity: 23 (12) WBC <5000 or ≥15,000 PPV 1.9 (30/1602) NPV 99.5 (4261/4283) Sensitivity: 58 (30) WBC <5000 or ≥20,000 PPV 2.3 (15/560) NPV 99.3 (5198/5235) Sensitivity: 29 (15)	Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				SBI (acute bacterial meningitis and bacteraemia) WBC <5000 PPV 4.5 (11/244) NPV 98.9 (5580/5641) Sensitivity: 15 (11) Spec: 4 (233) WBC ≥15,000 PPV 2.3 (31.1/1358) NPV 99.1 (4486/4527) Sensitivity: 43 (31) Spec: 77 (4486) WBC ≥20,000 PPV 3.2 (13/406) NPV 98.9 (5420/5479) Sensitivity: 18 (13) Spec: 93 (5420) WBC <5000 or ≥15,000 PPV 2.6 (42/1602) NPV 99. (4253/4283)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Sensitivity: 58 (42) Spec: 73 (4253) WBC <5000 or ≥20,000 PPV 3.7 (24/650) NPV 99.1 (5187/5235) Sensitivity: 33 (24) Spec: 89 (5187) Differentiating acute bacterial meningitis and isolated bacteraemia ANC AUC: 65 (51-78) WBC count AUC: 75 (63-88)	
Bressan 2010[44]	CRP, WBC, ANC	N=99 neonates with fever without source ED	SBI	Results (95% CI): Initial determination: fever <12 hours (all patients)	Observational design, small sample size. Indirectness: none.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		Italy		CRP (cut-off >20 mg/l) AUC: 0.78 (0.69-0.86) Sensitivity: 48 Specificity: 93.2 PPV 70.6 NPV 84.2 WBC (<5000/mm^3 or >15000/mm^3) AUC: 0.59 (0.49-0.69) Sensitivity: 28 Specificity: 87.7 PPV 43.75 NPV 78.1 ANC (cut-off >10000/mm^3) AUC: 0.77 (0.67-0.85) Sensitivity: 20 Specificity: 97.3 PPV 71.4 NPV 78	Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Initial determination: fever >12 hours (58 patients) CRP (cut-off >20 mg/l) AUC: 0.99 (0.92-1) Sensitivity: 100 Specificity: 96.2 PPV 71.4 NPV 78 WBC (<5000/mm^3 or >15000/mm^3) AUC: 0.79 (0.66-0.89) Sensitivity: 80 Specificity: 90.6 PPV 44.4 NPV 98 ANC (cut-off >10000/mm^3) AUC: 0.85 (0.73-0.93) Sensitivity: 80	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 100 PPV 100 NPV 98.2	
Davis 2015 [78]	CRP	N=60 Neonates with sepsis positive blood culture or sepsis negative blood culture UK. ICU	Detection of late-onset sepsis in VLBW infants	**Detection of late-onset sepsis** **CRP (cut-off >5.5 mg/dl)** AUC: 64.5 Sensitivity: 92 Specificity: 36	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
De 2014[85]	WBC, ANC	N=3893 Febrile 0-5 year olds. ED. Australia	Diagnosis of bacteraemia, SBI	Results (95% CI): WBC AUC, Any serious bacterial infection 65.3 (63.0-67.6) AUC, Bacteraemia 67.9 (59.8-75.9) Any serious bacterial infection WBC>15000/mm^3 Sensitivity: 47 (43-50) Specificity: 76 (74-77) WBC>20000/mm^3 Sensitivity: 26 (23-29)	Observational study. Indirectness: none. Risk of bias: High.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 90 (89-91) ANC AUC, Any SBI 63 (61.5-66.2) AUC, Bacteraemia 70.7 (63.1-78.2) Any serious bacterial infection **ANC** >10000/mm^3 Sensitivity: 41 (38-45) Specificity: 78 (76-79) **ANC** >15000/mm^3 Sensitivity: 21 (19-25) Specificity: 93 (92-94)	
Edgar 2010[91]	CRP	N=149 infants undergoing sepsis work-up NICU UK	Diagnosis of neonatal infection	CRP (cut-off 0.4 mg/l) AUC: 73 Sensitivity: 69.4 Specificity: 70.4 PPV 59.5 NPV 78.6	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Enguix 2001[95]	Neonates: CRP (cut-off 6.1 mg/l) Children: CRP (cut-off 22.1 mg/l)	N=46 neonates (3-30 days) N=70 children (2-12) Admitted to NICU or PICU	Diagnosis of bacterial sepsis	Neonates: CRP>6.1 mg/l AUC: 95 (88-1) Sensitivity: 95.8 Specificity: 83.6 PPV 80.2 NPV 96.7 Children: CRP>22.1 mg/l AUC: 93 (89-97) Sensitivity: 88.6 Specificity: 81.1 PPV 80.2 NPV 89.2	Observational design, possible selection bias (convenience sample), small sample size. Indirectness: none. Risk of bias: very high.
Fernandez Lopez 2003[98]	CRP (cut-off 27.5 mg/l) Total leukocytes (cut-off 16,500 /mm^3) Total neutrophils (cut-off >9576 /mm^3)	N=445 Children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	Diagnosis of sepsis	CRP>27.5 mg/l AUC: 81 (SD 0.02) Sensitivity: 78 Specificity: 75 PPV 88.5 NPV 54.9 Total leucocytes>16,500 /mm^3	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				AUC: 65 (SD 0.03) Sensitivity: 50.0 Specificity: 79.2 PPV 81.8 NPV 45.6 Total neutrophils>9576 /mm^3 AUC: 69 (SD 0.03) Sensitivity: 49.2 Specificity: 83.3 PPV 86 NPV 44	
Fischer 2000[102]	Total WBC count Total neutrophils CRP	N=154 Critically ill infants (median age 33.4 weeks) admitted to ICU. Switzerland	Culture-proven bloodstream infection	Total WBC count AUC: 61 Sensitivity: 37 Specificity: 86 Total neutrophils AUC: 93 Sensitivity: 86 Specificity: 85	Observational design, small sample size. Indirectness: high (66/143 infants were premature). Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				CRP AUC: 78 Sensitivity: 64 Specificity: 85	
Fouzas 2010[105]	CRP, WBC, Platelets	N=408 Infants aged 29 to 89 days admitted to the tertiary care paediatric unit. ED Greece	Diagnosis of SBI	Platelets ≥400,000/mm^3 Sensitivity: 85.4 Specificity: 45.9 PPV 34.8 NPV 90.3 Platelets ≥450,000/mm^3 Sensitivity: 82.5 Specificity: 70.5 PPV 48.6 NPV 92.3 Platelets ≥500,000/mm^3 Sensitivity: 52.4 Specificity: 77.7 PPV 44.3	Retrospective design, possible selection bias Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				NPV 82.9 Platelets ≥600,000/mm^3 Sensitivity: 22.3 Specificity: 90.2 PPV 43.4 NPV 77.5 AUC: 74 (70-79) WBC count>15,000/mm^3 Sensitivity: 52.4 Specificity: 78.7 PPV 45.4 NPV 83.0 AUC: 72 (67-76) CRP ≥2 mg/dl Sensitivity: 51.5 Specificity: 86.6 PPV 56.4 NPV 84.1	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				AUC: 75 (71-80)	
Freyne 2013[107]	CRP WBC	N=46 Infants aged 6 to 36 months with confirmed axillary temperature of >38.1C ED Ireland	Hospital diagnosis of evolving illness and confirmed bacterial sepsis	CRP >20 mg/l Sensitivity: 83.5 Specificity: 84.3 PPV 27.7 NPV 96.4 WCC <5000/mm^3 or >15000/mm^3 Sensitivity: 83.3 Specificity: 56.6 PPV 27.8 NPV 94.4	Observational design, small sample size Indirectness: none. Risk of bias: very high.
Galetto-Lacour 2003[112]	CRP, leucocytes, band	N=99 Children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination. ED Switzerland	diagnosis of SBI	CRP>40 mg/l Sensitivity: 79 (60-92) Specificity: 79 (67-88) PPV 90 NPV 61 Leucocytes ≥15 G/l Sensitivity: 52 (33-71) Specificity: 74 (62-84)	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				PPV 78 NPV 45 Band ≥1.5 G/l Sensitivity: 11 (2-28) Specificity: 93 (84-98) PPV 72 NPV 38 Leucocytes ≥15 G/l or Band ≥1.5 G/l Sensitivity: 55 (36-74) Specificity: 72 (61-83) PPV 80 NPV 46	
Gendrel 1999[121]	CRP	N= 360 Children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified. Hospital France	Hospital diagnosis of invasive bacterial infection, localised bacterial infection, viral infection.	CRP<20 mg/l 5/46 bacterial septicaemia/meningitis (group 1) 15/78 bacterial localised infections (group 2) 111/236 viral infections (group 3)	Observational design, small sample size, possible selection bias Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Discrimination between groups (1+2) and 3 CRP>10 mg/l Sensitivity: 98 Specificity: 50 PPV 50 NPV 98 CRP>20 mg/l Sensitivity: 83 Specificity: 71 PPV 60 NPV 89 CRP>40 mg/l Sensitivity: 73 Specificity: 88 PPV 76 NPV 86 Discrimination between groups 1 and (2+3)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				CRP>10 mg/l Sensitivity: 98 Specificity: 38 PPV 19 NPV 99.2 CRP>20 mg/l Sensitivity: 89 Specificity: 58 PPV 24 NPV 97.2 CRP>40 mg/l Sensitivity: 87 Specificity: 75 PPV 34 NPV 97.5	
Gomez 2010[127]	CRP	N=1018 Infants <3 months with fever without source.	SBI	Results (95% CI): CRP >70 mg/l AUC: 84.7 (75.4-94.0) Sensitivity: 69.6	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		ED Spain		Specificity: 93.8 PPV – Not reported NPV 99.3 CRP > 20 mg/l Sensitivity: 73.9 Specificity: 74.8 PPV – Not reported NPV – Not reported	
Gomez 2012[126]	CRP ANC, WBC	N=1112 Infants <3 months with fever without source. ED Spain	Diagnosis of serious bacterial infection or invasive bacterial infection)	CRP≥20 mg/l, WBC count ≥15,000/mm^3 and ANC ≥10,000/mm^3 were not found to be independent risk factors for IBI on multivariable analysis (data not shown). CRP AUC: serious bacterial infection 77.6 (74.1-81.1) AUC: invasive bacterial infection)74.7 (62.9-86.5)	Retrospective design. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				ANC AUC: serious bacterial infection 71.1 (67.4-74.8) AUC : invasive bacterial infection)I 62.9 (50.6-75.2) WBC AUC : serious bacterial infection 69.2 (65.5-72.9) AUC : invasive bacterial infection) 58.3 (46.0-70.6)	
Hatherill 1999[134]	CRP (cut-off >20 mg/l) CRP (cut-off >30 mg/l) CRP (cut-off >40 mg/l) CRP (cut-off >50 mg/l) WBC	N=175 Children admitted to PICU UK	Diagnosis of septic shock	CRP AUC: 83 (76-90) WBC AUC: 51 (41-60) CRP >20 mg/l Sensitivity: 91 Specificity: 62 PPV 66 NPV 89	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				CRP >30 mg/l Sensitivity: 81 Specificity: 70 PPV 69 NPV 82 CRP >40 mg/l Sensitivity: 79 Specificity: 77 PPV 74 NPV 82 CRP >50 mg/l Sensitivity: 76 Specificity: 80 PPV 76 NPV 80	
Hornik 2012[143]	ANC, I/T, Platelets, WBC	N=37,826 Neonates >72 hours of life admitted to NICU	Neonate diagnosis of bacterial sepsis	WBC<1000/mm^3 Sensitivity: 1.0 Specificity: >99.99	Retrospective design, possible selection bias (convenience sample). Indirectness: none.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC<5000/mm^3 Sensitivity: 7.0 Specificity: 96.1 WBC>20,000/mm^3 Sensitivity: 22.6 Specificity: 79.8 WBC>50,000/mm^3 Sensitivity: 1.0 Specificity: 99.1 ANC<1000/mm^3 Sensitivity: 2.4 Specificity: 98.0	Risk of bias: very high.
Hsiao 2006A[145]	WBC CRP ANC	N=429 Febrile infants ED USA	SBI	CRP, AUC: 78 WBC, AUC: 72 ANC, AUC: 70	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Isaacman 2002[146]	WBC (cut-off 17.1x10^3/l) CRP (cut-off 4.4mg/dL) ANC (cut-off 10.6x10^3/l)	N=256 Children aged between 3 and 36 months with fever. ED USA	Diagnosis of occult bacterial infection	WBC (cut-off 17.1x10^3/l) AUC: 69 (61-77) Sensitivity: 69 (51-89) Specificity: 80 (75-85) PPV 31 (20-43) NPV 95 (92-98) CRP (cut-off 4.4mg/dl) AUC: 71 (62-79) Sensitivity: 63 (43-82) Specificity: 81 (76-87) PPV 30 (18-43) NPV 94 (91-98) ANC (cut-off 10.6x10^3/l) AUC: 73 (65-81) Sensitivity: 69 (51-87) Specificity: 79 (73-84) PPV 32 (20-44) NPV 95 (91-98)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC (cut-off 17.1x10^3/l) or CRP≥3.1 AUC: 63 (53-71) Sensitivity: 76 (59-92) Specificity: 58 (51-64) PPV 19 (12-27) NPV 95 (91-99) ANC (cut-off 10.5x10^3/l) or CRP≥3.6 AUC: 66 (57-74) Sensitivity: 79 (64-95) Specificity: 50 (43-56) PPV 17 (10-23) NPV 95 (91-99) Multiple logistic regression model 1 (included age, temperature, length of illness CRP and ANC) Each cell increase of 1000x10^3/l in the ANC resulted in a risk increase of 1.15 for occult bacterial infection (OR 1.15, 95%CI1.07-1.24) after adjusting for CRP and length of	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				illness. Each 1 mg/dl increase in CRP resulted in a risk increase of 1.12 for occult bacterial infection (OR 1.12, 95%CI1.04-1.20, p0.003)after adjusting for ANC and length of illness. Multiple logistic regression model 2 (included age, temperature, length of illness CRP and WBC) Each cell increase of 1000x10^3 in the ANC resulted in a risk increase of 1.15 for occult bacterial infection (OR 1.15, 95%CI1.07-1.23, p<0.001) after adjusting for CRP and length of illness. Each 1 mg/dl increase in CRP resulted in a risk increase of 1.12 for occult bacterial infection (OR 1.12, 95%CI1.04-1.21, p0.003) after adjusting for WBC and length of illness.	
Jacquot	CRP (cut-off 0.6 mg/l)	N=73	Neonate late onset	CRP	Observational design, small sample

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
2009[147]		Neonates >72 hours of life admitted to NICU France	sepsis	AUC: 77 Sensitivity: 54 (47-69) Specificity: 86 (78-94) PPV 74 (64-84) NPV 75 (65-85)	size. Indirectness: none. Risk of bias: very high.
Kim 2015A[166]	Platelets (cut-off 68.0/µl)	N=2336 Very low birth weight infants Possibly ED. Korea	Diagnosis of sepsis	AUC: 69.2 Sensitivity: 59.3 Specificity: 76.5 PPV 66.7 NPV 70.3	Observational design, retrospective Indirectness: none. Risk of bias: very high.
Lacour 2001[178]	CRP (cut-off 40 mg/l) Leucocytes (cut off >15,000/mm^3)	N=124 Children aged 7 days to 36 months with fever without localising signs. ED Switzerland	Hospital diagnosis of serious bacterial infection	CRP (cut-off 40 mg/l) Sensitivity: 89 (72-98) Specificity: 75 (65-83) PPV 51 NPV 96 AUC: 88 Leucocytes (>15,000/mm^3) Sensitivity: 68 (48-84) Specificity: 77 (67-85)	Small sample size, possible selection bias. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				PPV 46 NPV 89	
Mahajan 2014[200]	ANC WBC	N=226 Well-appearing febrile children without obvious infection, ≥ 36 months old with documented fever (defined as rectal temperature measured in the ED or at home of ≥38°C if ≤3 months of age and ≥39°C if >3 months of age)	Diagnosis of serious bacterial infection	ANC (cut-off >10 x 10^9 cells/l) Sensitivity: 46.7 (28.8–65.4) Specificity: 88.1 (82.5–92.2) PPV 0.38 (0.23–0.55) NPV 0.91 (0.86–0.95) ANC (cut-off >13 x 10^9 cells/l) Sensitivity: 30.0 (15.4–49.6) Specificity: 94.3 (89.8–97.0) PPV 0.45 (0.24–0.68) NPV 0.90 (0.84–0.93) WBC (cut-off >15 x 10^9 cells/l) Sensitivity: 56.7 (37.7–74.0) Specificity: 76.3 (69.6–82.0) PPV 0.27 (0.17–0.40) NPV 0.92 (0.86–0.95)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC (cut-off >19 x 10^9 cells/l) Sensitivity: 46.7 (28.8–65.4) Specificity: 90.2 (84.9–93.8) PPV 0.15 (0.11–0.20) NPV 0.85 (0.80–0.89)	
Makhoul 2006[203]	CRP Immature neutrophil to total neutrophil (I/T) ratio	N=111 Neonates >72 hours of life admitted to NICU with clinically suspected late onset sepsis (LOS) Israel	Neonate late onset sepsis	Univariable analysis for variables associated with proven sepsis CRP >1.0 mg/dl: RR 2.85 (1.13-6.15) I/T >2: RR 5.13 (2.54-10.31) WBC <5000/mm^3, WBC >20 2000/mm^3, platelet count <150 000/mm^3: No association Multivariable analysis for variables associated with proven sepsis I/T >2: RR 4.89 (2.48-9.66)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.
Maniaci 2008[204]	WBC, ANC	N=234 Infants aged ≤90 days with a temperature ≥38.0˚C ED.	Hospital diagnosis of serious bacterial infection	ROC curve for definite serious bacterial infection versus no serious bacterial infection WBC count, AUC: 66 ANC, AUC: 74	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		USA		ROC curve for definite and possible serious bacterial infection versus no serious bacterial infection WBC count, AUC: 61 ANC, AUC: 66	
Manzano 2011[205]	CRP WBC ANC	N=328 Children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection. ED Canada	SBI	AUC ANC 80 (75-84) WBC 81 (76-85) CRP 88 (84-91) Diagnostic accuracy for detecting serious bacterial infection in fever without source CRP>17.7 mg/l Sensitivity: 94.4 (85.5-98.1) Specificity: 68.6 (66.9-69.3) PPV 37.2 (33.7-38.7) NPV 98.4 (95.9-99.5) WBC>14100x 10^6/l Sensitivity: 81.5 (70.3-89.3)	Observational design, small sample size. Indirectness: none. Risk of bias: low.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 70.8 (68.6-72.4) PPV 35.5 (30.6-38.9) NPV 95.1 (92.1-97.2) ANC>5200x 10^6/l Sensitivity: 87.0 (76.5-93.5) Specificity: 59.9 (57.8-61.1) PPV 29.9 (26.3-32.1) NPV 95.9 (92.1-97.2) Diagnostic accuracy for detecting serious bacterial infection when urinalysis was normal CRP>17.7 mg/l Sensitivity: 87.5 (53.6-97.8) Specificity: 69.7 (68.6-70.0) PPV) 8.3 (5.1-9.3) NPV 99.4 (97.9-99.9) WBC>14100x 10^6/l Sensitivity: 75.0 (41.5-92.8) Spec) 71.7 (70.6-72.2)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				PPV 7.7 (4.3-9.5) NPV 98.9 (97.5-99.7) ANC>5200x 10^6/l Sensitivity: 75.0 (41.4-92.8) Specificity: 59.8 (41.5-92.8) PPV 5.6 (3.1-6.9) NPV 98.7 (97.0-99.6)	
Nademi 2001[228]	WBC	N=141 Children with fever ED UK	Serious infection	WBC (cut-off >15000) Sensitivity: 10 Specificity: 95 PPV 44	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				NPV 72 WBC (cut-off >20000) Sensitivity: 29 Specificity: 93 PPV 63 NPV 76	
Nahum 2012[229]	CRP	N=121 Children aged 1 day-18 years after cardiac surgery with bypass	Differential diagnosis of early bacterial infection	CRP velocity (0 mg/dl per day) Sensitivity: 86.7 Specificity: 42.9 PPV 52 NPV 81.8 CRP velocity (1 mg/dl per day) Sensitivity: 80 Specificity: 73.8 PPV 68.6 NPV 83.8 CRP velocity (2 mg/dl per day) Sensitivity: 60	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 81 PPV 69.2 NPV 73.9 CRP velocity (3 mg/dl per day) Sensitivity: 50 Specificity: 90.5 PPV 78.9 NPV 71.7 CRP velocity (4 mg/dl per day) Sensitivity: 40 Specificity: 95.2 PPV 85.7 NPV 69 CRP velocity (5 mg/dl per day) Sensitivity: 26.7 Specificity: 97.6 PPV 88.9 NPV 65.1	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
Nosrati 2014[241]	CRP (cut off >2,4,6,10,20,30,40 mg/l) ANC Leucocyte count	N=401 Febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C in tertiary care. Israel	Hospital diagnosis of SBI	CRP (multivariable analysis) OR 1.042 (1.028-1.056), p<0.001 CRP>2 mg/l Sensitivity: 90 Specificity: 30 PPV 15 NPV 96 CRP>4 mg/l Sensitivity: 88 Specificity: 38 PPV 16 NPV 96 CRP>6 mg/l Sensitivity: 86 Specificity: 47 PPV 18 NPV 96 CRP>10 mg/l Sensitivity: 83 Specificity: 61	Retrospective design, possible selection bias Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				PPV 22 NPV 96 CRP>20 mg/l Sensitivity: 79 Specificity: 84 PPV 40 NPV 97 CRP>30 mg/l Sensitivity: 67 Specificity: 92 PPV 53 NPV 95 CRP>40 mg/l Sensitivity: 56 Specificity: 94 PPV 56 NPV 94 AUC: 81.9 (73.1-90.6)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				ANC AUC: 58.8 (48.9-68.6) Leukocyte count AUC: 57.4 (47.7-67.1)	
Olaciregui 2009[249]	CRP Leucocyte count	N=347 Neonates aged 4-90 days seen in the ED for fever. Spain	Diagnosis of serious bacterial infection, sepsis	Serious bacterial infection Leucocyte count AUC: 67 (63-73) Leucocyte count >10,000/µl Sensitivity: 73 (4-82) Specificity: 58 (52-64) PPV 35 (28-42) NPV 87 (82-92) Leucocyte count >15,000/µl Sensitivity: 38 (28-48) Specificity: 84 (80-88) PPV 43 (32-54) NPV 81 (77-85) CRP≥20 mg/l	Retrospective design, possible selection bias. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				AUC: 79 (75-84) Sensitivity: 64 (54-74) Specificity: 84 (80-88) PPV 55 (45-65) NPV 88 (84-92) CRP≥30 mg/l Sensitivity: 59 (48-70) Specificity: 89 (85-93) PPV 63 (52-74) NPV 87 (83-91) Sepsis/ bacteraemia CRP>30 mg/l Sensitivity: 56 (32-80) Specificity: 74 (69-79) PPV 9.6 (4-16) NPV 97 (95-99) Serious bacterial infection Multivariable analysis was	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				performed with the variables that were significant on univariable analysis (leucocytes, neutrophils, CRP and PCT): WCC (10^3/µl) OR 1.1 (1.03-1.16) CRP (≥30 mg/l) OR 6.6 (3.3-13.2)	
Pavcnick 2004[257]	CRP (cut-off 23 mg/l)	N=60 Neonates and children with SIRS and suspected infection NICU Slovenia	Sepsis	CRP AUC: 84 (57-89) Sensitivity: 70 Specificity: 89 PPV 53 NPV 94	Observational design, possible selection bias (possible convenience sample), small study size. Indirectness: none. Risk of bias: very high.
Pratt 2007[269]	ANC CRP WBC	N=128 Children with documented fever 39°C and found to have no localizing source of fever ED	SBI	CRP (≤12 hours, cut-off 3 mg/dl) Sensitivity: 67 Specificity: 74 CRP (≤12 hours, cut-off 5 mg/dl) Sensitivity: 50	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		USA		Specificity: 92 CRP (≤12 hours, cut-off 7 mg/dl) Sensitivity: 33 Specificity: 97 WBC (≤12 hours, cut-off 10000/mm^3) Sensitivity: 50 Specificity: 33 WBC (≤12 hours, cut-off 15000/mm^3) Sensitivity: 17 Specificity: 67 WBC (≤12 hours, cut-off 17500/mm^3) Sensitivity: 17 Specificity: 74	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				ANC (≤12 hours, cut-off 10000/mm^3) Sensitivity: 17 Specificity: 77 ANC (≤12 hours, cut-off 11000/mm^3) Sensitivity: 17 Specificity: 82 ANC (≤12 hours, cut-off 12000/mm^3) Sensitivity: 17 Specificity: 85 CRP (>12 hours, cut-off 3 mg/dl) Sensitivity: 100 Specificity: 63 CRP (>12 hours, cut-off 5 mg/dl) Sensitivity: 82	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 79 CRP (>12 hours, cut-off 7 mg/dl) Sensitivity: 73 Specificity: 81 WBC (>12 hours, cut-off 10000/mm^3) Sensitivity: 100 Specificity: 47 WBC (>12 hours, cut-off 15000/mm^3) Sensitivity: 82 Specificity: 69 WBC (>12 hours, cut-off 17500/mm^3) Sensitivity: 73 Specificity: 79	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				ANC (>12 hours, cut-off 10000/mm^3) Sensitivity: 64 Specificity: 81 ANC (>12 hours, cut-off 11000/mm^3) Sensitivity: 55 Specificity: 81 ANC (>12 hours, cut-off 12000/mm^3) Sensitivity: 55 Specificity: 84 CRP (≤12 hours) AUC: 68 (39-97) CRP (>12 hours) AUC: 92 (85-99)	

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC (≤12 hours) AUC: 37 (11-64) WBC (>12 hours) AUC: 85 (75-94) ANC (≤12 hours) AUC: 42 (15-69) ANC (>12 hours) AUC: 83 (72-94)	
Pulliam 2001[271]	CRP ANC WBC	N=77 Children aged 1-36 months, temperature ≥39˚C; clinically undetectable source of fever ED USA	Serious bacterial infection	CRP AUC: 90.5 (80.8-100.2) ANC AUC: 80.5 (70.5-90.5) WBC AUC: 76.1 (62.8-89.5)	Observational design, small sample size, convenience sample. Indirectness: none. Risk of bias: very high.
Rey 2007[274]	Leucocyte count CRP	N= 94 Children aged 62 (1-	Sepsis	Leucocyte count AUC: 53.2 (46.2-60.2)	Observational design, small sample size.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		203) months admitted to PICU Spain		CRP AUC: 75.0 (69.9-80.2) CRP>5.65 mg/dl Sensitivity: 72 Specificity: 66 CRP >6.55 mg/dl Sensitivity: 64 Specificity: 73	Indirectness: none. Risk of bias: very high.
Rudinsky 2009[276]	WBC	N=985 Infants and children under 3 months of age, home or ED temperature of ≥100.4˚F or if they were between 3 and 24 months of age and had a home or ED temperature ≥102.3˚F ED USA	SBI	WBC<5 Sensitivity: 0.05 (0.02-0.11) Specificity: 0.92 (0.90-0.94) WBC <5 or >15 Sensitivity: 0.47 (0.37-0.57) Specificity: 0.66 (0.63-0.70) WBC >10 Sensitivity: 0.72 (0.62-0.80) Specificity: 0.47 (0.43-0.51)	Retrospective design Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				WBC >15 Sensitivity: 0.42 (0.33-0.52) Specificity: 0.74 (0.71-0.78) WBC >20 Sensitivity: 0.16 (0.10-0.25) Specificity: 0.93 (0.91-0.95) WBC >25 Sensitivity: 0.02 (0.00-0.07) Specificity: 0.98 (0.96-0.99)	
Segal 2014[285]	CRP	N=373 Neonates or children with a rectal or oral temperature of ≥38˚C documented in the ED. ED	Bacterial infection	≤ 12 hours (cut off 2.1 mg/dl) AUC: 76 (63-88) Sensitivity: 72 (52-87) Specificity: 77 (64-86) > 12-24 hours (cut off 6 mg/dl)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
		Israel		AUC: 81 (69-92) Sensitivity: 68 (48-83) Specificity: 83 (69-92) > 24-48 hours (cut off 10.7 mg/dl) AUC: 87 (77-96) Sensitivity: 68 (47-84) Specificity: 90 (73-96) > 48 hours (cut off 12.6 mg/dl) AUC: 90 (84-97) Sensitivity: 80 (64-90) Specificity: 94 (85-97.5)	
Shaoul 2008[290]	ANC (cut-off >10,000 mm^3/l) CRP (cut-off >85mg/l) WBC (cut-off >15,000 mm^3/l)	N=425 Neonates or children attending paediatric ER with a fever >38°C NICU Israel	Positive blood culture	CRP >85mg/L Sensitivity: 70 Specificity: 67.6 PPV 60.3 CRP and ANC >10,000 or WBC >15,000	Retrospective design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Sensitivity: 84 Specificity: 27 PPV 48.8 CRP and ANC >10,000 and WBC >15,000 Sensitivity: 36 Specificity: 84.5 PPV 62.1	
Sherwin 2008[296]	ANC (cut off≥10 x 10^9/l) CRP (cut-off ≥ 18 pg/ml) Platelets (cut-off ≥ 100 x 10^9/l) WBC (cut-off ≥ 20 x 10^9/l)	N=164 Neonates (n=52) with late onset sepsis suspected sepsis and commenced on antibiotics NICU New Zealand	Neonate late onset sepsis	ANC AUC: 0.63 (0.46-0.81) Sensitivity: 33 (20-47) Specificity: 93 (86-100) PPV 75 (63-87) NPV 69 (56-82) CRP AUC: 0.72 (0.55-0.90) Sensitivity: 41 (25-57) Specificity: 94 (87-100) PPV 88 (77-98)	Observational design, possible selection bias (possible convenience sample). Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				NPV 63 (45-79) Platelets AUC: 0.70 (0.55-0.86) Sensitivity: 18 (7-29) Specificity: 93 (86-100) PPV 60 (46-74) NPV 66 (52-80) WBC AUC: 0.50 (0.33-0.68) Sensitivity: 22 (10-34) Specificity: 75 (62-88) PPV 36 (22-50) NPV 60 (46-74)	
Simon 2008[301]	CRP (threshold 20, 40 and 60 mg/l)	N=64 Aged 0-18 years with systemic inflammatory response syndrome (SIRS). PICU Canada	Bacterial/ non-bacterial SIRS	CRP AUC: 65 CRP threshold 20 mg/l Sensitivity: 95 Specificity: 24 PPV 44	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				NPV 90 CRP threshold 40 mg/l Sensitivity: 95 Specificity: 42 PPV 51 NPV 94 CRP threshold 60 mg/l Sensitivity: 59 Specificity: 55 PPV 46 NPV 68	
Thayyil 2005[308]	ANC, WBC, CRP	n=72 Children aged 1 to 36 months with fever >39˚C without localising signs. Hospital (ED paediatric units) UK	SBI	ANC AUC: 52 (36-71) WBC AUC: 56 (38-74) WBC >15x10^9/l Sensitivity: 50	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				Specificity: 53.1 NPV 89.5 PPV 11.8 CRP AUC: 0.66 (0.42-0.91) CRP >50 mg/l Sensitivity: 75 Specificity: 68.7 NPV95.6 PPV 23	
Trautner 2006[311]	WBC count, <15 and ≥15 x103 cells per mm3 ANC, <10 and ≥10 x103 cells per mm3	n=103 Children <18 years of age presenting to paediatric ED with rectal temperature ≥106˚F ED USA	SBI	WBC x10^3 cells per mm^3 <15 Frequency, n (%) 11 (55) ≥15 Frequency, n (%) 9 (45) OR 0.78 (0.29-2.08) ANC, x10^3 cells per mm^3	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Study	Test(s) and cut-off(s) for sensitivity, specificity, positive predictive value, negative predictive value	Population	Target condition	Outcomes (statistical measures) Sensitivity, % (range/median/95%CI) Specificity, % (range/median/95%CI) Positive predictive value (PPV), % Negative predicitive value (NPV), % ROC curve or area under the curve (range) Odds Ratio (95%CI)	Quality of the evidence
				<10 Frequency, n (%) 9 (45) ≥10 Frequency, n (%) 11 (55) OR 1.11 (0.41-2.96)	
Zant 2014[337]	CRP(cut-off ≥93 mg/l)	N=22 (25 liver transplantations) Paediatric patients who underwent liver transplantation Children's Hospital Germany	Detection of sepsis	AUC: 89 Sensitivity: 82 Specificity: 91 PPV 56 NPV 99	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

1
2

8.3.4.1 Clinical evidence summary tables, adults, children and neonates

Table 82: Clinical evidence summary: CRP, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP ≥125 mg/litre for predicting bloodstream infections in patients with suspected systemic infections.	1[1]	Sens 85 (55-98) Spec 81 (71-89) PPV 42 (23-63) NPV 97 (89-100)	NA	VERY LOW
CRP ≥125 mg/litre for predicting bloodstream infections in patients with suspected systemic infections.	1[1]	AUC 85 (63-96)	No serious imprecision	VERY LOW
CRP >10mg/litre for predicting bacteraemia in ED patients	1[2]	Sens 94 (86-98) Spec 18 (16-20) PPV 7 (6-9) NPV 98 (94-99)	NA	VERY LOW
CRP for predicting sepsis in postoperative patients admitted to ICU	1[3]	AUC 51.3 (41.2-61.4)	Serious	VERY LOW
CRP for predicting bacteraemia in hospitalised patients from whom blood cultures were drawn for sepsis	1[27]	AUC 0.53 (SE: 0.06)	NA	VERY LOW
CRP for predicting survival after infection in ICU patients with a diagnosis of infection	1[30]	AUC 40.7	NA	VERY LOW
CRP>128 mg/l for predicting sepsis/ severe sepsis in medico-surgical patients in ICU	1[54]	Sens 67 Spec 82 PPV 51 NPV 90	NA	VERY LOW
CRP for predicting sepsis/ severe sepsis in medico-surgical patients in ICU	1[54]	AUC 75.5 (64.0-86.0)	No serious imprecision	VERY LOW
CRP>128 mg/l for predicting sepsis,	1[52]	Sens 61	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
severe sepsis, and septic shock in medico-surgical patients in ICU		Spec 87 PPV 66 NPV 87		
CRP for predicting sepsis, severe sepsis, and septic shock in medico-surgical patients in ICU	1[52]	AUC 74 (67-81)	No serious imprecision	VERY LOW
CRP for predicting sepsis trauma patients	1[53]	AUC 48.9	NA	VERY LOW
CRP>100 mg/ml for predicting the infectious origin of any shock	1[69]	Sens 93±10 Spec 40±18	NA	VERY LOW
CRP for predicting sepsis in patients with shock	1[69]	AUC 85.4 (66.9-95.7)	No serious imprecision	VERY LOW
CRP for predicting 28-day mortality in post-op patients with severe sepsis	1[77]	AUC 61	NA	VERY LOW
CRP for predicting bacterial infection in ED patients with fever	1[82]	OR = 1.008 (1.001-1.014) (multivariable analysis)	No serious imprecision	VERY LOW
CRP>9 mg/l for predicting bacterial infection in ED patients with fever	1[82]	Sens. 99 Sepc. 15 PPV 71 NPV 83	NA	VERY LOW
CRP for predicting bacterial infection in ED patients with fever	1[82]	AUC 76 (67-85)	No serious imprecision	VERY LOW
CRP for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	AUC 84 (75-92)	No serious imprecision	VERY LOW
CRP>38 mg/l for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	Sens 79.7 Spec 57.9 PPV 88.1	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV 42.3		
CRP>50 mg/l for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	Sens 71.6 Spec 63.2 PPV 88.3 NPV 36.4	NA	VERY LOW
CRP>100 mg/l for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	Sens 63.5 Spec 94.7 PPV 97.9 NPV 40.0	NA	VERY LOW
CRP for predicting sepsis patients with cardiogenic shock	1[122]	AUC 83 (73-94)	No serious imprecision	VERY LOW
CRP (Ratio of follow-up CRP level to the initial CRP level (CRP ratio ≥0.7 defined as elevated)) for predicting bacteraemia in cirrhotic patients	1[130]	OR 19.12 (1.32-276.86)	No serious imprecision	VERY LOW
CRP for predicting bacterial and fungal Infections in immunocompromised patients	1[132]	AUC 0.76 (0.69-0.93)	No serious imprecision	VERY LOW
CRP>5 mg/l for predicting bacterial and fungal Infections in immunocompromised patients	1[132]	Sens: 100 Spec: 4 PPV: 40 NPV: 100	NA	VERY LOW
CRP>50 mg/l for predicting bacterial and fungal Infections in immunocompromised patients	1[132]	Sens: 94 Spec: 41 PPV: 51 NPV: 91	NA	VERY LOW
CRP>100 mg/l for predicting bacterial and fungal Infections in immunocompromised patients	1[132]	Sens: 83 Spec: 61 PPV: 58	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV: 85		
CRP>150 mg/l for predicting bacterial and fungal Infections in immunocompromised patients	1[132]	Sens: 68 Spec: 74 PPV: 63 NPV: 78	NA	VERY LOW
CRP>15.2 ng/ml, day 1, for predicting severe sepsis in patients with suspected ventilator-associated pneumonia	1[137]	Sens 86.4 Spec 65.2 PPV 70.4 NPV 83.3	NA	VERY LOW
CRP>15.2 ng/ml, day 1, for predicting severe sepsis in patients with suspected ventilator-associated pneumonia	1[137]	AUC 79.4 (66.4-92.5)	No serious imprecision	VERY LOW
CRP>15.75 ng/ml, day 7, for predicting severe sepsis in patients with suspected ventilator-associated pneumonia	1[137]	Sens 93.8 Spec 73.9 PPV 71.4 NPV 94.4	NA	VERY LOW
CRP>15.75 ng/ml, day 7, for predicting severe sepsis in patients with suspected ventilator-associated pneumonia	1[137]	AUC 78.3 (62.6-93.9)	No serious imprecision	VERY LOW
CRP>196 mg/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	Sens 92 Spec 60 PPV 23 NPV 98	NA	VERY LOW
CRP>196 mg/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	AUC 74	NA	VERY LOW
CRP>208 mg/l for predicting septic	1[139]	Sens 71	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
shock (day 0-7) in adults with fever in ICU		Spec 78 PPV 62 NPV 84		
CRP>208 mg/l for predicting septic shock (day 0-7) in adults with fever in ICU	1[139]	AUC 75	NA	VERY LOW
CRP>55 mg/l for predicting sepsis and septic shock/severe sepsis in patients diagnosed with SIRS in the ED	1[152]	Sens 81.2 (54.4-96.0) Spec =59.2 (51.0-66.7) PPV 16.5 (6.99-25.9) NPV 96.9 (93.1-100)	NA	VERY LOW
CRP>55 mg/l for predicting sepsis and septic shock/severe sepsis in patients diagnosed with SIRS in the ED	1[152]	AUC 72.5	NA	VERY LOW
CRP>6.84 mg/l for predicting sepsis/septic shock in ED and hospital patients	1[165]	Sens 87.5 Spec 63.5 PPV 50.9 NPV 92.2	NA	VERY LOW
CRP>6.84 mg/l for predicting sepsis/septic shock in ED and hospital patients	1[163,165]	AUC 81.9	NA	VERY LOW
CRP>8.88 mg/l for predicting mortality in ED and hospital patients	1[165]	Sens 85.7 Spec 66.7 PPV 29.3 NPV 96.7	NA	VERY LOW
CRP>8.88 mg/l for predicting mortality in ED and hospital patients	1[165]	AUC 72.3	NA	VERY LOW
CRP >67.5 mg/l for predicting 180-day mortality in ED patients	1[163,167]	Sens 84.86 (79.70-90.03) Spec 30.95 (26.79-35.10) PPV 32.37 (28.21-36.53) NPV 84.00 (78.56-89.43)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP >67.5 mg/l for predicting 180-day mortality in ED patients	1[167]	AUC 0.5620 (0.5053-0.6166)	No serious imprecision	VERY LOW
CRP >60 mg/l for predicting bacterial infection in hospital patients with SIRS	1[171]	Sens 86 (78-93) Spec 60 (46-73) PPV 79 NPV 73	NA	VERY LOW
CRP >60 mg/l for predicting bacterial infection in hospital patients with SIRS	1[171]	AUC 81 (73-86)	No serious imprecision	VERY LOW
CRP >8mg/l for predicting bloodstream infection in patients who had blood cultures taken at admission (multivariable analysis adjusted for body temperature, leucocyte count, CRP)	1[186]	OR=6.06 (0.82-44.6)	Serious	VERY LOW
CRP for predicting infection in patients in medico-surgical ICU	1[195]	AUC 58.0 (48.8-67.2)	Serious	VERY LOW
CRP for predicting sepsis in patients presenting to the ED with signs/symptoms of local infection or sepsis	1[198]	AUC 72	NA	VERY LOW
CRP>50 mg/l for predicting sepsis in ICU patients	1[215]	AUC 75 (63-86)	No serious imprecision	VERY LOW
CRP>50 mg/l for predicting sepsis in ICU patients	1[215]	Sens 88 Spec 23 PPV 45 NPV 71	NA	VERY LOW
CRP>93 mg/ml for predicting sepsis (septic complication during the first 5 postoperative days) in patients undergoing elective major surgical	1[216]	AUC 66.4 (49.3-83.5)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
procedures				
CRP>93 mg/ml for predicting sepsis (septic complication during the first 5 postoperative days) in patients undergoing elective major surgical procedures	1[216]	Sens 63 Spec 72 PPV 53 NPV 79	NA	VERY LOW
CRP>11 ng/ml for predicting sepsis in febrile patients	1[217]	AUC 79 (64-89)	No serious imprecision	VERY LOW
CRP>11 ng/ml for predicting sepsis in febrile patients	1[217]	Sens 87.1 (69.2-95.8) Spec 78.4 (61.3-89.6) PPV 77.1 NPV 87.9	NA	VERY LOW
CRP for predicting bacteraemia in patients with CAP	1[221]	AUC 67 (59-74)	No serious imprecision	VERY LOW
CRP>20 mg/l for predicting bacteraemia in patients with CAP	1[221]	Sens 96 Spec 9	NA	VERY LOW
CRP>50 mg/l for predicting bacteraemia in patients with CAP	1[221]	Sens 89 Spec 18	NA	VERY LOW
CRP>100 mg/l for predicting bacteraemia in patients with CAP	1[221]	Sens 81 Spec 33	NA	VERY LOW
CRP>200 mg/l for predicting bacteraemia in patients with CAP	1[221]	Sens 61 Spec 64	NA	VERY LOW
CRP>3.5 mg/dl for predicting bacteraemia in patients with fever	1[230]	Sens 75.0 Spec 40.4 PPV 60.8 NPV 56.8	NA	VERY LOW
CRP>3.5 mg/dl for predicting in patients with fever	1[230]	OR = 2.03 (0.93-446)	Serious	VERY LOW
CRP>3.5 mg/dl for predicting 21 day	1[230]	Sens 10.7	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
mortality in patients with fever		Spec 92.7 PPV 72.7 NPV 36.2		
CRP>3.5 mg/dl for predicting 21 day mortality in patients with fever	1[230]	OR = 1.51 (0.38-6.00)	Serious	VERY LOW
CRP >198 mg/l for predicting mortality in critically ill patients	1[245]	Sens 66 Spec 80 PPV 51 NPV 83	NA	VERY LOW
CRP >198 mg/l for predicting mortality in critically ill patients	1[245]	AUC 81.1	NA	VERY LOW
CRP for predicting of mortality in patients with traumatic brain injury or subarachnoid haemorrhage	1[246]	AUC Day 0: 31 AUC Mean all days (0-7): 68 AUC Peak CRP value: 63	NA	VERY LOW
CRP for predicting of mortality in patients with traumatic brain injury or subarachnoid haemorrhage	1[246]	Sens Day 0: 17 Sens Mean all days (0-7): 50 Sens Peak CRP value: 33	NA	VERY LOW
CRP>52 mg/l for predicting sepsis in patients with SIRS	1[253]	AUC 77.7 (56.9-80.0)	No serious imprecision	VERY LOW
CRP>52 mg/l for predicting sepsis in patients with SIRS	1[253]	Sens 75 (63-84.7) Spec 54.9 (49.2-69.1)	NA	VERY LOW
CRP (day 1) for predicting sepsis in patients with SIRS	1[260]	AUC 38.6 (23.0-54.3)	Serious	VERY LOW
CRP (day 2) for predicting sepsis in patients with SIRS	1[260]	AUC 53.3 (39.6-71.0)	Serious	VERY LOW
CRP for predicting in-hospital mortality in critically ill patients with suspected sepsis	1[261]	AUC 60 (48-72)	Serious	VERY LOW
CRP>50 mg/l for predicting sepsis in	1[265]	Sens 98.5	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
ICU patients		Spec 75		
CRP>8.7 mg/dl for predicting infection in critically ill patients in ICU	1[267]	Sens: 93.4 Spec: 86.1 PPV: 93.4 NPV: 86	NA	VERY LOW
CRP (maximum daily variation) for predicting ICU-acquired infection in ICU patients	1[268]	AUC 86.0 (75.2-93.3)	No serious imprecision	VERY LOW
CRP increase >4.1 mg/dl for predicting ICU-acquired infection in ICU patients	1[268]	Sens 92.1 Spec 71.4	NA	VERY LOW
CRP ≥70mg/l for predicting infection in ICU patients	1[289]	Sens 94 Spec 84 PPV 83 NPV 94	NA	VERY LOW
CRP ≥8 mg/dl for predicting sepsis in critically ill patients	1[299]	Sens 94.3 Spec 87.3 PPV 90.4 NPV 92.3	NA	VERY LOW
CRP ≥8 mg/dl for predicting sepsis in critically ill patients	1[299]	Sens 94.3 AUC 94 (89-98)	No serious imprecision	VERY LOW
CRP ≥3 mg/ml for predicting infection in elderly patients in hospital	1[303]	AUC 63	NA	VERY LOW
CRP ≥3 mg/ml for predicting infection in elderly patients in hospital	1[303]	Sens 92 Spec 36 PPV 30 NPV 94	NA	VERY LOW
CRP ≥3 mg/ml for predicting infection	1[303]	OR 3.4 (1.1-10.6)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
in elderly patients in hospital (multivariable analysis)			imprecision	
CRP for predicting sepsis in ED patients	1[313]	AUC 67	NA	VERY LOW
CRP>40 mg/dl for predicting sepsis in ED patients	1[313]	Sens 82.3 Spec 38.7 PPV 26.5 NPV 89.0	NA	VERY LOW
CRP>100 mg/dl for predicting sepsis in ED patients	1[313]	Sens 60.1 Spec 65.6 PPV 32.0 NPV 85.9	NA	VERY LOW
CRP>200 mg/dl for predicting sepsis in ED patients	1[313]	Sens 30.7 Spec 88.1 PPV 41.0 NPV 82.5	NA	VERY LOW
CRP > 100 mg/dl for predicting infection in critically ill patients in ICU	1[314]	Sens 59 Spec 57 PPV 62 NPV 54	NA	VERY LOW
CRP > 100 mg/dl for predicting infection in critically ill patients in ICU	1[314]	AUC 65 (46-78)	Serious	VERY LOW
CRP for predicting severe sepsis in ED patients with suspected infection (multivariable analysis)	1[316]	OR=1.02 (0.75-1.37)	Serious	VERY LOW
CRP for predicting sepsis in ED patients with suspected infection (multivariable analysis)	1[316]	OR=1.33 (1.10-1.61)	No serious imprecision	VERY LOW
CRP for predicting sepsis in ED patients	1[316]	AUC: 70 (65-74)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
with suspected infection (multivariable analysis)			imprecision	
CRP for predicting sepsis, including severe sepsis and septic shock in critically ill patients in ICU	1[318]	AUC 53.9 (43.0-64.5)	Serious	VERY LOW
CRP for predicting bacteraemia in patients with haematological malignancies after chemotherapy	1[320]	AUC 64	NA	VERY LOW
CRP for predicting bacteraemia in patients on general medical or infectious diseases ward	1[329]	AUC 72	NA	VERY LOW
CRP for predicting documented infections in patients who received chemotherapy for haematological malignancies and developed neutropenia	1[333]	AUC 61	NA	VERY LOW
CRP>30.8 mg/l for predicting documented infections in patients who received chemotherapy for haematological malignancies and developed neutropenia	1[333]	Sens 71 Spec 50 PPV 27 NPV 88	NA	VERY LOW
CRP for predicting bacteraemia in patients who received chemotherapy for haematological malignancies and developed neutropenia	1[333]	AUC 55	NA	VERY LOW
CRP>68.6 mg/l for predicting bacteraemia in patients who received chemotherapy for haematological malignancies and developed neutropenia	1[333]	Sens 46 Spec 73 PPV 20 NPV 91	NA	VERY LOW

Table 83: Clinical evidence summary: Band, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Band >10% for predicting infection in critically ill patients	1[57]	Sens 43 (28-59) Spec 92 (28-59) TP 18 FP 8 FN 24 TN 95	NA	VERY LOW
Band for predicting infection in critically ill patients	1[57]	AUC 74 (64-83)	No serious imprecision	VERY LOW
Band >8.5% for predicting sepsis in patients with SIRS in ICU	1[206]	AUC 80 (72 – 88)	No serious imprecision	VERY LOW
Band >8.5% for predicting sepsis in patients with SIRS in ICU	1[206]	Sens 84.3 Spec 71.4	NA	VERY LOW

Table 84: Clinical evidence summary: Creatinine, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Creatinine>20 mg/l for predicting septic shock in patients who had both blood cultures within 6 hours of suspected infection	1[17]	OR=4.31 (2.15-8.65)	No serious imprecision	VERY LOW

Table 85: Clinical evidence summary: Fibrinogen, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Fibrinogen for predicting sepsis in postoperative patients admitted to ICU	1[3]	AUC 56.3 (45.6-66.7)	Serious	VERY LOW

Table 86: Clinical evidence summary: Haemoglobin, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Hb ≤100 g/litre for predicting bacteraemia in patients with non-hospital acquired pneumonia	1[256]	OR=0.71 (0.09-5.7)	Serious	VERY LOW

Table 87: Clinical evidence summary: Lactate, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Lactate>4 for predicting bacteraemia in ED patients (univariable)	1[58]	p≤0.001	NA	VERY LOW
Lactate > 2mM for predicting severe sepsis in ED patients with suspected infection (multivariable analysis)	1[106]	OR=10.88 (6.51-18.19)	No serious imprecision	VERY LOW
Lactate > 2mM for predicting septic shock in ED patients with suspected infection (multivariable analysis)	1[106]	OR=6.36 (1.87-21.62)	No serious imprecision	VERY LOW
Lactate for predicting sepsis in ED patients with suspected infection	1[106]	AUC = 56.5 (50.8-61.6)	No serious imprecision	VERY LOW
Lactate for predicting severe sepsis in ED patients with suspected infection	1[106]	AUC = 79.2 (73.6-83.8)	No serious imprecision	VERY LOW
Lactate for predicting septic shock in ED patients with suspected infection	1[106]	AUC = 84.0 (71.9-91.2)	No serious imprecision	VERY LOW
Lactate>1.5 mmol/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	Sens 83 Spec 61 PPV 23 NPV 96	NA	VERY LOW
Lactate>1.5 mmol/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	AUC 75	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Lactate>1.7 mmol/l for predicting mortality (day 0-28) in adults with fever in ICU	1[139]	Sens 60 Spec 75 PPV 44 NPV 85	NA	VERY LOW
Lactate>1.7 mmol/l for predicting mortality (day 0-28) in adults with fever in ICU	1[139]	AUC 71	NA	VERY LOW
Lactate (hyperlactatemia ≥2.5 mmol/l) for predicting 28-day mortality in ICU patients with sepsis	1[150]	AUC At ICU admission: 0.52 AUC 12 hours after admission: 0.62 AUC 24 hours after admission: 0.68	NA	VERY LOW
Lactate at admission for predicting 180-day mortality in ED patients	1[167]	HR=1.10 (1.05-1.14)	No serious imprecision	VERY LOW
Lactate for predicting in-hospital mortality in ED patients with suspected infections	1[291]	AUC, POC lactate:72 AUC, laboratory lactate: 70	NA	VERY LOW

1 **Table 88: Clinical evidence summary: Leucocyte, adults**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
LAR (Leucocyte anti-sedimentation rate) for predicting bacteraemia in critically ill patients	1[33]	AUC 80 (64-95)	No serious imprecision	VERY LOW
Leukocyte count for predicting bacterial infection in ED patients with fever (multivariable analysis)	1[82]	OR = 1.125 (0.997-1.295)	Serious	VERY LOW
Leukocyte count≥4.0x10^9/l or ≤12.0x10^9/l for predicting bloodstream infection in patients who had blood cultures taken at admission (multivariable analysis adjusted for	1[186]	OR=1.07 (0.63-1.80)	Serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
body temperature, leucocyte count, CRP)				
Leucocytes >15000/microlitre for predicting mortality in critically ill patients	1[245]	Sens 36 Spec 80 PPV 31 NPV 83	NA	VERY LOW
Leucocytes >15000/microlitre for predicting mortality in critically ill patients	1[245]	AUC 62.0	NA	VERY LOW

Table 89: Clinical evidence summary: Lymphocyte, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Lymphocyte count for predicting bacteraemia in patients on general medical or infectious diseases ward	1[329]	AUC 70	NA	VERY LOW

Table 90: Clinical evidence summary: Neutrophils, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Neutrophils >80% for predicting bacteraemia in ED patients (multivariable)	1[58]	OR=1.76 (1.40-2.21)	No serious imprecision	VERY LOW
Neutrophil for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	AUC 65.83	NA	VERY LOW
DNI>12.3% for predicting sepsis and septic shock/severe sepsis in patients diagnosed with SIRS in the ED	1[152]	AUC 93.2	NA	VERY LOW
DNI>12.3% for predicting sepsis/septic	1[165]	Sens 88.6	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
shock in ED and hospital patients		Spec 90.3 PPV 77.5 NPV 95.5		
DNI>12.8% for predicting sepsis/septic shock in ED and hospital patients	1[165]	AUC 80.0	NA	VERY LOW
DNI>12.8% for predicting mortality in ED and hospital patients	1[165]	Sens 75.0 Spec 81.3 PPV 37.5 NPV 95.6	NA	VERY LOW
Neutrophil count >7.5x10^9 cells/l for predicting bacterial infection in hospital patients with SIRS	1[171]	Sens 74 (64-82) Spec 64 (50-76) PPV 82 NPV 57	NA	VERY LOW
Neutrophil count >7.5x10^9 cells/l for predicting bacterial infection in hospital patients with SIRS	1[171]	AUC 74 (66-81)	No serious imprecision	VERY LOW
Neutrophils≥2.0x10^9/l or ≤7.0x10^9/l for predicting bloodstream infection in patients who had blood cultures taken at admission (multivariable analysis adjusted for body temperature, leucocyte count, CRP)	1[186]	OR=1.07 (0.63-1.80)	Serious	VERY LOW
Neutrophil count for predicting bacteraemia in patients on general medical or infectious diseases ward	1[329]	AUC 66	NA	VERY LOW

Table 91: Clinical evidence summary: Platelets, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Platelets for predicting sepsis in	1[3]	AUC 73.6 (64.9-82.3)	No serious	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
postoperative patients admitted to ICU			imprecision	
Platelets <150 for predicting bacteraemia in ED patients (multivariable)	1[58]	OR=1.94 (1.50-2.52)	No serious imprecision	VERY LOW
Platelets for predicting in-hospital mortality in critically ill patients with suspected sepsis	1[261]	AUC 69 (59-79)	No serious imprecision	VERY LOW

1 **Table 92: Clinical evidence summary: Thrombin time, adults**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Thrombin time for predicting sepsis in postoperative patients admitted to ICU	1[3]	AUC 59.3 (45.6-66.9)	Serious	VERY LOW
Prothrombin time <60% for predicting septic shock in patients who had both blood cultures within 6 hours of suspected infection	1[17]	OR=5.33 (2.65-19.7)	No serious imprecision	VERY LOW
Thrombocyte count for predicting bacterial infection in ED patients with fever (multivariable analysis)	1[82]	0.996 (0.990-1.003)	Serious	VERY LOW
Antithrombin III (day 1) for predicting sepsis in patients with SIRS	1[260]	AUC 59.8 (24.4-76.0)	Serious	VERY LOW
Antithrombin III (day 2) for predicting sepsis in patients with SIRS	1[260]	AUC 62.8 (45.0-80.5)	Serious	VERY LOW
Thromboplastin time for predicting in-hospital mortality in critically ill patients with suspected sepsis	1[261]	AUC 63 (51-75)	No serious imprecision	VERY LOW
Anti-thrombin III (%) for predicting 28-day mortality in patients with known or suspected infection	1[298]	AUC 60.1	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Photothrombin time (seconds) for predicting 28-day mortality in patients with known or suspected infection	1[298]	OR=1.89 (1.38-2.58)	No serious imprecision	VERY LOW
Anti-thrombin III (%) for predicting 28-day mortality in patients with known or suspected infection	1[298]	AUC 57.4	NA	VERY LOW
Photothrombin time (seconds) for predicting 28-day mortality in patients with known or suspected infection	1[298]	OR=1.89 (1.38-2.58)	No serious imprecision	VERY LOW

Table 93: Clinical evidence summary: Urea, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Blood urea nitrogen for predicting bacteraemia in patients with CAP	1[221]	AUC 64 (57-71)	No serious imprecision	VERY LOW
Blood urea nitrogen>11mM for predicting bacteraemia in patients with CAP	1[221]	Sens 32 Spec 78	NA	VERY LOW

Table 94: Clinical evidence summary: WBC, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC for predicting bacteraemia in ED patients	1[56]	AUC 50 (30-70)	Serious	VERY LOW
WBC<4.3 or >11.4 cells/mm^3 for predicting bacteraemia in ED patients	1[56]	Sens 57 (31-83) Spec 66 (48-88) PPV 44 (22-67) NPV 81 (67-94)	NA	VERY LOW
WBC>12 x10^9/l for predicting infection	1[57]	Sens 52 (36-68)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
in critically ill patients		Spec 59 (49-69) TP 22 FP 42 FN 20 TN 61		
WBC<4 x10^9/l for predicting infection in critically ill patients	1[57]	Sens 10 (3-23) Spec 96 (90-99) TP 4 FP 4 FN 38 TN 99	NA	VERY LOW
WBC <4 or >12 for predicting bacteraemia in ED patients (univariable)	1[58]	p = 0.435	NA	VERY LOW
WBC count > 12,000mm^{-3} for predicting sepsis in ED patients with suspected infection (multivariable analysis)	1[106]	OR=1.83 (1.17-2.86)	No serious imprecision	VERY LOW
WBC for predicting sepsis/ severe sepsis in hospital patients with suspected infection	1[111]	AUC 66.71	NA	VERY LOW
WBC>20.3x10^9/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	Sens 58 Spec 84 PPV 33 NPV 94	NA	VERY LOW
WBC>20.3x10^9/l for predicting bloodstream infection (day 0-2) in adults with fever in ICU	1[139]	AUC 70	NA	VERY LOW
WBC>11.0x10^9/l for predicting sepsis and septic shock/severe sepsis in	1[152]	Sens 62.5 (35.4-84.8)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
patients diagnosed with SIRS in the ED		Spec 57.1 (49.1-64.9) PPV 12.6 (4.17-21.1) NPV 93.8 (88.5-99.1)		
WBC>11.0x10^9/l for predicting sepsis and septic shock/severe sepsis in patients diagnosed with SIRS in the ED	1[152]	AUC 53.6	NA	VERY LOW
WBC for predicting sepsis in patients presenting to the ED with signs/symptoms of local infection or sepsis	1[198]	AUC 53	NA	VERY LOW
WBC for predicting bacteraemia in patients with CAP	1[221]	AUC 58 (50-65)	Serious	VERY LOW
WBC≤5 or ≥20 x10^9/litre for predicting bacteraemia in patients with CAP	1[221]	Sens 22 Spec 84	NA	VERY LOW
WBC <4 or >20 x10^9/litre for predicting bacteraemia in patients with non-hospital acquired pneumonia	1[256]	OR=0.61 (0.3-7.17)	Serious	VERY LOW
WBC (day 1) for predicting sepsis in patients with SIRS	1[260]	AUC 55.1 (39.7-70.6)	Serious	VERY LOW
WBC (day 2) for predicting sepsis in patients with SIRS	1[260]	AUC 66.1 (52.2-79.9)	No serious imprecision	VERY LOW
WBC for predicting in-hospital mortality in critically ill patients with suspected sepsis	1[261]	AUC 53 (41-65)	Serious	VERY LOW
WBC (maximum daily variation) for predicting ICU-acquired infection in ICU patients	1[268]	AUC 66.8 (54.1-77.9)	No serious imprecision	VERY LOW
WBC≥10,000/mm^3 for predicting bacteraemia in geriatric patients	1[262]	Sens 43.5 Spec 59.4 PPV 8.8	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Eosinophil cell count ≤50 cells/mm^3 for predicting infection in ICU patients	1[289]	Sens 81 Spec 65 PPV 66 NPV 80	NA	VERY LOW
WBC ≤4000 or ≥12000 /mm^3 for predicting infection in elderly patients in hospital	1[303]	Sens 30 Spec 89 PPV 45 NPV 81	NA	VERY LOW
WBC ≤4000 or ≥12000 /mm^3 for predicting infection in elderly patients in hospital (univariable analysis)	1[303]	OR 3.5 (1.6-7.7)	No serious imprecision	VERY LOW
WBC <10^9/l for predicting sepsis, including severe sepsis and septic shock in immunocompromised patients	1[305]	Sens 63 Spec 60	NA	VERY LOW
WBC >10^9/l for predicting sepsis, including severe sepsis and septic shock in immunocompromised patients	1[305]	Sens 94 Spec 60	NA	VERY LOW
WBC ≥12000 /mm^3 for predicting infection in critically ill patients in ICU	1[314]	Sens 66 Spec 45 PPV 76 NPV 72	NA	VERY LOW
WBC ≥12000 /mm^3 for predicting infection in critically ill patients in ICU	1[314]	AUC 68 (49-81)	Serious	VERY LOW

Table 95: Clinical evidence summary: combination of tests, adults

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Band >10% and WBC >12 x10^9/l for predicting infection in critically ill	1[57]	Sens 26 (14-42) Spec 97 (92-99)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
patients		TP 11 FP 3 FN 31 TN 100		
CRP >10.0 mg/dl and lactate ≥4.0 mmol/l (compared to CRP ≤10.0 mg/dl and lactate <4.0 mmol/l, OR =1.00, reference) for predicting sepsis in patients with suspected infection (multivariable analysis adjusted for patient demographics and co-morbidities)	1[128]	OR 12.34 (6.81-22.34)	No serious imprecision	VERY LOW
CRP >10.0 mg/dl and lactate <4.0 mmol/l (compared to CRP ≤10.0 mg/dl and lactate <4.0 mmol/l, OR =1.00, reference) for predicting sepsis in patients with suspected infection (multivariable analysis adjusted for patient demographics and co-morbidities)	1[128]	OR 1.91 (1.22-2.98)	No serious imprecision	VERY LOW
CRP ≤10.0 mg/dl and lactate ≥4.0 mmol/l (compared to CRP ≤10.0 mg/dl and lactate <4.0 mmol/l, OR =1.00, reference) for predicting sepsis in patients with suspected infection (multivariable analysis adjusted for patient demographics and co-morbidities)	1[128]	OR 1.38 (0.58-3.24)	Serious	VERY LOW
CRP/albumin ratio at admission (cut-off >5.09) for predicting 180-day mortality in ED patients	1[167]	Sens 84.86 (79.70-90.03) Spec 30.95 (26.79-35.10) PPV 32.37 (28.21-36.53)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV 84.00 (78.56-89.43)		
CRP/albumin ratio at admission (cut-off >5.09 mg/dl) for predicting 180-day mortality in ED patients	1[167]	AUC 56.20 (50.53-61.66)	No serious imprecision	VERY LOW
CRP/albumin ratio at admission (cut-off >5.09 mg/dl) for predicting 180-day mortality in ED patients	1[167]	HR=1.06 (1.03-1.10)	No serious imprecision	VERY LOW
CRP+WBC for predicting sepsis in patients presenting to the ED with signs/symptoms of local infection or sepsis	1[198]	AUC 71	NA	VERY LOW
WBC + neutrophil percentage for predicting bloodstream infections in patients with burns	1[224]	AUC 62.4 (56.9-67.9)	No serious imprecision	VERY LOW
Lymphocyte count+Neutrophil count for predicting bacteraemia in patients on general medical or infectious diseases ward	1[329]	AUC 75	NA	VERY LOW
CRP+ Lymphocyte count+Neutrophil count for predicting bacteraemia in patients on general medical or infectious diseases ward	1[329]	AUC 78	NA	VERY LOW

8.3.4.2 Clinical evidence summary tables, children and neonates

Table 96: Clinical evidence summary: CRP, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP for predicting SBI in Children under 3 years with fever of unknown source	1[11]	AUC 85 (81-88)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP> 32 ng/mL for predicting SBI in Children under 3 years with fever of unknown source	1[11]	sens 84.0 spec 75.5	NA	VERY LOW
CRP> 20 ng/mL for predicting SBI in Children under 3 years with fever of unknown source	1[11]	Sens 88.3 (80.0-94.0) Spec 60.8 (55.2-66.3)	NA	VERY LOW
CRP> 40 ng/mL for predicting SBI in Children under 3 years with fever of unknown source	1[11]	Sens 71.3 (61.0-80.1) Spec 81.2 (76.4-85.4)	NA	VERY LOW
CRP> 80 ng/mL for predicting SBI in Children under 3 years with fever of unknown source	1[11]	Sens 46.0 (36.4-57.4) Spec 94.6 (91.5-96.8)	NA	VERY LOW
CRP for predicting SBI in Children under 3 years with fever of unknown source (Multivariable analysis)	1[11]	OR 1.02 (1.01-1.03)	No serious imprecision	VERY LOW
CRP +10 (48 hours) for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 90 Spec 70	NA	VERY LOW
CRP +11 (24 hours) for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 92 Spec 61	NA	VERY LOW
CRP +11 (48 hours) for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 87 Spec 89	NA	VERY LOW
CRP +15 (48 hours) for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 88 Spec 72	NA	VERY LOW
CRP +20 (48 hours) for predicting post-	1[20]	Sens 88	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
operative sepsis in children undergoing major surgery		Spec 76		
CRP for predicting SBI in febrile infants aged ≤3 months	1[29]	OR 1.21 (1.13-1.29)	No serious imprecision	VERY LOW
CRP>8mg/dl for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 23.5 (16.4-32.6) Spec 98.2 (97.1-98.9)	NA	VERY LOW
CRP>4mg/dl for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 44.1 (34.9-53.8) Spec 92.2 (90.1-93.8)	NA	VERY LOW
CRP>2mg/dl for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 55.9 (46.2-65.1) Spec 82.2 (79.3-84.7)	NA	VERY LOW
CRP >20 mg/l for predicting SBI in neonates with fever <12 hours without source	1[44]	Sens 48 Spec 93.2 PPV 70.6 NPV 84.2	NA	VERY LOW
CRP >20 mg/l for predicting SBI in neonates with fever <12 hours without source	1[44]	AUC 0.78 (0.69-0.86)	No serious imprecision	VERY LOW
CRP >20 mg/l for predicting SBI in neonates with fever >12 hours without source	1[44]	Sens 100 Spec 96.2 PPV 71.4 NPV 78	NA	VERY LOW
CRP >20 mg/l for predicting SBI in neonates with fever >12 hours without source	1[44]	AUC 0.99 (0.92-1)	No serious imprecision	VERY LOW
CRP >5.5 mg/dl for detection of late-onset sepsis in VLBW infants	1[78]	Sens 92 Spec 36	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP >5.5 mg/dl for detection of late-onset sepsis in VLBW infants	1[78]	AUC 64.5	NA	VERY LOW
CRP >0.4 mg/dl for detecting neonatal infection in infants undergoing sepsis work-up	1[91]	Sens 69.4 Spec 70.4 PPV 59.5 NPV 78.6	NA	VERY LOW
CRP >0.4 mg/dl for detecting neonatal infection in infants undergoing sepsis work-up	1[91]	AUC 73	NA	VERY LOW
CRP>6.1 mg/l for predicting bacterial sepsis in neonates admitted to NICU	1[95]	Sens 95.8 Spec 83.6 PPV 80.2 NPV 96.7	NA	VERY LOW
CRP>6.1 mg/l for predicting bacterial sepsis in neonates admitted to NICU	1[95]	AUC 95 (88-1)	No serious imprecision	VERY LOW
CRP>22.1 mg/l for predicting bacterial sepsis in children admitted to PICU	1[95]	Sens 88.6 Spec 81.1 PPV 80.2 NPV 89.2	NA	VERY LOW
CRP>22.1 mg/l for predicting bacterial sepsis in children admitted to PICU	1[95]	AUC 93 (89-97)	No serious imprecision	VERY LOW
CRP>27.5 mg/l for predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	1[98]	Sens 78 Spec 75 PPV 88.5 NPV 54.9	NA	VERY LOW
CRP>27.5 mg/l for predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	1[98]	AUC 81 (SD 0.02)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	Sens 64 Spec 85	NA	VERY LOW
CRP for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	AUC 78	NA	VERY LOW
CRP ≥2mg/dL for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 51.5 Spec 86.6 PPV 56.4 NPV 84.1	NA	VERY LOW
CRP for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	AUC 75 (71-80)	No serious imprecision	VERY LOW
CRP >20 mg/l for predicting bacterial sepsis	1[107]	Sens 83.5 Spec 84.3 PPV 27.7 NPV 96.4	NA	VERY LOW
CRP>40mg/L for predicting SBI in children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination.	1[112]	Sens 79 (60-92) Spec 79 (67-88) PPV 90 NPV 61	NA	VERY LOW
CRP>10mg/l for discrimination between bacterial septicaemia/meningitis + bacterial localised infections and viral infections in children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified	1[121]	Sens 98 Spec 50 PPV 50 NPV 98	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP>20mg/l for discrimination between bacterial septicaemia/meningitis + bacterial localised infections and viral infections in children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified	1[121]	Sens 83 Spec 71 PPV 60 NPV 89	NA	VERY LOW
CRP>40mg/l for discrimination between bacterial septicaemia/meningitis + bacterial localised infections and viral infections in children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified	1[121]	Sens 73 Spec 88 PPV 76 NPV 86	NA	VERY LOW
CRP>10mg/l for discrimination between bacterial septicaemia/meningitis and bacterial localised infections + viral infections in children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified	1[121]	Sens 98 Spec 38 PPV 19 NPV 99.2	NA	VERY LOW
CRP>20mg/l for discrimination between bacterial septicaemia/meningitis and bacterial localised infections + viral infections in children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified	1[121]	Sens 89 Spec 58 PPV 24 NPV 97.2	NA	VERY LOW
CRP>40mg/l for discrimination between bacterial septicaemia/meningitis and bacterial localised infections + viral infections in	1[121]	Sens 87 Spec 75 PPV 34 NPV 97.5	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified				
CRP >70 mg/l for predicting SBI in infants <3 months with fever without source	1[127]	Sens 69.6 Spec 93.8 PPV – Not reported NPV 99.3	NA	VERY LOW
CRP >70 mg/l for predicting SBI in infants <3 months with fever without source	1[127]	AUC 84.7 (75.4-94.0)	No serious imprecision	VERY LOW
CRP >20 mg/l for predicting SBI in infants <3 months with fever without source	1[127]	Sens 73.9 Spec 74.8	NA	VERY LOW
CRP for predicting of SBI in infants <3 months with fever without source	1[126]	AUC 77.6 (74.1-81.1)	No serious imprecision	VERY LOW
CRP for predicting of IBI (invasive bacterial infection) in infants <3 months with fever without source	1[126]	AUC 74.7 (62.9-86.5)	No serious imprecision	VERY LOW
CRP for predicting septic shock in children admitted to PICU	1[134]	AUC 83 (76-90)	No serious imprecision	VERY LOW
CRP>20 mg/l for predicting septic shock in children admitted to PICU	1[134]	Sens 91 Spec 62 PPV 66 NPV 89	NA	VERY LOW
CRP>30 mg/l for predicting septic shock in children admitted to PICU	1[134]	Sens 81 Spec 70 PPV 69 NPV 82	NA	VERY LOW
CRP>40 mg/l for predicting septic	1[134]	Sens 79	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
shock in children admitted to PICU		Spec 77 PPV 74 NPV 82		
CRP>50 mg/l for predicting septic shock in children admitted to PICU	1[134]	Sens 76 Spec 80 PPV 76 NPV 80	NA	VERY LOW
CRP for predicting occult bacterial infection in children aged between 3 and 36 months with fever	1[145]	AUC 78	NA	VERY LOW
CRP (cut-off 4.4mg/dL) for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	Sens 63 (43-82) Spec 81 (76-87) PPV 30 (18-43) NPV 94 (91-98)	NA	VERY LOW
CRP (cut-off 4.4mg/dL) for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	AUC 71 (62-79)	No serious imprecision	VERY LOW
Unit increase (1mg/dL) of CRP for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever (multivariable analysis adjusted for ANC and length of illness)	1[146]	OR 1.12 (1.04-1.20)	No serious imprecision	VERY LOW
CRP>0.6 mg/l for predicting late onset sepsis in neonates >72 hours of life admitted to NICU	1[147]	Sens 54 (47-69) Spec 86 (78-94) PPV 74 (64-84) NPV 75 (65-85)	NA	VERY LOW
CRP>0.6 mg/l for predicting late onset sepsis in neonates >72 hours of life	1[147]	AUC 77	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
admitted to NICU				
CRP>40 mg/l for predicting SBI in children aged 7 days to 36 months with fever without localising signs	1[178]	Sens 89 (72-98) Spec 75 (65-83) PPV 51 NPV 96	NA	VERY LOW
CRP>40 mg/l for predicting SBI in children aged 7 days to 36 months with fever without localising signs	1[178]	AUC 88	NA	VERY LOW
CRP for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	AUC 88 (84-91)	No serious imprecision	VERY LOW
CRP>17.7mg/l for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	Sens 94.4 (85.5-98.1) Spec 68.6 (66.9-69.3) PPV 37.2 (33.7-38.7) NPV 98.4 (95.9-99.5)	NA	VERY LOW
CRP velocity (0 mg/dl per day) for differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass	1[229]	Sens 86.7 Spec 42.9 PPV 52 NPV 81.8	NA	VERY LOW
CRP velocity (1 mg/dl per day) for differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass	1[229]	Sens 80 Spec 73.8 PPV 68.6 NPV 83.8	NA	VERY LOW
CRP velocity (2 mg/dl per day) for differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass	1[229]	Sens 60 Spec 81 PPV 69.2 NPV 73.9	NA	VERY LOW
CRP velocity (3 mg/dl per day) for	1[229]	Sens 50	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass		Spec 90.5 PPV 78.9 NPV 71.7		
CRP velocity (4 mg/dl per day) for differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass	1[229]	Sens 40 Spec 95.2 PPV 85.7 NPV 69	NA	VERY LOW
CRP velocity (5 mg/dl per day) for differential diagnosis of early bacterial infection in children aged 1 day-18 years after cardiac surgery with bypass	1[229]	Sens 26.7 Spec 97.6 PPV 88.9 NPV 65.1	NA	VERY LOW
CRP for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C (multivariable analysis)	1[241]	OR 1.042 (1.028-1.056)	No serious imprecision	VERY LOW
CRP for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	AUC 81.9 (73.1-90.6)	No serious imprecision	VERY LOW
CRP>2 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 90 Spec 30 PPV 15 NPV 96	NA	VERY LOW
CRP>4 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 88 Spec 38 PPV 16 NPV 96	NA	VERY LOW
CRP>6 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 86 Spec 47 PPV 18	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV 96		
CRP>10 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 83 Spec 61 PPV 22 NPV 96	NA	VERY LOW
CRP>20 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 79 Spec 84 PPV 40 NPV 97	NA	VERY LOW
CRP>30 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 67 Spec 92 PPV 53 NPV 95	NA	VERY LOW
CRP>40 mg/l for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	Sens 56 Spec 94 PPV 56 NPV 94	NA	VERY LOW
CRP count for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	AUC 79 (75-84)	No serious imprecision	VERY LOW
CRP≥20 mg/l for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	Sens 64 (54-74) Spec 84 (80-88) PPV 55 (45-65) NPV 88 (84-92)	NA	VERY LOW
CRP≥30 mg/l for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	Sens 59 (48-70) Spec 89 (85-93) PPV 63 (52-74) NPV 87 (83-91)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP≥30 mg/l for diagnosis of sepsis/ bacteraemia in neonates aged 4-90 days seen in the ED for fever	1[249]	Sens 56 (32-80) Spec 74 (69-79) PPV 9.6 (4-16) NPV 97 (95-99)	NA	VERY LOW
CRP≥30 mg/l for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever (multivariable analysis)	1[249]	OR 6.6 (3.3-13.2)	No serious imprecision	VERY LOW
CRP (cut-off 23 mg/l) for predicting sepsis in neonates and children with SIRS and suspected infection	1[257]	Sens 70 Spec 89 PPV 53 NPV 94	NA	VERY LOW
CRP (cut-off 23 mg/l) for predicting sepsis in neonates and children with SIRS and suspected infection	1[257]	AUC 84 (57-89)	No serious imprecision	VERY LOW
CRP (≤12 hours, cut-off 3 mg/dl) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 67 Spec 74	NA	VERY LOW
CRP (≤12 hours, cut-off 5 mg/dl) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 50 Spec 92	NA	VERY LOW
CRP (≤12 hours, cut-off 7 mg/dl) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 33 Spec 97		
CRP (>12 hours, cut-off 3 mg/dl) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 100 Spec 63	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP (>12 hours, cut-off 5 mg/dl)for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 82 Spec 79	NA	VERY LOW
CRP (>12 hours, cut-off 7 mg/dl)for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 73 Spec 81	NA	VERY LOW
CRP (≤12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 68 (39-97)	Serious	VERY LOW
CRP (>12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 92 (85-99)	No serious imprecision	VERY LOW
CRP for predicting SBI in children aged 1-36 months, temperature ≥39˚C; clinically undetectable source of fever	1[271]	AUC 90.5 (80.8-100.2)	No serious imprecision	VERY LOW
CRP for predicting sepsis in Children aged 62 (1-203) months admitted to PICU	1[274]	AUC 75.0 (69.9-80.2)	No serious imprecision	VERY LOW
CRP>5.65mg/dl for predicting sepsis in Children aged 62 (1-203) months admitted to PICU	1[274]	Sens 72 Spec 66	NA	VERY LOW
CRP>6.55mg/dl for predicting sepsis in Children aged 62 (1-203) months admitted to PICU	1[274]	Sens 64 Spec 73	NA	VERY LOW
CRP (≤ 12 hours, cut off 2.1mg/dL) for predicting bacterial infection in neonates or children with a rectal or	1[285]	AUC 76 (63-88)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
oral temperature of ≥38˚C				
CRP (≤ 12 hours, cut off 2.1mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	Sens 72 (52-87) Spec 77 (64-86)	NA	VERY LOW
CRP (> 12-24 hours, cut off 6mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	AUC 81 (69-92)	No serious imprecision	VERY LOW
CRP (> 12-24 hours, cut off 6mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	Sens 68 (48-83) Spec 83 (69-92)	NA	VERY LOW
CRP (>24-48 hours, cut off 10.76mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	AUC 87 (77-96)	No serious imprecision	VERY LOW
CRP (>24-48 hours, cut off 10.76mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	Sens 68 (47-84) Spec 90 (73-96)	NA	VERY LOW
CRP (>48 hours, cut off 12.6mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	AUC 90 (84-97)	No serious imprecision	VERY LOW
CRP (>48 hours, cut off 12.6mg/dL) for predicting bacterial infection in neonates or children with a rectal or oral temperature of ≥38˚C	1[285]	Sens 80 (64-90) Spec 94 (85-97.5)	NA	VERY LOW
CRP >85mg/L for predicting positive blood culture in neonates or children	1[290]	Sens 70 Spec 67.6	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
with a fever >38°C		PPV 60.3		
CRP≥ 18 pg/ml for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	AUC 0.72 (0.55-0.90)	No serious imprecision	VERY LOW
CRP≥ 18 pg/ml for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	Sens 41 (25-57) Spec 94 (87-100) PPV 88 (77-98) NPV 63 (45-79)	NA	VERY LOW
CRP>20 mg/L for discriminating bacterial/ non-bacterial SIRS in children aged 0-18 years with SIRS	1[301]	Sens 95 Spec 24 PPV 44 NPV 90	NA	VERY LOW
CRP>40 mg/L for discriminating bacterial/ non-bacterial SIRS in children aged 0-18 years with SIRS	1[301]	Sens 95 Spec 42 PPV 51 NPV 94	NA	VERY LOW
CRP>60 mg/L for discriminating bacterial/ non-bacterial SIRS in children aged 0-18 years with SIRS	1[301]	Sens 59 Spec 55 PPV 46 NPV 68	NA	VERY LOW
CRP for discriminating bacterial/ non-bacterial SIRS in children aged 0-18 years with SIRS	1[301]	AUC 65	NA	VERY LOW
CRP>50mg/l for predicting SBI in children aged 1 to 36 months with fever >39˚C without localising signs	1[308]	Sens 75 Spec 68.7 NPV95.6 PPV 23	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
CRP for predicting SBI in children aged 1 to 36 months with fever >39˚C without localising signs	1[308]	AUC 0.66 (0.42-0.91)	Serious	VERY LOW
CRP for predicting sepsis in paediatric patients who underwent liver transplantation	1[337]	AUC 89	NA	VERY LOW
CRP≥93mg/L for predicting sepsis in paediatric patients who underwent liver transplantation	1[337]	Sens 82 Spec 91 PPV 56 NPV 99	NA	VERY LOW

Table 97: Clinical evidence summary: Band, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Band ≥1.5G/L for predicting SBI in children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination.	1[112]	Sens 11 (2-28) Spec 93 (84-98) PPV 72 NPV 38	NA	VERY LOW

Table 98: Clinical evidence summary: Fibrinogen, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Fibrinogen 20% increase in 24 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 71 Spec 63	NA	VERY LOW
Fibrinogen 20% increase in 48 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 76 Spec 64	NA	VERY LOW

Table 99: Clinical evidence summary: Glucose, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Glucose 20% increase in 24 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 93 Spec 53	NA	VERY LOW
Glucose 20% increase in 48 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 90 Spec 63	NA	VERY LOW

Table 100: Clinical evidence summary: Leucocytes, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Total leucocytes>16,500 /mm^3 for predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	1[98]	Sens 50.0 Spec 79.2 PPV 81.8 NPV 45.6	NA	VERY LOW
Total leucocytes>16,500 /mm^3 for predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	1[98]	AUC 65 (SD 0.03)	NA	VERY LOW
Leucocytes ≥15G/L for predicting SBI in children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination.	1[112]	Sens 52 (33-71) Spec 74 (62-84) PPV 78 NPV 45	NA	VERY LOW
Leucocytes >15,000/mm^3 for predicting SBI in children aged 7 days to 36 months with fever without localising signs	1[178]	Sens 68 (48-84) Spec 77 (67-85) PPV 46 NPV 89	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Leukocyte count for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	AUC 57.4 (47.7-67.1)	Serious	VERY LOW
Leucocyte count for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	AUC 67 (63-73)	No serious imprecision	VERY LOW
Leucocyte count>10,000/µl for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	Sens 73 (4-82) Spec 58 (52-64) PPV 35 (28-42) NPV 87 (82-92)	NA	VERY LOW
Leucocyte count>15,000/µl for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever	1[249]	Sens 38 (28-48) Spec 84 (80-88) PPV 43 (32-54) NPV 81 (77-85)	NA	VERY LOW
Leucocyte count for predicting sepsis in Children aged 62 (1-203) months admitted to PICU	1[274]	AUC 53.2 (46.2-60.2)	Serious	VERY LOW

Table 101: Clinical evidence summary: Neutrophil, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
ANC for predicting SBI in Children under 3 years with fever of unknown source	1[11]	AUC 74 (70-78)	No serious imprecision	VERY LOW
ANC>6450/mm^3 for predicting SBI in Children under 3 years with fever of unknown source	1[11]	sens 81.8 spec 62.3	NA	VERY LOW
ANC>10,000/mm^3 for predicting SBI in Children under 3 years with fever of	1[11]	Sens 38.3 (28.5-48.9) Spec 67.8 (62.4-73.0)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
unknown source				
ANC for differentiating acute bacterial meningitis and isolated bacteraemia in febrile infants 3-89 days old	1[39]	AUC 65 (51-78)	No serious imprecision	VERY LOW
ANC >10000/mm^3 for predicting SBI in neonates with fever <12 hours without source	1[44]	Sens 20 Spec 97.3 PPV 71.4 NPV 78	NA	VERY LOW
ANC >10000/mm^3 for predicting SBI in neonates with fever <12 hours without source	1[44]	AUC 0.77 (0.67-0.85)	No serious imprecision	VERY LOW
ANC >10000/mm^3 for predicting SBI in neonates with fever >12 hours without source	1[44]	Sens 80 Spec 100 PPV 100 NPV 98.2	NA	VERY LOW
ANC >10000/mm^3 for predicting SBI in neonates with fever >12 hours without source	1[44]	AUC 0.85 (0.73-0.93)	No serious imprecision	VERY LOW
ANC for predicting any SBI in febrile 0-5 year olds	1[85]	AUC 63 (61.5-66.2)	No serious imprecision	VERY LOW
ANC for predicting bacteraemia in febrile 0-5 year olds	1[85]	AUC 70.7 (63.1-78.2)	No serious imprecision	VERY LOW
ANC >10000/mm^3 for predicting any SBI in febrile 0-5 year olds	1[85]	Sens 41 (38-45) Spec 78 (76-79)	NA	VERY LOW
ANC >15000/mm^3 for predicting any SBI in febrile 0-5 year olds	1[85]	Sens 21 (19-25) Spec 93 (92-94)	NA	VERY LOW
Total neutrophils>9576 /mm^3 for	1[98]	Sens 49.2	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital		Spec 83.3 PPV 86 NPV 44		
Total neutrophils>9576 /mm^3 for predicting sepsis in children between 1 and 36 months of age treated for fever in paediatric ED and admitted to hospital	1[98]	AUC 69 (SD 0.03)	NA	VERY LOW
Total neutrophils for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	Sens 86 Spec 85	NA	VERY LOW
Total neutrophils for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	AUC 93	NA	VERY LOW
ANC for predicting of SBI in infants <3 months with fever without source	1[126]	AUC 71.1 (67.4-74.8)	No serious imprecision	VERY LOW
ANC for predicting of IBI (invasive bacterial infection) in infants <3 months with fever without source	1[126]	AUC 62.9 (50.6-75.2)	No serious imprecision	VERY LOW
ANC<1000/mm^3 for predicting bacterial sepsis in neonates >72 hours of life admitted to NICU	1[143]	Sens 2.4 Spec 98.0	NA	VERY LOW
ANC for predicting occult bacterial infection in children aged between 3 and 36 months with fever	1[145]	AUC 70	NA	VERY LOW
ANC (cut-off $1.6x10^3$/L) for predicting occult bacterial infection (OBI) in children aged between 3 and 36	1[146]	Sens 69 (51-87) Spec 79 (73-84) PPV 32 (20-44)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
months with fever		NPV 95 (91-98)		
ANC (cut-off 1.6 x10^3/L) for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	AUC 73 (65-81)	No serious imprecision	VERY LOW
Unit increase (1000x10^3/L) of ANC for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever (multivariable analysis adjusted for CRP and length of illness)	1[146]	OR 1.15 (1.07-1.24)	No serious imprecision	VERY LOW
ANC (cut-off >10 x 10^9 cells/l) for predicting SBI in well-appearing febrile children without obvious infection, ≥ 36 months old with documented fever	1[200]	Sens 46.7 (28.8–65.4) Spec 88.1 (82.5–92.2) PPV 0.38 (0.23–0.55) NPV 0.91 (0.86–0.95)	NA	VERY LOW
ANC (cut-off >13 x 10^9 cells/l) for predicting SBI in well-appearing febrile children without obvious infection, ≥ 36 months old with documented fever	1[200]	Sens 30.0 (15.4–49.6) Spec 94.3 (89.8–97.0) PPV 0.45 (0.24–0.68) NPV 0.90 (0.84–0.93)	NA	VERY LOW
Immature neutrophil to total neutrophil (I/T) ratio >2 to diagnose late onset sepsis in neonates >72 hours of life admitted to NICU with clinically suspected late onset sepsis (multivariable analysis)	1[203]	RR 4.89 (2.48-9.66)	No serious imprecision	VERY LOW
ANC for discriminating definite SBI v no SBI in infants aged ≤90 days with a temperature ≥38.0˚C	1 [204]	AUC 74	NA	VERY LOW
ANC for discriminating definite and possible SBI v no SBI in infants aged	1[204]	AUC 66	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
≤90 days with a temperature ≥38.0˚C				
ANC for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	AUC 80 (75-84)	No serious imprecision	VERY LOW
ANC>5200x 10^6/l for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	Sens 87.0 (76.5-93.5) Spec 59.9 (57.8-61.1) PPV 29.9 (26.3-32.1) NPV 95.9 (92.1-97.2)	NA	VERY LOW
ANC for diagnosis of SBI in febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C	1[241]	AUC 58.8 (48.9-68.6)	Serious	VERY LOW
ANC (≤12 hours, cut-off 10000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 17 Spec 77	NA	VERY LOW
ANC (≤12 hours, cut-off 11000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 17 Spec 82	NA	VERY LOW
ANC (≤12 hours, cut-off 12000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 17 Spec 85	NA	VERY LOW
ANC (>12 hours, cut-off 10000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 64 Spec 81	NA	VERY LOW
ANC (>12 hours, cut-off 11000/mm^3) for predicting SBI in children with documented fever 39°C and found to	1[269]	Sens 55 Spec 81	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
have no localizing source of fever				
ANC (>12 hours, cut-off 12000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 55 Spec 84	NA	VERY LOW
ANC (≤12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 42 (15-69)	Serious	VERY LOW
ANC (>12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 83 (72-94)	No serious imprecision	VERY LOW
ANC for predicting SBI in children aged 1-36 months, temperature ≥39˚C; clinically undetectable source of fever	1[271]	AUC 80.5 (70.5-90.5)	No serious imprecision	VERY LOW
ANC≥10 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	AUC 0.63 (0.46-0.81)	Serious	VERY LOW
ANC≥10 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	Sens 33 (20-47) Spec 93 (86-100) PPV 75 (63-87) NPV 69 (56-82)	NA	VERY LOW
ANC for predicting SBI in children aged 1 to 36 months with fever >39˚C without localising signs	1[308]	AUC 52 (36-71)	Serious	VERY LOW
ANC≥10,000/mm^3 for predicting SBI in children<18 years of age presenting to paediatric ED with rectal temperature ≥106˚F	1[311]	OR 1.11 (0.41-2.96)	Serious	VERY LOW

1 **Table 102: Clinical evidence summary: Platelets, children and neonates**

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Platelets 20% increase in 24 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 93 Spec 39	NA	VERY LOW
Platelets 20% increase in 48 hours for predicting post-operative sepsis in children undergoing major surgery	1[20]	Sens 95 Spec 19	NA	VERY LOW
Platelets ≥400,000/mm^3 for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 85.4 Spec 45.9 PPV 34.8 NPV 90.3	NA	VERY LOW
Platelets ≥450,000/mm^3 for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 82.5 Spec 70.5 PPV 48.6 NPV 92.3	NA	VERY LOW
Platelets ≥500,000/mm^3 for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 52.4 Spec 77.7 PPV 44.3 NPV 82.9	NA	VERY LOW
Platelets ≥600,000/mm^3 for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 22.3 Spec 90.2 PPV 43.4 NPV 77.5	NA	VERY LOW
Platelets for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	AUC 74 (70-79)	No serious imprecision	VERY LOW
Platelets (cut-off 68.0/µl) for predicting sepsis in very low birth weight infants	1[166]	Sens 59.3 Spec 76.5 PPV 66.7	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV 70.3		
Platelets (cut-off 68.0/µl) for predicting sepsis in very low birth weight infants	1[166]	AUC 69.2	NA	VERY LOW
Platelets≥100 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	AUC 0.70 (0.55-0.86)	No serious imprecision	VERY LOW
Platelets≥100 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	Sens 18 (7-29) Spec 93 (86-100) PPV 60 (46-74) NPV 66 (52-80)	NA	VERY LOW

Table 103: Clinical evidence summary: WBC, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC for predicting SBI in Children under 3 years with fever of unknown source	1[11]	AUC 71 (66-75)	No serious imprecision	VERY LOW
WBC> 10,470/mm^3 for predicting SBI in Children under 3 years with fever of unknown source	1[11]	sens 84.9 spec 47.4	NA	VERY LOW
WBC> 15,000/mm^3 for predicting SBI in Children under 3 years with fever of unknown source	1[11]	Sens 51.6 (41.0-62.1) Spec 75.5 (70.3-80.2)	NA	VERY LOW
WBC for predicting SBI in febrile infants aged ≤3 months	1[29]	OR 1.1 (1.06-1.15)	No serious imprecision	VERY LOW
WBC >15,000/µL for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 48 (38.6-57.6) Spec 84.1 (81.4-86.5)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC >20,000/µL for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 21.6 (14.7-30.5) Spec 95.2 (93.5-96.5)	NA	VERY LOW
WBC>15,000 or <5,000/µL for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 50 (40.5-59.5) Spec 78.1 (75-80.8)	NA	VERY LOW
WBC>20,000 or <400K/µL for predicting SBI in febrile infants aged ≤3 months	1[29]	Sens 21.6 (14.7-30.5) Spec 92.1 (90-93.8)	NA	VERY LOW
WBC≥5,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 79 (63-90) Spec 5 (4-6)	NA	VERY LOW
WBC≥10,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 61 (43-76) Spec 42 (40-44)	NA	VERY LOW
WBC≥15,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 45 (29-62) Spec 78 (76-79)	NA	VERY LOW
WBC≥20,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 24 (11-40) Spec 93 (92-94)	NA	VERY LOW
WBC≥25,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 13 (4-28) Spec 98 (97-99)	NA	VERY LOW
WBC≥30,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 5 (1-2) Spec 99 (99-100)	NA	VERY LOW
WBC≥15,000 or <5,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 66 (49-80) Spec 72 (71-74)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC≥20,000 or <5,000/mm^3 for predicting bacteraemia in febrile infants 0-89 days old	1[38]	Sens 45 (29-62) Spec 88 (87-89)	NA	VERY LOW
WBC<5,000/mm^3 for predicting bacteraemia in febrile infants 3-89 days old	1[39]	Sens 6 PPV 1.2 NPV 99.1	NA	VERY LOW
WBC≥15,000/mm^3 for predicting bacteraemia in febrile infants 3-89 days old	1[39]	Sens 52 PPV 2.0 NPV 99.4	NA	VERY LOW
WBC≥20,000/mm^3 for predicting bacteraemia in febrile infants 3-89 days old	1[39]	Sens 23 PPV 1.9 NPV 99.5	NA	VERY LOW
WBC<5,000 or ≥15,000/mm^3 for predicting bacteraemia in febrile infants 3-89 days old	1[39]	Sens 58 PPV 1.2 NPV 99.1	NA	VERY LOW
WBC<5,000/mm^3 or ≥20,000 for predicting bacteraemia in febrile infants 3-89 days old	1[39]	Sens 29 PPV 2.3 NPV 99.3	NA	VERY LOW
WBC<5,000/mm^3 for predicting SBI (acute bacterial meningitis and bacteraemia) in febrile infants 3-89 days old	1[39]	Sens 15 Spec: 4 PPV 4.5 NPV 98.9	NA	VERY LOW
WBC≥15,000/mm^3 for predicting SBI (acute bacterial meningitis and bacteraemia) in febrile infants 3-89 days old	1[39]	Sens 43 Spec: 77 PPV 2.3 NPV 99.1	NA	VERY LOW
WBC≥20,000/mm^3 for predicting SBI (acute bacterial meningitis and	1[39]	Sens 18 Spec: 93	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
bacteraemia) in febrile infants 3-89 days old		PPV 3.2 NPV 98.9		
WBC<5000 or ≥15,000/mm^3 for predicting SBI (acute bacterial meningitis and bacteraemia) in febrile infants 3-89 days old	1[39]	Sens 58 Spec: 73 PPV 2.6 NPV 99.0	NA	VERY LOW
WBC<5000 or ≥20,000/mm^3 for predicting SBI (acute bacterial meningitis and bacteraemia) in febrile infants 3-89 days old	1[39]	Sens 33 Spec: 89 PPV 3.7 NPV 99.1	NA	VERY LOW
WBC for differentiating acute bacterial meningitis and isolated bacteraemia in febrile infants 3-89 days old	1[39]	AUC 59 (49-69)	Serious	VERY LOW
WBC <5000/mm^3 or >15000/mm^3 for predicting SBI in neonates with fever <12 hours without source	1[44]	Sens 28 Spec 87.7 PPV 43.75 NPV 78.1	NA	VERY LOW
WBC <5000/mm^3 or >15000/mm^3 for predicting SBI in neonates with fever <12 hours without source	1[44]	AUC 77 (67-85)	No serious imprecision	VERY LOW
WBC <5000/mm^3 or >15000/mm^3 for predicting SBI in neonates with fever >12 hours without source	1[44]	Sens 80 Spec 90.6 PPV 44.4 NPV 98	NA	VERY LOW
WBC <5000/mm^3 or >15000/mm^3 for predicting SBI in neonates with fever >12 hours without source	1[44]	AUC 79 (66-89)	No serious imprecision	VERY LOW
WBC for predicting any SBI in febrile 0-5 year olds	1[85]	AUC 65.3 (63.0-67.6)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC for predicting bacteraemia in febrile 0-5 year olds	1[85]	AUC 67.9 (59.8-75.9)	No serious imprecision	VERY LOW
WBC>15000/mm^3 for predicting any SBI in febrile 0-5 year olds	1[85]	Sens 47 (43-50) Spec 76 (74-77)	NA	VERY LOW
WBC>20000/mm^3 for predicting any SBI in febrile 0-5 year olds	1[85]	Sens 26 (23-29) Spec 90 (89-91)	NA	VERY LOW
WBC for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	Sens 37 Spec 86	NA	VERY LOW
WBC for predicting culture-proven bloodstream infection in critically ill infants (median age 33.4 weeks) admitted to ICU	1[102]	AUC 61	NA	VERY LOW
WBC>15,000/mm^3 for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	Sens 52.4 Spec 78.7 PPV 45.4 NPV 83.0	NA	VERY LOW
WBC for predicting SBI in infants aged 29 to 89 days admitted to the tertiary care paediatric unit	1[105]	AUC 72 (67-76)	No serious imprecision	VERY LOW
WCC <5000/mm^3 or >15000/mm^3 for predicting bacterial sepsis	1[107]	Sens 83.3 Spec 56.6 PPV 27.8 NPV 94.4	NA	VERY LOW
WBC for predicting of SBI in infants <3 months with fever without source	1[126]	AUC 69.2 (65.5-72.9)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC for predicting of IBI (invasive bacterial infection) in infants <3 months with fever without source	1[126]	AUC 58.3 (46.0-70.6)	Serious	VERY LOW
WBC for predicting septic shock in children admitted to PICU	1[134]	AUC 51 (41-60)	Serious	VERY LOW
WBC<1000/mm^3 for predicting bacterial sepsis in neonates >72 hours of life admitted to NICU	1[143]	Sens 1.0 Spec >99.99	NA	VERY LOW
WBC<5000/mm^3 for predicting bacterial sepsis in neonates >72 hours of life admitted to NICU	1[143]	Sens 7.0 Spec 96.1	NA	VERY LOW
WBC>20,000/mm^3 for predicting bacterial sepsis in neonates >72 hours of life admitted to NICU	1[143]	Sens 22.6 Spec 79.8	NA	VERY LOW
WBC>50,000/mm^3 for predicting bacterial sepsis in neonates >72 hours of life admitted to NICU	1[143]	Sens 1.0 Spec 99.1	NA	VERY LOW
WBC for predicting occult bacterial infection in children aged between 3 and 36 months with fever	1[145]	AUC 72	NA	VERY LOW
WBC (cut-off 17.1x10^3/L) for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	Sens 69 (51-89) Spec 80 (75-85) PPV 31 (20-43) NPV 95 (92-98)	NA	VERY LOW
WBC (cut-off 17.1x10^3/L) for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	AUC 69 (61-77)	No serious imprecision	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC (cut-off >15 x 10^9 cells/l) for predicting SBI in well-appearing febrile children without obvious infection, ≥ 36 months old with documented fever	1[200]	Sens 56.7 (37.7–74.0) Spec 76.3 (69.6–82.0) PPV 0.27 (0.17–0.40) NPV 0.92 (0.86–0.95)	NA	VERY LOW
WBC (cut-off >19 x 10^9 cells/l) for predicting SBI in well-appearing febrile children without obvious infection, ≥ 36 months old with documented fever	1[200]	Sens 46.7 (28.8–65.4) Spec 90.2 (84.9–93.8) PPV 0.15 (0.11–0.20) NPV 0.85 (0.80–0.89)	NA	VERY LOW
WBC for discriminating definite SBI v no SBI in infants aged ≤90 days with a temperature ≥38.0˚C	[204]	AUC 66	NA	VERY LOW
WBC for discriminating definite and possible SBI v no SBI in infants aged ≤90 days with a temperature ≥38.0˚C	[204]	AUC 61	NA	VERY LOW
WBC for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	AUC 81 (76-85)	No serious imprecision	VERY LOW
WBC>14100x 10^6/l for predicting SBI in children aged 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection	1[205]	Sens 81.5 (70.3-89.3) Spec 70.8 (68.6-72.4) PPV 35.5 (30.6-38.9) NPV 95.1 (92.1-97.2)	NA	VERY LOW
WBC≥15,000/mm^3 for predicting serious infection in children with fever	1[228]	Sens 10 Spec 95 PPV 44 NPV 72	NA	VERY LOW
WBC≥20,000/mm^3 for predicting serious infection in children with fever	1[228]	Sens 29 Spec 93 PPV 63	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
		NPV 76		
WCC (10^3/µl) for diagnosis of SBI in neonates aged 4-90 days seen in the ED for fever (multivariable analysis)	1[249]	OR 1.1 (1.03-1.16)	No serious imprecision	VERY LOW
WBC (≤12 hours, cut-off 10000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 50 Spec 33	NA	VERY LOW
WBC (≤12 hours, cut-off 15000/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 17 Spec 67	NA	VERY LOW
WBC (≤12 hours, cut-off 17500/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 17 Spec 74	NA	VERY LOW
WBC (>12 hours, cut-off 10000/mm^3)for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 100 Spec 47	NA	VERY LOW
WBC (>12 hours, cut-off 15000/mm^3)for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 82 Spec 69	NA	VERY LOW
WBC (≤12 hours, cut-off 17500/mm^3) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	Sens 73 Spec 79	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC (≤12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 37 (11-64)	Serious	VERY LOW
WBC (>12 hours) for predicting SBI in children with documented fever 39°C and found to have no localizing source of fever	1[269]	AUC 85 (75-94)	No serious imprecision	VERY LOW
WBC for predicting SBI in children aged 1-36 months, temperature ≥39˚C; clinically undetectable source of fever	1[271]	AUC 76.1 (62.8-89.5)	No serious imprecision	VERY LOW
WBC<5 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.05 (0.02-0.11) Spec 0.92 (0.90-0.94)	NA	VERY LOW
WBC<5 or >15 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.47 (0.37-0.57) Spec 0.66 (0.63-0.70)	NA	VERY LOW
WBC>10 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.72 (0.62-0.80) Spec 0.47 (0.43-0.51)	NA	VERY LOW
WBC>15 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.42 (0.33-0.52) Spec 0.74 (0.71-0.78)	NA	VERY LOW

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
WBC>20 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.16 (0.10-0.25) Spec 0.93 (0.91-0.95)	NA	VERY LOW
WBC>25 for predicting SBI in infants and children under 3 months of age, temperature of ≥100.4˚F, or if they were between 3 and 24 months of age and had temperature ≥102.3˚F	1[276]	Sens 0.02 (0.00-0.07) Spec 0.98 (0.96-0.99)	NA	VERY LOW
WBC≥20 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	AUC 50 (33-68)	Serious	VERY LOW
WBC≥20 x 10^9/l for predicting late onset sepsis in neonates with late onset sepsis suspected sepsis and commenced on antibiotics	1[296]	Sens 22 (10-34) Spec 75 (62-88) PPV 36 (22-50) NPV 60 (46-74)	NA	VERY LOW
WBC for predicting SBI in children aged 1 to 36 months with fever >39˚C without localising signs	1[308]	AUC 56 (38-74)	Serious	VERY LOW
WBC >15x10^9/l for predicting SBI in children aged 1 to 36 months with fever >39˚C without localising signs	1[308]	Sens 50 Spec 53.1 NPV 89.5 PPV 11.8	NA	VERY LOW
WBC≥15,000/mm^3 for predicting SBI in children<18 years of age presenting to paediatric ED with rectal temperature ≥106˚F	1[311]	OR 0.78 (0.29-2.08)	Serious	VERY LOW

Table 104: Clinical evidence summary: Combination of tests, children and neonates

Risk factors/outcomes/population	Number of studies	Effect and CI	Imprecision	Quality of evidence
Leucocytes ≥15G/L or Band ≥1.5G/L for predicting SBI in children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination.	1[112]	Sens 55 (36-74) Spec 72 (61-83) PPV 80 NPV 46	NA	VERY LOW
WBC (cut-off 17.1x103/L) or CRP≥3.1 for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	Sens 76 (59-92) Spec 58 (51-64) PPV 19 (12-27) NPV 95 (91-99)	NA	VERY LOW
WBC (cut-off 17.1x103/L) or CRP≥3.1 for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	AUC 63 (53-71)	No serious imprecision	VERY LOW
ANC (cut-off 10.5x103/L) or CRP≥3.6 for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	Sens 79 (64-95) Spec 50 (43-56) PPV 17 (10-23) NPV 95 (91-99)	NA	VERY LOW
ANC (cut-off 10.5x10^3/L) or CRP≥3.6 for predicting occult bacterial infection (OBI) in children aged between 3 and 36 months with fever	1[146]	AUC 66 (57-74)	No serious imprecision	VERY LOW
CRP>85mg/L and ANC >10,000 mm^3/L or WBC >15,000 mm^3/L, for predicting positive blood culture in neonates or children with a fever >38°C	1[290]	Sens 84 Spec 27 PPV 48.8	NA	VERY LOW
CRP>85mg/L and ANC >10,000 mm^3/L and WBC >15,000 mm^3/L, for predicting positive blood culture in neonates or children with a fever >38°C	1[290]	Sens 36 Spec 84.5 PPV 62.1	NA	VERY LOW

8.3.5 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Table 105: UK costs of blood tests

Test	GP Point of care	GP Send to lab Error! Reference ource not found.(a)(b)	Ambulance Point of care	ED or ward Point of care	ED or ward Send to lab(c)
Glucose	YES(a)	£2.40	YES(a)	Usually done on blood gas machine. See row below.	£3.40
Blood gas: pH, bicarbonates, lactate, glucose, Na, K	NA – but possible	NA	NA	£11.70 (e)	(use POC)
Lactate	NA – but possible	£6.20	£2.04(g)	(See blood gas)	£5.90
Full blood count (haemoglobin, platelets, white cell count, lymphocytes, neutrophils)	NA	£2.42	NA	NA	£3.10
Immature to total neutrophil ratio (I/T)	NA	Not routinely available Blood film (special) £7.65	NA	NA	NA
Bands or toxic granulations	NA	Blood film (special) £7.65	NA	NA	NA(f)
Biochemical tests (renal function, liver function, urea, electrolytes, creatinine)	NA	Renal: £2.64 LFT: £2.88	NA	NA	£5.00
Clotting screen (INR, APTR, fibrinogen, haematocrit)	NA	£5.12	NA	NA	£4.70
Thrombin time (TT)	NA	£15.48	NA	NA	£13.30
C-reactive protein (CRP)	NA – but possible	£1.12	NA	NA – but possible	£3.90

YES: available, cost tbc; NA: Not available currently; POC: Point of care; LFT: Liver function test

(a) Cost would be very small as equipment cost would be spread over many patients so cost would mainly be cost of the strips.

(b) This would involve sending to lab (for example, at local hospital) and would take several hours at best for reply.

(c) Source: KCL Viapath. Provided by Anthony Wierzbicki.

(d) Source: Southampton Hospital NHS trust. Provided by GDG Chair. Lab would usually be within the hospital, but would still take time for results.

(e) Source: Southampton Hospital NHS trust. Provided by GDG Chair.
(f) Rarely available in UK
(g) Source: CQUIN: Lactate Monitoring Device Appraisal. Provided by GDG member (April 2015). This is the average cost per test strip. Average price of the device is £275, however on a per patient basis the cost of the machine would be small.

8.3.6 Evidence statements

Clinical

All the evidence included in the review was of very low quality. The results for all the blood tests were inconclusive. No clear sense of whether sensitivity or specificity increased or decreased with increasing blood test thresholds could be ascertained from the reported data. There was considerable variation in the participant inclusion criteria and the settings.

Economic

No relevant economic evaluations were identified.

8.3.7 Recommendations and link to evidence

Recommendations	**The evidence for diagnostic accuracy of routine blood tests is discussed below and recommendations for blood tests are included in recommendations 44,51,59,66,74,82.** **12 years and over** **44. For adults and children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:** **• arrange for immediate review by the senior clinical decision maker** **• carry out a venous blood test for the following:** **– blood culture** **– full blood count** **– C reactive protein** **– urea and electrolytes** **– creatinine** **– clotting screen** **– blood gas to include lactate measurement** **• give a broad-spectrum antimicrobial at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.4** **• discuss with consultant.** **51. For adults and children and young people aged 12 years and over with suspected sepsis and 2 or more moderate to high risk criteria, carry out a venous blood test for the following :** **• blood culture** **• full blood count** **• C reactive protein** **• urea and electrolytes**

	• creatinine • blood gas for lactate • arrange for a clinician to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria. 5-11 years 59. For children aged 5- 11 years who have suspected sepsis and 1 or more high risk criteria: • arrange for immediate review by the senior clinical decision maker • carry out a venous blood test for the following: – blood culture – full blood count – C reactive protein – urea and electrolytes – creatinine – clotting screen – blood gas for glucose and lactate 66. For children aged 5-11 years with suspected sepsis and 2 or more moderate to high risk criteria: • carry out a venous blood test for the following : – blood culture – full blood count – C reactive protein – urea and electrolytes – creatinine – blood gas for lactate • arrange for a clinician to review the person's condition and test results within 1 hour of meeting moderate to high risk criteria. Children aged under 5 years 74. For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria: • arrange for immediate review by the senior clinical decision maker • carry out a venous blood test for the following: – blood culture – full blood count – C reactive protein – urea and electrolytes – creatinine – clotting screen – blood gas for glucose and lactate

	• **give parentral antibiotics (with 1 hour of identifying that they meet any high risk criteria; see section 8.4)** • **discuss with consultant.** **82.For children aged under 5 years with suspected sepsis and 2 or more moderate to high risk criteria:** • **carry out a venous blood test for the following :** – **blood culture** – **full blood count** – **C reactive protein** – **urea and electrolytes** – **creatinine** – **blood gas for lactate** • **arrange for a clinician to review the person's condition and test results within 1 hour of meeting 2 or more moderate to high risk criteria.**
Relative values of different outcomes	Diagnostic test accuracy studies were used in this review where accuracy of a given blood test was measured against a reference standard (blood culture proven infection, composite definitions of sepsis), and sensitivity, specificity, positive predictive value, negative predictive value, ROC curve and area under the curve were reported where available. The GDG also regarded the clinical outcome of all-cause mortality to be an appropriate reference standard. Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with sepsis would have serious implications, including death. Sensitivity was important because the misclassification of an individual without sepsis would result in inappropriate administration of antibiotics. The GDG considered all-cause mortality to be a critical outcome.
Trade-off between clinical benefits and harms	The consequences of missing a diagnosis of sepsis are severe, as the mortality rate in sepsis is high. People with sepsis can be difficult to identify. Simple blood tests that would identify people with sepsis and/or people at risk of poor outcomes would be helpful in identifying those who require interventions rapidly. A test which performs poorly will give false reassurance and be of potential harm. A test which if normal or low would allow people to be safely discharged would be helpful in settings such as emergency departments. High specificity indicates ability to correctly identify people who do not have the problem being tested for. Given the possible consequences of missing sepsis the GDG were looking for very high specificity values of at least 80%. The evidence indicated that commonly available blood tests had poor performance overall for diagnosis. Many studies reported AUC only without information as to sensitivities and specificities at specific thresholds. A number of potential blood tests were included in the protocol but the GDG were aware that the two tests most commonly used as possible indicators of inflammation were CRP and WCC. **C Reactive Protein (CRP)** The results for CRP were inconclusive. Critically ill patients in ICU without sepsis have a high CRP indicating in keeping with CRP being a marker for inflammation from any cause. In such a scenario CRP would be unlikely to be a pivotal factor in making a decision on treatment options. Considering the clinical scenarios where CRP might be useful to rule out sepsis such as in emergency departments the specificity values

	were unacceptably low. CRP is usually undetectable in blood. Levels of 10 mg/l had a specificity of 18% to detect bacteraemia in an Australian emergency department study (Adams 2005[2]). Using a level of 5 0mg/l in a study in emergency department in the Netherlands (De Jager 2010[81]) increased specificity to 37% which is still unacceptability low to be used as a 'rule out' test in such a serious diagnosis. Values for sensitivity and specificity for CRP were better in children than in adults but the disparate nature of the evidence and the low quality of evidence combined with the difficulty in taking blood from young children meant the GDG did not think CRP added sufficient benefit to decision making to recommend that it be used in this way. **White Cell Count (WCC)** A high WBC can indicate infection, but a low or normal level can indicate a lack of response to infection and this may be particularly seen when infection is overwhelming. The use of WCC in assessing people who might have sepsis is therefore inherently difficult. The GDG were interested in sensitivity and specificity for both low and high values and many studies in people being assessed for sepsis report results in this way. The results for WCC were inconclusive for sensitivitity and the specificity was not adequate to be able to rule out series infection using WCC in settings where this would be of most benefit. Some studies reported on individual white cell types such as neutrophils but these has similar specificity to total WCC. Immature neutrophils (or bands) are produced as part of the pathway of development of neutrophils. An increase in immature cells in the bloodstream is understood to be caused by a response of the bone marrow to infection. These may be an early sign of infecton but research is at an early stage and insufficent evidence was found to make any recommendation. Immature neutrophils are not regularly reported in England. The results for neutrophils were inconclusive. The GDG were aware of developing research in this area which would inform further guidance. **Lactate** Very few studies assessing lactate were found in the initial evidence review and the evidence was inconclusive (see 8.1). A specific diagnostic accuracy review examining clinical outcomes was added and this is discussed further in section 8.3.9. **Clotting** The dysfunction associated with sepsis can alter the body's ability to clot. The evidence was inadequate to consider recommending routine assessment of clotting to either diagnose clotting or to predict outcomes and the GDG did not therefore make a recommendation to assess clotting factors for these purposes.
Economic considerations	No economic evidence was identified for this question. The benefit of recognising sepsis early comes from the benefit that early treatment can provide, as early diagnosis is an enabler of early treatment. Therefore the cost effectiveness of a test comes from the management that the test indicates, and a test with high sensitivity and specificity is generally more cost effective than a test with low sensitivity and specificity. A test with a high sensitivity will appropriately identify the people who correctly have sepsis and will lead to a low number of false negatives. False negatives will not receive treatment when they should have and may therefore deteriorate and require further downstream costs. A test with a high specificity will correctly rule out people without sepsis and will lead to a low number of false positives. False positives will receive treatment that they did not need which would be an unnecessary use of resources.

	The GDG were presented with costs of the various tests in different settings. Some tests such as bands or immature to total neutrophil ratio are not routinely available, and would require a change in practice to implement. Blood glucose is measured by gas machine in the ED, but via test strips in GP/primary care. Costs for GP/primary care do not need to be included as blood glucose level would not be checked in this setting if a person's GPs may be concerned the patient has sepsis. It was noted that if thrombin time is recommended, it is expensive if done separately and is sometimes included in clotting screens, but not always. Most tests were in the region of a few pounds, with blood gas and clotting tests (combining the tests labelled clotting tests and thrombin time together) being the most expensive. The test costs can vary between hospitals based on individual laboratory arrangements. The clinical review identified many studies looking at a variety of tests and also some in combination. However the data could not be meta-analysed and was generally of very low quality. The tests also generally had a trade-off whereby if sensitivity was high then specificity would be low or vice versa. Low sensitivity would mean missing people which might be considered more important than unnecessarily observing or treating people given the high mortality associated with sepsis. Overall the GDG agreedthat no test should be taken in isolation, and test results should be taken together with clinical factors when making a decision. The GDG recommended tests that are generally considered current practice (full blood count, CRP, lactate, creatinine, clotting screen, Urea/Electrolytes), and also specified which risk groups should have which tests, so there needs to be a suspicion of sepsis along with some additional criteria (from the stratification) for tests to take place. The GDG agreed that the turnaround of the tests should happen quickly with an appropriate clinician interpreting them. This may put pressure on laboratories, and also on staff to be present in a timely manner, however the benefit that timely management would bring such as early administration of antibiotics, was considered to outweigh these costs. This recommendation is not likely to have a large cost impact.
Quality of evidence	Overall, the quality of evidence was very low. In many studies the description of selection of patients was limited, and it was unclear if selection was random or consecutive. The majority of studies had small numbers of patients, and the studies were unlikely to be sufficiently powered to take into account measurement variability. The majority of the studies did not provide sufficient information on the timing the blood test and the determination the diagnosis using the reference standard. In most studies it was unclear if physicians treating patients had been blinded to the index blood test result. There was significant variability amongst the included studies. The data could not be meta-analysed which contributed to the GDG lack of confidence in the evidence. • The inclusion criteria varied amongst the studies and were ill-defined. Some of this was inevitable as definitions of sepsis and severe sepsis have changed over time but in other cases terms such as bacteraemia were used when it was clear that the population were severely ill. • The settings in which the symptoms were assessed were not clear for example hospitalised patients on a general ward or ICU, or patients presenting to the ED. • For each sign or symptom, there was inconsistency on how the threshold was defined or what the abnormal value was. • The reference standard varied amongst the included studies. In addition the studies used differing definitions for sepsis, severe sepsis, progression to

	septic shock, bacteraemia, and serious bacterial infection.
Other considerations	The GDG considered that the evidence indicated that blood tests had poor performance overall for diagnosis or prognosis. Blood markers such as CRP and WCC can however be of use in monitoring of a patient's condition and other blood tests may be required for ensuring safety of interventions. The GDG therefore made recommendations for blood tests to be performed for those patients at high levels of risk who were more likely to need intervention and monitoring. The GDG agreed that patients in the high risk category should receive a clotting screen when bloods are taken as this group are most likely to need vascular access using a centrial line and a clotting screen is normal practice before this is carried out. The rationale for assessment of lactate, renal function tests and tests for disemminated intravascular coagulation (DIC) are discussed in sections 8.3.9, 8.3.15 and 8.3.21. Glucose measurement is important for children who may have an abnormal glucose level when unwell but this is not sepsis specific. People who will receive antibiotics should have a blood culture performed before they receive antibiotics (see chapter 14). The delivery of IV antibiotics and taking of blood cultures require venous access and the GDG agreed that required blood tests should be taken at the same time. People with two or more high to moderate risk criteria need the results of blood tests to further stratify their risk and the GDG therefore recommended that they should have blood tests and have the results of these reviewed within an hour of meeting high to moderate criteria. Blood tests for people at other risk levels are at the discretion of the clinican assessing the person with suspected sepsis. Research recommendations - see 8.3.8 and appendix N. (1) The evidence assesed for this guideline indicated that current blood tests are generally not helpful when assessing people suspected of sepsis to allow diagnosis of serious infection and initiation of appropriate antibiotics. During the development of this guideline NICE published Diagnostic guidance on use of procalcitonin (PCT) (DG18). The guidance found a lack of evidence for use of procalcitonin and the GDG agreed that it was a high priority recommendation to assess use of PCT specifically and other biomarkers as point of care tests to improve diagnosis of sepsis. The GDG therefore developed a research recommendation in this area (2) The reviews of scoring tools, signs and symptoms and blood tests did not find good evidence for tests that would rule out sepsis. This is an issue of significant important in emergency departments where people are often seen by junior staff who have to decide whether the person should be discharged. Decision rules to rule out sepsis would be useful in these situations and might consist of combination of clinical signs and blood simple blood tests.

8.3.8 Research recommendation

Please see appendix N for more detail.

2. **What is the clinical and cost effectiveness of procalcitonin (PCT) point-of-care tests at initial triage for diagnosis of serious infection and the initiation of appropriate antibiotic therapy?**

3. **Is it possible to derive and validate a set of clinical decision rules or a predictive tool to rule out sepsis which can be applied to patients presenting to hospital with suspected sepsis?**

8.3.19 Review question: In people with suspected sepsis how accurate is blood lactate to identify worsening sepsis?

For full details see review protocol in Appendix C.

Table 106: PICO characteristics of review question

Population	People with suspected sepsis or severe sepsis
Index test	Initial blood lactate
Reference standards	These were intended to be 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
Statistical measures	Sensitivity Specificity
Study design	Observational studies that included diagnostic accuracy analyses

8.3.10 Clinical evidence

A search was conducted for prospective and retrospective observational studies that examined the diagnostic test accuracy of blood lactate for the early identification of people likely to experience worsening sepsis.

Seventeen studies[50,55,97,106,139,150,168,191,193,211,263,273,284,312,321-323] were identified (**Table 107**). Two of the included papers were in children[168,284]. These have been highlighted in the review but are presented alongside adult study data as there had been no *a priori* plans to stratify for age.

The aim of this review was to identify a blood lactate threshold at which an individual with suspected sepsis should receive urgent care. Diagnostic test accuracy data was considered the most informative data because the sensitivity and specificity data are derived at a given threshold. Clinical outcomes were considered the most appropriate given the objective was to identify people likely to have poorer prognosis. The review identified studies with sensitivity and specificity data for the following outcomes; all-cause mortality, development of septic shock and ICU admission. It was not possible to conduct meta-analysis of the diagnostic accuracy data because of

This review did not utilise ORs because a lactate level above a particular threshold may give a statistically significant and strong effect for an increased odds of the outcome (for example OR (95%CI): 3.4(2.8-4.5)) but if the same data yields a sensitivity of (for example) 60% for that threshold then even though there is an increase in odds, the accuracy of the test may not be acceptable. It was therefore considered that odds ratios would not be helpful for formulating recommendations for the use of lactate in the context prioritising people with suspected sepsis for urgent care.

Evidence from the included studies is summarised in the clinical evidence profiles below (**Table 108**, **Table 109**, **Table 110**, **Table 111** and **Table 112**). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix L.

Results have been stratified by initial lactate levels (defined by the mean in a study) according to the following; <2, 2-4 and >4 mmol/l. This stratification was based on the GDG's understanding that the differing levels would represent different degree of severity of initial sepsis, which would influence how predictive lactate was of death or disease progression. All included papers provided sensitivity and specificity data but most provided the information at a limited number of different thresholds. Hence the authors of all of these were also contacted for further diagnostic accuracy data at a range of thresholds. One study author[323] responded accordingly and the additional data provided was added to the review. Some other papers only included area under ROC curve data (see excluded study list in Appendix L. The authors of these papers were contacted for more information on the sensitivities and specificities at each threshold which they used to derive the ROC curve data. One study author[273] provided this information, and so this paper has been included.

Table 107: Summary of studies included in the review

Study	Population	Test(s)	Target condition	Quality of evidence
Casserly 2015[50]	n=19,945 adults with sepsis Hospitals (n=218) Patient data from the	Lactate	In-hospital mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded

Study	Population	Test(s)	Target condition	Quality of evidence
	Surviving Sepsis Campaign database USA Initial lactate 2-4 mmol/l Mean age: unclear Other characteristics: unclear			to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Caterino 2009[55]	n=935 adults with sepsis ED USA Initial lactate: 2-4 mmol/l but not clear Mean (SD) age: 79.1 (8.3) years	Lactate	30-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Femling 2014[97]	n=378 adults with sepsis or severe sepsis ICU USA Initial lactate >4 mmol/l APACHE score: 17 in those who died; 14 in survivors Median (IQR) age: 59 (57-60) years	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Freund 2012[106]	n=462 adults with suspected infection ED France Initial lactate <2 mmol/l Mean (SDS) age: 64 (20) years	Lactate	Sepsis Severe sepsis Sepsis shock	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Hoeboer 2012[139]	n=101 adults with fever in ICU The Netherlands Initial lactate <2 mmol/l SOFA score: 2 to 14 Age was between 19 and 81 years	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment , which would possibly affect outcome.
Jansen 2009[149]	n=394 adults with sepsis ICU The Netherlands	Lactate	28 day mortality	Risk of bias: very serious, principally due to physicians treating patients not being blinded to the lactate status. This means that lactate levels

Study	Population	Test(s)	Target condition	Quality of evidence
	Initial lactate 2-4 mmol/l APACHE II: 18 Mean (SD) age: 65 (16) years			could affect treatment, which would possibly affect outcome.
Kim 2013A[168]	n=65 adults with sepsis ICU South Korea Initial lactate >4 mmol/l PRISM III score: 16.5 Mean (SD) age: 10(6.1) years	Lactate clearance	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Linder 2009[191]	n=233 adults with fever and suspected infection Infectious diseases clinic Sweden Initial lactate 2-4 mmol/l SIRS score: 2.38 Age ranged from 18-92 years	Lactate	Severe sepsis with or without septic shock	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Lorente 2009[193]	n=192 adults with severe sepsis ICU Spain Initial lactate 2-4 mmol/l APACHE II score: 19 Median (IQR) age: 60 (49-70) years	Lactic acid	ICU mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Marty 2013[211]	n=94 adults with sepsis ICU France Initial lactate >4 mmol/l SAPS 2: 60 Mean (SD) age: 58 (16) years	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Phua 2008[263]	n=77 adults with septic shock admitted to ICU within 24 hours Initial lactate 2-4 mmol/l APACHE II score: 26.9 Mean (SD) age: 55 (16) years in survivors and 54 (17) years in non-	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.

Study	Population	Test(s)	Target condition	Quality of evidence
	survivors			
Puskarich 2013[273]	n=187 adults with sepsis Tertiary hospitals ED USA Initial lactate >4 mmol/l SOFA score: 6 in survivors and 9.5 in non-survivors Mean (SD) age: 60 (16.7) years in survivors and 67 (13.7) years in non-survivors	Lactate	In-hospital survival	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Scott 2012[284]	n=239 children with sepsis ED USA Initial lactate 2-4 mmol/l Mean age: unclear but all children and most 2-12 years	Lactate	ICU admission	Risk of bias: Serious; convenience sample used.
Trzeciak 2007[312]	n=1177 adults with infection Urban Medical Centre (ED, ICU and non-ICU wards) USA Initial lactate 2-4 mmol/l Age unclear but 48% were between 50 and 75 years	Lactate	In-hospital `mortality	Risk of bias: very serious, principally due to physicians treating patients not being blinded to the lactate status. This means that lactate levels could affect treatment, which would possibly affect outcome.
Vorwerk 2009[321]	n=307 adults with sepsis ED UK Initial lactate 2-4 mmol/l MEDS score: 7.9 Mean age: 66.6 years in survivors and 79.7 years in non-survivors)	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Wacharasint 2012[322]	n=665 adults with septic shock ICU Canada	Lactate	28-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The

Study	Population	Test(s)	Target condition	Quality of evidence
	Initial lactate 2-4 mmol/l APACHE II score: 27 Mean age approximately 62 years			assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Walker 2013[323]	n=78 adults with sepsis ICU admitted directly from ED UK Initial lactate 2-4 mmol/l APACHE II score: 24.9 Median (IQR) age: 56(40-66) years	Lactate	30-day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.

8.3.11 Clinical evidence summary table: Initial lactate

8.3.11.1 Strata 1: Studies where the mean initial lactate in each study was >4 mmol/l

8.3.11.1.1 Initial lactate and all-cause mortality

Table 108: Diagnostic accuracy profile for initial lactate and all-cause mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of >4 mmol/l and in-hospital mortality								
Femling 2014[97] Puskarich 2013[273] [c]	n=378 n=187	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.54 (0.46-0.63) 0.64	0.52 (0.46-0.5) 0.47	VERY LOW
Threshold of ≥5 mmol/l and 28-day mortality (CHILDREN)								
Kim 2013A[168]	n=65	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.44 (0.21-0.69)	0.81 (0.67-0.91)	VERY LOW
Threshold of ≥5.4 mmol/l and 28-day mortality								
Marty 2013[211]	n=94	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.77 (0.63-0.87)	0.55 (0.39-0.70)	VERY LOW

(a) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.

(b) Confidence intervals sufficiently variable to reduce confidence in the estimate.

(c) Study reported sensitivity and specificity for <4 mmol/l to predict survival. It can be easily shown on a 2x2 table that the sensitivity and specificity for >4 mmol/l to predict mortality can be derived by simply switching sensitivity and specificity values.

8.3.11.2 Strata 2: Studies where the mean initial lactate in each study was 2-4 mmol/l

8.3.11.2.1 Initial lactate and all-cause mortality

Table 109: Diagnostic accuracy profile for initial lactate and all-cause mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥1 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	1.0	0.0	VERY LOW
Threshold of ≥1.4 mmol/l and 28-day mortality								
Wacharasint 2012[322]	n=665	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.86	0.27	VERY LOW
Threshold of ≥2.01 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.96	0.08	VERY LOW
Threshold of ≥2.3 mmol/l and 28-day mortality								
Wacharasint 2012[322]	n=665	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.60	0.55	VERY LOW
Threshold of ≥2.4 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.88	0.13	VERY LOW
Threshold of ≥2.5mmol/l and 28-day mortality								
Jansen 2009A[150]	n=394	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.44 (0.28-0.60)	0.57 (0.46-0.67)	VERY LOW
Threshold of ≥2.95 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.8	0.18	VERY LOW
Threshold of ≥3.1 mmol/l and ICU mortality								
Lorente 2009[193]	n=192	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.55	0.75	VERY LOW
Threshold of ≥3.5 mmol/l and 28-day mortality								
Phua 2008[263]	n=77	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.53	0.71	VERY LOW
Threshold of ≥3.55 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.76	0.37	VERY LOW

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥4.0 mmol/l and 28-day mortality/in-hospital mortality								
Vorwerk 2009[321] Trzeciak2007[312] Caterino 2009[55] [c] Casserly2015[50]	n=307 n=1177 n=935 n=19945	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[d]	0.49 (0.35 – 0.63) 0.19 (0.15-0.23) 0.29 (0.17-0.42) 0.41 (0.40-0.42)	0.74 (0.65-0.82) 0.93 (0.91-0.94) 0.95 (0.94-0.97) 0.73 (0.72-0.74)	VERY LOW
Threshold of ≥4.15 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.76	0.38	VERY LOW
Threshold of ≥4.4 mmol/l and 28-day mortality								
Wacharasint 2012[322]	n=665	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.36	0.82	VERY LOW
Threshold of ≥4.5 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.68	0.39	VERY LOW
Threshold of ≥5.05 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.64	0.44	VERY LOW
Threshold of ≥5.6 mmol/l and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.52	0.54	VERY LOW

(a) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.

(b) Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Some studies failed to give raw data and so CIs could not be calculated.

(c) Unclear if this was from the <2 strata or 2-4 strata. Consideration of the categorical data given suggested that mean lactate would have been very close to 2, and so this has been placed in the 2-4 strata

(d) In Vorwerk 2009 only, confidence intervals sufficiently variable to reduce confidence in the estimate.

8.3.11.2.2 Initial lactate and ICU admission

Table 110: Diagnostic accuracy profile for initial lactate and ICU admission

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥4.0 mmol/l for predicting later ICU admission (CHILDREN)								
Scott 2012[284]	n=239	Serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.26 (0.09-0.51)	0.94 (0.90-0.97)	VERY LOW

(a) Risk of bias mainly due to lack of evidence that the sampling was consecutive or random.
(b) Confidence intervals sufficiently variable to reduce confidence in the estimate.

8.3.11.2.3 Initial lactate and worsening sepsis

Table 111: Diagnostic accuracy profile for lactate and worsening of sepsis with or without septic shock

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥2.5 mmol/l and severe sepsis with/without shock								
Linder 2009[191]	233	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.25	0.975	VERY LOW

(a) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment which would possibly affect outcome.
(b) Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Studies failed to give raw data and so CIs could not be calculated.

8.3.11.3 Strata 3: Studies where the mean initial lactate in each study was ≤2 mmol/l

8.3.11.3.1 Initial lactate and all-cause mortality

Table 112: Diagnostic accuracy profile for initial lactate and all-cause mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥1.7 mmol/l for predicting 28-day mortality								
Hoeboer 2012[139]	n=101	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.60	0.75	VERY LOW
Threshold of ≥2 mmol/l for predicting in hospital mortality or ICU admission								

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Freund 2012[106]	n=462	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.54 (0.45-0.64)	0.76 (0.72-0.81)	VERY LOW

1 *(a) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect*
2 *treatment, which would possibly affect outcome.*
3 *(b) Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Some studies failed to give raw data and so CIs could not be calculated for*
4 *those.*

8.3.12 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Table 113: UK costs of lactate testing

Test	GP Send to lab [(a)(b)]	Ambulance Point of care	ED or ward Point of care	ED or ward Send to lab[(C)]
Lactate	£6.20	£2.04[(c)]	£11.70 Blood gas: (test include: pH, bicarbonates, lactate, glucose, Na, K)	£5.90

pH = measure of acid base balance; Na = measure of sodium, K = Potassium

(a) This would involve sending to lab (for example, at local hospital) and would take several hours at best for reply.

(b) Source: KCL Viapath. Provided by Anthony Wierzbicki.

(c) Source: CQUIN: Lactate Monitoring Device Appraisal. Provided by GDG member (April 2015). This is the average cost per test strip. Average price of the device is £275, however on a per patient basis the cost of the machine would be small.

8.3.13 Evidence statements

Clinical

The evidence from the seventeen studies included in the review was of very low quality for all outcomes. The highest sensitivity was found in one study with a blood lactate threshold of 1 mmol/l for the outcome of all-cause mortality. However the population all had initial lactates of >2 mmol/l at baseline and at this threshold the level was not specific. Generally as the thresholds increased up to >5.4 mmol/l the sensitivity was lower and the specificity increased for the outcome of all-cause mortality. Two studies using thresholds in the range of 2-4 mmol/l found that specificity was higher compared with sensitivity for the outcome of ICU admission. One study using a threshold of <2 mmol/l found that specificity was higher compared with sensitivity for the composite outcome of in-hospital mortality or ICU admission.

Economic

No relevant economic evaluations were identified.

1

8.3.14 Recommendations and link to evidence

Recommendations	**The evidence for diagnostic accuracy of lactate to identify worsening sepsis is discussed below and the main recommendations informed by this review are recommendations 45,46,47,52,53,54,60,61,62,67,75,76,77,83** **12 years and over** **45. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre, or blood pressure less than 90 mmHg:** • **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5 and** • **refer to critical care for review of central venous access and initiation of inotropes or vasopressors and admission to critical care** **46. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:** • **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.** **47. For adults and children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:** • **consider giving fluids (in line with recommendations in section 8.5).** **52. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury , treat as high risk and follow recommendations 44-50.** **53. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:** • **repeat structured assessment at least hourly** • **ensure review by a senior clinical decision maker within 3 hours of meeting moderate to high risk criteria for consideration of antibiotics.** **54. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:**

- **manage the definitive condition**

- **if appropriate, discharge with information (see recommendations 121 and 122) depending on the setting.**

5-11 years

60. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate over 4 mmol:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria in line with recommendations in section 8.5) and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care**

61. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

62. For children aged 5-11 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- **consider giving fluids in line with recommendations in section 8.5.**

67. For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 59 to 65.

Children aged under 5 years

75. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre:

- **give fluids (in line with recommendations in section 8.5) and**
- **refer to critical care for review of central access and initiation of inotropes or vasopressors and admission to critical care.**

76. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- **give fluids as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.5.**

77. For children aged under 5 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre, consider giving fluids in line with recommendations in section 8.5.

	83. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 74 to 81.
Relative values of different outcomes	Diagnostic test accuracy studies were used in this review and the GDG identified all-cause mortality at 28 days, ICU admission, hospitalisation and length of stay as appropriate reference standards for poor sepsis outcomes. Sensitivity was regarded as critical, as sensitivity measures the ability of the test to identify those with the target condition (poor sepsis outcomes). Specificity was also important, as specificity measures the ability of the test to identify those who do not have the target condition (worsening sepsis).
Trade-off between clinical benefits and harms	The evidence was complicated by different settings and different populations. The highest sensitivity for detecting mortality of 100% was seen with a threshold of 1.0 mmol/l, but this was in a patient sample who all had initial lacates of >2 mmol/l at baseline and so this result is an artefact of a threshold that selected every person as 'positive' for predicted mortality. Consequently the specificity was 0%. This threshold is therefore equivalent to assuming that all are at risk of developing worsening sepsis leading to death. More meaningful results are the sensitivity of 86% seen in one study in the >4 mmol/l stratum and in one at the 2-4 mmol/l stratum. These were at thresholds of 2 and 1.4 mmol/l respectively. A sensitivity of 86% indicates a 14% false negative rate and thus would imply not identifying 14% of those at risk of death. Specificity at this threshold was very low, and would not represent much improvement compared to treating everyone with suspected sepsis as though they were likely to have worsening sepsis. At higher thresholds even less useful sensitivities were seen, accompanied by steadily improving specificities. In the context of this review, poor sensitivity indicates a failure to detect those likely to have worsening sepsis. This could lead to serious consequences or death if the test was used to decide whether the patient should not be treated.
Economic considerations	No economic evidence was identified for this question. A lactate test in hospital is relatively cheap. It is usually done using a blood gas machine along with other tests, or as a lab based test. It is part of routine practice for patients suspected as sepsis. The purpose of this question is to identify a lactate level or threshold which is a good predictor that the patient's sepsis has a worse prognosis. The benefit of a prognostic tool comes from the management that it indicates. A tool/test is more likely to be cost effective if it has a high sensitivity and high specificity. In other words; correctly identifies those patients who are in need of more aggressive treatment and more likely to die (true positives) and also correctly identifies those patients who do not currently require more aggressive treatment (true negatives). A tool with a low sensitivity will miss a lot of people (false negatives) with worsening sepsis at the detriment to the health of those patients. A tool with low specificity will find many false positives who are incorrectly labelled as having worsening sepsis and will thus face unnecessary and potentially expensive and harmful interventions. Providing more aggressive treatment at a lower threshold would mean more people would receive the additional interventions such as being referred to ICU which would have resource and cost implications. Therefore the threshold needs to be a balance between low enough to catch the people who have developed severe sepsis but high enough that there are not a lot of people being treated unnecessarily. The GDG agreed that the lactate level is informative; however the clinical evidence showed a mixed picture and was generally of very low quality. A tiered recommendation was made of different actions based on the lactate level of the

	patient. With the patients seen as more severe (suspected sepsis and high risk factors for mortality accompanied with a high lactate level of >4) receiving the more intensive treatment and monitoring. Lactate measurement out of hospital is a point of care cost involving a handheld device and strips. The strips are not very expensive but have a use by date. In hospital lactate can be measured via the blood gas machine, or a sample sent to the lab. The GDG confirmed that GPs would not send tests to the lab for immediate sepsis diagnosis due to the need for immediacy of results, and that therefore the point of care costs would only be relevant in this setting or if the patient is seen by an ambulance or paramedic. The evidence for use of lactate was not adequate to recommend its use in these settings. The pathway in the guideline recommends lactate when deciding on critical care referral, fluids and consultant input. Point of care testing for lactate is therefore not required out of hospital unless transfer to hospital is prolonged and decisions about out of hospital care are required.
Quality of evidence	Quality of evidence was generally very low. One reason was high levels of imprecision or the lack of any measures of precision. Another reason was very serious risk of bias, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. In some of the studies the description of selection of participants was limited. The GDG agreed therefore that they could not be confident in the evidence due to poor quality.
Other considerations	The GDG were interested in whether lactate could be used a discriminating factor to indicate which patients required more urgent and aggressive treatment. The GDG discussed the relative importance of sensitivity and specificity, mainly the risk of missing people with sepsis against the harm to the population of treating people unnecessarily. However the evidence indicated a high sensitivity occurred mainly with lower lactate levels. Information on how many people this would identify is not available, but the GDG considered that a lactate of 2 mmol/l would pick up many people with less serious infections. The GDG concluded that the evidence was not strong enough to justify determining a particular lactate threshold on a rule in or rule out basis. The GDG considered whether lactate had a place in the pathway for people with suspected sepsis. They considered that the context in which lactate would be used was important. The evidence suggested that specificity was higher at higher lactate levels indicating that those patients with higher lactate levels were more likely to have poor prognosis. Lactic acid is an indication of poor perfusion and higher levels of lactate are consistent with a more compromised circulatory system. The GDG considered that as a group mortality is higher in the group of patients who have higher lactate level. The GDG therefore agreed to make a recommendation informed by the evidence and their experience. The pathway recommends that lactate level should not be used to decide who receives antibiotics but that all patients with suspicion of sepsis and high risk criteria should be given antibiotics . The GDG agreed that those patients with a lactate of greater than 4mmol/l should receive IV fluids, be referred to critical care and have involvement of consultant. People with lactate between 2mmol/l and 4mmol/l require IV fluids and discussion with the consultant and those whose lactate is less then 2mmol/l should also be discussed with consultant. High risk patients require reasssement for response to treatment and this includes reassement of lactate. This is discussed further in chapter 13.

8.3.15 Review question: In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis??

For full details see review protocol in Appendix C.

Table 114: PICO characteristics of review question

Population	People with suspected sepsis, severe sepsis or septic shock
Index test	Initial serum creatinine
Reference standards	These outcomes were intended to be gold 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
Statistical measures	Sensitivity Specificity Positive Predictive Value Negative Predictive Value ROC curve or area under the curve Odds ratio: univariate analyses only included if no multivariate analyses reported
Key confounders for studies reporting odds ratios	No pre-specified confounders
Study design	Observational studies that included diagnostic accuracy analyses

8.3.16 Clinical evidence

A search was conducted for prospective and retrospective observational studies that examined the diagnostic test accuracy of creatinine for the early identification of people likely to experience worsening sepsis.

Four adult studies.[138,184,291,297] There was no evidence found for the outcomes of ICU admission, hospitalisation or length of stay.

The aim of this review was to determine if raised creatinine levels were indicative of worsening sepsis, and as such, clinical outcomes were considered the most appropriate. Both diagnostic test accuracy statistics and ORs were considered to be informative. Firstly, ORs were examined to determine if there was an association of increased creatinine and poor prognosis, and diagnostic accuracy statistics could identify a threshold at which a patient should receive urgent care.

If a study reported both multivariate and univariate ORs then only the multivariate results were reported. It was not possible to conduct meta-analysis of the diagnostic accuracy data nor the ORs due to heterogeneity in the populations, settings, and outcomes between the included studies. No evidence was found for the outomes of ICU admission, hospitalisation or length of stay.

Table 115: Summary of studies included in the review

Study	Test(s)	Population	Outcome	Outcomes (statistical measures)	Quality of evidence

Study	Test(s)	Population	Outcome	Outcomes (statistical measures)	Quality of evidence
Hjortrup 2015[138]	Pre-admission serum creatinine	n=222 patients with severe sepsis ICU Denmark	28-day mortality	Serum creatinine AUC: 0.50 (0.42–0.58) Cut-off: ≥1.7 mg/dl (150.3 µmol/L) Sensitivity: 0.38 Specificity: 0.70 PPV: 0.62 NPV: 0.48	Convenience sample from the Scandinavian Starch for Severe Sepsis and Septic Shock (6S) RCT[259,259] Risk of bias: very high.
Leedahl 2014[184]	Serum creatinine within first 12 hours	n=390 patients with septic shock ICU USA	28-day mortality	Serum creatinine level increase, per 0.1 mg/dl (8.8 µmol/L) (n=333 patients with measured serum creatinine available) AUC: 0.54 (0.47-0.61) Univariate OR (95% CI): 0.95 (0.87-1.05) Multivariate OR (95%CI): 0.88 (0.79-0.98)	Retrospective observational design Risk of bias: very high.
Shapiro 2010A[293]	Serum creatinine level obtained in ED	n=661 patients with suspected sepsis ED USA	In-hospital mortality	AUC: 0.73 cut-off >0.7 mg/dl Sensitivity: 0.83 (0.75-0.94) Specificity: 0.17 (0.14-0.20) OR (95% CI): 1.27 (0.58-2.80) cut-off >1.7 mg/dl Sensitivity: 0.41 (0.28-0.54) Specificity: 0.81 (0.78-0.84) OR (95% CI): 2.94 (1.7-5.1)	Secondary analysis of prospective cohort (convenience sample)[294,295] Risk of bias: very high.
Shmuely 2000[297]	Serum creatinine level obtained in ED	n=2722 ED patients with bacteraemia USA	In-hospital mortality	Initial creatinine >3.0 mg/dl (265.2 µmol/L) Multivariate OR (95%CI): 1.7 (1.0-2.7)	Observational design, unclear description of multivariate analysis. Severity of sepsis unclear as study states patients with bacteraemia and mentions septic shock. Risk of bias: very high.

1

8.3.17 Clinical evidence summaries for serum creatinine

8.3.17.1 Clinical evidence summary: diagnostic accuracy

Table 116: Diagnostic accuracy profile for initial creatinine and all-cause mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≥1.7 mg/dl (150.3 µmol/L) and 28 day mortality								
Hjortrup 2015[138]	n=222	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.38	0.70	VERY LOW
Threshold of >0.7 mg/dl (61.9 µmol/L) and in-hospital mortality								
Shapiro 2010[291]	n=661	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.83 (0.75-0.94)	0.17 (0.14-0.20)	VERY LOW
Threshold of >1.7 mg/dl (150.63 µmol/L) and in-hospital mortality								
Shapiro 2010[291]	n=661	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.41 (0.28-0.54)	0.81 (0.78-0.84)	VERY LOW

(d) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the creatinine status and that the study selected participants from previously published RCT. The assumed lack of blinding means that creatinine levels could affect treatment, which would possibly affect outcome.

(e) Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Some studies failed to give raw data and so CIs could not be calculated.

(f) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the creatinine status and that the study selected participants from previously published prospective cohort study. The assumed lack of blinding means that creatinine levels could affect treatment, which would possibly affect outcome.

8.3.17.2 Clinical evidence summary: creatinine and odds ratios for clinical outcomes

Risk factor /outcomes/population	Study (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect and CI in single study	GRADE
Creatinine level increase, per 0.1 mg/dl (8.8 µmol/L) and 28-day mortality Septic shock patients in ICU	Leedahl 2014[184] (n=333)	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Multivariate OR (95%CI): 0.88 (0.79-0.98)	LOW

Risk factor /outcomes/population	Study (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect and CI in single study	GRADE
Initial creatinine >0.7 mg/dl (61.9 µmol/L) for and in-hospital mortality Patients with suspected sepsis	Shapiro 2010[291] (n=661)	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[cd]	OR (95% CI): 1.27 (0.58-2.80)	VERY LOW
Initial creatinine >1.7 mg/dl (150.3 µmol/L) for predicting in-hospital mortality Patients with suspected sepsis	Shapiro 2010[291] (n=661)	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[d]	OR (95% CI): 2.94 (1.7-5.1)	VERY LOW
Initial creatinine >3.0 mg/dl (265.2 µmol/L) for predicting in-hospital mortality ED patients with bacteraemia	Shmuely 2000[297] (n=2722)	Very serious[e]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Multivariate OR (95%CI): 1.7 (1.0-2.7)	VERY LOW

(a) Risk of bias mainly due to retrospective observational design and the lack of evidence that physicians treating patients were blinded to the creatinine status. The assumed lack of blinding means that creatinine levels could affect treatment, which would possibly affect outcome.

(b) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the creatinine status and that study selected participants from previously published RCT. The assumed lack of blinding means that creatinine levels could affect treatment, which would possibly affect outcome.

(c) Confidence intervals sufficiently variable to reduce confidence in the estimate.

(d) Unadjusted odds ratio.

(e) Risk of bias mainly due to lack of evidence that physicians treating patients were blinded to the creatinine status. The assumed lack of blinding means that creatinine levels could affect treatment, which would possibly affect outcome.

8.3.18 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

8.3.19 Evidence statements

Clinical

The evidence from the four studies included in the review was of low to very low quality for the outcome of all-cause mortality. A low threshold of ≥7 mg/l for serum creatinine resulted in a relatively low sensitivity and very low specificity, while a higher threshold of ≥17 mg/l resulted in a very low sensitivity and a relatively low specificity. The evidence identified suggested that higher values for serum creatinine could be an indicator for worsening sepsis.

Economic

No relevant economic evaluations were identified.

8.3.20 Recommendations and link to evidence

Recommendations	**The evidence for accuracy of creatinine to identify worsening sepsis is discussed below and the main recommendations this informs are recommendations 52,67,83.** **52. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 44 to 50.** **67. For children aged 5 to 11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 59 to 65.** **83. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk and follow recommendations 74 to 81.**
Relative values of different outcomes	Diagnostic test accuracy studies and studies reporting ORs were used in this review, and the GDG identified all-cause mortality at 28 days, ICU admission, hospitalisation and length of hospital stay as appropriate reference standards for poor sepsis outcomes. The GDG considered sensitivity as critical, because a raised creatinine is a sign of kidney dysfunction and missing a case will have severe consequences for the patient. The GDG considered specificity less important, because the identification of false positives was more acceptable in the context of the patient outcome of kidney failure. No evidence was found for the outcomes of ICU admission, hospitalisation or

	length of hospital stay.
Trade-off between clinical benefits and harms	Sepsis can lead to multiple-organ damage and the kidney is one of the organs frequently affected. Creatinine is a marker for kidney damage and it was the aim of this review to determine if raised creatinine levels were indicative of worsening sepsis and to identify a threshold at which a patient should receive urgent care. A threshold of ≥17 mg/l for initial creatinine for identifying 28 day all-cause mortality resulted in a very low sensitivity of 38% and a relatively low specificity of 70%. Using the same threshold to identify in-hospital mortality, sensitivity and specificity were slightly higher, with 41% and 81%, respectively. A lower threshold of 7 mg/l resulted in a sensitivity of 83% and a specificity of 17%, meaning that 17% of people at risk of death would not be identified. At the same time the low specificity of 17% would result in a very high number of people being falsely identified as at risk of death.
Economic considerations	No economic evidence was identified for this question. No additional cost would apply as creatinine testing is usually part of routine tests, but currently no decision making is based on it. However testing more of the population for creatinine or testing more frequently may increase costs (for example testing those at low risk of sepsis). If creatinine is used as a discriminator of severity, different thresholds will have different implications. A low threshold will mean more people are treated more aggressively (and involve additional resources) because they are thought to be worsening. A high threshold may mean some people that are worsening may being missed. A test with a low sensitivity will have a high number of false negatives and miss people that are deteriorating, and a test with a low specificity have a high number of false positives and will treat people more aggressively who actually are not deteriorating. In general a test with higher sensitivity and specificity will be more cost effective. It was noted that creatinine can be done as a point of care test, however the GDG are not recommending that creatinine point of care testing specifically be used. Creatinine would be done undertaken alongside standard blood tests. The GDG agreed that creatinine is not a point of care test and assessment of renal function is normal practice in unwell patients. They also agreed that creatinine is a marker of organ dysfunction and therefore people with evidence of acute kidney injury, as defined by existing guidance, should be considered high risk which would initiate more intensive treatment.
Quality of evidence	Overall, the quality of evidence was very low. The description of selection of patients was limited, and it was unclear if selection was random or consecutive. In most studies it was unclear if physicians treating patients had been blinded to the creatinine result. Two of the four studies only reported unadjusted odds ratios. The GDG agreed therefore that they could not be confident in the evidence due to the low quality.
Other considerations	The GDG agreed that creatinine is a marker of organ dysfunction and if a person with suspected sepsis did have abnormal renal function it would be a cause for concern. However the difficulty in an acute presentation is that the baseline kidney function of the patient is unlikely to be known, and baseline kidney function may differ for different groups, particularly the elderly. Setting a specific threshold of creatinine as a marker of deterioration is very difficult. The GDG considered that the proportion of people who have sepsis and acute kidney injury without other evidence of abnormal physiology is likely to be very small. A large proportion of patients with sepsis however are likely to be elderly, and therefore more likely to have existing poor kidney function, so either a low threshold or acute kidney injury as a single risk factor might mean giving antibiotics to a large number of elderly people with mild acute kidney injury who turn out to have another cause for their clinical presentation. Additionally, different Trusts have different levels of normal creatinine

	because of population mix. The GDG considered that the presence of acute kidney injury in a person with one moderate to high risk criteria indicated that they required more urgent assessment and intervention. They used consensus to recommend that people with moderate to high risk criteria should be treated as high risk if they have evidence of acute kidney injury (AKI). The GDG agreed that the definition of acute kidney injury is already the subject of guidance and therefore agreed that AKI should be defined as by the NICE guideline CG169 Acute Kidney Injury.

8.3.21 Review question: In people with suspected sepsis what is the extent to which disseminated intravascular coagulation (DIC) affects clinical outcomes? For full details see review protocol in Appendix C.

Table 117: PICO characteristics of review question

Population	People with suspected sepsis, severe sepsis or septic shock
Index test	Disseminated intravascular coagulation (DIC)
Reference standards	These outcomes were intended to be reference standard measures that a worsening of sepsis had taken place: • All-cause mortality at 28 days (or nearest time point) • Hospitalisation • ICU admission • Length of hospital stay
Statistical measures	Odds ratio: univariate analyses only included if no multivariate analyses reported
Key confounders for studies reporting odds ratios	No pre-specified confounders
Study design	Observational studies

8.3.22 Clinical evidence

A search was conducted for prospective and retrospective observational studies that examined the association of DIC for the early identification of people likely to experience worsening sepsis.

Five studies in adults were identified.[114-117,247] . Two of the studies were validations of a score developed by the Japanese Association of Acute Medicine Sepsis Registry Study group, namely the Japanese Association of Acute Medicine DIC diagnostic score (JAAM DIC score) [115, 116] One study used the JAAM DIC score to evaluate epidemiology and outcome of severe sepsis in Japanese ICUs[247]. One study used the JAAM DIC for the identification of patients with DIC in the evaluation of DIC and inflammatory processes[117], and similarly a second study used the International Society on Thrombosis and Haemostasis DIC criteria. [114]

DIC is characterised by the widespread activation of coagulation, the suppression of anticoagulation pathways and the inhibition of fibrinolysis. DIC is not a risk factor for sepsis, rather a severe complication of sepsis. In this sense, the review is not a prognostic study examining whether DIC is a risk factor for sepsis, the review is a determination of the extent to which DIC affects the outcome of patients with sepsis. Diagnostic test accuracy data was not used in this review because the objective was not to identify a threshold (value of score) at which a patient should receive urgent care.

If a study reported multivariate and univariate ORs then only the multivariate results were reported. No evidence was found for the outcomes of hospitalisation, ICU admission, and length of hospital stay. It was not possible to conduct meta-analysis of the data due to heterogeneity in the derivations of the ORs.

1 **Table 118: Summary of studies included in the review**

Study	Blood sample collection and DIC definition	Population	Outcome	Outcomes (statistical measures)	Quality of evidence
Gando 2007[114]	Blood samples were collected within24 hours of diagnosis. ISTH	N=45 ICU, SIRS/sepsis Japan	All-cause mortality	**All-cause mortality** DIC score (n=45 patients with measured serum creatinine available) Multivariable OR (95%CI): 4.225 (1.418-12.584)	Observational design Indirectness: none. Risk of bias: very high.
Gando 2007A[117]	Blood samples were collected within 24 hours of diagnosis based on SIRS/sepsis criteria. ISTH (>5), Japanese Ministry of Health and Welfare (>7)	N=48 ICU, SIRS/sepsis Japan	All-cause mortality	**All-cause mortality** DIC as a risk factor for death (n=48) Univariable OR (95% CI): 40.5 (4.544-360.9)	Observational design Indirectness: none. Risk of bias: very high.
Gando 2008[116]	Blood samples were taken on admission to critical care centres and daily thereafter. JAAM DIC, ISTH	N=329 ICU, DIC (34.7% sepsis) Japan	28 day all-cause mortality	**28-day all-cause mortality** SIRS criteria (n=329 patients) Multivariable OR (95%CI): 2.289 (0.964-5.434) JAAM DIC score (n=329) Stepwise method OR (95%CI): 1.223 (1.004-1.489)	Observational design Indirectness: very serious. Risk of bias: very high.
Gando 2013[115]	Blood samples were taken on admission to the ICU and daily thereafter. JAAM DIC	N=624 ICU, severe sepsis Japan	28 day all-cause mortality	**28 day all-cause mortality** DIC score as Day-1 predictor of 28-day mortality (n=624 at time of inclusion) Stepwise regression OR (95%CI): 1.282 (1.141-1.439)	Observational design Indirectness: none. Risk of bias: very high.

Study	Blood sample collection and DIC definition	Population	Outcome	Outcomes (statistical measures)	Quality of evidence
Ogura 2014[247]	Blood samples were taken on admission to the ICU and daily thereafter. JAAM DIC	N=624 with severe sepsis ICU, severe sepsis Japan	28 day mortality, in-hospital all-cause mortality	**28 day all-cause mortality** DIC score (n=624 at time of inclusion) Multivariable OR (95%CI): 1.733 (1.094-2.747) **Hospital all-cause mortality:** DIC score (n=624 at time of inclusion) Stepwise method OR (95%CI): 1.546 (1.008-2.370)	Observational design Indirectness: none. Risk of bias: very high.

ISTH denotes International Society on Thrombosis and Haemostasis, JAAM denotes Japanese Association of Acute Medicine, SIRS denotes systemic inflammatory response syndrome.

1

8.3.23 Clinical evidence summary for disseminated intravascular coagulation

3 **Table 119: Disseminated intravascular coagulation (DIC) and all-cause mortality**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with DIC (95% CI)
28-day mortality - Gando 2008[116]	329 (1 study)	VERY LOW[1,2] due to risk of bias, indirectness	1.22 (1.00 to 1.49)	See comment	-[4]
28-day mortality - Gando 2013[115]	624 (1 study)	VERY LOW[1] due to risk of bias	1.28 (1.14 to 1.44)	See comment	-[4]
28-day mortality - Ogura 2014[247]	624 (1 study)	VERY LOW[1] due to risk of bias	1.73 (1.09 to 2.75)	See comment	-[4]
In-hospital mortality - Gando 2007[114]	45 (1 study)	VERY LOW[1,3] due to risk of bias, imprecision	4.22 (1.42 to 12.59)	See comment	-[4]
In-hospital mortality - Gando 2007A[117]	48 (1 study)	VERY LOW[1,3] due to risk of bias, imprecision	40.50 (4.54 to 360.98)	See comment	-[4]
In-hospital mortality - Ogura 2014[247]	624 (1 study)	VERY LOW[1] due to risk of bias	1.55 (1.01 to 2.37)	See comment	-[4]

[1] Risk of bias mainly due to the lack of evidence that physicians treating patients were blinded to the DIC status. The assumed lack of blinding means that knowledge of DIC could affect treatment, which would possibly affect outcome.
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments)
[3] Downgraded by 1 increment due to a very imprecise result expressed by a very wide confidence interval
[4] N/A as only adjusted or unadjusted OR was provided

8.3.24 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Unit costs of tests that make up a DIC score are provided below to aid consideration of cost effectiveness.

Table 120: Costs of POC coagulation tests and laboratory coagulation tests

Intervention	Cost per patient	Source
Laboratory coagulation tests		
Clotting screen (INR, APTR, fibrinogen, haematocrit)	£4.70	Southampton Hospital NHS trust. Provided by GDG Chair
Thrombin time (TT)	£13.30	Southampton Hospital NHS trust. Provided by GDG Chair
Platelet count	£3.10	Southampton Hospital NHS trust. Provided by GDG Chair (note that this cost is for a full blood count)

Abbreviations: INR = international normalised ratio; APTR = Activated partial thromboplastin time ratio

8.3.25 Evidence statements

Clinical

The evidence from the five studies included in the review was of very low quality for the outcome of all-cause mortality. The evidence showed that DIC was a risk factor for mortality using the both the Japanese Association of Acute Medicine DIC diagnostic score and the International Society on Thrombosis and Haemostasis DIC criteria.

Economic

No relevant economic evaluations were identified.

8.3.26 Recommendations and link to evidence

Recommendations	No recommendation was made for measurement of DIC.
Relative values of different outcomes	The critical outcomes considered for this review were all-cause mortality, hospitalisation, ICU admission, and length of hospital stay. Mortality was the only outcome reported.
Trade-off between clinical benefits and harms	The evidence showed that DIC was a risk factor for mortality. Only adult populations with sepsis or systemic inflammatory response syndrome (SIRS) were included and the two of studies took place in intensive care settings as part of the validation of a DIC score. The GDG did not think that any clinical benefit would be likely if DIC was tested for early in the course of sepsis.

	No studies were identified in children.
Economic considerations	No economic evidence was identified for this question. DIC is a score made up of the results of four different blood parameters. The cost for this could be as high as £30 per person and potentially higher as test costs can vary per hospital. Some of the components of the score are tests that are routinely done for patients suspected of sepsis. But some of them like fibrinogen and d-dimer are not routinely undertaken and will involve additional costs if recommended. A test with a low sensitivity will miss people that are worsening, and a test with a low specificity will treat people more aggressively who actually are not worsening. In general a test with higher sensitivity and specificity will be more cost effective. However different thresholds will have different implications. A low threshold will mean more people are treated more aggressively because they are thought to be worsening. A high threshold may mean some people that are worsening are being missed. Although the GDG acknowledged that DIC means the patient is very unwell, this does not help to discriminate between patients of different levels of severity. The DIC score is not commonly used in the UK, and given that it has not been proven to be a discriminator of severity and the cost is high; the GDG therefore chose to not make a recommendation.
Quality of evidence	The evidence included in this review was of very low quality. This was largely due to very high risk of bias and indirectness. The very high risk of bias rating was due to small patient numbers in two studies, a lack of blinding to potentially confounding patient characteristics, as well as a lack of reference standards. There was very serious indirectness for the outcome of all-cause mortality in one studybecause only 34.7% of the study population had sepsis.
Other considerations	The GDG acknowledged that people with DIC are severely ill and as a result have a higher risk of mortality. They considered that DIC alone was unlikely to be a useful discriminatory factor in initial assessment and management as it is a confounder. The GDG therefore did not make any recommendations for measurement of DIC.

18.4 Antimicrobial treatments

8.4.1 Introduction

The management of sepsis consists of a bundle of actions to be taken as soon as possible after diagnosis. Antimicrobials are one of the main pillars of sepsis treatment. Identifying the most appropriate type of antimicrobials and giving them promptly will increase the possibility of people surviving an episode of sepsis. At the same time giving broad spectrum antibiotics to people who do not need them can lead to the development of antimicrobial resistances.

An evidence review was conducted to identify the most appropriate timing for antimicrobial treatment.

No systematic review was carried out to establish the most clinically and cost effective antimicrobial treatment. This was due to differences in the source of infection and different infection patterns in different areas. Recommendations on particular antibiotic use in children were adapted from recommendations in Fever in under 5s guideline (CG160) and the Meningitis (Bacterial) and Meningococcal Septicameia guideline (CG102).

8.4.2 Review question: What are the most clinically and cost effective timings of IV or IM (parenteral) empiric antimicrobial treatments in patients with a) septic shock b) severe sepsis without shock c) sepsis?

For full details see review protocol in Appendix C.

Table 121: PICO characteristics of review question

Population	People with or at risk of developing sepsis or severe sepsis
Intervention	Empiric antimicrobial treatment
Comparison	Early versus late initiation of treatment
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for disease progression Important: • Duration of hospital stay. • Duration of critical care stay. • Number of organs supported (change in SOFA score). • Adverse events (inability to tolerate drugs).
Study design	Systematic reviews, RCTs and cohort studies

8.4.3 Clinical evidence

We searched for randomised trials and cohort studies comparing the effectiveness of early (up to 12 hours) antimicrobial therapies versus delayed administration, as initial empirical treatment for patients with sepsis, severe sepsis or septic shock. No randomised trials were found. Twenty cohort studies were included in the review.[31,49,79,99,100,109,110,119,120,148,159,174,179,194,214,242,272,327,328,332,338] Only two studies (Fusco 2015[109] and Weiss 2014[327]) were in paediatric population; all the others were conducted in adult population.

The included studies are summarised in **Table 122** (ICU setting, adult population: nine studies), **Table 123** (GP, ED, or hospital setting, adult population: nine studies), and **Table 124** (PICU setting, paediatric population: two studies). In some studies in the ICU setting, antimicrobial treatment might have started before admission to ICU; however the in-hospital mortality outcome was measured after ICU admission.

Six studies in an adult population and one study in a paediatric population were excluded from the analysis because they did not report the adjusted OR for mortality (Fusco 2015[109] reported median length of stay, Garnacho-Montero 2010[120] and Jalili 2013[148] only reported univariable analysis, de Groot 2015[79] and Wisdom 2015[328] reported univariable analysis and adjusted hazard ratio, and Karvellas 2015[159] and Zhang 2015B[338] reported the association between a delay of administration and mortality/length of stay).

Evidence from the included studies is summarised in the clinical evidence summary below (Section 8.4.3.1). See also the study selection flow chart in Appendix B, study evidence tables in Appendix E, forest plots in Appendix D, GRADE tables in Appendix G and excluded studies list in Appendix H.

Table 122: Summary of studies included in the review. Setting: ICU. Adult population

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
Bloos 2014[32]	Patients were divided into the following groups according to the timing of antimicrobial treatment: previous AT, 0 to 1 hours, 1 to 3 hours, 3 to 6 hours and >6 hours	n=1011 Germany ICU Patients with proven or suspected infection with at least one new organ dysfunction	- 28-day mortality. (Multivariable analysis, adjusted for inadequate empirical antimicrobial therapy, age, initial SOFA, and maximum serum lactate level, and further covariates) <1h versus >1 h after onset of organ dysfunction OR 0.96 (0.69-1.33)	Study quality Risk of bias: high (prospective study, consecutive patients enrolled)
Ferrer 2009[99]	Patients were divided into the following groups according to the timing of broad-spectrum antibiotic treatment: previous AT, 0 to 1 hours, 1 to 3 hours, 3 to 6 hours and >6 hours	n=2796 Spain ICU Adult patients with severe sepsis or septic shock	- In-hospital mortality (Broad-spectrum antibiotics. Propensity-adjusted logistic regression model) Time zero=time of presentation 0-1 hours (n=510) OR 0.67 (0.50-0.90) 1-3 hours (n=572)OR 0.80 (0.60-1.06) 3-6 hours (n=290) OR 0.87 (0.62-1.22)	Study quality Risk of bias: moderate (observational design, prospective study, consecutive patients enrolled, large sample size)
Ferrer 2014[100]	Antibiotic administrati	n=17990 Multiple	-In-hospital mortality (logistic regression model, adjusted for Sepsis severity score, ICU	Study quality Risk of bias:

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
	on at 0-1 hours, 1-2 hours,2-3 hours, 3-4 hours, 4-5 hours, 5-6 hours and >6 hours	countries (Europe, USA, South America) ICU Patients with severe sepsis and septic shock	admission source (ED, ward, ICU), and geographic region) Time zero=time of presentation 0-1hours: OR 1.00 (referent) 1-2 hours: OR 1.07 (0.97-1.18) 2-3 hours: OR 1.14 (1.02-1.26) 3-4 hours: OR 1.19 (1.04-1.35) 4-5 hours: OR 1.24 (1.06-1.45) 5-6 hours: OR 1.47 (1.22-1.76) >6 hours: OR 1.52 (1.36-1.70)	high (retrospective, large sample size, time to mortality not reported)
Garnacho-Montero 2010[120]	Comparison of outcomes of patients who received initial antibiotics within 4 hours of arrival with those whose treatment began later	n=125 Spain Hospital (some patients also required ICU admission) Patients with bacteraemic pneumococcal community-acquired pneumonia	Time zero=time of arrival -In-hospital mortality (Bivariate analysis. 1st antibiotic dose) Survivors: 3 hours (15 minutes-64 hours), Non-survivors: 5 hours (40 minutes-14 hours) p value 0.563 - In-hospital mortality (bivariate analysis. 1st antibiotic dose ≥4 hours); Survivors: 44/104 (42%), Non-survivors: 12/21 (57%) p value 0.212 - In-hospital mortality (Cox proportional hazard model. 1st antibiotic dose ≥4 hours) HR 1.909 (0.797-4.570)	Study quality Risk of bias: high (prospective, consecutive patients, but small sample size)
Kumar 2006[174]	Empiric antimicrobial therapy delay	N=2731 Canada ICU Adults with septic shock (ICU or tertiary care institution)	- In-hospital mortality Each hour of delay in initiation of effective antimicrobial therapy associated with mean decrease in survival of 7.6% (range 3.6 –9.9) 1st versus 2nd hour delay in antimicrobial therapy Adjusted: OR 1.67 (1.12-2.48) Time zero=time of onset of persistent/recurrent hypotension - In-hospital mortality per hour delay Multivariable analysis (adjusted): OR 1.119 (1.103–1.136)	Study quality Risk of bias: high (retrospective study, large sample size) No indirectness
Larche 2003[179]	Empiric antimicrobial therapy delay, <2 hours versus >2 hours	n=88 France ICU Critically ill cancer	- 30-day mortality (Multivariable analysis, adjusted for severity of illness) Antibiotic administration >2 hours OR 7.04 (1.17-42.21)	Study quality Risk of bias: very high (retrospective study, small sample size)

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
		patients with septic shock		
Nygard 2014[242]	Patients with community acquired severe sepsis were treated with antibiotics in either <6 hours or ≥6 hours after admission.	n=220 Norway ICU Patients with severe sepsis.	- In-hospital mortality (multivariable analysis, backward stepwise selection, with initial treatment >6hours after admission, n=211) OR 2.48 (1.02-6.02)	Study quality Risk of bias: high (prospective study, consecutive recruitment, but small sample size)
Yokota 2014[332]	Patients were treated with antibiotic treatment in either <1 hour or ≥1 hour.	n=1279 Brazil ICU Patients with proven severe sepsis or septic shock	- in-hospital mortality (multivariable analysis of for time to therapy <1 hour and ≥1 hour) OR 0.771 (0.589-1.010)	Study quality Risk of bias: very high (Retrospective cohort study)
Zhang 2015B[338]	Not reported	n=1058 USA ICU Patients with severe sepsis or septic shock and a positive blood culture	Independent association between delay in appropriate antimicrobial treatment and hospital LOS: each hour delay in the administration of appropriate antimicrobial treatment resulted in a 0.134-day increase in postinfection hospital LOS Risk of bias: very high; Indirectness of outcome: No indirectness Independent association between delay in appropriate antimicrobial treatment and ICU LOS: each hour delay in the administration of appropriate antimicrobial treatment resulted in a 0.095-day increase in post-infection ICU LOS	Risk of bias: very high, retrospective study design

Table 123: Summary of studies included in the review. Setting: GP, ED, or hospital. Adult population

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
Cartwright 1992[49]	Parenteral antibiotics prior to	N=360 UK GP and	- Mortality: Group 1 (antibiotic given): n= 88 (95%) survived, n=5 (5%) died	Study quality Risk of bias: very high

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
	admission to hospital	hospital Patients (children and adults) with meningococcal disease	Group 2 (antibiotic not given): n= 224 (91%) survived, n= 22 (9%) died RR 0.60 (0.23-1.54)	(retrospective, small sample size, time point not reported)
De Groot 2015[79]	Antibiotic administration from time at ED registration	N=1168 The Netherlands ED Patients with suspected infections	Protocol outcome 1: 28-day mortality - Actual outcome: 28-day mortality; Group 1 (antibiotic <1h): n= 48/431 died; Group 2 (antibiotic 1-3h): n= 51/547 died; Group 3 (antibiotic >h): n= 13/190 died. PIRO group 1-7 (n=413): Time<1h (reference) HR 1. Time 1-3h: HR 2.55 (0.36-18.25). Time>3h HR 5.31 (0.43-68.16) PIRO group 7-14 (n=532): Time<1h (reference) HR 1. Time 1-3h: HR 1.25 (0.62-2.31). Time>3h HR 0.86 (0.28-2.63) PIRO group >14 (n=223): Time<1h (reference) HR 1. Time 1-3h: HR 0.99 (0.53-1.87). Time>3h HR 1.11 (0.40-3.08)	Study quality Risk of bias: high (observational design)
Gaieski 2010[110]	Triage to antibiotic therapy ≤1 hour, >1 hour, ≤2 hours, >2 hours, ≤3 hours, >3 hours, ≤4 hours, >4 hours, ≤5 hours, >5 hours	n= 261 USA ED Patients undergoing early goal-directed therapy for severe sepsis or septic shock	- In-hospital mortality (Triage to ED antibiotics) Multivariable analysis adjusted for potential confounders ≤1 h versus >1 h: OR 0.51 (0.21–1.22) ≤2 h versus >2 h: OR 0.72 (0.38–1.37) ≤3 h versus >3 h: OR 0.64 (0.32–1.29) ≤4 h versus >4 h: OR 0.80 (0.35–1.84) ≤5 h versus >5 h: OR 0.86 (0.56–6.15)	Study quality Risk of bias: very high (retrospective, small sample size)
Jalili 2013[148]	Empiric antibiotic door-to-needle time <1h 1-2h >2h	n=145 Iran ED Sepsis: n=145 APACHE score ≤10: n=55 (38%) APACHE score 11-20: n=62 (43%) APACHE score >20: n=27 (19%)	- In-hospital mortality: overall population Group 1 (door-to-antibiotic time <1h): n=1/26 (4%) Group 2 (door-to-antibiotic time 1-2h): n= 16/80 (20%) Group 3 (door-to-antibiotic time >2h): n= 14/38 (37%), p=0.005 - In-hospital mortality according to APACHE score Door-to-antibiotic time <1h APACHE score ≤10: n=0/13 (0%) APACHE score 11-20: n=0/11 (0%) APACHE score >20: n=1/2 (50%) Door-to-antibiotic time 1-2h	Study quality Risk of bias: high (prospective, consecutive patients, but small sample size)

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
			APACHE score ≤10: n=0/30 (0%) APACHE score 11-20: n=6/38 (16%) APACHE score >20: n= 10/12 (83%) Door-to-antibiotic time >2h APACHE score ≤10: n=0/12 (0%) APACHE score 11-20: n=1/13 (8%) APACHE score >20: n=13/13 (100%)	
Karvellas 2015[159]	Not reported	n=126 USA, Saudi-Arabia, Canada Medical centres Adult cirrhotic patients with spontaneous peritonitis-associated septic shock	Multivariable analysis of in-hospital mortality due to hourly time delay to appropriate antimicrobial therapy: OR 1.86 (1.10-3.14), p=0.02	Study quality Risk of bias: very high, retrospective study design, small sample size, inclusion criteria clearly reported Indirectness: cirrhotic patients with septic shock
Lueangarun 2012[194]	Timing: Group 1: <1 h Group 2: 1-6 h Group 3: >6 h	n=229 Thailand Hospital (medical wards) Patients with sepsis (13.5%), severe sepsis (25.3%) and septic shock (61.1%)	- Overall mortality Group 1 (<1 h) n=144 (63.0%) Group 2 (1-6 h) n=150 (65.3%) Group 3 (>6 h) n=184 (80.5%) <3hours versus >3 hours (time zero= time of diagnosis) OR 1.92 (1.08-3.42)	Study quality Risk of bias: very high (retrospective design, small sample size). No indirectness
Menendez 2012[214]	Antibiotics within 6 hours of arrival at the emergency department	n= 4137 Spain Hospital Patients with community-acquired pneumonia (CAP) and sepsis	<6 hours versus >6 hours - 30-day mortality (multivariable analysis for whole population) OR 0.67 (0.50-0.89) - 30-day mortality (multivariable analysis for non-severe sepsis) OR 0.44 (0.24-0.82) - 30-day mortality (multivariable analysis for severe sepsis) OR 0.69 (0.48-1.015) - Length of hospital stay (multivariable	Study quality Risk of bias: moderate (large, prospective study)

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
			analysis for whole population) OR 0.80 (0.71-0.91) - Length of hospital stay (multivariable analysis for non-severe sepsis) OR 0.73 (0.58-0.92) - Length of hospital stay (multivariable analysis for severe sepsis) OR 0.94 (0.77-1.16)	
Puskarich 2011[272]	Patients were treated with antibiotics and received hourly increments.	n=300 USA ED Patients with proven or suspected sepsis who received the initial treatment at ED	- In-hospital mortality (multivariable analysis, antibiotics treatment >1h of ED triage) OR 1.81 (0.74-4.44) - In-hospital mortality (multivariable analysis, antibiotics treatment >2h of ED triage) OR 1.07 (0.54-2.16) - In-hospital mortality (multivariable analysis, antibiotics treatment >3h of ED triage) OR 0.66 (0.27-1.63) - In-hospital mortality (multivariable analysis, antibiotics treatment >4h of ED triage) OR 0.39 (0.08-1.90) - In-hospital mortality (multivariable analysis, antibiotics treatment >5h of ED triage) OR 0.69 (0.07-6.86)	Study quality Risk of bias: high (Pre-planned analysis of non-blinded RCT, small sample size)
Wisdom 2015[328]	Not reported	n=220 Australia Tertiary hospital Uncomplicated sepsis (n=102), severe sepsis (n=118)	HR for in-hospital mortality according to time from triage to antibiotics for all patients: ≤1 hr (n=27): HR 1 1-3 hr (n=72): HR 1.69 (0.73-3.92), p=0.22 3-6 hr (n=61): HR 1.12 (0.47-2.92), p=0.72 >6 hr (n=60): HR 1.75 (0.75-5.09), p=0.20 HR for in-hospital mortality according to time from triage to antibiotics for patients with uncomplicated sepsis: ≤1 hr (n=6): HR 1 1-3 hr (n=31): HR 1.65 (0.19-14.10), p=0.65 3-6 hr (n=35): HR 0.67 (0.07-6.19), p=0.72 >6 hr (n=30): HR 0.57 (0.06-5.70), p=0.63 HR for in-hospital mortality according to time from triage to antibiotics for patients with severe sepsis: ≤1 hr (n=21): HR 1 1-3 hr (n=41): HR 1.49 (0.58-3.86), p=0.41 3-6 hr (n=26): HR 1.50 (0.53-4.25), p=0.44 >6 hr (n=30): HR 2.25 (0.91-5.59), p=0.08	Study quality Risk of bias: very high, retrospective study design, inclusion criteria not fully stated, timing not reported, only HRs reported

1 **Table 124: Summary of studies included in the review. Setting: PICU. Paediatric population**

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
Fusco 2015[109]	Time from first fluid bolus order to time of first appropriate antimicrobial administration	n=72 USA PICU Patients with ICD-9 sepsis diagnosis (septicaemia, severe sepsis or septic shock)	Time to first antimicrobial agent: median LOS in days (IQR) ≤1 hr (n=24) versus >1 hr (n=48): 381.5 (IQR 275.7-597.7) versus 243.9 (IQR 135.6-563.4), p=0.08 ≤2 hr (n=28) versus >2 hr (n=44): 381.5 (IQR 274.8-606.3) versus 227.7 (IQR 129.4-482.1), p=0.03 ≤3 hr (n=41) versus >3 hr (n=31): 308.0 (IQR 235.8-616.0) versus 219.7 (IQR 127.4-441.0), p=0.05 ≤4 hr (n=49) versus >4 hr (n=23): 290.4 (IQR 185.8-603.1) versus 272.6 (IQR 131.4-441.0), p=0.14 ≤5 hr (n=53) versus >5 hr (n=19): 290.3 (IQR 178.1-603.1) versus 272.6 (IQR 131.4-441.0), p=0.26 ≤6 hr (n=59) versus >6 hr (n=13): 287.6 (IQR 164.0-599.5) versus 332.4 (IQR 141.0-459.2), p=0.89 Time to first antimicrobial agent: median LOS in days (IQR) ≤1 hr (n=24) versus >1 hr (n=48): 263.7 (IQR 115.6-536.2) versus 99.6 (IQR 53.5-216.3), p=0.02 ≤2 hr (n=28) versus >2 hr (n=44): 223.0 (IQR 98.6-435.3) versus 99.6 (IQR 61.6-247.3), p=0.11 ≤3 hr (n=41) versus >3 hr (n=31): 184.0 (IQR 79.3-482.2) versus 93.7 (IQR 49.6-203.4), p=0.06 ≤4 hr (n=49) versus >4 hr (n=23): 172.0 (IQR 65.9-402.9) versus 98.2 (IQR 60.1-215.8), p=0.23 ≤5 hr (n=53) versus >5 hr (n=19): 169.0 (IQR 65.1-402.9) versus 98.2 (IQR 63.4-193.6), p=0.35 ≤6 hr (n=59) versus >6 hr (n=13):163.0 (IQR 64.0-381.5) versus 98.2 (IQR 67.1-265.8), p=0.67	Study quality Risk of bias: very high Retrospective observational study, inclusion criteria not fully reported, small sample size
Weiss 2014[327]	Time from sepsis recognition to initial treatment and appropriate treatment.	n=130 USA PICU Patients with severe sepsis or	- PICU mortality (univariable analysis of initial treatment <1h and >1h of sepsis recognition) OR 1.67 (0.35-7.91) - PICU mortality (univariable analysis of initial treatment <2h and >2h of sepsis recognition) OR 2.43 (0.74-7.99) - PICU mortality (univariable analysis of initial	Study qualityRisk of bias: very high Retrospective observational study, inclusion criteria clearly reported,

Study	Empiric antimicrobial drug and timings of initiation	Population	Outcomes	Comments
		septic shock	treatment <3h and >3h of sepsis recognition) OR 3.92 (1.27-12.06) - PICU mortality (univariable analysis of initial treatment <4h and >4h of sepsis recognition) OR 3.60 (1.23-10.52) - PICU mortality (multivariable analysis; initial treatment >3 h after sepsis recognition) OR 3.83 (1.06-13.82) - PICU mortality (multivariable analysis; appropriate treatment >3 h after sepsis recognition) OR 3.23 (0.90-11.62)	univariable analysis for most outcomes reported, small sample size

8.4.3.11 Clinical evidence summary tables

Table 125: <1 hour versus >1 hour, adult population

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <1h versus >1h (multivariable analysis) (95% CI)
Mortality	- (8 studies)	VERY LOW[2] due to risk of bias	OR 0.87 (0.81 to 0.94)	See comment	-[1]
Mortality - ICU setting	- (6 studies)	VERY LOW[2] due to risk of bias	OR 0.88 (0.81 to 0.95)	See comment	-[1]
Mortality - ED setting	- (2 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.53 (0.28 to 0.99)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 126: <2 hours versus >2 hours, adult population

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <2h versus >2h (multivariable analysis) (95% CI)
Mortality	- (4 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.73 (0.51 to 1.04)	See comment	-[1]
Mortality - ICU setting	- (1 study)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.14 (0.02 to 0.88)	See comment	-[1]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <2h versus >2h (multivariable analysis) (95% CI)
Mortality - ED setting	- (3 studies)	VERY LOW[2] due to risk of bias	OR 0.78 (0.54 to 1.12)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **Table 127: <3 hours versus >3 hours, adult population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <3h versus >3h (multivariable analysis) (95% CI)
Mortality	- (6 studies)	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	OR 0.7 (0.57 to 0.86)	See comment	-[1]
Mortality - ICU setting	- (1 study)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.8 (0.6 to 1.07)	See comment	-[1]
Mortality - ED setting	- (5 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.62 (0.47 to 0.82)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **Table 128: <4 hours versus >4 hours, adult population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <4h versus >4h (multivariable analysis) (95% CI)
Mortality	41 (2 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 1.03 (0.49 to 2.14)	125 per 1000	-[1]
Mortality - ED setting	- (2 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 1.03 (0.49 to 2.14)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

2 **Table 129: <5 hours versus >5 hours, adult population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <5h versus >5h (multivariable analysis) (95% CI)
Mortality	- (2 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 1.07 (0.24 to 4.77)	See comment	-[1]
Mortality - ED setting	- (2 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 1.07 (0.24 to 4.77)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <5h versus >5h (multivariable analysis) (95% CI)
risk of bias [3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

1

2 **Table 130: <6 hours versus >6 hours, adult population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <6h versus >6h (multivariable analysis) (95% CI)
Mortality	- (3 studies)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.72 (0.58 to 0.9)	See comment	-[1]
Mortality - ICU setting	- (2 studies)	VERY LOW[2,3,4] due to risk of bias, imprecision, indirectness	OR 0.79 (0.57 to 1.08)	See comment	-[1]
Mortality - ED setting	- (1 study)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.67 (0.5 to 0.9)	See comment	-[1]
[1] Absolute effect not estimable as the crude event rate for the control group was not provided [2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs [4] I2=60% (p=0.11)					

1 **Table 131: Hourly treatment delay, ICU, adult population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Hourly treatment delay (ICU) (95% CI)
In-hospital mortality	- (1)	VERY LOW[2] due to risk of bias	OR 1.12 (1.1 to 1.14)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2

3 **Table 132: Parenteral antibiotics prior to admission to hospital (GP)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Parenteral antibiotics prior to admission to hospital (GP) (95% CI)
Mortality	- (1)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.58 (0.21 to 1.58)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

4

5 **Table 133: <1 hour versus >1 hour, PICU, paediatric population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <1h versus >1h (PICU) (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <1h versus >1h (PICU) (95% CI)
PICU mortality	- (1)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.6 (0.13 to 2.86)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **Table 134: <2 hours versus >2 hours, PICU, paediatric population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <2h versus >2h (PICU) (95% CI)
PICU mortality	- (1)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.41 (0.13 to 1.35)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

2

3 **Table 135: <3 hours versus >3 hours, PICU, paediatric population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <3h versus >3h (PICU) (95% CI)
PICU mortality	- (1)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.25 (0.08 to 0.79)	See comment	-[1]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <3h versus >3h (PICU) (95% CI)

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 136: <4 hours versus >4 hours, PICU, paediatric population**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	OR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with <4h versus >4h (PICU) (95% CI)
PICU mortality	- (1)	VERY LOW[2,3] due to risk of bias, imprecision	OR 0.28 (0.1 to 0.81)	See comment	-[1]

[1] Absolute effect not estimable as the crude event rate for the control group was not provided
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3

8.4.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

The recommendations on antimicrobial use for children are adapted from existing NICE guidelines on infection, and where use of specific antibiotics have been stated these are costed up below. Due to differences in the source of infection and different infection patterns in different areas, not all recommendations from this guideline (notably those for adults) state a specific type of antibiotic, as local guidance should be followed.

Most doses depend on weight and duration of treatment. Maximum doses have been used here as conservative estimates.

Table 137: UK costs of antimicrobials

Drug	Population	Cost per unit	Dose	Total cost	Source of dose data
Benzylpenicillin	Children under 16. In a community setting.	2 vials of 600mg = £4.67	1.2g single dose	£4.67	BNF [a]
Ceftriaxone	Children under 16. In a hospital setting	1 vial of 2000mg = £19.10	4g daily (max dose) Duration of 10 days	£382	Dosage from BNF. Duration of dose from recommendations in Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline 102). [b]
Amoxicillin	Children under 3 months who should be given an additional antibiotic active against listeria	1 vial of 1000mg =£1.92	100mg/kg every 8 hours Duration of 14 days	£40.32	Dosage from BNF. Duration of dose from recommendations in Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline 102). [c]
Benzylpenicillin	Neonates	2 vials of 600mg = £4.67	25 mg/kg every 12 hours Duration of 7 days	£4.63	Neonatal infection guideline (NICE guideline 149). [d]
Gentamicin	Neonates	10mg/ml in 5ml ampoule = £11.25	5mg/kg every 36 hours Duration of 5	£11.48	Neonatal infection guideline(NICE guideline 149). [d]

Drug	Population	Cost per unit	Dose	Total cost	Source of dose data
			days (3 doses in 5 days)		
Ceftriaxone	Neonates more than 41 weeks corrected age and not receiving calcium infusion.	1 vial of 2000mg = £19.10	50mg/kg once a day. Duration of 7 days	£11.36	Recommendation made in this guideline. Frequency of dose from BNF: once daily. Assumed given for 7 days. (d)
Cefotaxime	40 weeks corrected age or below or receiving an intravenous calcium infusion.	10 vials of 2000mg = £37.50	50mg/kg every 8 hours Duration 7 days	£6.69	Recommendation made in this guideline. Frequency of dose from BNF: give every 8 hours for severe infections. Assumed given for 7 days (d)

(a) Source of drug costs: BNF [155]
(b) Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) prior to urgent transfer to hospital: Child 10–17 years; 1.2 g, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer.
(c) From BNF: For children 2-4g daily (used for meningitis). From meningitis under 16 guideline: In children and young people aged 3 months or older with unconfirmed, uncomplicated but clinically suspected bacterial meningitis, treat with intravenous ceftriaxone for at least 10 days
(d) From BNF: Neonate 7 days to 28 days; 50–100 mg/kg every 8 hours. From meningitis in children guideline: In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. Average weight of 5kg was used.
(e) Used average weight of a newborn of 3.4kg to calculate dose.

8.14.5 Evidence statements

Clinical

The evidence included from the observational studies was of very low quality for all outcomes. Eight of the twenty studies included did not report adjusted odds ratios for mortality and were therefore not included in the analysis. Comparison of the evidence for benefit for reduction in mortality for antibiotics within 1 hour versus 3 hours was inconclusive because of differences in the populations and settings.

Economic

No relevant economic evaluations were identified.

8.24.6 Recommendations and link to evidence

8.42.6.1 Recommendations on timing of antimicrobial

	The evidence for timing of antibiotics is discussed below . This informs recommendations 44,53,59,68, 74,84 as follows:
Recommendations	**12 years and over**

44. For adults and children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker**
- **carry out a venous blood test for the following :**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas to include lactate measurement**
- **give a broad-spectrum antimicrobial at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria) in line with recommendations in section 8.4**
- **discuss with consultant.**

53. For adults and children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:

- **repeat structured assessment at least hourly**
- **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.**

5-11 years

59. For children aged 5 to 11 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker**
- **carry out a venous blood test for the following:**
  - **blood culture**
  - **full blood count**
  - **C reactive protein**
  - **urea and electrolytes**
  - **creatinine**
  - **clotting screen**
  - **blood gas for glucose and lactate**
- **give people a broad-spectrum antimicrobial (see section 8.4) at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria)**
- **discuss with consultant.**

68. For children aged 5 to 11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:

	• **repeat structured assessment at least hourly** • **ensure review by a senior decision maker within 3 hours of meeting 2 or more moderate to high risk criteria for consideration of antibiotics.** **Children aged under 5 years** **74. For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria:** • **arrange for immediate review by the senior clinical decision maker** • **carry out a venous blood test for the following:** – **blood culture** – **full blood count** – **C reactive protein** – **urea and electrolytes** – **creatinine** – **clotting screen** – **blood gas for glucose and lactate** • **give parentral antibiotics (within 1 hour of identifying that they meet any high risk criteria; see section 8.4)** • **discuss with consultant.** **84. For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:** • **repeat structured assessment at least hourly** • **ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criterion for consideration of antibiotics.** **General** **90. Pre-alert secondary care (through GP or ambulance service) when any high risk criteria are met in a person with suspected sepsis outside of a hospital, and transfer them immediately.** **91. Ensure urgent assessment mechanisms are in place to deliver antibiotics when high risk criteria are met in secondary care (within 1 hour of meeting a high risk criterion).** **92. Ensure GPs and ambulance services have mechanisms in place to give antibiotics in the pre-hospital setting if transfer time is likely to be more than 1 hour.**
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days, health-related quality of life and admission to critical care to be critical outcomes. Important outcomes were duration of hospital stay, duration of critical care stay, number of organs supported (change in SOFA score), and adverse events (inability to tolerate drugs).

	All-cause mortality was the only available outcome reported by all included studies. Only one study compared length of hospital stay for antimicrobial treatment administered before or after 6 hours. No evidence was found for the remaining outcomes listed above.
Trade-off between clinical benefits and harms	Antibiotics are a cornerstone of treatment for people with sepsis. Prompt administration of antibiotics increases the possibility of people surviving an episode of sepsis. An individual is unlikely to suffer harm from receiving an antibiotic they do not need, but at a population level antibiotic resistance will increase if broad spectrum antibiotics are given to patients who do not need them. The clinical evidence in adults showed a reduction in all-cause mortality when antibiotics were administered within up to 3 hours. Comparison of the evidence for reduction in mortality for antibiotics within 1 hour versus 3 hours indicated that there may be no additional benefit of early therapy. However, the populations in the 2 timing groups were different, and participant inclusion criteria varied across the studies, therefore no conclusion could be made on the relative benefits The GDG considered that recommending antibiotics within one hour for those at highest risk would ensure that those people with highest risk would benefit, but that it was appropriate to recommend a 3 hour window for people at moderate to high risk without organ dysfunction. There was less evidence for the paediatric population: of the two studies included, one was excluded from the analysis because it only reported median (IQR) length of stay; the other was a retrospective single-centre observational study of children in PICU with severe sepsis and septic shock. The GDG considered that the recommendations made for adults should be used for children.
Economic considerations	No economic evidence was identified for this question. The cost of antimicrobials is not likely to differ if they are given at different timings. However the implication of giving them early based on certain signs is that you will be giving them to a broader population, some of which will not have sepsis. Giving antibiotics more broadly based on a low level of suspicion (before further information such as tests for example) will also have an impact on the antibiotic resistance of the population in the longer term. If they are to be administered in primary care, this may also have an impact on resources such as more training needed, management of antimicrobial stock and storage, being able to undertake tests. Also if they should be given early this might mean on the way to hospital and may also have implications for ambulances. On the other hand delayed administration of antibiotics in order to confirm a diagnosis beforehand may result in patients deteriorating and more downstream resources needed. Care of patients with sepsis can be very expensive particularly for patients on ICU because there is a high nurse to patient ratio on ICU and continuous monitoring needed. This approach may also lead to a risk of mortality if patients worsen because of delayed administration. The GDG considered that the health gains for those who may need antibiotics would outweigh the additional cost of providing them early. The clinical evidence showed that for adults, administering antibiotics in less than one hour had a clear clinical benefit in terms of reduction in mortality. The time at which an hour would begin from is when the criteria for high suspicion of sepsis is met, not when a definitive diagnosis happens. Based on previous reviews on signs and symptoms, and also GDG consensus, the GDG agreed that anyone considered to meet any of the high risk factors for sepsis should receive antibiotics. The population that is being discussed here as being given antibiotics is potentially large as it is those that are suspected of sepsis and categorised as high risk of mortality (based on risk factors and tests). The actual prevalence of sepsis is unknown due to the underlying condition often being reported as the cause rather than the systemic condition itself.

	However there could be as high as over 100,000 admissions due to sepsis per year, with the mortality rate being relatively high (around 30%). It has been reported that there may be over 37,000 deaths from severe sepsis annually in the UK. The GDG considered that their categorisations of people suspected of sepsis into high risk, moderate to high risk, and low risk, would appropriately capture the sepsis population and the more aggressive interventions (such as antibiotics) would only be for the individuals considered to be of high risk of deterioration from suspected sepsis, rather than all suspected. Administering antibiotics is part of the treatment for sepsis, however sepsis is not always well recognised in practice. Therefore although the antibiotics recommendations here are only for those suspected of sepsis and with high risk factors, the increased recognition of sepsis from this guideline may lead to more use of broad spectrum antibiotics.
Quality of evidence	The evidence for all the outcomes is of very low quality. The major risk of bias of the studies included in the review was their observational design. Study investigator knowledge of when the antibiotic was administered may have affected the clinical decision making. The GDG agreed therefore that they could not be confident in the evidence due to the low quality.
Other considerations	The GDG used the evidence and their experience of current treatment of sepsis to make recommendations. They agreed that current practice is to implement sepsis 6, and sepsis bundles but the reliability of implementation varies. According to the report of the emergency departments clinical audit 2013-2014[309], there was an improvement across all quartiles of performance for the administration of antibiotics within 1 hour of arrival and prior to leaving the ED, compared to the 2011 audit. Antibiotics given prior to leaving the ED is at a median of 94% and within the first hour of attendance has increased from 27% to 32%. The GDG noted that most of the evidence compares antibiotic administration before and after 1 hour, while there is limited evidence for other timing of administration (2-6 hours). The studies used slightly different criteria for inclusion and it was not possible to perform subgroup analysis by disease severity from the available evidence. The GDG noted that early treatment is recommended in other NICE guidance, for example CG191 Pneumonia, but that guideline recommends time to antibiotics <3 hours. The GDG discussed how a recommendation to give antibiotics within one hour could be implemented. The studies varied in terms of 'time zero' with some measuring time from when criteria were met and others from diagnosis. The GDG agreed that the choice of 'time zero' was crucial and should be clearly identified if this recommendation is to be audited. The GDG agreed that timing should start from when 'sepsis' criteria are objectively met i.e. when diagnosis should be made, rather than when it actually is. They agreed that using this time the recommendations were more likely to improve practice. Recognising sepsis is one of the biggest challenges in care. The GDG discussed whether antibiotics should be given in primary care or ambulance. They recognised that this would mean that GP surgeries and ambulances would need to stock broad spectrum antibiotics which they were likely to use only rarely. Most of the evidence is from intensive or hospital/ED setting, and only one study was conducted in primary care or community setting (Cartwright 1992 analysed the effect of parenteral antibiotics prior to admission to hospital on mortality, in children and adults with meningococcal disease). The GDG were concerned that giving antibiotics in primary care would result in a delay in transfer of people to hospital. More evidence on likely numbers and benefit would be required before recommending treatment in primary care which would be a change in practice. The GDG agreed it was better to improve performance of current system rather than introduce a new system with untested consequences. The priority should

	be to ensure rapid transport to hospital with the emergency department alerted to the patient's arrival. If someone is clearly recognised to have sepsis than time to antibiotics should be considered to run from that time. The GDG agreed that the majority of people in England are within an hour of a hospital. For this reason they did not recommend that ambulance services should be equipped to give antibiotics to people with sepsis. However in more remote areas where there is delay in getting to emergency departments it may be appropriate for local services to plan interventions by paramedics. Ideally blood cultures should be taken before antibiotics are given. Although the evidence available pertained to adults, the GDG considered it appropriate to extrapolate to children. The Meningitis (bacterial) and Meningococcal septicaemia guideline CG102 recommends that children with suspected meningitis or septicaemia are given parenteral antibiotics at the earliest opportunity, either in primary or secondary care but that transfer to hospital should not be delayed to give antibiotics. CG102 found no evidence for prescribing outside the hospital setting but recognised that this is standard advice and that GP practices and other settings may have benzylpenicillin available.

8.4.6.2 Recommendations on choice of antimicrobial treatments

No evidence review was carried out for choice of antimicrobial agents. This would not have informed national recommendations as choice of antimicrobial depends on local guidelines. The recommendation on taking of blood cultures is included here because of its association with the the use of antibiotics but a discussion of the use of blood cultures is in section 14 Finding the source of infection. The recommendations for specific antibiotics here are taken from other NICE guidance as well as being informed by GDG expertise.

Recommendations	**93. For patients in hospital who have suspected infections, take microbiological samples before prescribing an antimicrobial and review the prescription when the results are available. For people with suspected sepsis, take blood cultures before antibiotics are given. [This recommendation is adapted from Antimicrobial stewardship (NICE guideline NG15)]** **94. If meningococcal disease is specifically suspected (fever and purpuric rash) give appropriate doses of parenteral benzyl penicillin in community settings and intravenous ceftriaxone in hospital settings. [This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE clinical guideline 102)]** **95. For people aged 18 years and above who need an empirical intravenous antimicrobial for a suspected infection but who have no confirmed diagnosis, use an intravenous antimicrobial from the agreed local formulary and in line with local (where available) or national guidelines. [This recommendation is adapted from Antimicrobial stewardship(NICE guidance NG15)]** **96. For people aged up to 17 years with suspected community acquired sepsis of any cause give ceftriaxone 80 mg/kg once a**

	day with a maximum dose of 4g daily at any age. [This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline CG102)] **97. For people aged up to 17 years with suspected sepsis who are already in hospital, or who are known to have previously been infected with ceftriaxone-resistant bacteria, consult local guidelines for choice of antibiotic.** **98. For children younger than 3 months, an additional antibiotic active against listeria (for example, ampicillin or amoxicillin) should be given. [This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]** **99. Treat neonates presenting in hospital with suspected sepsis with intravenous benzylpenicillin and gentamicin [This recommendation is from Neonatal infection (NICE guideline CG149)]** **100. Treat neonates who are more than 40 weeks postmenstrual age who present with community acquired sepsis with ceftriaxone 50 mg/kg unless already receiving an intravenous calcium infusion at the time. If 40 weeks postmenstrual age or below or receiving an intravenous calcium infusion use cefotaxime 50 mg/kg.**
Relative values of different outcomes	Not applicable
Trade-off between clinical benefits and harms	The GDG agreed that a dose of empiric antibiotic is unlikely to cause harm to an individual patient except where a patient has an allergy which is severe enough to cause an anaphylactic reaction. However sepsis is life threatening with antibiotic administration one of the main treatments and the potential benefit outweighs the risk unless the person has known severe allergy. Using high or maximal dosage then stopping antimicrobial treatment when no longer necessary is accepted asbest means to lower the risk of resistance developing.
Economic considerations	No relevant economic evaluations were identified. Antibiotics are a vital part of the treatment for a patient with sepsis. In general the costs of antibiotics tend to be low, although some newer generation antibiotics can be more expensive. From the review on the timing of antibiotic administration, the GDG recommended administering antibiotics within one hour from identifying any high risk factors alongside a suspicion of sepsis, as this had a clear clinical benefit in terms of reduction in mortality. Escalation of care for patients who have sepsis and deteriorate can be very expensive as they would need to be treated on ICU where they are continually monitored. The GDG considered that the health benefits for those who may need antibiotics would outweigh the additional cost of providing them early. This is also likely the case for the type of antibiotic, as the costs involved in treating a sepsis patient whose condition has worsened would far outweigh the initial antibiotic cost. The GDG decided that a recommendation should be made stating that patients should be given antibiotics at the maximum dose. Given the high mortality rate associated with sepsis, this was considered to be appropriate in order for the antibiotic to be as effective as possible. Although antibiotics may have side effects, this would be far outweighed by the mortality associated with the condition, should

	the treatment be ineffective.
Quality of evidence	The recommendations are informed by other NICE guidance and expert option.
Other considerations	The evidence from the review on timing for antibiotics indicates that people with sepsis benefit from receiving antibiotics within 1-2 hours from diagnoses. For some patients the source of sepsis may be clear and either the source or a specific clinical context may dictate the choice of antibiotic. There are several disease or condition specific NICE guidelines which have made recommendations for antibiotic use e.g. pneumonia guideline (CG191), neutropenic sepsis guideline (CG151). Many people will however require empiric antibiotic treatment. The GDG were advised by a co-opted expert and agreed that an appraisal of evidence would not provide definitive evidence of which antibiotic to use. Patterns of infection can be different in different areas and patterns of anti- microbial resistance changes. The choice of empiric antibiotic in adults needs to be informed and monitored by local knowledge. The GDG were aware of a recommendation from NICE Anti-microbial stewardship guideline about use of empiric antibiotics and agreed to cross-refer to that recommendation.. The GDG did consider that ideally individual trusts should work together to ensure neighbouring areas had similar recommendations and that ideally regional or if possible national guidance might be available. CG102 also recommends that atni-mocribial samples are taken before antibiotics where possible and the GDG added the use of blood cultures as these are specific for people suspected of sepsis.NICE guideline CG102 recommends benzylpenicillin or ceftriaxone to children and young people with meningitis or meningococcal disease depending on setting. Following review of the evidence in that guideline the GDG considered it appropriate to adapt the recommendations to include treatment for adults with suspected meningococcal disease as they were unaware of evidence that would make that inappropriate NICE guidance for broad spectrum antibiotics already exisits for seriously ill children and young people where cause is unclear The GDG reviewed the evidence and recommendations in these guidelines and decided that the evidence reviews were relevant and appropriate and evidence unlikely to have changed. They therefore adapted these for use in children and young people with sepsis. The Fever in under 5s guideline (CG160) recommends a third-generation cephalosporin (for example, cefotaxime or ceftriaxone) until culture results are available and that infants younger than 3 months should have an agent active against listeria (for example, ampicillin or amoxicillin) added to their regime. The Meningitis (CG102) guideline recommends ceftriaxone on the basis of clinical and cost effectiveness data. The GDG therefore agreed to recommend ceftriaxone as the antibiotic of choice in children and young people with suspected sepsis with an agent active against listeria added up to 3 months. Neonates can also receive ceftriaxone if 41 weeks corrected age and not receiving an intravenous calcium infusion. In premature babies ceftriaxone may exacerbate hyperbilirubinaemia and ceftriaxone should therefore be used if 40 weeks corrected age or below or receiving an intravenous calcium infusion. Children and young people already in hospital require different regiemes. The GDG were unable to make a specific recommendation for children and young people from 1 month to 17 years and made a recommendation that choice of antibiotic required local guidelines. The neonatal sepsis guideline already has a recommendation for neonates with in hospital with suspected sepsis and the GDG included it here for completeness. The GDG developed a recommendation to remind practitioners that people with sepsis should be given the maximal recommended dose. People with sepsis have a potentially life-threatening illness and require adequate dose of antibiotic which is more likely to be achieved with maximal doses.

1
2

18.5 IV fluid administration

8.5.1 Introduction

Sepsis is a whole-body inflammatory response to an infection. The dilatation of blood vessels leads to haemodynamic changes, low blood pressure and tissue oxygenation. In severe cases the pathophysiological processes can lead to circulatory shock. Intravenous fluid resuscitation is therefore one of the main pillars and paramount in the initial phase of sepsis management.

This section aims to identify which patients with sepsis would benefit from IV fluid resuscitation and which type of fluid, alone or in combination, is the most clinically and cost effective.

8.5.2 Review question: What is the most clinical and cost effective a) immediate/bolus IV fluid, b) volume/dosage of immediate/bolus IV fluid resuscitation, and c) rate of administration of immediate/bolus IV fluids in patients with sepsis?

For full details see review protocol in Appendix A.

Table 138: PICO characteristics of review question

Population	People at risk of developing or diagnosed with severe sepsis and septic shock
Intervention	Fluid administration to be initiated within 6 hours after diagnosis. IV fluids: • Crystalloid • Colloid • Albumin • Blood or blood product
Comparison	• Immediate initiation versus no or later initiation • High volume versus low volume • Fast versus slow rate of administration
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis Important: • Duration of hospital stay • Duration of critical care stay • Number of organs supported • Time to reversal of shock • Adverse events (long-term disability; short-term heart failure)
Study design	Systematic reviews, RCTs, cohort studies

8.5.3 Clinical evidence

This evidence review was performed to complement the NICE guidelines on IV fluids in adults[231] and children (due for publication in December 2015) by looking for research specific to sepsis. We searched for RCTs and cohort studies comparing the effectiveness of the type, volume and timing of administration of intravenous fluids for patients with sepsis, severe sepsis or septic shock. Eight studies were included in this review; five RCTs[88,142,225,279,281], two retrospective cohort studies[108,213],

and one systematic review[254]. Only one study was in a paediatric population[281]. The included studies are summarised in **Table 139** below. Evidence from these studies is summarised in the clinical evidence summary below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L. Additional data on length of stay are presented in Tables **Table 152Table 156**.

The included studies did not provide any information on fluids that had been given to patients as part of the early goal-directed therapy (EGDT) or any other concomitant treatment which had been part of the EGDT.

Table 139: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Study design and length of follow-up
Dolecek 2009[88]	n=30 Intervention 1: 20% albumin 100 ml every 12 hours for a maximum of 72 hours n=26 Intervention 2: 6% HES 130/0,4 250 ml every 6 hours for a maximum of 72 hours	n=56 adults Severe sepsis Czech Republic	28-day mortality	RCT Follow-up: 72 hours
Fuller 2010[108]	n=34 Intervention 1: Packed red blood cells + EGDT, average of 4.56 units per patient n=93 Intervention 2: EGDT only	n=93 adults Septic shock USA	Hospital mortality Hospital length of stay ICU length of stay	Retrospective cohort study Follow-up: unclear
Holst 2014[142]	n=502 Intervention 1: Leukoreduced red blood cells if blood concentration of haemoglobin had decreased below ≤7 g/dl (low threshold group); crossmatched, prestorage leukoreduced red cells suspended in a saline-adenine-glucose-mannitol solution. Duration: entire ICU stay, maximum of 90 days after randomisation (n=496) Intervention 2: Leukoreduced red blood cells if blood concentration of	n=998 adults Septic shock Denmark, Finland, Norway, Sweden	90-day mortality	RCT Follow-up: 90 days

Study	Intervention and comparison	Population	Outcomes	Study design and length of follow-up
	haemoglobin had decreased below ≤9 g/dl (high threshold group); crossmatched, prestorage leukoreduced red cells suspended in a saline-adenine-glucose-mannitol solution. Duration: entire ICU stay, maximum of 90 days after randomisation			
McInthyre 2007[213]	Type of fluid: n=235 Intervention 1: Crystalloid - crystalloid n=258 Intervention 2: Colloid + crystalloid Quantity of fluid (includes crystalloids, colloids and blood products): n=210 Intervention 1: 0-2 litres n=186 Intervention 2: 2-4 litres n=100 Intervention 3: >4 litres	n=496 adults Severe sepsis Canada	Type of fluid: Hospital mortality ICU mortality Hospital length of stay Quantity of fluid (includes crystalloids, colloids and blood products): Hospital mortality ICU mortality Hospital length of stay	Retrospective cohort study Follow-up: 24 hours
Myburgh 2012[225]	n=979 Intervention 1: Hydroxyethyl starch. 6% HES 130/0.4 in 0.9%-saline 500-ml bags. Maximum dose of 50 ml/kg/day, followed by open-label 0.9% saline for the remainder of the 24-hour period. Duration 90 days max. Concurrent medication/care: at the discretion of treating clinician n=958 Intervention 2: Saline. 0.9% saline 500-ml bags. Maximum dose of 50 ml/kg/day, followed by	n=1937 adults Sepsis Australia, New Zealand	90-day mortality	RCT Follow-up: 90 days

Study	Intervention and comparison	Population	Outcomes	Study design and length of follow-up
	open-label 0.9% saline for the remainder of the 24-hour period. Duration 90 days max. Concurrent medication/care: at the discretion of treating clinician			
Patel 2014[254]	n=2068 Intervention 1: median albumin exposure: 175.0 g (16.0-180.0 g) in a median volume of 1.7 l (0.4-3.4 l). Duration: median of 3 days (40 minutes - 28 days) n=2122 Intervention 2: crystalloids (0.9% saline, Ringer's lactate) n=156 Intervention 3: colloids (HES, gelatin)	n=4190 adults Sepsis of any severity Multiple countries	Mortality	Systematic review Follow-up: unclear
SAFE 2011[279]	n=603 Intervention 1: 4% albumin in 500 ml bottles n=615 Intervention 2: 0.9% Sodium Chloride BP (saline) in 500 ml bottles	n=1218 adults Severe sepsis Australia, New Zealand	28-day mortality	RCT Follow-up: 28 days
Santhanam 2008[281]	n=80 Intervention 1: 20-40 ml of Ringer lactate/kg over 15 minutes plus dopamine if therapeutic goals were not achieved. n=80 Intervention 2: 20 ml of Ringer lactate/kg over 20 minutes plus dopamine if therapeutic goals were not achieved	n=160 children aged 1 month to 12 years Septic shock India	Cumulative 72-hour survival	RCT Follow-up: until discharge or death

1 **Abbreviations: EGDT=early goal-directed therapy; HES=hydroxyethyl starch**

8.5.3.1 Clinical evidence summary tables

Table 140: 6% HES versus 0.9% saline in adults with sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 6% HES versus 0.9% saline (95% CI)
90-day mortality	1921 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.07 (0.92 to 1.25)	237 per 1000	17 more per 1000 (from 19 fewer to 59 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 141: Crystalloid versus colloid plus crystalloid in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with crystalloid versus colloid + crystalloid (95% CI)
Hospital mortality	493 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.92 (0.75 to 1.12)	469 per 1000	38 fewer per 1000 (from 117 fewer to 56 more)
ICU mortality	493 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.8 (0.62 to 1.02)	384 per 1000	77 fewer per 1000 (from 146 fewer to 8 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 142: 20% albumin versus 6% HES in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 20% albumin versus 6% HES (95% CI)
28-day mortality	56 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.58 (0.18 to 1.83)	231 per 1000	97 fewer per 1000 (from 189 fewer to 192 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 143: 4% albumin versus 0.9% Sodium Chloride BP in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 4% albumin versus 0.9% Sodium Chloride BP (95% CI)
28-day mortality (univariate analysis)	1218 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.74 to 1.02)	353 per 1000	46 fewer per 1000 (from 92 fewer to 7 more)
28-day mortality (multivariate analysis)	919 (1 study)	HIGH	OR 0.71 (0.52 to 0.97)	355 per 1000	-[3]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Adjusted odds ratio.

Table 144: Albumin versus crystalloids in adults with sepsis

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Control	Risk difference with albumin versus crystalloids (95% CI)
Mortality	3878 (1 study)	MODERATE[1] due to indirectness	RR 0.93 (0.86 to 1.01)	393 per 1000	28 fewer per 1000 (from 55 fewer to 4 more)

[1] Downgraded by 1 increment because of differences regarding the study population.

1

2 **Table 145: Albumin versus colloids in adults with sepsis**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with albumin versus colloids (95% CI)
Mortality	299 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.02 (0.76 to 1.36)	372 per 1000	7 more per 1000 (from 89 fewer to 134 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment because of differences regarding the study population.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3

4 **Table 146: Packed red blood cells (PRBC) plus EGDT versus EGDT only in adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PRBC + EGDT versus EGDT (95% CI)
Hospital mortality	93 (1 study)	VERY LOW[1] due to imprecision	RR 1.21 (0.71 to 2.08)	339 per 1000	71 more per 1000 (from 98 fewer to 366 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PRBC + EGDT versus EGDT (95% CI)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 147: Red blood cells (RBC) for low threshold (≤7 g/dl) versus high threshold (≤9 g/dl) in adults with septic shock

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with RBC at low versus high threshold (95% CI)
90-day mortality	998 (1 study)	MODERATE[1] due to indirectness	RR 0.97 (0.84 to 1.11)	450 per 1000	13 fewer per 1000 (from 72 fewer to 49 more)
90-day mortality - >70 years of age	358 (1 study)	MODERATE[1] due to indirectness	RR 1.01 (0.84 to 1.23)	530 per 1000	5 more per 1000 (from 85 fewer to 122 more)
90-day mortality - 70 years or younger	640 (1 study)	MODERATE[1] due to indirectness	RR 0.93 (0.77 to 1.13)	402 per 1000	28 fewer per 1000 (from 92 fewer to 52 more)

[1] Intervention does not fall within the 6-hour time frame (the GDG acknowledged that protocolised care usually required fluids to be given within the first 6 hours).

Table 148: 0-2 litres versus 2-4 litres of fluids in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 0-2L versus 2-4L (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 0-2L versus 2-4L (95% CI)
Hospital mortality	396 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.84 to 1.3)	441 per 1000	22 more per 1000 (from 71 fewer to 132 more)
ICU mortality	396 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.89 (0.67 to 1.17)	355 per 1000	39 fewer per 1000 (from 117 fewer to 60 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 149: 0-2 litres versus >4 litres of fluids in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 0-2L versus >4L (95% CI)
Hospital mortality	310 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.03 (0.79 to 1.33)	450 per 1000	13 more per 1000 (from 94 fewer to 149 more)
ICU mortality	310 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.56 to 1.04)	410 per 1000	94 fewer per 1000 (from 180 fewer to 16 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 150: 2-4 litres versus >4 litres of fluids in adults with severe sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 2-4L versus >4L (95% CI)
Hospital mortality	286 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.98 (0.75 to 1.28)	450 per 1000	9 fewer per 1000 (from 112 fewer to 126 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with 2-4L versus >4L (95% CI)
ICU mortality	286 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.79 (0.59 to 1.05)	450 per 1000	94 fewer per 1000 (from 185 fewer to 22 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 151: High volume (20-40 ml Ringer lactate/kg) versus low volume (20 ml Ringer lactate/kg) in children with septic shock

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with High volume versus low volume (95% CI)
Cumulative 72-hour survival	147 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 0.93 (0.77 to 1.14)	753 per 1000	53 fewer per 1000 (from 173 fewer to 105 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 152: Additional data (data could not be meta-analysed): packed red blood cells (PRBC) plus EGDT versus EGDT only for adults with septic shock

Study	Comparator	Outcome	PRBC + EGDT		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
Fuller 2010[108]	EGDT	**Duration of hospital stay**					
		Hospital length of stay	25.9 days	34	12.5 days	59	Very high
		Duration of critical care stay					
		ICU length of stay	11.4 days	34	3.8 days	59	Very high

Note: it is unclear whether the results of hospital and ICU length of stay are median or mean values.

Table 153: Additional data (data could not be meta-analysed) : crystalloid versus colloid plus crystalloid for adults with severe sepsis

Study	Comparator	Outcome	Crystalloid		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
McInthyre 2007[213]	Colloid	**Duration of hospital stay**					
		Hospital length of stay (median, IQR)	13 days (7-27)	235	15 days (6-26)	258	Very high

Table 154: Additional data(data could not be meta-analysed): 0-2 litres versus 2-4 litres of fluids for adults with severe sepsis

Study	Comparator	Outcome	0-2L		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
McInthyre 2007[213]	2-4 litres	**Duration of hospital stay**					
		Hospital length of stay (median, IQR)	14 days (8-28)	210	13.5 days (6-26)	186	Very high

Table 155: Additional data (data could not be meta-analysed): 0-2 litres versus >4 litres of fluids for adults with severe sepsis

Study	Comparator	Outcome	0-2 litres		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
McInthyre 2007[213]	>4 litres	**Duration of hospital stay**					
		Hospital length of stay (median, IQR)	14 days (8-28)	210	17 days (6-28)	100	Very high

Table 156: Additional data (data could not be meta-analysed): 2-4 litres versus >4 litres of fluids for adults with severe sepsis

Study	Comparator	Outcome	2-4 litres		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
McInthyre 2007[213]	>4 litres	**Duration of hospital stay**					
		Hospital length of stay (median, IQR)	13.5 days (6-26)	186	17 days (6-28)	100	Very high

8.5.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[129] These are listed in Appendix M, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

1 Unit costs

2 Table 157: UK costs of IV Fluids

IV Fluid	ADULTS: Cost of fluid for resuscitation (2000 ml)[a]	CHILDREN: Cost of fluid for 500 ml pre-mixed bag (unless stated otherwise)[b]
Crystalloids		
0.45% sodium chloride	-	£0.90
0.9% Sodium Chloride	£1.40	£0.63
0.9% sodium chloride + potassium (pre-mixed) • 10mmol potassium in 500 ml 0.9% sodium chloride • 20mmol potassium in 500 ml 0.9% sodium chloride	- -	£0.71 £0.76
Hartmann's Solution	£1.70	
Plasma-lyte M	£1.84	
Plasma Lyte 148	-	1000 ml = £1.59
Ringer's Lactate	£5.00	£0.76
Colloids		
Volplex	£7.60	
Isoplex	£7.80	
Gelofusine/Gelaspan 4%	£9.60	
Geloplasma	£10.00	
6% Venofundin	£25.20	
6% Tetraspan	£26.00	
6% Voluven	£30.00	
6% Volulyte	£30.60	
10% Tetraspan	£39.60	
Albumins		
5% Albumin	£122.08	
4.5% Albumin	£136.24	£33.75
Blood products[c]		
Packed red blood cells	£121.85	£48.99 (neonatal red cells)
Fresh frozen plasma	£28.46	£50.02 (neonatal MBFFP [65 ml non-UK Sourced]) £178.03 (Paediatric MBFFP [275 ml non-UK Sourced])
Platelets	£193.15	£86.28 (Neonatal platelets)

Pooled cryoprecipitate (5 packs)	£177.57	£1,080.48 (MB cryoprecipitate-pooled [non-UK sourced])

(a) Source: IV fluid guideline for adults
(b) Source: IV fluid guideline for children
(c) Source: NHS Blood and Transplant Price List 2014/15

Note that in addition to the costs of the products themselves there will be handling and administration costs from the laboratory. Goal directed therapy also may involve further tests.

8.5.5 Evidence statements

Clinical

The evidence included in this review was of moderate to very low quality.

Adults with sepsis, severe sepsis or septic shock:

Evidence from seven studies on head to head comparison of different types of IV fluids found that there was no clinically important difference for the outcomes of mortality and hospital length of stay. A multivariable analysis in one study indicated that patients receiving albumin had a higher chance of death at 28 days compared to those receiving saline.

Children with sepsis, severe sepsis or septic shock:

The evidence from one study did not show any clinically important difference for mortality at 72 hours between different dosages of IV fluids.

Economic

No relevant economic evaluations were identified.

8.5.6 Recommendations and link to evidence

Recommendations	**People over 16 years** **101. If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of 500 ml over less than 15 minutes. [This recommendation is from Intravenous fluid therapy in over 16s in hospital (NICE guideline CG174)]** **102. If children and young people up to 16 years need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. [This recommendation is from Intravenous fluid therapy in children (NICE guideline NG29)]** **103. If neonates need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–**

	154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes. [This recommendation is from Intravenous fluid therapy in children and young people in hospital (NICE guideline TBC)] **104. Reassess patient after completion of the intravenous fluid bolus, and if no improvement give second bolus. If there is no improvement after second bolus alert consultant to attend (in line with recommendations 50, 65 and 80).** **105. Use a pump or syringe if no pump available to deliver fluids for resuscitation to people with suspected sepsis who need fluids in bolus form.** **106. Do not use tetrastarch for fluid resuscitation for people with sepsis. [This recommendation is adapted from Intravenous fluid therapy in over 16s in hospital (NICE clinical guideline CG174)].** **107. Consider human albumin solution 4–5% for fluid resuscitation only in patients with sepsis with shock. [This recommendation is adapted from Intravenous fluid therapy in over 16s in hospital (NICE guideline CG174)].**
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days, health-related quality of life and admissionto critical care to be critical outcomes. Important outcomes were duration of hospital stay, duration of critical care stay, number of organs supported and time to reversal of shock. Potential harm from inappropriate fluid administration is fluid overload or heart failure and this was also included as outcome.
Trade-off between clinical benefits and harms	The GDG acknowledged that a NICE clinical guideline on intravenous fluid administration in adults (CG174) and a guideline on intravenous fluids in children (NG29) had already been published. The GDG also acknowledged that the NICE guideline on intravenous fluid administration in adults included a recommendation for patients with severe sepsis. This evidence review was to review whether there was any sepsis specific evidence omitted from IV fluids guidelines or published since those guidelines. **Type of fluids** NICE guidance recommends crystalloids for resuscitation. This review did not find any evidence to suggest that was not appropriate for people with sepsis. The evidence indicated no benefit from adding colloids to crystalloids in people with sepsis. NICE CG 174 recommended consideration of albumin for severe sepsis. That recommendation was informed by the SAFE study, which compared albumin and saline for fluid resuscitation in intensive care. The SAFE study (2004) found limited evidence of a treatment effect that favours albumin in a predefined subgroup of patients with severe sepsis. A follow-up paper (SAFE 2011) presented more detailed data on the severe sepsis subgroup. A multivariate analysis showed that albumin was independently associated with a decreased 28-day mortality.. The GDG decided that the recommendation in CG174 was appropriate for people with severe sepsis and that in practice this would be instituted only by specialists and not used for initial resuscitation.

	Albumin versus other colloids The evidence from the two studies included in this review did not show any clinically important difference for albumin versus other colloids. **Use of blood products** The GDG acknowledged that the evidence from the two studies included in this review did not show any clinically important difference for the use of blood products. Blood products may be important for people with sepsis but are unlikely to be used at an early stage in resuscitation and their use is more appropriate for consideration by specialists in individual cases. The GDG therefore decided not to make a recommendation. **Volume of fluids** The GDG acknowledged that the evidence from the two studies included in this review did not show any clinically important difference for the quantities of fluids compared in the two studies. The GDG agreed that an initial fluid bolus of 500 ml as recommended in the IV Fluid guideline could be recommended as long as the patient's vital status was continuously reassessed. The Surviving Sepsis Campaign currently recommends up to 30 ml per kilogram of crystalloids as an initial bolus. In the case of children the GDG agreed that they had not found any evidence to change the recommendations made by the IV fluids in children guideline which had included children with sepsis. The GDG acknowledged that the FEAST study[202] generated controversy in paediatric care because it suggested that in an African setting, giving a fluid bolus was potentially harmful. Maitland (2011) had already been included in the IV fluids in children guideline and is further discussed in other considerations. In conclusion, the GDG agreed that this review did not provide any evidence that would alter the existing IV fluid recommendations for adults and children.
Economic considerations	An economic evaluation was identified but excluded due to limited applicability and methodological limitations. More information on this can be found in appendix M. The cost effectiveness of the type of fluid will depend on its cost as well as any additional benefit that a more expensive fluid can provide. Higher volumes or more aggressive rates of administration will consume more resources. However a more effective fluid may reduce downstream resource use of further interventions and potentially reduce length of stay. The GDG were presented with the cost of the types of fluids and blood products. Crystalloids are the cheapest type of fluid and albumin the most expensive; however the doses given may affect the overall cost. The population that is being discussed here as being given fluids is potentially large as it is those that are suspected of sepsis and categorised as high risk of mortality (based on risk factors and tests). The actual prevalence of sepsis is unknown due to the underlying condition often being reported as the cause rather than the systemic condition itself. However there could be as high as over 100,000 admissions due to sepsis per year, with the mortality rate being relatively high (around 30%). The GDG decided that the population that should be administered fluids are those suspected of sepsis with high risk criteria and a lactate level above 2. These are considered an unwell group of patients, and fluids are a standard part of managing patients with sepsis. Those at high risk and lactate less than 2 are considered for fluids. The categorisation of patients into risk groups based on signs and symptoms and then further based on test results means that the most aggressive interventions are only given to patients likely to be most at risk and who would benefit from the

	interventions such as fluids. The IV fluids guidelines for adults and children recommend crystalloids. The clinical review data identified could not be meta-analysed and no one fluid appeared clinically better than another. The GDG agreed that the recommendations made in the IV fluids guidelines were appropriate and likely to be cost effective for the sepsis population, given that crystalloids have the lowest acquisition cost of all the fluids. Crystalloids are used in current practice therefore this recommendation is unlikely to have a cost impact. There may even be a cost saving if implementing the recommendation means switching from other more expensive fluids to using crystalloids. The IV fluid guideline for adults also recommends albumin for patients with severe sepsis. The GDG agreed this was an appropriate recommendation based on clinical findings from the SAFE study which found reduced mortality at 28 days from using albumin over saline. A reduced mortality from albumin may offset its incremental cost above the comparator to the extent that it could become cost effective, as those patients that remain alive in the albumin arm would accrue more QALYs. Although cost effectiveness of albumin remains uncertain without evidence, the recommendation is only to consider their use and only in the severe sepsis group. In practice this would be instituted only by specialists and not used for initial resuscitation. This recommendation may have a cost impact; however it may also already be incorporated into practice from the IV fluids in adults guideline.
Quality of evidence	The evidence included in this review was of moderate to very low quality, largely due to risk of bias and imprecision. A lack of blinding to study interventions or potentially confounding patient characteristics, as well as the observational study design of some of the included studies were the main reasons for an increased risk of bias. The GDG agreed therefore that they could not be confident in the evidence due to the low quality.
Other considerations	The GDG noted that there was some evidence for current treatment standards for people with sepsis from Early Goal Directed Therapy (EGDT) trials. Data from the Protocolised Management in Sepsis (ProMISe) study which had been performed in UK emergency departments indicated that at baseline people included in the study had received a median of 2l of fluid. Patients were required to have received a litre of fluid over 60 minutes for recruitment to the trial. These studies were not part of this review as the EGDT trials assessed the effectiveness of a treatment bundle, and thus the clinical effectiveness of IV fluids could not independently assessed. These studies are further discussed in chapter 12. The GDG discussed the FEAST study [202]. The FEAST study did not fit the study population defined in the protocol for this review but had been widely discussed in the paediatric sepsis community. The FEAST study showed that fluid boluses (20-40ml/kg) significantly increased 48-hour mortality in severely ill African children with impaired perfusion compared with maintenance fluid. The study was excluded from formal review because the study population consisted of children with severe febrile illness or respiratory distress rather than sepsis. The study authors collected data on working diagnoses, that is, diagnoses used by practitioners at admission that were not confirmed by diagnostic procedures. The rationale behind using working diagnoses was the fact that the availability of diagnostic facilities is limited in large parts of Sub-Saharan Africa and medical professionals need a simple and effective treatment approach for their patients. Vague details about the study population are given in the online appendix. One of the subgroup analyses was on people with a positive malaria serology. However, only 16% of the study population had a working diagnosis of septicaemia, significantly less than children with a negative malaria serology. The IV fluids in children guideline acknowledged that the FEAST evidence challenges whether boluses should be used for resuscitation in resource-limited

	settings for children with shock who did not have hypotension. However, the guideline concluded that although this was an important finding, the situation was not directly applicable to the UK clinical setting. The GDG discussed the 6S study (Perner 2012), which showed an increased risk of death for people with severe sepsis who were treated with hydroxyethyl starch (HES) compared to those treated with Ringer acetate. The European Medicines Agency concluded in December 2014 that HES was contraindicated in critically ill patients or patients with sepsis or burns and this is thereore no longer available. NICE CG 174 recommends albumin in 'severe sepsis'. The terminology being used for describing sespsis and its complications is changing and the term 'severe sepsis' will cease to be used. The GDG reviewed the evidence and using their experience considered that the appropriate population for the use of albumin is a patient with sepsis and shock. The wording in the recommendation has therefore been changed from 'severe sepsis' to 'septis with shock'. NICE CG174 is a guideline for people over 16 years. The GDG agreed following the review of evidence for this guideline that this is also elevant to people less than 16 years and therefore have adapted the recommendation to include all popultations in the guideline. The GDG wished to make it explicit that IV fluids should be given promptly and quickly. They therefore included a recommendation indicating that fluids should be given by syringe if a pump was not available. They also chose to include a recommendation to make explicit the need to repeat fluids if the patient does not respond and to ensure appropriate consultant input. Appropriate consultant input is discussed in section 8.6. The recommendations for intravenous fluids are made with the understanding that intravenous fluids are primarily given in acute hospital settings. The GDG were aware that it can be possible to give fluids in ambulance and other settings. They agreed that overall the priority was to ensure a patient is transferred as quickly as possible to an acute hospitaland therefore did not make a specific recommendation about delivery of fluids in other settings. .

18.6 Escalation of care

8.6.1 Introduction

Specialised critical care teams and rapid response teams have become increasingly involved in the management of critically ill patients. Being looked after by specialised healthcare staff has been shown to positively influence patient outcome. It is paramount that sepsis patients receive appropriate and timely treatment, some of which can only be delivered in certain settings.

8.6.2 Review question: When is the most appropriate time for care of people with sepsis to be directed to a) a senior healthcare professional, and b) critical care providers?

For full details see review protocol in Appendix A.

Table 158: PICO characteristics of review question

Population	People at risk of developing severe sepsis and septic shock
Intervention	Escalation of care
Comparison	Early versus late escalation of care
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis Important: • Duration of hospital stay. • Duration of critical care stay. • Number of organs supported. • Adverse events (long-term disability; short-term heart failure)
Study design	Systematic reviews, RCTs, cohort studies conducted in the UK

8.6.3 Clinical evidence

We searched for randomised controlled trials and cohort studies conducted in the UK that assessed early versus delayed escalation of care in people with sepsis, severe sepsis or septic shock. No studies were identified that met the protocol inclusion criteria. Therefore the GDG decided to include studies published outside of the UK and two prospective cohort studies[283,300] and one before and after study[315] were identified. In addition, it was decided to include a case-control study[240]conducted in the UK.

Three studies[283,300,315] were in adult populations and one study was in children[240] . The included studies are summarised in **Table 184** below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix L.

1 **Table 159: Summary of studies included in the review**

Study	Intervention and comparison (if applicable)	Population	Outcomes	Comments
Ninis 2005[240]	Management failures: not under care of paediatrician, failure of supervision by consultant Patient assessment failures: failure to recognise complications, failure to recognise severity Clinical practice failures: failure to administer inotropes, failure to administer fluids (too little versus adequate, too much versus adequate) Length of follow-up: unclear	n=498 children (143 cases, 355 matched controls) Meningococcal disease, setting unclear UK	Risk factors for death	Case-control study in children with meningococcal disease. Children who died from meningococcal disease during the study period were matched by age with three survivors (controls) from the same region of the country. Multivariable analyses showing risk factors for death.
Schramm 2011[283]	n=268 Baseline group: training of nurses and house staff on sepsis pathophysiology, recognition of severe sepsis, and practical aspects of central venous pressure and $ScvO_2$ n=284 Weekly activation group: weekly feedback on compliance with the sepsis resuscitation bundle n=432 Sepsis response team (SRT) activation group Length of follow-up: unclear	n=984 adults Severe sepsis or septic shock, ICU USA	Mortality, multiple logistic regression analysis showing the association of hospital death with the study intervention periods	Prospective cohort study comparing three different bundle/intervention groups. The multivariable analysis showing the association of hospital death with the study intervention periods uses the baseline group as a reference. 22 episodes were excluded from the multivariable mortality analysis because they were repeat ICU admissions.
Silverman 2011[300]	n=19 Intervention 1: Pre-bundle group n=186	n=273 adults Severe sepsis or septic shock, ICU	Mortality Length of stay on the ICU	Prospective cohort study comparing three bundles at three different time periods.

Study	Intervention and comparison (if applicable)	Population	Outcomes	Comments
	Intervention 2: Bundle group: tasks that were to be accomplished as soon as possible over the 6 h immediately after the identification of sepsis: measure serum lactate level; obtain blood cultures before antibiotic administration; administer broad-spectrum antibiotics within 3 h of emergency department admission and within 1 h of non–emergency department admission; treat hypotension and/or increased lactate level with fluids with a minimum of 20 ml/kg of crystalloid; in the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/l maintain adequate CVP and central venous oxygen saturation (achieve a CVP of >8 mmHg, achieve central venous oxygen saturation ($ScvO_2$) >70% or mixed venous oxygen saturation (SvO_2) >65%); consider low-dose steroids for vasopressor-unresponsive septic shock; consider activated Drotrecogin alfa; glucose control to maintain serum glucose level <150 mg/dl (range, 90–140 mg/dl); maintain inspiratory plateau pressures <30 cm water for mechanically ventilated patients n=68 Intervention 3: Bundle-plus group: SICU led by a surgical intensivist Length of follow-up: unclear	USA		
Umscheid 2015[315]	Early warning response system (EWRS): all in-patients and non-critical care services screened continuously. If a patient met the EWRS criteria	Derivation cohort n=4575 adults (alerts in pre-implementation period	Adverse events	Pre-implementation/post-implementation study of early warning response system.

Study	Intervention and comparison (if applicable)	Population	Outcomes	Comments
	threshold, an alert was sent to the covering provider and rapid response coordinator. Length of follow-up: not applicable	n=595, alerts in post-implementation period n=545) Sepsis, acute inpatient units USA		

Table 160: Clinical evidence summary: escalation of care

Study	Intervention and comparison	Population	Outcomes	Limitations
Ninis 2005[240]	Management failures Patient assessment failures Clinical practice failures	n=498 children (143 cases, 355 matched controls)	Independent risk factors for death (multivariable analysis): Not under care of paediatrician: OR 66.0 (95% CI 3.6-1210) Failure of supervision by consultant: OR 19.5 (95% CI 1.8-213) Failure to recognise complications: OR 3.33 (95% CI 0.7-17) Failure to recognise severity: OR 0.51 (95% CI 0.1-2.5) Failure to administer inotropes: OR 23.7 (95% CI 2.6-213) Too little versus adequate fluid therapy: OR 1.49 (95% CI 0.2-12) Too much versus adequate fluid therapy: OR 19.4 (95% CI 0.2-1560)	Case-control study Serious indirectness (children with meningococcal disease) Very high risk of bias (unclear setting, case-control study, patient selection)
Schramm 2011[283]	n=268 Baseline group n=284 Weekly activation group n=432 SRT (sepsis response team) activation group	n=984 adults	Mortality: 81/268 baseline group, 78/284 weekly feedback group, 93/432 SRT activation group Multiple logistic regression analysis showing the association of hospital death with the study intervention periods (n=962): Baseline group (n=267): OR 1 Weekly feedback group (n=272): OR 1.013 (95% CI 0.685-1.497) SRT group (n=423): OR 0.657 (95% CI 0.456-0.945)	Prospective cohort study Serious indirectness (setting, comparison of different time periods rather than escalation of care) Very high risk of bias (differences in population numbers between study periods, study design)
Silverman 2011[300]	n=19 Intervention 1: Pre-bundle group n=186 Intervention 2: Bundle group n=68	n=273 adults	Mortality rate: 42% in the pre-bundle group, 28% in the bundle group, 20% in the bundle-plus group Length of stay (mean, SD); 38 days (31) in the pre-bundle group, 29 days (36) in the bundle group, 22 days (15) in the bundle-plus group	Prospective cohort study Serious indirectness (setting, comparison of time periods with different intervention protocols and not escalation of care) Very high risk of bias (no adjusted analysis of mortality rates, study

Study	Intervention and comparison	Population	Outcomes	Limitations
	Intervention 3: Bundle-plus group			design)
Umscheid 2015[315]	Early warning response system (EWRS)	derivation cohort n=4575 adults (alerts in pre-implementation period n=595, alerts in post-implementation period n=545)	Mortality: OR 0.98 (95% CI 0.63-1.53) Mortality within 30 days of alert: OR 0.69 (95% CI 0.38-1.26) Mortality or inpatient hospice transfer: OR 0.65 (95% CI 0.33-1.29) Renal replacement therapy: OR 0.82 (95% CI 0.27-2.43)	Pre-implementation/post-implementation study No indirectness High risk of bias (study design, unadjusted odds ratios)

8.6.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

8.6.5 Evidence statements

Clinical

The evidence was of very low quality for all of the outcomes.

Adults:

The evidence suggested that being looked after by a senior clinician or a specialised team was associated with a reduced mortality. One study showed that the implementation of an early automated warning system resulted in lower mortality rates although the effect might not be clinically important.

Children:

One study in children with meningococcal disease showed that the mortality risk was reduced if they received treatment from a paediatrician rather than a healthcare professional not specialised in paediatric medicine. Failure to receive sufficient supervision of junior staff (management failure), and not receiving adequate inotropes were also found to be independently associated with an increased risk of death.

Economic

- No relevant economic evaluations were identified.

8.6.6 Recommendations and link to evidence

Recommendations	**The evidence for escalation of care is discussed below and specific reference to escalation of care is included in recommendations 44, 50 ,59,74.** **44. For adults and children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:** • **arrange for immediate review by the senior clinical decision maker** • **carry out a venous blood test for the following :** – **blood culture** – **full blood count** – **C reactive protein** – **urea and electrolytes** – **creatinine**

– **clotting screen**

– **blood gas to include lactate measurement**

- **give a broad-spectrum antimicrobial at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet a high risk criteria) in line with recommendations in section 8.4**
- **discuss with consultant.**

50. Alert a consultant to attend in person if an adult, child or young person aged 12 years or over with suspected sepsis and any high risk criteria fails to respond within one hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **systolic blood pressure persistently below 90mmHg**
- **reduced level of consciousness despite resuscitation**
- **respiratory rate over 30 breaths per minute**
- **lactate not reduced by more than 20% within 1 hour.**

59. For children aged 5- 11 years who have suspected sepsis and 1 or more high risk criteria:

- **arrange for immediate review by the senior clinical decision maker**
- **carry out a venous blood test for the following:**

– **blood culture**

– **full blood count**

– **C reactive protein**

– **urea and electrolytes**

– **creatinine**

– **clotting screen**

– **blood gas for glucose and lactate**

- **give people a broad-spectrum antimicrobial (see section 8.4) at the maximum recommended dose as soon as possible (within 1 hour of identifying that they meet any high risk criteria)**
- **discuss with consultant.**

65. Alert a consultant to attend in person if a child aged 5-11 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- **reduced level of consciousness despite resuscitation**
- **heart rate or respiratory rate fulfil high risk criteria**
- **lactate remains over 2 mmol/litre after one hour.**

	74. For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria: • **arrange for immediate review by the senior clinical decision maker** • **carry out a venous blood test for the following:** – **blood culture** – **full blood count** – **C reactive protein** – **urea and electrolytes** – **creatinine** – **clotting screen** – **blood gas for glucose and lactate** • **give parentral antibiotics (within 1 hour of identifying that they meet any high risk criteria; see section 8.4)** • **discuss with consultant.** **80. Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:** • **reduced level of consciousness despite resuscitation** • **heart rate or respiratory rate fulfil high risk criteria** • **lactate over 2 mmol/litre after 1 hour.**
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days, health-related quality of life, and admission to critical care to be critical outcomes. Length of stay on the ICU, length of hospital stay, the number of organs supported, and adverse events were considered important outcomes. Mortality was the only outcome reported by the included studies.
Trade-off between clinical benefits and harms	The evidence showed that escalation of care to senior healthcare professionals or critical care providers caused a reduction in mortality. Being looked after by intensivists or teams specialised in the treatment of sepsis, as well as receiving bundled care had a positive effect on mortality reduction. One study showed that the implementation of an early warning response system for adults with sepsis resulted in fewer deaths although the effect might not be clinically important. Another study in children with meningococcal disease identified a failure of adequate escalation of care to be an independent risk factor for mortality. Not being looked after by a paediatrician, failure to receive sufficient supervision of junior staff (management failure), and not receiving adequate inotropes were found to be independently associated with an increased risk of death.The GDG acknowledged that the evidence from the included study in children had resulted in a change of practice, as it showed that senior involvement in the therapeutic process was needed, and children had worse outcomes when treated in adult settings..
Economic considerations	No economic evidence was identified for this question. Escalation of care to a more senior clinician/team will involve costs associated with the more senior staff and also the opportunity cost of their time.

	The cost effectiveness of early escalation of care will depend upon what benefit that additional level of care can bring to the patient. If a more senior clinician or closer supervision can pick up changes that might have been missed and even led to death had care not been escalated, then this is likely to be a cost effective strategy. Therefore how to decide when care should be escalated or for which patients may be important because this is likely to be more cost effective for the higher risk groups, and this links to other reviews which looked at which tools best predict the progression of sepsis. Although the clinical studies identified did not fit the protocol exactly, they generally showed that escalation of care in some form reduces mortality. Two studies from the clinical review also showed that escalation of care in some form led to a reduction in the length of ICU stay. The GDG agreed that the input of a senior clinician was important and decided that patients categorised as high risk would have their case discussed with a consultant. The most severe high risk group (lactate more than 4 mmol/l) should also have their cases referred to critical care, for consideration of admission to critical care setting. The discussion with the consultant could be via the telephone, although the GDG debated when a consultant should attend physically, and agreed that attendance would be appropriate if any high risk patient had not 'improved significantly' after one hour of initiation of fluids. A significant improvement is measured by vital signs and lactate level and is defined above. It is then the role of the senior clinicians to decide on further interventions that might be appropriate for the patient. Although discussion with a consultant and particularly attendance would have associated costs and opportunity costs, the GDG agreed that seeking the opinion of a consultant was important because of the potential high mortality of sepsis with shock.
Quality of evidence	The evidence included in this review was generally of very low quality. This was largely due to study design, risk of bias and indirectness. Indirectness existed for both the study populations and the assessed interventions. No studies were identified that fully matched all criteria of the study protocol. The protocol limited the inclusion of studies to RCTs or cohort studies conducted in the UK and published after 1999 only. The included studies therefore were cohort studies from the USA, a pre-implementation/post-implementation study from the USA, and a case-control study from the UK. The GDG agreed to include these four studies in this review to provide a basis for discussion and inform recommendations for escalation of care. Three studies were of an observational study design and one study was a case-control study. Observational studies are inferior to RCTs as they offer more potential for bias, for example in patient selection where the composition of treatment groups may differ in terms of patient important characteristics leading to possible confounding. Case-control studies are especially prone to selection bias, limiting its generalisability to populations. The observational rather than experimental study design cannot provide strong evidence for the effect of an intervention..
Other considerations	. The GDG defined appropriate levels of care in several areas of pathway. They considered that a medically qualified practitioner, usually a GP should see people with risk factors for sepsis if they were first seen by non-medical practitioners such as a pharmacist or ambulance personnel. The GDG considered that people with suspected sepsis and high risk criteria should be seen in hospital by professionals with adequate training to start initial assessment and treatment. The GDG were aware that the NICE guideline on acute illness in adults in hospital (CG50) defined competencies required for healthcare professionals looking after acutely ill adults but wished to define further the grade of health professional who should be involved with care of people with suspected sepsis and high risk criteria. The GDG considered that people with suspected sepsis needed early assessment and treatment from healthcare professionals who would be able to

	recognise how unwell the person is and act independently in initiating treatment. The ability to perform a clinical assessment and make a judgememnt about the likelihood of sepsis is important. The GDG used the term 'senior clinical decision maker' to signify the grade of doctor they considered appropriate. The GDG recognised that local arrangements may include appropriately trained advanced nurse practitioners but wished to emphasise that the practitioner seeing the person needs to be able to prescribe antibiotics. . For people over 18 years old the GDG recommended a doctor of grade CT3/ST3 or above, or an advanced nurse practitioner, who could prescribe antibiotics, depending on local arrangements. The GDG agreed that for children and young people up to and including 17 years old a 'senior clinical decision maker' is a paediatric qualified doctor of grade ST4 or above. The GDG considered that all people with high risk criteria could should be discussed with a consultant and made recommendations for consultant attendance for those people not responding to initial resuscitation. The GDG agreed these criteria by consensus. The criteria for attendance of the consultant are lack of response to initial fluids and anitbiotics. For adults, children and young people 12 years and over this is a blood pressure less than 90mmHg, reduced level of consciousness, respiratory rate over 30breaths per minute and a lactate level which had not reduced by 20% over an hour. For children less than 12 years the criteria are reduced level of consciousness, heart rate or respiratory rate meeting high risk criteria or lactate remaining above 2 mmmol/litre. (The evidence on lactate clearance and the use of scores for monitoring is discussed in section 13.6). The GDG recognised that consultant attendance might be a challenge to current working practices but were clear that the responsible consultant for these severely ill patients could come from a variety of specialists such as anaesthetics, acute medicine or emergency care. The GDG were aware of similar arrangements for other serious situations such as trauma. CG50 Acutely ill patients in hospital already recommends that if the team caring for the patient considers that admission to a critical care area is clinically indicated, then the decision to admit should involve both the consultant caring for the patient on the ward and the consultant in critical care. The GDG agreed for people without high risk criteria should be assessed by medical qualified practitioners with prescribing rights but specificed that people with high to moderate risk criteria in whom a definitive diagnosis could not be reached should be assessed by a senior clinical decision mnaker within 3 hours for consideration of antibiotics (see section 8.4.5).

8.6.7 Research recommendations

Please see Appendix N for more detail.

4. A UK sepsis registry should be established to collect clinical and epidemiological data to provide information to support clinical audit to inform the research agenda.

5. What effect will the NICE sepsis guideline have on patient care processes and outcomes in the UK over the next 5 years?

9 Inotropic agents and vasopressors

9.1 Introduction

Sepsis management consists of a bundle of actions to be taken as soon as possible after diagnosis. Inotropic agents, which alter heart muscle contractions, and vasopressors, which cause the constriction of blood vessels, are important parts of sepsis treatment. Some agents have characteristics of both.

This section aims to assess the benefit and cost effectiveness of inotropic agents and vasopressors, both alone and in combination, and identify the most appropriate time for the provision of treatment.

9.2 Review question: What is the most clinical and cost effective inotropic agent or vasopressor for early management of people with severe sepsis? What are the most clinically and cost effective timings of inotropic agents and vasopressors in patients with severe sepsis?

For full details see review protocol in Appendix C.

Agents listed in the protocol can either be classified as inotropic agents or vasopressors, and some agents have characteristics of both classes. To avoid a conflict of definitions, inotropic agents or vasopressors are reported as given by the papers where possible. The term 'inotropes' is used in the data extraction protocol, and therefore that term is given in the clinical evidence tables for all agents.

The terms 'norepinephrine' and 'epinephrine' are used instead of 'noradrenaline' and 'adrenaline' as these are the terms given in the included studies.

Table 161: PICO characteristics of review question

Population	People at risk of developing severe sepsis
Intervention(s)	Inotropic agents and vasopressors: • Milrinone • Enoximone • Dobutamine • Dopamine • Dopexamine • Adrenalin/epinephrine • Noradrenaline/norepinephrine • Vasopressin • Metaraminol
Comparison(s)	• Inotropic agents and vasopressors compared to each other • Early versus late initiation
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis

	Important: • Duration of hospital stay • Duration of critical care stay • Number of organs supported • Adverse events (long-term disability; short-term heart failure)
Study design	RCTs, systematic reviews, cohort studies (if not enough RCT evidence is found)

Cohort studies were only considered for inclusion if not enough evidence from RCTs was found. Studies on levosimendan were excluded as this agent is not licensed in the UK.

To avoid a conflict of definitions we used the terms inotropic agents and vasopressors as given by the investigators of the included studies.

9.3 Clinical evidence

We searched for randomised controlled trials and cohort studies comparing the effectiveness of the type and timing of administration of inotropic agents or vasopressors for patients with sepsis, severe sepsis or septic shock. Twenty studies were included in the review; seventeen RCTs[14,18,180,188,201,207,210,212,218,226,255,277,278,282,286,287,319] and three retrospective cohort studies[21,25,209] . One of the included studies was in children[319]; the others were on adults only. All studies are summarised in **Table 162: Summary of studies included in the review** below. Evidence from these studies is summarised in the clinical evidence summary below (Section 9.3.1). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

1 **Table 162: Summary of studies included in the review**

Study	Intervention and comparison	Population	Outcomes	Comments
Annane 2007 (CATS trial)[14]	n=161 Intervention 1: Inotrope - Adrenalin/epinephrine. Starting dose: 0.2 µg/kg/min, titration based on mean blood pressure (more or less than 70 mmHg). Duration not reported. Concurrent medication/care: With or without placebo (depending on comparison treatment, i.e. norepinephrine alone or with dobutamine) n=169 Intervention 2: Inotrope - Any combination. Starting dose: 0.2 µg norepinephrine/kg/min, titration based on mean blood pressure (more or less than 70 mmHg), with or without 5 µg dobutamine/kg/min (depending on mean blood pressure). Duration not reported. Concurrent medication/care: Not reported	n=330 adults Septic shock ICU, France	Number of deaths at 7 days Number of deaths at 14 days Number of deaths at 28 days Number of deaths at 90 days Mortality at discharge from intensive care Mortality at discharge from hospital Length of stay in intensive care Adverse events during catecholamine infusion Adverse events after catecholamine infusion	RCT
Bai 2014[21]	n=213 Intervention 1: Inotrope – Noradrenalin/norepinephrine. Dosage not reported. Concurrent medication/care not reported Hourly delay of norepinephrine administration	n=213 adults Septic shock ICU, China	Time from onset of septic shock to initial norepinephrine administration as an independent determinant of 28-day mortality	Retrospective cohort study
Beck 2014[25]	n=4376 Intervention 1: Inotrope –	n=6514 adults	Delay of vasopressor administration as an independent	Retrospective cohort study

Study	Intervention and comparison	Population	Outcomes	Comments
	Noradrenalin/norepinephrine. Dosage not reported. Concurrent medication/care not reported n=3502 Intervention 2: Inotrope – Dopamine. Dosage not reported. Concurrent medication/care not reported n=1466 Intervention 3: Inotrope – Phenylephrine. Dosage not reported. Concurrent medication/care not reported n=793 Intervention 4: Inotrope – Dobutamine. Dosage not reported. Concurrent medication/care not reported n=708 Intervention 5: Inotrope – Vasopressin. Dosage not reported. Concurrent medication/care not reported n=313 Intervention 6: Inotrope – Epinephrine. Dosage not reported. Concurrent medication/care not reported	Septic shock ICU, Canada/USA/Saudi-Arabia	determinant of in-hospital mortality	Serious indirectness: Phenylephrine is not included in the study protocol
De Backer 2010[18]	n=858, septic shock n=542 Intervention 1: Inotrope - Dopamine. Dose determined by body weight. Dopamine could be increased or decreased by 2 µg/kg/min. Maximal dose of study drug: 20 µg/kg/min.. Duration 28 days. Concurrent medication/care: Open-label norepinephrine added if patient was still hypotensive after the maximum dose had been administered. n=821, septic shock n=502 Intervention 2: Inotrope - Noradrenalin/norepinephrine. Dose determined by	n=1679 adults, 62% of which had septic shock Septic shock ICU, Belgium/Austria/Spain	28-day mortality	RCT Pre-defined subgroup analysis of people with septic shock

Study	Intervention and comparison	Population	Outcomes	Comments
	body weight. Norepinephrine could be increased or decreased by 0.02 µg/kg/min. Maximal dose of study drug: 0.19 µg/kg/min. Duration 28 days. Concurrent medication/care: Open-label norepinephrine added if patient was still hypotensive after the maximum dose had been administered.			
Lauzier 2006[180]	n=13 Intervention 1: Inotrope - Vasopressin. 0.04-0.20 U/min (source of study drug: Ferring, Toronto, Ontario). Duration not reported. Concurrent medication/care: When maximal dose of drug was reached, administration of the other drug was allowed as rescue therapy if mean arterial pressure was still below 70 mmHg. Dobutamine was used if cardiac index decreased below 3 l/min/m^2 despite adequate fluid resuscitation. Either crystalloids or colloids (25% albumin or pentastarch 10%) were used to maintain pulmonary artery occlusion pressure greater than 12 mmHg. Antimicrobials, corticosteroids, analgesia, insulin used if needed n=10 Intervention 2: Inotrope - Noradrenalin/norepinephrine. 0.1-2.8 µg/kg/min (source of study drug: Sabex, Boucherville, Quebec). Duration not reported. Concurrent medication/care: When maximal dose of drug was reached, administration of the other drug was allowed as rescue therapy if mean arterial pressure was still below 70 mmHg. Dobutamine was used if cardiac index decreased below 3 l/min/m^2 despite adequate fluid resuscitation. Either crystalloids or colloids (25% albumin or pentastarch 10%) were used to maintain pulmonary artery occlusion pressure greater than 12	n=23 persons aged 16 and older Septic shock ICU, Canada/France	ICU mortality	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	mmHg. Antimicrobials, corticosteroids, analgesia, insulin used if needed			
Levy 1997[188]	n=15 Intervention 1: Inotrope - Adrenalin/epinephrine. Infusions were started at 0.3 µg/kg/min and titrated on MAP at 5-min intervals to obtain an MAP >80 mmHg with a stable or increased cardiac index. Duration not reported. Concurrent medication/care: histamine receptor (H_2) blocker by a continuous infusion (50 mg bolus of ranitidine followed by a continuous infusion of 10 mg/h), dopamine up to a dose of 20 µg/kg per min during the first hour n=15 Intervention 2: Inotrope - Any combination. Infusions were started at 0.3 µg/kg per min and titrated on MAP at 5-min intervals to obtain an MAP >80 mmHg with a stable or increased cardiac index; dobutamine infused as a fixed dose of 5 µg/kg per min. Duration Not reported. Concurrent medication/care: histamine receptor (H_2) blocker by a continuous infusion (50 mg bolus of ranitidine followed by a continuous infusion of 10 mg/h), dopamine up to a dose of 20 µg/kg per min during the first hour	n=30 adults Septic shock ICU, France	Mortality	RCT
Mahmoud 2012[201]	n=30 Intervention 1: Inotrope - Any combination. Starting dose of 0.05 µg/kg/min of norepinephrine (dose was gradually increased to 0.1 µg/kg/min), patients continued on a dose of 0.1 µg/kg/min; dobutamine was added in a starting dose of 3 µg/kg/min and increased in increments of 2 µg/kg/min up to 20 µg/kg/min. Duration not reported. Concurrent medication/care: traditional sepsis treatments (fluids, antibiotics, glucose control, respiratory support)	n=60 adults Septic shock ICU, Egypt	28-day mortality ICU length of stay SOFA score at start SOFA score at 24 hours	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	n=30 Intervention 2: Inotrope - Any combination. Starting dose of 0.05 µg/kg/min of norepinephrine (dose was gradually increased to 0.1 µg/kg/min), patients continued on a dose of 0.1 µg/kg/min; epinephrine was added in a starting dose of 0.05 µg/kg/min and increased in increments of 0.03 µg/kg/min up to 0.3 µg/kg/min. Duration not reported. Concurrent medication/care: traditional sepsis treatments (fluids, antibiotics, glucose control, respiratory support)		SOFA score at 48 hours SOFA score at 72 hours SOFA score at 96 hours Acute coronary syndrome Arrhythmias Cerebral stroke Limb ischaemia	
Marik 1994[207]	n=10 Intervention 1: Inotrope - Noradrenalin/norepinephrine. Titrated during a period of 20 minutes to achieve an MAP greater than 75 mmHg; once target MAP was achieved no alteration in rate of infusion was permitted until the end of the study period. Duration not reported. Concurrent medication/care: Midazolam and morphine infusions for sedation, vecuronium infusion for neuromuscular blockade n=10 Intervention 2: Inotrope - Dopamine. Titrated during a period of 20 minutes to achieve an MAP greater than 75 mmHg and to keep the pulse rate less than 150 bpm; once target MAP was achieved no alteration in rate of infusion was permitted until the end of the study period. Duration not reported. Concurrent medication/care: Midazolam and morphine infusions	n=20 adults Septic shock ICU, USA	Mortality	RCT Patients receiving mechanical ventilation

Study	Intervention and comparison	Population	Outcomes	Comments
	for sedation, vecuronium infusion for neuromuscular blockade			
Martin 1993[210]	n=16 Intervention 1: Inotrope - Noradrenalin/norepinephrine. 0.5 µg/kg/min at an infusion of 2 ml/min; 2 ml-increments allowed up to a maximum of 5 µg/kg/min (infusion rate of 20 ml/min). Duration not reported. Concurrent medication/care: respiratory support, volume expansion, fluid resuscitation (colloids, crystalloids), blood products if haematocrit below 33%, 5 µg/kg/min epinephrine if patient did not respond to treatment n=16 Intervention 2: Inotrope - Dopamine. 2.5 µg/kg/min at an infusion of 2 ml/min; 2 ml-increments allowed up to a maximum of 25 µg/kg/min (infusion rate of 20 ml/min). Duration not reported. Concurrent medication/care: respiratory support, volume expansion, fluid resuscitation (colloids, crystalloids), blood products if haematocrit below 33%, addition of 1.7 (1.8) µg/kg/min norepinephrine if not responding to dopamine, plus 5 µg/kg/min epinephrine if patient did not respond to treatment	(n=32) adults Septic shock ICU, France	Hospital mortality	RCT
Martin 2015[209]	n=324 Intervention 1: Inotrope - Norepinephrine. Maximum dosage of norepinephrine was 0.79 µg/kg per minute (IQR 0.03-10 µg/kg per minute). Duration 60 hours (IQR 2-648 hours). Concurrent medication/care: dobutamine, isoproterenol, epinephrine, terlipressin, hydrocortison	n=324 adults Septic shock ICU, France	Mortality	Retrospective cohort study
Mathur 2007[212]	n=25 Intervention 1: Inotrope - Dopamine. Dose range: 10-25	n=50 adults	Mortality	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	µg/kg/min, increments of 2.5 µg/kg/min every 15 minutes. Duration not reported. Concurrent medication/care: Crystalloids, red blood cells n=25 Intervention 2: Inotrope - Noradrenalin/norepinephrine. Dose range: 0.5-2.5 µg/kg/min, increments of 0.25 µg/kg/min every 15 minutes. Duration not reported. Concurrent medication/care: Crystalloids, red blood cells	Septic shock ICU, India		
Morelli 2009 (TERLIVAP trial)[218]	n=15 Intervention 1: Inotrope - Vasopressin. Continuous infusion of 0.03 U vasopressin per minute. Duration 48 hours. Concurrent medication/care: Open-label norepinephrine if the goal MAP of 70 (5) mmHg was not achieved with study drug infusion, IV fluids to maintain central venous pressure of 8-12 mmHg and PAOP between 12 and 18 mmHg during 48-hour study period, packed red blood cells if haemoglobin concentrations decreased below 8 g/dl, dobutamin was administered in doses up to 20 µg/kg/min to achieve SvO_2 values of 65% or more, IV hydrocortisone (200 mg/day), open-label norepinephrine infusions after end of study period, sedation with sulfentanil and midazolam n=15 Intervention 2: Inotrope - Noradrenalin/norepinephrine. 15 µg norepinephrine per minute. Duration 48 hours. Concurrent medication/care: Open-label norepinephrine if the goal MAP of 70 (5) mmHg was not achieved with study drug infusion, IV fluids to maintain central venous pressure of 8-12 mmHg and PAOP between 12 and 18 mmHg	n=45 adults Septic shock ICU, Italy	ICU mortality Length of stay on the ICU Requiring renal replacement therapy New-onset of tachyarrhythmias	RCT 3-arm trial (vasopressin, norepinephrine, terlipressin), only 2 arms (vasopressin, norepinephrine) extracted

Study	Intervention and comparison	Population	Outcomes	Comments
	during 48-hour study period, packed red blood cells if haemoglobin concentrations decreased below 8 g/dl, dobutamin was administered in doses up to 20 µg/kg/min to achieve SvO_2 values of 65% or more, IV hydrocortisone (200 mg/day), open-label norepinephrine infusions after end of study period, sedation with sulfentanil and midazolam			
Myburgh 2008[226]	n=76 Intervention 1: Inotrope - Adrenalin/epinephrine. 15 mg epinephrine in 250 ml 5% dextrose water. Duration not reported. Concurrent medication/care: Additional therapies as required n=82 Intervention 2: Inotrope - Noradrenalin/norepinephrine. 15 mg norepinephrine in 250 ml 5% dextrose water. Duration not reported. Concurrent medication/care: Additional therapies as required	n=280 adults Septic shock ICU, Australia	Mortality at 28 days Mortality at 90 days	RCT Serious indirectness: a priori sepsis subgroup of larger study population
Patel 2010[255]	n=134 Intervention 1: Inotrope - Dopamine. 5-20 µg per kg per min. Duration not reported. Concurrent medication/care: Suspected or confirmed septic shock patients were initially resuscitated with either crystalloid or colloid infusions to a CVP greater than or equal to 8 mmHg. If they continued to have a MAP less than 60 mmHg or a systolic blood pressure less than 90 mmHg after adequate fluid resuscitation, they were considered candidates for randomisation. A vasopressor administration protocol guided the administration and dosing titration of vasopressor agents to achieve a MAP greater than or equal to 60 mmHg or a systolic pressure greater than or equal to 90 mmHg. If the predetermined maximum dose was	n=252 adults Septic shock ICU, USA	28-day mortality Length of stay in the hospital Length of stay in intensive care Incidence of arrhythmias	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	reached for the initial vasopressor (dopamine, 20 µg/kg/min or norepinpehrine, 20 µg/min), then the addition of vasopressin at a continuous infusion dose (0.04 U/min) was initiated. Patients who required additional hemodynamic support to meet the goals were then started on an infusion of phenylephrine (25-200 µg/min), which was titrated to reach the goal hemodynamic parameters n=118 Intervention 2: Inotrope - Noradrenalin/norepinephrine. 5-20 µg/min. Duration not reported. Concurrent medication/care: Suspected or confirmed septic shock patients were initially resuscitated with either crystalloid or colloid infusions to a CVP greater than or equal to 8 mmHg. If they continued to have a MAP less than 60 mmHg or a systolic blood pressure less than 90 mmHg after adequate fluid resuscitation, they were considered candidates for randomisation. A vasopressor administration protocol guided the administration and dosing titration of vasopressor agents to achieve a MAP greater than or equal to 60 mmHg or a systolic pressure greater than or equal to 90 mmHg. If the predetermined maximum dose was reached for the initial vasopressor (dopamine, 20 µg/kg/min or norepinephrine, 20 µg/min), then the addition of vasopressin at a continuous infusion dose (0.04 U/min) was initiated. Patients who required additional hemodynamic support to meet the goals were then started on an infusion of phenylephrine (25-200 µg/min), which was titrated to reach the goal hemodynamic parameters			
Ruokonen 1993[277]	n=5	n=10 adults	Mortality	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 1: Inotrope - Noradrenalin/norepinephrine. Not reported. Duration not reported. Concurrent medication/care: Crystalloids, fresh frozen plasma and HES to maintain a paOP of 8-12 mmHg, 2 µg/kg/min dopamine to maintain renal perfusion n=5 Intervention 2: Inotrope - Dopamine. Not reported. Duration not reported. Concurrent medication/care: Crystalloids, fresh frozen plasma and HES to maintain a paOP of 8-12 mmHg	Septic shock ICU, Finland		
Russell 2008[278]	n=396 Intervention 1: Inotrope - Noradrenalin/norepinephrine. 15 mg norepinephrine in 250-ml intravenous bags of 5% dextrose water with final concentrations of 60 µg of norepinephrine per ml. Infusion was started at 5 ml/hour and increased by 2.5 ml/hour every 10 minutes during first hour to achieve a constant target rate of 15 ml/hour. Duration not reported. Concurrent medication/care: Open-label vasopressors to maintain a constant target mean arterial pressure n=406 Intervention 2: Inotrope - Vasopressin. 30 U vasopressin in 250-ml intravenous bags of 5% dextrose water with final concentrations of 0.12 U vasopressin/ml. Infusion was started at 5 ml/hour and increased by 2.5 ml/hour every 10 minutes during first hour to achieve a constant target rate of 15 ml/hour. Duration not reported. Concurrent medication/care: Open-label vasopressors to maintain a target mean arterial pressure	(n=802) persons aged 17 and older Septic shock ICU, Australia/Canada/USA	Death from any cause at 28 days 90-day mortality Length of stay in the hospital Length of stay on the ICU	

Study	Intervention and comparison	Population	Outcomes	Comments
Schmoelz 2006[282]	n=20 Intervention 1: Inotrope - Dopexamine. 2 µg/kg/min in a concentration of 1.0 mg/ml (infusion rate of 0.12 ml/kg). Duration not reported. Concurrent medication/care: Not reported n=21 Intervention 2: Inotrope - Dopamine. 3 µg/kg/min in a concentration of 1.5 mg/ml (infusion rate of 0.12 ml/kg). Duration not reported. Concurrent medication/care: Not reported	n=61 adults; 41 in the arms extracted Septic shock ICU, Germany	28-day mortality	RCT 3-arm study (dopexamine, dopamine, placebo), only 2 arms (dopexamine, dopamine) extracted
Seguin 2002[286]	n=11 Intervention 1: Inotrope - Adrenalin/epinephrine. Starting dose of 0.1 µg/kg per minute, increased by steps of 0.2 µg/kg per minute every 5 minutes to reach mean systemic arterial pressure between 70-80 mmHg. Duration not reported. Concurrent medication/care: Not reported n=11 Intervention 2: Inotrope - Any combination. Norepinephrine: starting dose of 0.1 µg/kg per minute, increased by steps of 0.2 µg/kg per minute every 5 minutes to reach mean systemic arterial pressure between 70-80 mmHg Dobutamine: continuous infusion of 5 µg/kg per minute. Duration not reported. Concurrent medication/care: Not reported	n=22 adults Septic shock ICU, France	Mortality	RCT
Seguin 2006[287]	n=10 Intervention 1: Inotrope - Adrenalin/epinephrine. Epinephrine titration from 0.2 µg/kg/min with increments of 0.2 µg/kg/min every 3 minutes; increase of epinephrine by steps of 0.2 µg/kg/min until MAP between 70 and 80 mmHg. Duration not reported. Concurrent medication/care: Fluid infusion, mechanical	n=22 adults Septic shock ICU, France	Mortality rate at 28 days Mortality rate at 90 days	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	ventilation n=12 Intervention 2: Inotrope - Any combination. Dopexamine titration from 0.5 µg/kg/min with increments of 0.5 µg/kg/min every 3 minutes; norepinephrine titration from 0.2 µg/kg/min with increments of 0.2 µg/kg/min every 3 minutes; increase norepinephrine by 0.2 µg/kg/min if cardiac index is 3.0 l/min/m^2 or more; increase dopexamine by 0.5 µg/kg/min if cardiac index is below 3.0 l/min/m^2. Duration not reported. Concurrent medication/care: Fluid infusions, mechanical ventilation			
Ventura 2015[319]	n=63 Intervention 1: Inotrope - Dopamine. Up to three doses if no response: 5 µg/kg/min (1st dose), 7.5 µg/kg/min (2nd dose), 10 µg/kg/min (3rd dose). Duration 20-minute intervals. Concurrent medication/care: initial fluid bolus of 20 ml crystalloids/kg in 20 minutes, repeated if no response, and repeated again if no response (plus initiation of study drug protocol). Antibiotics within the first 6 hours n=57 Intervention 2: Inotrope - Epinephrine. Up to three doses if no response: 0.1 µg/kg/min (1st dose), 0.2 µg/kg/min (2nd dose), 0.3 µg/kg/min (3rd dose). Duration 20-minute intervals. Concurrent medication/care: initial fluid bolus of 20 ml crystalloids/kg in 20 minutes, repeated if no response, and repeated again if no response (plus initiation of study drug protocol). Antibiotics within the first 6 hours.	n=120 children Septic shock PICU, Brazil	28-day mortality	RCT Statistically significant differences between dopamine and epinephrine groups: Duration of resuscitation: 33.6 (57) hours versus 16.1 (23.6) hours Renal replacement therapy: 11 (17.4%) versus 6 (10.5%)

9.3.1 Clinical evidence summary

Table 163: Clinical evidence summary: Norepinephrine versus vasopressin for adults with septic shock

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine versus vasopressin (95% CI)
28-day mortality	778 (1 study)	MODERATE[1] due to imprecision	RR 1.11 (0.93 to 1.33)	354 per 1000	39 more per 1000 (from 25 fewer to 117 more)
90-day mortality	771 (1 study)	MODERATE[1] due to imprecision	RR 1.13 (0.97 to 1.31)	439 per 1000	57 more per 1000 (from 13 fewer to 136 more)
ICU mortality	53 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.26 (0.72 to 2.21)	393 per 1000	102 more per 1000 (from 110 fewer to 475 more)
Requiring renal replacement therapy at 48 hours	30 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.6 (0.68 to 3.77)	333 per 1000	200 more per 1000 (from 107 fewer to 923 more)
New onset of tachyarrhythmias	30 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 4 (0.5 to 31.74)	67 per 1000	200 more per 1000 (from 33 fewer to 1000 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 164: Clinical evidence summary: Norepinephrine versus dopamine for adults with septic shock

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Control	Risk difference with norepinephrine versus dopamine (95% CI)
28-day mortality	252 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.86 (0.66 to 1.13)	500 per 1000	70 fewer per 1000 (from 170 fewer to 65 more)
Mortality	80 (3 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.82 (0.59 to 1.15)	700 per 1000	126 fewer per 1000 (from 287 fewer to 105 more)
Hospital mortality	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.7 (0.36 to 1.37)	625 per 1000	188 fewer per 1000 (from 400 fewer to 231 more)
Incidence of arrhythmias	252 (1 study)	LOW[1] due to risk of bias	RR 0.31 (0.18 to 0.53)	381 per 1000	263 fewer per 1000 (from 179 fewer to 312 fewer)
Length of stay in the hospital	252 (1 study)	LOW[1] due to risk of bias			The mean length of stay in the hospital in the intervention groups was 0.7 lower (4.36 lower to 2.96 higher)
Length of stay on the ICU	252 (1 study)	LOW[1] due to risk of bias			The mean length of stay on the icu in the intervention groups was 0.7 higher (1.15 lower to 2.55 higher)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 165: Clinical evidence summary: Norepinephrine versus epinephrine for adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine versus epinephrine (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine versus epinephrine (95% CI)
28-day mortality	158 (1 study)	MODERATE[1] due to imprecision	RR 1.31 (0.76 to 2.24)	224 per 1000	69 more per 1000 (from 54 fewer to 277 more)
90-day mortality	156 (1 study)	MODERATE[1] due to imprecision	RR 1.18 (0.76 to 1.83)	311 per 1000	56 more per 1000 (from 75 fewer to 258 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 166: Clinical evidence summary: Dopexamine versus dopamine for adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with dopexamine versus dopamine (95% CI)
28-day mortality	41 (1 study)	LOW[1] due to imprecision	RR 1.31 (0.41 to 4.2)	190 per 1000	59 more per 1000 (from 112 fewer to 610 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3

4 **Table 167: Clinical evidence summary: Norepinephrine plus dobutamine versus epinephrine for adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + dobutamine versus epinephrine (95% CI)
28-day mortality	330 (1 study)	MODERATE[1] due to imprecision	RR 0.86 (0.65 to 1.14)	398 per 1000	56 fewer per 1000 (from 139 fewer to 56 more)
90-day mortality	330 (1 study)	HIGH	RR 0.96 (0.78 to 1.19)	522 per 1000	21 fewer per 1000 (from 115 fewer to 99 more)
7-day mortality	330 (1 study)	MODERATE[1] due to imprecision	RR 0.81 (0.54 to 1.21)	248 per 1000	47 fewer per 1000 (from 114 fewer to 52 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + dobutamine versus epinephrine (95% CI)
14-day mortality	330 (1 study)	MODERATE[1] due to imprecision	RR 0.75 (0.54 to 1.04)	348 per 1000	87 fewer per 1000 (from 160 fewer to 14 more)
Mortality	52 (2 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.58 to 1.71)	500 per 1000	0 fewer per 1000 (from 210 fewer to 355 more)
Mortality at discharge from ICU	330 (1 study)	HIGH	RR 0.95 (0.75 to 1.21)	466 per 1000	23 fewer per 1000 (from 116 fewer to 98 more)
Mortality at discharge from hospital	330 (1 study)	HIGH	RR 0.93 (0.75 to 1.15)	522 per 1000	37 fewer per 1000 (from 130 fewer to 78 more)
Number of serious adverse events during catecholamine infusion	330 (1 study)	LOW[1] due to imprecision	RR 0.91 (0.63 to 1.31)	267 per 1000	24 fewer per 1000 (from 99 fewer to 83 more)
Number of serious adverse events after catecholamine infusion	330 (1 study)	LOW[1] due to imprecision	RR 1.03 (0.49 to 2.19)	75 per 1000	2 more per 1000 (from 38 fewer to 89 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

1

2 **Table 168: Norepinephrine plus dopexamine versus epinephrine for adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + dopexamine versus epinephrine (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + dopexamine versus epinephrine (95% CI)
28-day mortality	22 (1 study)	LOW[1] due to imprecision	RR 0.56 (0.11 to 2.7)	300 per 1000	132 fewer per 1000 (from 267 fewer to 510 more)
90-day mortality	22 (1 study)	LOW[1] due to imprecision	RR 0.62 (0.18 to 2.16)	400 per 1000	152 fewer per 1000 (from 328 fewer to 464 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 169: Clinical evidence summary: Norepinephrine plus epinephrine versus norepinephrine plus dobutamine for adults with septic shock**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + epinephrine versus norepinephrine + dobutamine (95% CI)
28-day mortality	60 (1 study)	LOW[1] due to imprecision	RR 0.94 (0.57 to 1.53)	533 per 1000	32 fewer per 1000 (from 229 fewer to 283 more)
SOFA score at start	60 (1 study)	MODERATE[1] due to imprecision			The mean sofa score at start in the intervention groups was 0.8 higher (2.31 lower to 3.91 higher)
SOFA score at 24 hours	60 (1 study)	MODERATE[1] due to imprecision			The mean sofa score at 24 hours in the intervention groups was 0.7 higher (2.41 lower to 3.81 higher)
SOFA score at 48 hours	60 (1 study)	MODERATE[1] due to imprecision			The mean sofa score at 48 hours in the intervention groups was 0.6 higher (2.49 lower to 3.69 higher)
SOFA score at 72 hours	60 (1 study)	MODERATE[1] due to imprecision			The mean sofa score at 72 hours in the intervention groups was 0.6 higher (2.72 lower to 3.92 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with norepinephrine + epinephrine versus norepinephrine + dobutamine (95% CI)
SOFA score at 96 hours	60 (1 study)	MODERATE[1] due to imprecision			The mean sofa score at 96 hours in the intervention groups was 0.8 higher (2.62 lower to 4.22 higher)
Acute coronary syndrome	60 (1 study)	LOW[1] due to imprecision	RR 1 (0.07 to 15.26)	33 per 1000	0 fewer per 1000 (from 31 fewer to 475 more)
Arrhythmias	60 (1 study)	LOW[1] due to imprecision	RR 0.67 (0.21 to 2.13)	200 per 1000	66 fewer per 1000 (from 158 fewer to 226 more)
Cerebral stroke	60 (1 study)	LOW[1] due to imprecision	Not estimable	See comment	-[2]
Limb ischaemia	60 (1 study)	LOW[1] due to imprecision	RR 0.67 (0.12 to 3.71)	100 per 1000	33 fewer per 1000 (from 88 fewer to 271 more)

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] No events reported in either group

Table 170: Additional data (data could not be meta-analysed): Timing of inotropes/vasopressor administration for adults with septic shock

Study	Intervention and comparison	Population	Baseline characteristics	Outcomes
Bai 2014[21]	n=213 Noradrenalin/norepinephrine	(n=213) adults ICU Septic shock	Age, mean (SD): survivors: 58.2 (11.9); non-survivors 59.5 (14.4) APACHE II, mean (SD): 28.4 (4.2) Serum lactate at onset, mean (SD): 4.3 (1.4)	Time from onset of septic shock to initial norepinephrine administration as independent determinant of 28-day mortality The adjusted OR of death was 1.392 (95% CI, 1.138-1.702) per hour delay of administration of norepinephrine

Study	Intervention and comparison	Population	Baseline characteristics	Outcomes
				Risk of bias: High
Beck 2014[25]	n=4376 Intervention 1: Noradrenalin/norepinephrine n=3502 Intervention 2: Dopamine n=1466 Intervention 3: Phenylephrine n=793 Intervention 4: Dobutamine n=708 Intervention 5: Vasopressin n=313 Intervention 6: Epinephrine	n=6514 adults ICU Septic shock	Age, mean (SD): 62.1 (16.1) APACHE II, mean (SD): 26.1 (8.2) Serum lactate on day 1, mean (SD): 4.8 (4.4)	Delay of vasopressor administration as independent determinant of in-hospital mortality The adjusted OR of death was 1.02 (95% CI, 1.01-1.03) for overall delay of administration of vasopressor Risk of bias: High

1

2 **Table 171: Additional data (data could not be meta-analysed): Norepinephrine versus vasopressin for adults septic shock**

Study	Comparator	Outcome	Norepinephrine		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
Morelli 2009[218]	Vasopressin	**Duration of critical care stay**					
		ICU length of stay	17 days (7-23)	15	17 days (5-27)	15	High
Russell 2008[278]	Vasopressin	**Duration of critical care stay**					
		ICU length of stay	16 days (8-32)	382	15 days (7-29)	396	Low
		Duration of hospital stay					
		Hospital length of stay	26 days (15-53)	382	27 days (13-52)	396	Low

Table 172: Additional data (data could not be meta-analysed): Norepinephrine plus dobutamine versus epinephrine for adults with septic shock

Study	Comparator	Outcome	Norepinephrine plus dobutamine		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
Annane 2007[14]	Epinephrine	**Duration of critical care stay**					
		ICU length of stay	16 days (6-32)	169	15 days (7-31)	161	Low

Table 173: Additional data (data could not be meta-analysed): Norepinephrine plus dobutamine versus norepinephrine plus epinephrine for adults with septic shock

Study	Comparator	Outcome	Norepinephrine plus dobutamine		Comparator		Risk of bias
			Results	No. analysed	Results	No. analysed	
Mahmoud 2012[201]	Norepinephrine plus epinephrine	**Duration of critical care stay**					
		ICU length of stay	7 days (4-11)	30	6 days (5-10)	30	Low

Table 174: Additional data (data could not be meta-analysed): effects of treatment on mortality

Study	Intervention and comparison	Population	Outcomes
De Backer 2010[18]	n=858, septic shock n=542 Intervention 1: Dopamine n=821, septic shock n=502 Noradrenalin/norepinephrine	n=1679 adults, 62% of which had septic shock Septic shock, ICU	Overall effect of treatment on mortality did not differ between those who received dopamine and those who received norepinephrine. The confidence interval for the hazard ratio crossed the line of no effect.
Ventura 2015[319]	n=63 Intervention 1: Dopamine	n=120 children	Multiple logistic regression: dopamine versus epinephrine: OR 6.51 (95% CI 1.12-37.80)

Study	Intervention and comparison	Population	Outcomes
	n=57 Intervention 1: Epinephrine	Septic shock, PICU	

1

2 **Table 175: Additional data (data could not be meta-analysed): effects of dosage on mortality**

Study	Intervention and comparison	Population	Outcomes
Martin 2015[209]	n=324 Intervention 1: Norepinephrine	n=324 adults Septic shock, ICU	Dose of norepinephrine greater than 1 µg/kg/min as an independent predictor of mortality: OR 9.7 (95% CI 4.5-23)

3

9.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Table 176: UK costs of inotropes/vasopressors

Drug	Units	Cost per unit (a)
Noradrenaline/ norepinephrine	4ml (1mg/ml)	£4.40
Adrenaline/epinephrine	10ml (100µg/ml)	£6.99
Vasopressin (argipressin (synthetic vasopressin))	1ml (20 Units/ml)	£22.50
Milrinone (Primacor)	10ml (1mg/ml)	£19.91
Enoximone	20ml (5mg/ml)	£15.02
Dopamine	5ml (40mg/ml)	£3.88
Dopexamine (dopacard)	5ml (10mg/ml)	£25.20
Dobutamine	50ml (5mg/ml)	£7.50

(a) Source: BNF [155]

An average dose will generally depend on the weight of the patient, their response to treatment, and how long they are given treatment for. Examples of the cost of averages doses for some of the drugs can be seen below:

- Noradrenaline dose from GDG estimate: 4mg in 50mls at an infusion rate of 10ml/ hour, for a duration of 48 hours = 38.4mg ≈ 10 injections = £44
- Vasopressin dose from clinical evidence: 0.03 U vasopressin per minute for a duration of 48 hours = 86.4 units ≈ 5 injections = £112.50

In addition to the cost of the interventions are the liquids that the interventions might need to be diluted in, however the cost of these is likely to be small.

9.5 Evidence statements

Clinical

The evidence in this review was of ranged from high to very low quality for the outcomes

Adults with septic shock:

RCT evidence from sixteen studies on head to head comparisons of inotropic agents or vasopressors found that there was no clinically important difference for the outcomes of mortality, length of stay in hospital and ICU settings, the number of organs supported, and adverse events.

One retrospective cohort study assessing the effect of a delay in inotrope or vasopressor therapy suggested that a delay might increase mortality. A second retrospective study found a trend for increased mortality with therapy delay.

One RCT study indicated that a norepinephrine dose greater than 1 µg/kg/min might be an independent predictor of death.

Children with septic shock:

One RCT study in children indicated that epinephrine might be potentially more clinically effective than dopamine for the outcome of mortality. However children in the dopamine group had a significantly longer resuscitation period and were more likely to receive renal replacement therapy than children in the epinephrine group.

Economic

No relevant economic evaluations were identified.

9.6 Recommendations and link to evidence

Recommendations	No specific recommendation was made for use of intropes or vasopressors
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days, health-related quality of life, and admission to critical care to be critical outcomes. Length of stay on the ICU, length of hospital stay, the number of organs supported, and adverse events were considered important outcomes. Mortality was the only outcome reported by all included studies.
Trade-off between clinical benefits and harms	**Type of inotropic agent or vasopressor** The clinical evidence did not show any clinically important difference between different types of inotropic agents or vasopressors with regards to mortality or length of stay in hospital and intensive care settings. One study found that adults receiving norepinephrine were less likely to develop arrhythmias than adults receiving dopamine. No evidence was found for the outcomes of health-related quality of life, admission to critical care, and the numbers of organs supported. **Timing of inotrope or vasopressor administration** This review identified two retrospective cohort studies analysing the effect of a delay in inotrope administration on mortality. Both studies were on adults with septic shock of similar age and severity of illness. One study found that a delay might increase mortality. The second study suggested only a mild trend for increased mortality with therapy delay. There was no evidence for a delay of inotrope or vasopressor administration in children. No evidence was found for the outcomes of health-related quality of life, admission to critical care, length of stay, the numbers of organs supported, and adverse events.

	Dosage of inotrope or vasopressor administration One RCT study indicated that a norepinephrine dose greater than 1 µg/kg/min might be an independent predictor of death. The study was in adults with septic shock on the ICU. There was no evidence for children. No evidence was found for the outcomes of health-related quality of life, admission to critical care, length of stay, the numbers of organs supported, and adverse events. The GDG agreed that hypotensive patients need blood pressure support. Vasopressors, particularly noradrenaline, are standard practice for treatment for hypotensive patients with sepsis in the UK. The pathway developed for people with suspected sepsis and high risk criteria, which includes people with low blood pressure, is for rapid resuscitation with IV fluids and critical care involvement. The GDG discussed whether to make a recommendation for inotrope/vasopressor use but agreed that this would be part of a package of care such as central vascular access and critical care input. The evidence did not suggest that earlier treatment was required. The GDG agreed that referral to appropriate specialised care for these people was paramount and that making a recommendation about intoropes/vasopressors separately from that bundle of care was unlikely to be helpful. The GDG considered that it was the role of critical care to decide on inotropes or vasopressors and therefore worded the recommendation about referral to critical care to include consideration of inotropes and vasopressors. .
Economic considerations	No economic evidence was identified for this question. The GDG were presented with the unit costs of the different inotropes and vasopressors. An average dose will depend on the weight of the patient, their response to treatment, and how long they are given treatment for, therefore this is difficult to estimate and is patient specific. In addition to the cost of the interventions are the liquids that the interventions might need to be diluted in, however the cost of these is likely to be small. The clinical data has not identified which inotrope or vasopressor might be the most effective, or any significant difference in resource use between different interventions. The timing of when the interventions should be administered is partly dependent upon the identification of people with severe sepsis or at risk of developing severe sepsis. These are the subject of other questions within this guideline. The GDG agreed that if a patient is not responding to fluids, senior input should be sought, who will then decide what further interventions the patient might need. Inotropes and vasopressors generally need a central line inserted which is usually done in ICU so the patients will have to be moved to ICU for these drugs to be administered. A concern may be the delay in admitting patients to the ICU due to delays or capacity issues. The specific type of inotrope or vasopressor to be used will be decided by the senior clinician. Inotropes and vasopressors are commonly used in the management of patients with sepsis who are not responding to fluid resuscitation; therefore this recommendation is unlikely to have a cost impact.
Quality of evidence	The evidence included in this review was generally of moderate to very low quality. This was largely due to high risk of bias and imprecision. The evidence for mortality at 90 days, and at discharge from the ICU and the hospital for norepinephrine versus dobutamine was of high quality.
Other considerations	The GDG discussed the issue around terminology regarding inotropic agents and vasopressors. It was acknowledged that the agents included in the review protocol could be classified as either inotropes or vasopressors, with some of them having characteristics of both groups. The terms used in this review are those given by the study investigators themselves.

10 Using oxygen

Sepsis is a whole-body inflammatory response to an infection. Haemodynamic changes and respiratory failure can lead to a reduced tissue oxygenation. Giving high-flow oxygen may help prevent a metabolic acidosis and maintain an aerobic metabolism. It is current practice to provide supplementary oxygen as part of sepsis management.

This section aims to determine the impact of treatment with oxygen in people with sepsis in relation to patient outcomes.

10.1 Review question: Is the use of supplemental oxygen clinically and cost effective in patients with sepsis?

For full details see review protocol in Appendix C.

Table 177: PICO characteristics of review question

Population	People with or at risk of developing sepsis or severe sepsis: • hypo-oxygenated people • not hypo-oxygenated people
Intervention	Treatment with oxygen
Comparison	No treatment with oxygen
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis Important: • Duration of hospital stay • Duration of critical care stay • Number of organs supported • Time to reversal of shock • Adverse events (long term disability; short-term heart failure)
Study design	Systematic reviews and RCTs. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of treatment with oxygen on the outcomes will be considered.

10.2 Clinical evidence

No relevant clinical studies on supplemental oxygen (neither RCTs nor cohort) were identified.

10.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

10.4 Evidence statements

Clinical

No relevant studies for the use of oxygen in patients with sepsis were identified.

Economic

No relevant economic evaluations were identified.

10.5 Recommendations and link to evidence

Recommendations	**108. Give oxygen to achieve a target saturation of 94-98% for adult patients or 88-92% for those at risk of hypercapnic respiratory failure.** **109. Oxygen should be given to children with suspected sepsis who have signs of shock or oxygen saturation (SpO_2) of less than 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO_2 of greater than 92%, as clinically indicated.[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]**
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days health-related quality of life, and rate of admission to ICU to be critical outcomes. Length of ICU stay, length of hospital stay, number of organs supported and time to reversal of shock, and adverse events were considered important outcomes.
Trade-off between clinical benefits and harms	No evidence (RCT or observational studies) of benefit or harm was identified. The requirement for oxygen for people who are acutely unwell is generally dependent on the underlying cause of illness and the presence of reduced oxygen levels. Oxygen is generally considered to be of benefit if oxygen levels are low. Oxygen treatment is known not to improve subjective feelings of breathlessness and can be harmful if people are at risk of hypercapnia such as people with COPD as it may precipitate respiratory failure.
Economic considerations	No health economic evidence was identified for this question. Providing oxygen is likely to have a low cost. Maintaining adequate concentrations of oxygen is important to avoid hypoxia and long term organ damage, however some vulnerable groups like patients with respiratory conditions will be at risk of hypercapnic respiratory failure and more caution is required in prescription of oxygen. Given that no clinical evidence was identified, and current practice already involves using supplemental oxygen which is recognised to be an important part of the management of sepsis; a recommendation was made in line with current practice. This recommendation is not likely to have a cost impact.
Quality of evidence	No clinical evidence was found. The recommendation is based on existing guidance from the British Thoracic Society (BTS), the Fever in under 5s guideline (CG160) and GDG opinion.
Other considerations	No specific evidence was found for use of oxygen in patients with sepsis. The GDG were aware that supplemental oxygen for acutely ill patients is standard practice in people with reduced oxygen levels. No evidence was found to refute this

Recommendations	**108. Give oxygen to achieve a target saturation of 94-98% for adult patients or 88-92% for those at risk of hypercapnic respiratory failure.** **109. Oxygen should be given to children with suspected sepsis who have signs of shock or oxygen saturation (SpO_2) of less than 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO_2 of greater than 92%, as clinically indicated.[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]**
	practice in people with sepsis. In recent trials of Early Goal Directed Therapy (EGDT) supplemental oxygen was given to patients with O2 saturations of less than93%. The GDG agreed to use guidelines for oxygen use in acutely ill people developed by the British Thoracic Society (BTS) [243] to inform their recommendations. These are the accepted national guidelines in use of oxygen and the GDG agreed that without specific evidence to contradict these, it was preferable to ensure consistency in recommendations for people who are acutely unwell. The BTS has been awarded NICE accreditation for its clinical guideline production. An updated (2015) version of recommendations for Emergency Oxygen Use in Adult patients is currently being developed. The BTS recommend supplemental oxygen to maintain O^2 saturation between 94 and 98% for acutely ill patient who are not at risk of hypercapnia. A lower target, between 88 and 92% is recommended for people with a past history or prone to hypercapnic respiratory failure. The NICE Fever in under 5s guideline (CG160)[232] makes a recommendation on the use of use of oxygen in children. The guideline found no evidence on the use of oxygen in children which examined the effect upon outcome of administering oxygen to the child with symptoms and signs of serious illness. A consensus recommendation was made to use oxygen to correct hypoxaemia. The GDG reviewed the recommendation and agreed that the recommendation would apply to children less than 12 years.

11 Acid-base balance (use of bicarbonate)

11.1 Introduction

Sepsis is a whole-body inflammatory response to an infection. Haemodynamic changes, renal failure and reduced tissue oxygenation can lead to a metabolic acidosis. Intravenous fluid resuscitation, one of the main pillars of sepsis management, can aggravate the acidosis and result in serious complications. Understanding the role of acid-base balance in the management of sepsis is therefore of the utmost importance.

This section aims to determine the impact of acid-base balance correction; the use of bicarbonate, in people with sepsis.

11.2 Review question: Is acid-base balance (that is, the use of bicarbonate) clinically and cost effective in people with sepsis?

For full details see review protocol in Appendix C.

Table 178: PICO characteristics of review question

Population	People with or at risk of developing sepsis or severe sepsis
Intervention	Bicarbonate
Comparison	No bicarbonate
Outcomes	**Critical:** • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis **Important:** • Duration of hospital stay • Duration of critical care stay • Number of organs supported • Time to reversal of shock • Adverse events (long term disability; short-term heart failure)
Study design	Systematic reviews and RCTs. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of timing of acid-base balance correction on the outcomes will be considered.

11.3 Clinical evidence

One case-control study was included in the review[93]; this is summarised in **Table 179** below. No relevant RCTs were identified. Evidence from the study is summarised in the clinical evidence summary below (**Table 180** and **Table 181**) See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

Table 179: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Elsolh	Bicarbonate	n=36 patients	**28-day mortality** Intervention:	Observational

Study	Intervention and comparison	Population	Outcomes	Comments
2010[93]	versus no bicarbonate (case-control study)	and 36 controls, all with septic shock. USA	n=10 (28% [14-45%]), Control: n=12 (33% [19-51%]; (p=0.79) **Duration of critical care stay** Intervention: median 44.5 h [34-54], Control: median 55 h [39-60]; (p=0.01) **Time to reversal of shock** Intervention: median 11.5 days [6.0-16.0], Control: median 16.0 days [13.5-19.0]; (p=0.09)	design, small sample size; very high risk of bias. No indirectness.

1

2

Table 180: Clinical evidence summary: bicarbonate versus no bicarbonate (28-day mortality)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bicarbonate versus no bicarbonate (95% CI)
28-day mortality	72 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.83 (0.41 to 1.68)	333 per 1000	57 fewer per 1000 (from 197 fewer to 227 more)

[1] *Case-control study. Small sample size*
[2] *Confidence interval crossed both standard MIDs*

Table 181: Clinical evidence summary: bicarbonate versus no bicarbonate (duration of critical care stay; time to reversal of shock)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Median time (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bicarbonate versus no bicarbonate (95% CI)
Duration of critical care stay	72 (1 study)	VERY LOW[1] due to risk of bias	Bicarbonate group: 44.5 [34-54] hours Control group: 55 [39-60] hours (p=0.01, as reported by the author)	-	-
Time to reversal of shock	72 (1 study)	VERY LOW[1] due to risk of bias	Bicarbonate group: 11.5 [6.0-16.0] days Control group: 16.0 [13.5-19.0] days (p=0.09, as reported by the author)	-	-

[1] *Case-control study. Small sample size*

11.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Table 182: Intervention cost

Drug	Units	Cost per unit [(a)]
Sodium Bicarbonate	8.4% (50ml)	£12.15

(a) Source: BNF[155]

This cost may vary as the dose is dependent on the patient's weight and also how long they are given the intervention for.

11.5 Evidence statements

Clinical

One case-control study was identified for this review. The evidence was of very low quality for all outcomes. There was no clinically important difference in using bicarbonate versus not using bicarbonate in patients with sepsis.

Economic

No relevant economic evaluations were identified.

11.6 Recommendations and link to evidence

Recommendations	No recommendation was made.
Relative values of different outcomes	The GDG considered mortality, health-related quality of life, and admission to critical care to be critical outcomes. Length of stay on the ICU and in hospital, and the number of organs supported were important outcomes, while adverse events were considered to be less important outcomes. Evidence from one included study for three outcomes was found: 28-day mortality, duration of critical care stay, and time to shock reversal.
Trade-off between clinical benefits and harms	The evidence did not show any benefit or harm in using bicarbonate in patients with sepsis.
Economic considerations	No relevant economic evaluations were identified for this question. Bicarbonate is not very expensive (£12.15 for 50ml) however the total cost is

	uncertain as the overall dose used is patient dependent. It may also involve some nursing time. Only one clinical study was identified and the effect of bicarbonate on mortality was not clinically significant. There was some reduction in critical care stay reported in the paper, and critical care stay is very expensive, however this also had a large confidence interval, and the paper was judged to be of very low quality. Bicarbonate is not used in current practice for sepsis patients, and given the lack of evidence; the GDG decided that they could not make a positive recommendation. They discussed the possibility of making a negative recommendation and were of the view that this might be confusing, as bicarbonate is not currently used. It was therefore decided to make no recommendation.
Quality of evidence	Only one study was included in the review, a case-control study. The evidence for the three outcomes reported (28-day mortality, duration of critical care stay, and time to reversal of shock) is of very low quality, mainly due to very high risk of bias.
Other considerations	The GDG discussed whether or not to make a recommendation against the use of bicarbonate. They considered that it is not routine practice to give bicarbonate at present for people with sepsis, although bicarbonate might be required for the management of other underlying diseases, for example, renal disease or as part of further intensive care management. As it is not current routine practice to give bicarbonate as part of early management, the GDG decided that a recommendation would be potentially confusing and therefore did not make a recommendation.

1

12 Early goal-directed therapy (EGDT)

12.1 Introduction

The management of sepsis consists of a bundle of actions to be taken as soon as possible after diagnosis. Early goal-directed therapy (EGDT) is a protocolised approach to the management of severe sepsis during the first six hours after diagnosis. The treatment bundle includes antimicrobials, fluid resuscitation, inotropic agents or vasopressors, and continuous monitoring of haemodynamic parameters to ensure an adequate blood flow and tissue oxygenation. While early trials have shown a significant survival benefit for patients receiving EGDT, more recent studies could not identify any difference between EGDT and what is considered to be standard therapy.

The guideline scope did not include review of EGDT. The guideline focus is on early recognition and initial management and treatment and not appropriate intensive monitoring such as that used iin EGDT. The GDG were aware however of recent trials in emergency departments and that routine care in the trials was an indication of high standard routine care. Given the lack of good quality trial evidence for individual interventions in very early sepsis, the GDG were interested in the information available from the EGDT trials on standard care.

12.2 Review question: What is the clinical and cost effectiveness of implementing early goal-directed therapy (EGDT) for people with sepsis?

For full details see review protocol in Appendix C.

Table 183: PICO characteristics of review question

Population	People at risk of developing or diagnosed with severe sepsis. Strata (by severity disease): • sepsis • severe sepsis • septic shock Subgroups: the following groups will be considered separately if data are available: • children • adults • pregnant women • people at higher risk of infection Setting: All settings in which NHS care is provided
Intervention	EGDT
Comparison(s)	• Usual care • Other resuscitation strategies
Outcomes	Critical: • 28 day all-cause mortality (or the nearest time point) • Health-related quality of life (for example, as assessed by SF-12 or EQ-5D) • Admission to critical care as a proxy for progression to severe sepsis Important: • Duration of hospital stay

	• Duration of critical care stay • Number of organs supported (for example, SOFA score) • Time to reversal of shock • Adverse events (long term disability; short-term heart failure).
Study design	Systematic reviews RCTs

12.3 Clinical evidence

A recent systematic review[13] assessing the randomised clinical trial evidence for EGDT in the resuscitation of patients presenting to the ED with septic shock, was identified and included in this evidence report. The systematic review aimed to address the primary question of whether EGDT when compared with other resuscitation strategies, was associated with a survival benefit. The review by Angus et al included 11 studies, of which five[158,220,258,275,330] enrolled patients presenting to the ED with septic shock and were suitable for assessment of the primary objective. These studies also matched our protocol criteria and were included in this evidence report.

The systematic review is summarised in **Table 184: Summary of systematic review included in this review** below and further details can be found in Appendix H. **Table 185: Summary of study and baseline characteristics of included trials of EGDT in septic shock** below provides a summary of the key included trial and baseline population characteristics, and **Table 186** provides a summary of the EGDT protocol and outcomes in each of these studies. Further details of the included studies, including study design, settings, inclusion criteria, study outcome results, and any subgroup analyses carried out in the individual studies, is given in **Table 187**.

Table 188 summarises particular therapies (fluids, vasopressor, dobutamine, blood transfusion and time to first antimicrobial) delivered during the six hour resuscitation period in each study. A more detailed breakdown of these and other therapies delivered to each study arm during the ProMISe, the UK study, has been given in **Table 189** and **Table 190**. **Table 191** details authors' description of assessments and procedures carried out pre-randomisation in each study (inclusion criteria to the trial).

The evidence is further summarised in the GRADE clinical evidence summary (**Table 192**). See also forest plots in Appendix K and GRADE tables in Appendix J.

Table 184: Summary of systematic review included in this review

Study	Intervention and comparison	Population	Outcomes	Comments
ANGUS 2001 [13]	EGDT with either usual care or another resuscitation strategy that did not incorporate EGDT EGDT defined as the protocolised administration of IV fluids, vasoactive agents and red cell transfusion to achieve the	Adult and paediatric populations with septic shock	Authors only analysed studies that reported mortality Primary outcome: mortality identified as primary outcome for that study • 28- day mortality • 90-day mortality Secondary outcomes:	11 studies were included. Analysis was carried out on 5 studies in the ED setting. See appendix for full details of systematic review

Study	Intervention and comparison	Population	Outcomes	Comments
	predetermined haemodynamic goals of CVP, MAP, $ScvO_2$		• ICU admission rate • ICU duration of stay • Hospital duration of stay	

Abbreviations: CVP – central venous pressure; MAP – mean arterial pressure; ScvO2 – central venous oxygen saturation; ICU – intensive care unit; SR: systematic review

Table 185: Summary of study and baseline characteristics of included trials of EGDT in septic shock

Study	Country	N	Male (%)	Mean age (years): EGDT, control	Single or multicentre	Illness severity scores: EGDT, control
RIVERS 2001[275]	USA	263	50.6	67.1, 64.4	Single centre	APACHE II: 21.4, 20.4
JONES 2010[156]	USA	300	54.3	59.8, 61.6	Multicentre	SAPS II: 44.8, 44.1
ProCESS 2014[330]	USA	1341	55.4	60, 62	Multicentre	APACHE II: 20.7, 20.8
ARISE 2014[258]	Australasia	1600	59.8	62.7, 63.1	Multicentre	APACHE II: 15.8, 15.4
ProMISe 2015[220]	UK	1260	57	66.4, 64.3	Multicentre	APACHE II: 18.7, 18.0

Abbreviations: N: number of patients; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; Control was usual care or another non-EDGT resuscitation strategy.

Table 186: Summary of EGDT protocol and outcome of included studies

Study	EGDT group	Control group[a]	Survival benefit	Primary mortality	
				EGDT	Control
Standard EGDT versus usual care					
RIVERS 2001[275]	ScvO2 ≥ 70% CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	Yes: 28d/60d/in-hospital mortality	29.2%	44.4%
ProCESS 2014[330]	ScvO2 ≥ 70% CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	Usual care or Protocolised standard care[b]	No: 60d/in-hospital mortality	21.0%	18.5%
ARISE 2014[258]	ScvO2 ≥ 70% CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	Usual care	No: 28d/90d/ICU/in-hospital mortality	18.6%	18.8%
ProMISe 2015[c220]	ScvO2 ≥ 70% CVP ≥ 8 mmHg MAP ≥ 65 mmHg	Usual care	No: 28d/90d/ICU/in-hospital mortality	29.5%	29.2%
Standard EGDT versus lactate clearance					
JONES 2010[156]	ScvO2 ≥ 70%	Lactate	No: in-hospital	22.7%	16.7%

Study	EGDT group	Control group[a]	Survival benefit	Primary mortality	
				EGDT	Control
	CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	clearance ≥ 10% CVP ≥ 8-12 mmHg MAP ≥ 65 mmHg UO ≥ 0.5 ml/kg/h	mortality		

(a) The control group was usual care or another non-EDGT resuscitation strategy
(b) Protocol-based standard therapy in the ProCESS trial used components which were less aggressive than those used for EGDT. In contrast to the triggers in the EGDT protocol, protocol-based standard therapy recommended packed red-cell transfusion only if the haemoglobin level was <7.5 g/dL
(c) ProMISe investigators adapted EGDT from the original algorithm7as follows: arterial catheter recommended, not mandated; option to use SBP as a blood pressure goal, rather than solely MAP; minimum goals set for CVP and MAP, rather than a range.
(d) Abbreviations: CVP – central venous pressure; MAP – mean arterial pressure; ScvO2 – central venous oxygen saturation

1 **Table 187: Further details of studies included in review**

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
RIVERS 2001[275]	EGDT versus standard care **EGDT** (n=130): CVC inserted for continuous monitoring of patients' CVP and $Scv0_2$. Early structured treatment provided based on subjects' CVP,MAP and $Scv0_2$ measurements **Standard care** (n=133): Patients treated at clinicians' discretion according to a protocol for hemodynamic support with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture obtained in the ED before the administration of antibiotics	n=263 Single centre, open label RCT, USA Adult patients who presented to the ED with severe sepsis, septic shock, or the sepsis syndrome, fulfilment of two of four criteria for the SIRS and a SBP no higher than 90 mmHg (after a crystalloid-fluid challenge of 20 to 30 ml per kg of body weight over a 30-min period) or a blood lactate concentration of ≥4 mmol/litre	For standard therapy versus EGDT respectively: • Mortality: ○ In-hospital mortality, no(%): - All patients: 59(46.5) versus 38 (30.5), RR (95% CI): 0.58 (95% CI 0.38–0.87), P=0.009; - Patients with severe sepsis: 19 (30.0) versus 9 (14.9), RR (95% CI): 0.46 (0.21–1.03), p=0.06; - Patients with septic shock: 40 (56.8) versus 29 (42.3), RR (95% CI): 0.60 (0.36–0.98), P=0.04; - Patients with sepsis syndrome: 44 (45.4) 35 (35.1), RR (95% CI): 0.66 (0.42–1.04), P=0.07 ○ 28-day mortality, no(%): 61 (49.2) versus 40 (33.3), RR (95% CI) 0.58 (0.39–0.87), P=0.01 ○ 60-day mortality, (no(%): 70 (56.9) versus 50 (44.3), RR (95% CI) 0.67 (0.46–0.96), P=0.03 • Organ dysfunction and coagulation variables, 7-72 hours after start of therapy: ○ APACHE II score: 15.9±6.4 versus 13.0±6.3, P<0.001 ○ SAPS II: 42.6±11.5 versus 36.9±11.3, P<0.001 ○ MODS: 6.4±4.0 versus 5.1±3.9, P<0.001 ○ Prothrombin time (sec): 17.3±6.1 versus 15.4±6.1, P=0.001 ○ Concentration of fibrin-split products (µg/dl): 62.0±71.4 versus 39.2±71.2, P<0.001 ○ Concentration of D-dimer: 5.65±9.06 versus 3.34±9.02, P=0.006 ○ Partial thromboplastin (sec): 37.0±14.2 versus 34.6±14.1, P=0.06 ○ Fibrinogen concentration (mg/dl) 358±134 versus 342±134, P=0.21	Duration of study: March 1997 – March 2000 Subgroup analyses not reported

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
			○ Platelet count (per mm3): 144,000±84,000 versus 139,000±82,000, P=0.51 • Consumption of healthcare resources: ○ Mean duration of vasopressor therapy: 2.4±4.2 versus. 1.9±3.1 days, P=0.49 ○ Mean duration of mechanical ventilation: 9.0±13.1 versus. 9.0±11.4 days, P=0.38 Mean length of hospital stay: 13.0±13.7 versus. 13.2±13.8 days, P=0.54	
JONES 2010A[156]	EGDT versus lactate clearance. **EGDT** (n=150): CVC inserted for continuous monitoring of patients' CVP and Scv02. Early structured treatment provided based on subjects' CVP,MAP and Scv02 measurements **Lactate clearance** group (n=150): resuscitated to normalise CVP, MAP, and lactate clearance of ≥ 10%	n=300 Multicentre (3 centres), non-inferiority RCT, USA Patients with severe sepsis or septic shock; patients aged > 17 years with confirmed or presumed infection, have ≥ 2 or SIRS criteria, and have hypoperfusion evidenced by either a SBP < 90 mmHg after a minimum of 20 mL/kg rapid volume challenge or a blood lactate concentration of ≥ 36 mg/dL (4 mmol/L)	For lactate clearance versus EGDT respectively: • In-hospital mortality, no. (%): ○ ITT: 25 (17) versus 34 (23), 6 (−3 to 15) ○ Per protocol: 25 (17) versus 33 (22), 5 (−3 to 14) • Median time from ED triage to eligibility: 111 mins (IQR 56–192 mins) versus 105 mins (IQR 60–175 mins), (P=0.67) • Median time from eligibility to study entry: 14 mins (IQR, 1–48 mins) versus 13 mins (IQR, 1–55 mins), (P=0.72) • Mean (SD) amount of IV fluid administered prior to enrolment: 2.3 L(1.4 L) versus 2.4 L (1.4L), (P =0.37) • Length of ICU stay (days), mean (SD), 5.9 (8.46) versus 5.6 (7.39), P=0.75 • Length of hospital stay, mean (SD): 11.4 (10.89) versus 12.1 (11.68), P=0 .60 • Hospital complications: ○ Ventilator-free days, mean (SD): 9.3 (10.31) versus 9.9 (11.09), P=0.67 ○ Multiple organ failure, no. (%): 37 (25) versus 33 (22), P=0.68 ○ Care withdrawn, no. (%): 14 (9) versus 23 (15), P=0.15	Duration of study: January 2007 – January 2009 Subgroup analyses not reported

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
			• SOFA score, median (IQR): ○ At timepoint 0: 6 (4–9) versus 6 (4–9), P=0.71 ○ At 24 hours: 8 (5–11) versus 7 (5–11), P=0.98 ○ At 48 hours: 4 (2–7) versus 5 (2–7), P=0.90 ○ At 72 hours: 3 (1–6) versus 3 (1–6), P=0.62 • SAPS II score ○ At timepoint 0: 44.8 (18.4) versus 44.1 (17.3), P=0. 69 ○ At 72 hours: 33.4 (14.1) versus 34.6 (17.2), P=0. 54 • MEDS score ○ At timepoint 0: 10.9 (3.9) versus 10.6 (3.4), P=0.46 ○ At 72 hours: 8.4 (4.2) versus 8.4 (4.5) P=0.93 • Glasgow coma scale ○ At timepoint 0: 13 (4.1) versus 13 (3.7), P=0.67 ○ At 24 hours: 12 (4.3) versus 12 (3.9), P=0.68 ○ At 48 hours: 13 (3.7) versus 13 (3.5), P=0.91 ○ At 72 hours: 15 (3.1) versus 14 (4.0), P=0.04	
ProCESS 2014 [330]	EGDT versus PSC (Protocolised Standard Care) versus Usual care **EDGT** (n=439): CVC inserted for continuous monitoring of patients' CVP and $Scv0_2$. Early structured treatment provided based on subjects' CVP,MAP and	n=1341 Multicentre (31 EDs) open-label RCT, USA Adults if within 6 hours after presentation to the ED they had presumed infection, ≥2 SIRS criteria, and either refractory hypotension	For Protocol-based EGDT, PSC, and Usual care respectively: • Mortality: ○ in-hospital mortality at 60 days: 92/439 (21.0%), 81/446 (18.2%), 86/456 (18.9) P=0.83 ○ all-cause mortality at 90 days: 129/405 (31.9%), 128/415 (30.8%), 139/412 (33.7%), P=0.66 • Admission to critical care as a proxy for progression to severe sepsis: ○ admission to the ICU: 401/439 (91.3%), 381/446 (85.4%), 393/456 (86.2%), P=0.01	Duration of study: March 2008 – May 2013 Subgroup analyses: No difference in any categories: Pre-hoc subgroup analyses: • age, sex, race

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
	Scv02 measurements. **PSC:** (n=446): Protocol for administration of fluids and vasoactive agents to reach goals for SBP and shock index without requirement for central venous monitoring **Usual Care** (n=456): attending physicians provided routine care. Study measurements and treatments were based on physicians'/ sites' standard practices	or a serum lactate level ≥ 4 mmol/L	• Duration of hospital stay: ○ Mean length of stay in the hospital; 11.1 days (±10), 12.3 days (±12.1), 11.3 days (±10.9), P=0.25 • Duration of critical care stay: ○ Mean length of stay on the ICU; Protocol-based EGDT (n=401, 91.3%): 5.1 days (±6.3), Protocol-based standard therapy (n=381, 85.4%): 5.1 days (±7.1), Usual care (n=393, 86.2%): 4.7 days (±5.8) • New organ failure in the first week (no./total no. (%)): ○ Cardiovascular: 269/439 (61.3%),: 284/446 (63.7%), 256/456 (56.1%) ○ Respiratory: 165/434 (38.0%), 161/441 (36.5%), 146/451 (32.4%) ○ Renal: 12/382 (3.1%), 24/399 (6.0%), 11/397 (2.8%) • Duration of organ support (days): ○ Cardiovascular : 2.6±1.6, 2.4±1.5, 2.5±1.6, P=0.52 ○ Respiratory: 165/434 (38.0%), 161/441 (36.5%), 146/451 (32.4%) ○ Renal: 12/382 (3.1%), 24/399 (6.0%), 11/397 (2.8%) • Adverse events ○ Serious adverse events: 23 (5.3%) versus 22 (4.9%) versus 37 (8.1%)	• source of infection • enrolment criterion (refractory hypotension or elevated serum lactate level) Post-hoc subgroup analyses • APACHE II score • Baseline serum lactate • Time from detection of shock until randomisation
ARISE 2014[258]	EGDT versus usual care **EGDT** (n=796): CVC inserted for continuous monitoring of patients' CVP and Scv02. Early structured treatment provided	n=1600 Multicentre (51 centres) open-label RCT, Australia, New Zealand, Finland, Hong Kong, Ireland	For EGDT versus Usual care respectively: • Mortality at 28-days: ○ all-cause mortality at 90 days: 147/792 (18.6%) versus 150/796 (18.8%), P=0.90 ○ all-cause mortality at 28 days: 177/792 (14.8%) versus 127/797 (15.9%), P=0.53	Duration of study: 5 October 2008 – 23 April 2014 Subgroup analyses: No difference in any categories • Country

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
	based on subjects' CVP,MAP and Scv02 measurements **Usual care** (n=804): • Arterial line and a CVC inserted if considered clinically appropriate • ScVO2 measurement not permitted during the 6 hour intervention period • Decisions about the location of care delivery, investigations, monitoring, and all treatments were made at the discretion of the treating clinician	Adults if within 6 hours after presentation to the ED they had presumed infection, ≥2 SIRS criteria, and either refractory hypotension or hypoperfusion	• Duration of hospital stay: ○ median length of stay in the hospital: 8.2 days (4.9-16.7) versus 8.5 days (4.9-16.5), P=0.89 • Duration of critical care stay: ○ median length of stay on the ICU: 2.8 days (1.4-5.1) versus 2.8 days (1.5-5.7), P=0.81 ○ median length of stay in the ED: 1.4 hours (0.5-2.7) versus 2.0 hours (1.0-3.8), P<0.001 • Number of organs supported: ○ receipt of vasopressor support: 605/793 (76.3%) versus 525/798 (65.8%), P<0.001 ○ receipt of renal-replacement therapy: 106/793 (13.4%) versus 108/798 (13.5%), P=0.94 ○ receipt of mechanical ventilation: 238/793 (30%) versus 251/798 (31.5%), P=0.52 • Serious adverse events: 56 (7.1%) versus 42 (5.3%), P=0.15	• APACHE II < 25 versus >25 • Presence or absence of invasive mechanical ventilation • Presence or absence of refractory hypotension • Lactate level (<4.0mmol/l or<4.0mmol/L) • IV fluid administration (<20ml/kg or >20ml/kg of body weight)
PROMISE 2015[220]	EGDT (modified) versus usual care **EGDT** (n=630): Arterial catheter recommended, not mandated; option to use SBP as a blood pressure goal,	n=1260 Multicentre (56 NHS sites), open-label RCT, UK Adults (≥18 years of age) if within 6 hours after presentation	For EGDT versus Usual care respectively: • Mortality: ○ all-cause mortality at 90 days: 184/623 (29.5%) versus 181/620 (29.2%) ○ all-cause mortality at 28 days: 155/625 (24.8%) versus 152/621 (24.6%) • Duration of hospital stay : ○ median length of stay in hospital (days, IQR): 9(4-21) versus 9 (4-18),	Duration of study: 16 February 2011 – 24 July 2014 Subgroup analyses: No difference in any categories (P = 0.39 to 0.72 for interaction):

Study	Treatment schedule (intervention and comparator)	Population (N, country and setting, inclusion criteria)	Outcomes (results)	Comments
	rather than solely MAP; minimum goals set for CVP and MAP, rather than a range **Usual care** (n=630): Decisions about the location of care delivery, investigations, monitoring, and all treatments were made at the discretion of the treating clinician (see Table 8 for further details)	to the ED; they had a known or presumed infection, ≥ 2 SIRS criteria and either refractory hypotension (SBP <90 mmHg; or MAP <65 mmHg, despite resuscitation with at least 1 litre IV fluids within 60 minutes) blood lactate level, ≥4 mmol per litre)	P=0.46 • Duration of critical care stay: ○ - median length of stay on ICU (days, IQR): 2.6 (1.0-5.8) versus 2.2 (0.0-5.3), P=0.005 ○ - median length of stay in ED (hours, IQR): 1.5 (0.4-3.1) versus 1.3 (0.4-2.9), P=0.34 • Number of organs supported: ○ SOFA score at 6 hours: 6.4 (±3.8) versus 5.6 (±3.8), P<0.001 ○ SOFA score at 72 hours: 4.0 (±3.8) versus 3.7 (±3.6), P=0.056 ○ receipt of advanced cardiovascular support : 230/622 (37%) versus 190/614 (30.9%), P=0.026 ○ receipt of advanced respiratory support: 179/620 (28.9%) versus 175/615 (28.5%), P=0.90 ○ receipt of renal support: 88/620 (14.2%) versus 81/614 (13.2%), P=0.62 • Health-related quality of life: ○ EQ-5D at 90 days: 0.609 ±0.319 versus 0.613 ±0.312, P=0.88 • Adverse events ○ serious adverse events: 30 (4.8%) versus 26 (4.2%), P=0.58	• degree of protocolised care used in the usual-care group • age • MEDS score • SOFA score • time from presentation at the ED to randomisation

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; MODS: Multiple Organ Dysfunction Scale; SOFA: Sequential Organ Failure Assessment; MEDS: Mortality in Emergency Department Sepsis; PSC: Protocolised Standard Care (Protocol-based standard therapy in the ProCESS trial used components which were less aggressive than those used for EGDT. In contrast to the triggers in the EGDT protocol, protocol-based standard therapy recommended packed red-cell transfusion only if the haemoglobin level was <7.5 g/dL); EQ-5D: European Quality of Life-5 Dimensions (questionnaire which ranges from 0 (death) to 1 (perfect health), with higher scores indicating a better quality of life)

Table 188: Interventions delivered between randomisation and 6 hours post-randomisation

Study	Fluids (ml)		Vasopressor (%)		Dobutamine (%)		Blood transfusion (%)		Time to first antimicrobial (mins), median (IQR)	
	EDGT	Control	EDGT	Control	EDGT	Control	EDGT	Control	EDGT	Control
Primary objective										
• RIVERS 2001[275]	4981±2984	3499±2499	27.4	30.3	13.7	0.8	64.1	18.5	NA	NA
• JONES 2010A[156]	4300±2210	4500±2360	75.3	72.0	72.0	5.3	3.3	7.3	115 (66-170)	115 (62-180)
• ProCESS 2014[330]	2805±1957	2783±1880	54.9	48.1	5.7	1.0	14.4	7.9	NA	NA
• ARISE 2014[258]	1964±1415	1713±1401	66.6	57.8	15.4	2.6	13.6	7.0	70 (38-114)	67 (39-110)
• ProMISe 2015[220]	2226±1443	2202±1271	53.3	46.6	18.1	3.8	8.8	3.8	NA[a]	NA[a]

(a) All patients in the ProMISe trial received antimicrobials prior to randomisation

Table 189: ProMISe study (UK) 5: Interventions delivered at baseline

Intervention	EGDT (N = 625)	Usual resuscitation (N = 626)
Total intravenous fluida, no/total no (%)	612/625 (97.9)	606/625 (97.0)
Total intravenous fluid, mL	1890 ± 1105	1965 ± 1149
Median total intravenous fluid (IQR), mL	1950 (1000, 2500)	2000 (1000, 2500)
Intravenous colloidb, no/total no (%)	-	-
Intravenous colloid, mL	-	-
Median intravenous colloid (IQR), mL	-	-
Intravenous crystalloidb no/total no (%)	-	-
Intravenous crystalloid, mL	-	-
Vasopressors , no/total no (%)	15/625 (2.4)	21/626 (3.4)
Red cell transfusion, no/total no (%)	-	-
Red cells transfusion, mL	-	-
Median red cell transfusion (IQR), mL	-	-
Dobutamine, no/total no (%)	2/625 (0.3)	0/626 (0.0)
Mechanical ventilation, no/total no (%)	40/625 (6.4)	28/626 (4.5)
Sedatives, no/total no (%)	-	-
Neuromuscular blocking agent, no/total no (%)	-	-
Supplemental O2c, no/total no (%)	397/539 (73.7)	407/542 (75.1)
Platelets, no/total no (%)	-	-
Platelets, mL	-	-
Median platelets (IQR), mL	-	-
Fresh frozen plasma, no/total no (%)	-	-
Fresh frozen plasma, mL	-	-
Median fresh frozen plasma (IQR), mL	-	-
Co-interventions for the source of sepsis	-	-
Surgery, no/total no (%)	0/625 (0.0)	0/626 (0.0)
Activated Protein C, no/total no (%)	-	-
Steroids, no/total no (%)admission (IQR) — hr	31/625 (5.0)	25/626 (4.0)
Antimicrobial (change since ED), no/total no (%)	-	-

Plus-minus values are means ±SD.

(a) Includes IV crystalloid and colloid administration > 20mL and all blood product administration at baseline. Includes IV fluid administration > 20mL at all other time points.

(b) Includes IV fluid administration > 20mL.

(c) At baseline supplemental O2 is based on FiO2.

Table 190: ProMISe study (UK) 5: Interventions delivered during the 0-6 hour intervention period

Intervention	EGDT (N = 625)	Usual resuscitation (N = 626)
Supplemental O_2 - no./total no.	558/623 (89.6)	557/625 (89.1)

Intervention	EGDT (N = 625)	Usual resuscitation (N = 626)
(%)		
Insertion of CVC line with $ScvO_2$ monitoring capability - no./total no. (%) Timing of insertion - no. (%) • Before hour 1 • Hour 1 to hour 2 • Hour 2 to hour 3 • Hour 3 to hour 4 • Hour 4 to hour 5 • Hour 5 to hour 6	545/624 (87.3) • 459 (84.5) • 67 (12.3) • 15 (2.8) • 2 (0.4) • 0 (0.0) • 0 (0.0)	2/625 (0.3) N/A at all timepoints
Insertion of any CVC - no./total no. (%)	575/624 (92.1)	318/625 (50.9)
• Time from randomization to insertion - hr	1.2 ± 0.9	1.8 ± 1.7
• Median time from randomization to insertion (IQR) - hr	1.1 (0.8, 1.5)	1.4 (0.6, 2.9)
Insertion of arterial catheter - no./total no. (%)	462/623 (74.2)	389/625 (62.2)
• Time from randomization to insertion - hr	1.3 ± 1.6	1.2 ± 1.7
• Median time from randomization to insertion (IQR)	1.1 (0.4, 1.9)	1.0 (0.2, 1.9)
• Any intravenous fluid† - no./total no. (%)	609/623 (97.8)	604/625 (96.6)
• Any intravenous fluid – mL	2226 ± 1443	2022 ± 1271
• Median total any intravenous fluid (IQR) - mL [b]	2000 (1150, 3000)	1784 (1075, 2775)
• Intravenous colloid - no./total no. (%) [b]	197/623 (31.6)	180/625 (28.8)
• Intravenous colloid - mL	1062 ± 801	913 ± 627
• Median intravenous colloid (IQR) - mL	1000 (500, 1500)	750 (500, 1000)
• Intravenous crystalloid† - no./total no. (%) [b]	584/623 (93.7)	597/625 (95.5)
• Intravenous crystalloid - mL	1963 ± 1357	1767 ± 1178
• Median intravenous crystalloid (IQR) - mL	1750 (999, 2750)	1500 (900, 2380)
• Vasopressors - no./total no. (%)	332/623 (53.3)	291/625 (46.6)
• Red cell transfusion - no/total no. (%)	55/623 (8.8)	24/625 (3.8)
• Red cell transfusion - mL	426 ± 209	540 ± 294
• Median red cell transfusion (IQR) - mL	309 (285, 577)	535 (305, 607)

Intervention	EGDT (N = 625)	Usual resuscitation (N = 626)
• Dobutamine - no./total no. (%)	113/623 (18.1)	24/625 (3.8)
• Mechanical ventilation - no./total no. (%)	126/623 (20.2)	119/625 (19.0)
• Sedatives - no./total no. (%)	138/623 (22.2)	130/625 (20.8)
• Neuromuscular blocking agent - no./total no. (%)	53/623 (8.5)	40/625 (6.4)
• Critical care admission - no./total no. (%)	551/625 (88.2)	467/626 (74.6)

(a) Plus-minus values are means ±SD.
(b) Included in this category is the administration of more than 20mL of an IV fluid
(c) ProMISe investigators adapted EGDT from the original algorithm7as follows: arterial catheter recommended, not mandated; option to use SBP as a blood pressure goal, rather than solely MAP; minimum goals set for CVP and MAP, rather than a range. All patients received antimicrobials prior to randomisation.

Table 191: Descriptions of pre-randomisation assessments and procedures for all patients, and usual or standard care arm included trials

Study	Author's description of pre-randomisation assessments and procedures[a]	Author's description of usual/standard care arm
RIVERS 2001[275]	Fulfilment of 2 of 4 SIRS criteria and a SBP no higher than 90 mmHg (after a crystalloid-fluid challenge of 20 to 30 ml per kg of body weight over a 30-minute period) or a blood lactate concentration of≥ 4 mmol per litre.	After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians' discretion according to a protocol for haemodynamic support with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture were obtained in the ED before the administration of antibiotics. Antibiotics were given at the discretion of the treating clinicians. Antimicrobial therapy was deemed adequate if the in vitro sensitivities of the identified microorganisms matched the particular antibiotic ordered in the ED.
JONES 2010A[156]	Confirmed or presumed infection, ≥ SIRS criteria hypoperfusion evidenced by either a SBP < 90mmHg after a minimum of 20 mL/kg rapid volume challenge or a blood lactate concentration of ≥36 mg/dL (4mmol/L).	Control group description: In the lactate clearance group, clinicians used lactate clearance instead of $ScvO_2$ as the last resuscitation goal in the protocol and targeted a lactate clearance of at least 10%.
ProCESS 2014[330]	Suspected infection, ≥ 2 SIRS criteria, refractory hypotension (SBP <90mmHg despite IV fluid challenge of 20-30cc/kg over a 30 minute period, or evidence of hypoperfusion (a blood lactate concentration > 4mmol/L)	When a subject is randomised to usual care, the existing care providers will remain in charge of the subject's care, and no prompts or study materials will be provided. Study data mirroring that collected in the EGDT and PSC arms will be collected by the site study coordinator.
ARISE 2014[258]	Suspected or confirmed infection AND • ≥ SIRS criteria: ○ Core temperature <36.0°C or >38.0°C ○ HR >90 BPM ○ Respiratory rate (RR) >20 breaths per minute or $PaCO_2$ <32 mmHg or the requirement for invasive MV for an acute process ○ WCC >12.0 x 10^9/L or <4.0 x 10^9/L or >10% immature band forms AND • Evidence of refractory hypotension OR hypoperfusion	Once a patient has been randomised to standard care, they will continue to be cared for by the appropriate treating clinical team. Investigations, monitoring and treatment will be instituted if clinically indicated. An arterial catheter and a CVC may be inserted by the clinical team if considered clinically appropriate. Study materials will not be provided and ScvO2 measurement will not be performed. As soon as practicable, and in keeping with usual practice, patients randomised to the standard care arm will be admitted for in-patient care. As clinically indicated, patients requiring ICU admission will be transferred to ICU as soon as possible, where conventional ICU care will be delivered.

Study	Author's description of pre-randomisation assessments and procedures[a]	Author's description of usual/standard care arm
	○ Refractory hypotension is confirmed by the presence of a SBP <90 mm Hg or MAP < 65 mm Hg after a 1000ml IV fluid challenge within 60 minutes (including IV fluids administered pre-hospital) ○ Hypoperfusion is confirmed by the presence of a blood lactate concentration ≥4.0 mmol/L AND ○ The first dose of IV antimicrobial therapy is commenced prior to randomisation	
ProMISe 2015[220]	Standard care[c] should include the following assessments or procedures that are required to evaluate the suitability of patients for the trial: ○ in patients with suspected or confirmed infection this should include having arterial or venous blood lactate measurement to assess for the presence of hypoperfusion; ○ a first dose of IV antimicrobial therapy commenced prior to randomisation. Additional investigations and evaluation of the suspected infection will occur as part of standard clinical management. It is also expected that a minimum IV fluid challenge of one litre fixed bolus within 60 minutes, will be given as part of standard resuscitation for patients with suspected or confirmed infection and evidence of hypotension.	For patients randomised to usual resuscitation, all investigations, monitoring and treatment will be instituted, as considered appropriate, by the treating clinician(s). For these patients, the ProMISe early, goal-directed, resuscitation protocol and associated intervention arm equipment will not be provided. As soon as practicable, and according to local practice, patients should be admitted for in-patient care and transferred to an appropriate hospital location.

(a) Pre-randomisation procedures and assessments were the inclusion criteria for the trial
(b) Abbreviations: SIRS criteria: systemic inflammatory response criteria; WCC: White blood cell count; MV: mechanical ventilation
(c) In addition to the above, and also of interest was the timing of CVC insertion. Personal communication with the ProMISe study investigators revealled that 21 patients (3.4%) in each group had had a CVC inserted prior to randomisation. These patients were included within the 575 and 318 patients in EGDT and usual care groups, respectively, who had a CVC in place during hours 0-6 of the trial.

Table 192: Clinical evidence summary: EGDT versus Control (Usual care or other non-EGDT resuscitation strategies) for septic shock

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with EGDT versus Control (95% CI)
Primary mortality outcome of each study	4735 (5 studies)	LOW due to risk of bias[1], inconsistency[2]	RR 1.01 (0.9 to 1.12)	224 per 1000	2 more per 1000 (from 22 fewer to 27 more)
90 day all-cause mortality	4063 (3 studies)	MODERATE due to risk of bias[1]	RR 0.99 (0.89 to 1.11)	267 per 1000	3 fewer per 1000 (from 29 fewer to 29 more)
ICU admission	4180 (3 studies)	LOW[1] due to risk of bias[1], inconsistency[2]	RR 1.11 (1.09 to 1.14)	830 per 1000	91 more per 1000 (from 75 more to 116 more)
ICU length of stay for patient admitted to ICU (days)	3876 (4 studies)	MODERATE[2] due to risk of bias[1]			The mean ICU length of stay for patients admitted to ICU (days) in the intervention groups was 0.02 lower (0.47 lower to 0.43 higher)

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2]Downgraded by 1 or 2 increments because:

- The point estimate varies widely across studies, unexplained by subgroup analysis.
- The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis
- Heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis.

12.4 **Economic evidence**

Published literature

One economic evaluation was identified with the relevant comparison and has been included in this review.[220] This is summarised in the economic evidence profile below (Table 193) and the economic evidence tables in Appendix I.

See also the economic article selection flow chart in Appendix F.

Table 193: Economic evidence profile: EGDT versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Mouncey 2015[220]	Directly applicable [(a)]	Potentially serious limitations[(b)]	Within RCT economic evaluation (ProMISe trial) comparing a resuscitation protocol (EGDT) with usual care. Cost utility analysis with 90 day time horizon using EQ-5D elicited from 90 day survivors of trial, and resource use costed from trial.	£989	-0.001	Usual care is dominant	A probabilistic analysis showed that EGDT has less than 20% probability of being cost effective at thresholds of £20,000 and £30,000. The results did not vary in various sensitivity analyses.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) UK study from an NHS perspective. Uses EQ-5D. Sources of costs from relevant UK sources and resource use from RCT.

(b) Adverse events not taken account of in cost effectiveness analysis. Methodology behind probabilistic analysis unclear. Short time horizon

National Clinical Guideline Centre, 2016
492

12.5 Evidence statements

Clinical

Low and moderate quality evidence from one systematic review found no survival benefit of EGDT over usual care.

Economic

One cost utility analysis identified that EGDT was dominated by usual care.

12.6 Recommendations and link to evidence

Recommendations	No recommendation was made regarding EGDT.
Relative values of different outcomes	The GDG considered all-cause mortality at 28 days health-related quality of life, and rate of admission to ICU to be critical outcomes. Length of ICU stay, length of hospital stay, number of organs supported and time to reversal of shock, and adverse events were considered important outcomes.
Trade-off between clinical benefits and harms	The included study was a relevant and recent systematic review. From this review we included five open-label RCTs in adult patients with septic shock, which reported the above outcomes. Of particular interest to the GDG were three large multicentre studies, ProMiSe, ARISE and PRoCESS which all contradicted an earlier single-centre study, which had been the basis of the EGDT strategy of protocolised care for patients with severe sepsis. Of these three studies, the GDG suggested that the UK ProMiSe study was of high clinical importance due to its generalisabilty to the UK population. This study also carried the highest weighting in our analysis due to its large sample size. Data from all five included RCTs was presented to the GDG, with meta-analyses of overall primary mortality, 90-day mortality, ICU admission and ICU length of stay. For the overall primary mortality outcome, analysis included all five RCTs. The results were consistent, confirming a lack of survival benefit of EGDT, with the exception of the 2001 US Rivers et al trial. There were many suggestions given by the GDG for this difference, as well as discussion of shortcomings of this trial. These included doubt over the plausibility of the reported effect size (which can sometimes be inflated in small single-centre studies), limited external validity to patients outside the location of the trial, and unequal allocation of resources (e.g. patients in the intervention arm may have received extra attention from researchers and higher levels of clinical surveillance than the control arm because of knowledge that they were participating in a trial, a phenomenon known as the 'Hawthorne Effect'). The other outcomes; 90-day mortality, ICU admission and ICU length of stay were analysed for ProMiSe, ARISE and PRoCESS. For 90-day mortality there was also no difference between EGDT and control arms. EGDT was however associated with an increased ICU admission rate, despite there being no difference in ICU length of stay. It was discussed that by definition, patients receiving EGDT were more likely to be admitted to ICU since if they had central venous catheter (with or without $ScVO_2$ monitoring), they would by default be in ICU. The GDG also noted that, an explanation for the similarity between groups in ICU length of stay could be

	attributed to the fact that by nature of all patients being participants in a large trial, both groups would have continued to receive a high standard of care. The GDG also suggested that the standard of current clinical practice has evolved to be higher in more recent years, and this could be an explanation for the finding of no difference in length of stay, as well as no overall significant benefit from EGDT. These findings generally do not support the use of the specific protocolised care used in these trials, but they do indicate that the high standard of usual care for suspected sepsis/sepsis patients achieved in the trials should be an aim for the future.
Economic considerations	One cost utility analysis was identified (Mouncey 2015) comparing EDGT with usual care. This is a within trial economic evaluation based on the ProMISe trial. The paper was rated as directly applicable with potentially serious limitations. It used an NHS perspective and EQ-5D to measure quality of life. Some of the limitations include that the time horizon was 90 days, and also no adverse events were included, also some of the methodology is unclear. The study found that EGDT is more expensive and less effective, in other words EGDT is dominated by usual care. Resources are likely to be required in setting up a formal EGDT resuscitation protocol, such as training costs – training staff to follow and implement the protocol and the opportunity cost of staff time that would be involved in this. This might depend on setting, for example if in ED then equipment might also need to be upgraded such as monitors for oxygen saturation monitoring. EGDT will also usually consume more resources as a protocol is followed which will mean more 'aggressive' use of interventions, for example, fluids, central venous access, inotropes/vasopressors, and blood products. Whether this more expensive intervention is cost effective will depend on the benefit it provides, and the clinical review identified that all except one trial showed no difference in mortality between EGDT and usual care. The GDG agreed that as the standard of care is much higher in recent times, EGDT or a formal resuscitation protocol in general would provide no benefit in clinical practice, as the evidence has confirmed. It was noted that usual care in a trial is likely to be of a higher standard than usual care in practice, and therefore setting a high standard of usual care for suspected sepsis/sepsis patients is the overall aim. The GDG did not make a recommendation because no clinical benefit was identified, and making a do not use recommendation might be misinterpreted, so theyconsidered that continuation of current practice was the best way forward.
Quality of evidence	The included systematic review was of high quality and directly relevant to our review question. The evidence from the included RCTs was generally of moderate to low quality. This was due to risk of bias as all outcomes were downgraded by one increment due to lack of blinding. The lack of blinding was inevitable, since it would be almost impossible to study intensive investigator-blinded $ScvO_2$-guided resuscitation. While lack of blinding and knowledge of allocation could have influenced outcomes, the meta-analyses showed no difference between EGDT and control groups for most outcomes. Furthermore, the three multicentre trials were methodologically harmonised and well-conducted. They were precise; highly powered to detect differences; the groups were matched at baseline; data was analysed by the intention-to-treat principle; and there was a very good follow-up rate for the primary outcome.
Other considerations	The GDG did not consider it appropriate to make a recommendation on EGDT. They considered that the standard of routine care in the trials was very high and they were concerned that a recommendation saying not to carry out EGDT would be misinterpreted. The GDG were also aware that the individual patient data from EGDT studies is currently being analysed and the findings from this may inform whether some patients would benefit from this approach.

	In order for the GDG to understand how usual care was defined in the trials, and to identify ways in which the current standard of usual care in the UK could potentially be improved, additional data from the UK ProMISe study supplementary protocols and appendices, were presented and discussed. A detailed description of assessments, procedures, and interventions administered to patients prior to randomisation, at baseline, and during hours 0-6 in the trial were considered. The GDG noted the range of baseline blood lactate concentration, ranging from 1.6 to 8.7 mmol/L in each arm. Also of interest was the timing of CVC insertion to answer the earlier question as the guideline scope had included this as a qustrion. : The ProMISe study investigators, following personal communication, provided data on this, with 21 patients (3.4%) in each group having had a CVC inserted prior to randomisation. These patients were included within the 575 and 318 patients in EGDT and usual care groups, respectively, who had a CVC in place during hours 0-6 of the trial. Thus it is evident that a minimum number of patients required central venous access before more intensive treatment and monitoring as carried out in the the trial.

13 Monitoring

13.1 Review question: In people with sepsis or severe sepsis, what is the clinical and cost effectiveness of scoring systems, and specified blood markers (lactate clearance) in monitoring response to treatment?

For full details see review protocol in Appendix C.

Table 194: PICO characteristics of review question

Population	People with suspected sepsis or severe sepsis
Prognostic tests	1) Use of scoring systems (PEWS, MEWS, NEWS, early warning scores) 2) lactate
Outcomes	1) Use of scoring systems (PEWS, MEWS, NEWS, early warning scores) Critical outcomes: • Mortality. • Clinical resolution (up to and including end of treatment). • Health-related quality-of-life (up to 30 days). • Critical care admission. Important outcomes: • Treatment failure. • Appropriate or inappropriate use of antibiotics. • Duration of treatment. • Hospital re-admission (30 days). • Length of hospital stay. • Complications (including relapse; 30 days). 2) lactate • All-cause mortality at 28 days (or nearest time point) • ICU admission • Hospitalisation • Length of hospital stay
Study design	Systematic reviews Cohort studies

13.2 Clinical evidence for lactate clearance

Six studies[16,86,211,237,273,323] assessed the diagnostic accuracy of percentage lactate clearance over 0-6 hours.

Results have been stratified by initial lactate levels (defined by the mean in a study): <2, 2-4 and >4 mmol/litre. This stratification was based on the GDG's belief that the differing levels would represent different levels of initial sepsis, which would influence how predictive lactate and lactate clearance were of death or disease progression.

1 **Table 195: Summary of included studies**

Study	Population	Test(s)	Target condition	Quality of evidence
Arnold 2009[16]	n=166 ED patients with severe sepsis Initial lactate >4 mmol/litre SOFA score: 3.6 Mean (sd) age 66(15) years	Lactate clearance	In-hospital mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Dettmer 2015[86]	n=132 with sepsis ED USA Initial lactate >4 mmol/litre SOFA score: 4.8 Mean age: 61.6(15.8) years	Lactate	28 day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Marty 2013[211]	n=94 ICU France Initial lactate >4 mmol/litre SAPS 2: 60 Mean age: 58(16) years	Lactate Lactate clearance	28 day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Nguyen 2004[237]	n=111 patients with sepsis or septic shock admitted to the ED USA Initial lactate >4 mmol/litre APACHE II: 20.2Mean age: 64.9(16.7) years	Lactate clearance	In hospital mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. `
Puskarich 2013[273]	n=187 with sepsis Tertiary hospitals USA Initial lactate >4 mmol/litre SOFA score: 6 in survivors and 9.5 in non-survivors Mean (sd) age: 60(16.7) years in survivors and 67(13.7) years in non-survivors	Lactate Lactate clearance	In hospital survival	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.
Walker 2013[323]	n=78 with sepsis ICU admitted directly from ED UK	Lactate Lactate Clearance	30 day mortality	Risk of bias: very serious, principally due to lack of evidence that physicians treating patients were blinded

Study	Population	Test(s)	Target condition	Quality of evidence
	Initial lactate 2-4 mmol/litre APACHE II score: 24.9 Median (IQR) age: 56(40-66) years			to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome.

1

13.2.1 Clinical evidence profiles for lactate clearance (0 to 6 hours). Strata 1: Studies where the mean initial lactate in each study was ≥4 mmol/litre

Table 196: Diagnostic accuracy profile for lactate clearance (from 0-6 hours) in predicting mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≤ - 7.7% (0-6 hours) and 28-day mortality[c]								
Marty 2013[211]	n=94	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.63(0.49-0.76)	0.56 (0.40-0.72)	VERY LOW
Threshold of <10% (0-6 hours) and in-hospital mortality								
Arnold 2009[16]	n=166	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.24(0.11-0.40)	0.95(0.90-0.98)	VERY LOW
Nguyen 2004[237]	n=111					0.45	0.84	
Puskarich 2013[273] [d]	n=187					0.21	0.86	
Threshold of ≤40% (time not clear) and 28-day mortality								
Dettmer 2015[86]	n=132	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.87(0.69-0.96)	0.59 (0.49-0.69)	VERY LOW
Threshold of <50% (0-6 hours) and 28-day mortality								
Puskarich 2013[273] [e]	n=187	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.84	0.45	VERY LOW

(a) Risk of bias mainly due to to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment , which would possibly affect outcome.

(b) Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Some studies failed to give raw data and so CIs could not be calculated.

(c) Study reported a threshold of -7.7%. It is highly unlikely that such an extreme threshold (set at a level of increasing lactate associated with the very worst prognosis) would be this sensitive. Hence it is likely that the negative sign simply (but erroneously) denotes 'clearance', rather than a negative clearance (which strictly denotes an increase in lactate).

(d) Study reported sensitivity and specificity for > 10% to predict survival. It can be easily shown on a 2x2 table that the sensitivity and specificity for <10% to predict mortality can be derived by simply switching sensitivity and specificity values.

(e) Study reported sensitivity and specificity for > 50% to predict survival. It can be easily shown on a 2x2 table that the sensitivity and specificity for <50% to predict mortality can be derived by simply switching sensitivity and specificity values.

13.2.2 Clinical evidence profiles for lactate clearance (0 to 6 hours). Strata 2: Studies where the mean initial lactate in each study was 2-4 mmol/litre

Table 197: Diagnostic accuracy profile for lactate clearance (from 0-6 hours) in predicting mortality

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality
Threshold of ≤58% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.96	0.23	VERY LOW
Threshold of ≤49.8% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.92	0.49	VERY LOW
Threshold of ≤39.2% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.88	0.56	VERY LOW
Threshold of ≤36% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.88	0.64	VERY LOW
Threshold of ≤29.8% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.76	0.67	VERY LOW
Threshold of ≤18.9% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.68	0.82	VERY LOW
Threshold of ≤9.4% (0-6 hours) and 30-day mortality								
Walker 2013[323]	n=78	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	0.48	0.87	VERY LOW

(a) Risk of bias mainly due to to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment , which would possibly affect outcome.

(b) B Confidence intervals sufficiently variable to reduce confidence in the estimate, or no confidence intervals given. Studies failed to give raw data and so CIs could not be calculated.

13.2.3 Clinical evidence profiles for lactate clearance (0 to 6 hours). Strata 3: Studies where the mean initial lactate in each study was ≤2 mmol/litre

No data found.

13.3 **Clinical evidence for use of scoring systems**

Four studies were included in the review.[160-162,223] Evidence from these are summarised in the clinical summary table (**Table 198**). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix L.

All four included studies are conducted on an indirect population (surgical or acutely ill medical patients), not sepsis specific. Despite the indirect population, those were the only studies that reported change in a scoring system (abbreviated ViEWS) over a period of time. There is also to note that all four studies are retrospective analysis of data from the same database (MediTech, Canada). The quality of the evidence was evaluated using the QUADAS-2 checklist for diagnostic accuracy studies.

Table 198: Summary of included studies

Study	Population	Test(s)	Target condition	Results	Quality of evidence
Kellett 2013[162]	n=18,827 surgical patients	Abbreviated ViEWS (does not include mental status)	In-hospital mortality	Outcome by changes between the first and second abbreviated ViEWS recording: when examined according to the initial abbreviated ViEWS recorded, there was no statistically significant change in in-hospital mortality associated with either an increase or decrease in abbreviated ViEWS Outcome by changes between the first and third abbreviated ViEWS recording: there was no statistically significant difference in the in-hospital mortality of the patients with an increase (52.2% of patients) or a decrease in score (17.1% of patients).	Retrospective design, single centre, low number of in-hospital death. Indirectness: Surgical patients, not specific to sepsis. Risk of bias: very high.
Kellett 2013A[161]	n=18,853 acutely ill medical patients	Abbreviated ViEWS (does not include mental status)	In-hospital mortality	Outcome by changes between the first and second abbreviated ViEWS recording: when examined according to the initial abbreviated ViEWS recorded there was no statistically significant change in in-hospital mortality associated with either an increase or decrease in abbreviated ViEWS Outcome by changes between the first and third abbreviated ViEWS recording: there was no statistically significant difference in the in-hospital mortality of the patients with an increase (17.1% of patients) or a decrease in score (18.3% of patients) of only one point for any value of the initial abbreviated ViEWS	Retrospective design, single centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.
Kellett 2015[160]	n=44,531 acutely ill	Abbreviated ViEWS (does	30-day in-hospital	30-day mortality: 4.6% (2067 patients)	Retrospective design, single

Study	Population	Test(s)	Target condition	Results	Quality of evidence
	medical patients	not include mental status)	mortality	The ViEWS weighted points that increased the most in patients who died and decreased the most in survivors were those for respiratory rate (0.54 and -0.14, respectively). The ViEWS weighted points that decreased the least in patients who died was temperature (0.12), and in survivors points for both oxygen saturation and systolic blood pressure were unchanged whilst points for temperature increased by 0.07. In patients who died there was little change in the weighted score for temperature, and most of the change in oxygen saturation and systolic blood pressure was in the 24 hours before death	centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.
Murray 2014[223]	n=44,531 acutely ill medical patients	Abbreviated ViEWS (does not include mental status)	30-day in-hospital mortality	OR for admissions with an increased AbEWS averaged over 12 h compared with those who decreased their score. For patients with initial score 0-2: OR 1.58 (1.08-2.30) For patients with initial score 3-6: OR 2.17 (1.75-2.69) For patients with initial score ≥7: OR 1.79 (1.39-2.31) Within a day of admission, the averaged daily AbEWS of patients with an admission AbEWS of 0-2 trended upwards, with the averaged score of those who died within 30 days rising more steeply. In contrast the averaged daily AbEWS of all patients admitted with an AbEWS on admission ≥7 trended downwards, with the averaged score of those who would die falling more slowly. The trajectories of patients with an AbEWS on admission 3-6 diverged: survivors trending downwards and non-survivors upwards.	Retrospective design, single centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.

1

13.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

13.5 Evidence statements

Clinical

Lactate clearance

The evidence from the six studies included in the review was of very low quality.

Blood lactate clearance from 0-6 hours (>4 mmol/l) stratum

Moderate sensitivity and specificity was found at a threshold of < -7.7% for blood lactate clearance for the outcome of all-cause mortality. At a threshold of <10% sensitivity was lower while specificity increased. In contrast at a threshold of <50% sensitivity was higher and specificity decreased.

Blood lactate clearance from 0-6 hours (2-4mmol/litre stratum)

As the threshold of blood lactate changed from <9.4% to <49.8% sensitivity increased and specificity decreased for the outcome of all-cause mortality

Use of scoring systems

Four retrospective cohort studies, from the same database, were identified for this review. The evidence was of very low quality due to study design and the population indirect (not sepsis specific). The evidence was insufficient to determine the minimum change in score to trigger intervention, nor to establish how often the score is to be repeated. No evidence was identified for paediatric population.

Economic

No relevant economic evaluations were identified.

13.6 Recommendations and link to evidence

Recommendations	**Sepcific recommendations on monitoring are included in recommendations 48,49,50,63,64,65, 78,79,80** **48. Monitor people with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients in acute hospital settings. [This recommendation is from Acute illness in adults in hospital (NICE guideline CG50)].** **49. Monitor the mental state of adults and children and young people aged 12 years and over with suspected sepsis. Consider**

using a scale such as the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

50. Alert a consultant to attend in person if an adult, child or young person aged 12 years or over with suspected sepsis and any high risk criteria fails to respond within one hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- Systolic blood pressure persistently below 90mmHg
- reduced level of consciousness despite resuscitation
- respiratory rate over 30 breaths per minute
- lactate not reduced by more 20% within 1 hour.

63. Monitor children with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is from Acutely ill patients in hospital (NICE guideline CG50)].

64. Monitor the mental state of children aged 5-11 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

65. Alert a consultant to attend in person if a child aged 5- 11 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- reduced level of consciousness despite resuscitation
- heart rate or respiratory rate fulfil high risk criteria
- lactate remains over 2 mmol/litre after one hour.

78. Monitor children aged under 5 with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. [This recommendation is adapted from Acutely ill patients in hospital (NICE guideline CG50)].

79. Monitor the mental state of children aged under 5 years with suspected sepsis. Consider using the Glasgow Coma Score (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.

80. Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- reduced level of consciousness despite resuscitation

	• **heart rate or respiratory rate fulfill high risk criteria** • **lactate over 2 mmol/litre after 1 hour.**
Relative values of different outcomes	**Monitoring the person who is unwell with sepsis can be done using physiological and clinical parameters such as heart rate or mental state or biochemical markers or a combination of these. The GDG were interested in outcomes that would reflect effect on serious morbidity or mortality.** **Lactate clearance** **The GDG agreed that the critical outcomes for lactate clearance were measures of worsening of sepsis. They agreed to include mortality at 28 days (or nearest time point), ICU admission, hospitalisation and length of hospital stay** **Scoring systems** **For scoring systems the GDG agreed critical outcomes were mortality, clinical resolution (up to and including end of treatment), health-related quality-of-life (up to 30 days) and** critical care admission. Important outcomes were treatment failure, appropriate or inappropriate use of antibiotics, duration of treatment,hospital re-admission (30 days), length of hospital stay and complications (including relapse; 30 days). The statistical measures considered to assess the accuracy of the tools are: area under the curve (AUC), through ROC analysis; relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for the patient outcomes listed above and for those in higher or lower risk groups; sensitivity; specificity; positive predictive value (PPV); negative predictive value (NPV).
Trade-off between clinical benefits and harms	Monitoring is useful if it can identify people who are not responding to treatment or who are deteriorating. If a score can not do this accurately harm may come to people because of a lack of recognition that they are not responding or that they are deteriorating. Recommending a score or measure which is not sufficiently accurate or sensitive to change risks false reassurance of health care practitioners and is potentially harmful.The studies available found no evidence that changes in score were associated with changes in critical outcomes. For lactate clearance - In the >4 mmol/litre stratum a sensitivity of 0.87 was observed at a threshold of 50%. In the 2-4 mmol/litre stratum a sensitivity of 96% was observed at a threshold of 58%. These results imply that respectively 13% and 4% of those at risk of death would not be identified. Specificity was 0.59 and 0.23 respectively. The GDG considered that this sensitivity and specificity values were acceptable but the evidence available either did not specify a time period or specified a 0-6 hours time period. This evidence could therefore not inform monitoring in early phases of presentation.
Economic considerations	No economic evidence was identified for this question. As with a diagnostic question, the benefit of using a risk score/test in identifying the status of the patient is the intervention/management that the prognostic test will indicate. The tests are likely to be cheap as the scores only take a small amount of staff time, but lactate testing is most likely more expensive and is usually done on a blood gas machine. The sensitivity and specificity of a test in identifying a condition may be different to that of identifying subtle changes in a condition. In general, a more accurate test is more likely to be cost effective if it picks up more changes in the patient's condition. The frequency of the tests is important because the optimal timing is frequently enough to pick up changes that need intervention and not miss anything, but not too

	frequent that the costs of testing would then outweigh the benefit. The clinical evidence did not meet the protocol; however was the only evidence identified. Monitoring is included in the NICE guideline CG50 Acutely Ill Patients in Hospital. The GDG made a consensus recommendation that monitoring should be more frequent in the group at highest risk and ideally be continuous monitoring, but at least every 30 minutes. Patients in the high to moderate risk category should have a minimum of hourly monitoring which can change if the patients categorisation changes. The GDG also agreed that lactate was an important measure to assess physiological response to resusitation, and lactate should be measured again 1 hour after the administration of IV fluids. , This along with other measures that would generally be included in a scoring tool, will help determine if care should be escalated to a consultant attendance. The GDG could not recommend a specific scoring system to use for monitoring. Some scores give an indication of how frequently patients should be monitored based on the results of the score. For example the National Early Warning Score (NEWS) states patients should be monitored every hour if they are score 5 or more '. However the patients the recommendations from this guideline apply to have suspected sepsis and the GDG considered that during early assessment they should have more frequent monitoring. . The GDG weighed up the trade-off of costs and benefits in their decision making and although monitoring more frequently is expected to use more staff time, the population being monitored can deteriorate rapidly and picking up changes can potentially mean mortality is avoided as a patients condition can then be escalated to a consultant being called and referral to critical care ,where continuous monitoring can occur. An additional concern was the possibility that patients with only moderate to high risk criteria for example would automatically get hourly monitoring which may be an overuse of resources. However some of the people will have sepsis and will benefit from additional monitoring. The benefit and potential harm avoided from monitoring the high risk group group more frequently will outweigh the additional resource use for the few patients who may not have needed such frequent monitoring.
Quality of evidence	Lactate clearance Quality of evidence was generally very low. One reason was high levels of imprecision or the lack of any measures of precision. Another reason was very serious risk of bias, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. Scoring systems No direct evidence was found for the use of scoring systems in monitoring sepsis. The evidence included is indirect because the population is not sepsis specific, but those were the only studies that report changes in score over a period of time. The GDG acknowledged the limited quality of the included studies. All the studies are retrospective cohort studies, analysing data from the same database and therefore, prone to bias due to their design. The GDG noted that the study populations had a high mean age (mean age ranging between 55.8 and 67.5 years), and considered that an older population cannot tolerate deterioration in physiology like a younger population could do and that changes in physiology might have a more significant association with outcomes in younger people. Older people are however more likely to be acutely unwell. Overall, the quality of evidence is very low.

Other considerations	The GDG used informal consensus to make recommendations for monitoring. The GDG recognised that evidence was insufficent to inform a recommendation on the use of lactate clearance. They used consensus to recommend that a lack of response to resuscitation could be assessed by a reduction in lactate by 20% in adults, children and young people over 12 years and by a lactate over 2 mmol/l in children less than 12 years (see section 8.6). They agreed not to make a recommendation for the use of lactate clearance for continued monitoring in adults or children. The GDG recognised that NICE CG50 makes recommendations for use of scores and track and trigger systems for acutely ill adults in hospital. CG50 recommends that physiological measurements should be repeated every 12 hours unless frequency altered by senior staff or freuqncy should increase if abnormal physiology is detected. It advises that thresholds for triggering actions should be decided locally. The review for this guideline did not find any sepsis specific information on sensitivity of scores to change and the GDG therefore made consensus recommendations on use of individual parameters to assess response to initial resuscitation rather than recommending a change in score (see section 8.6). The GDG agreed to adapt the recommendations from CG50 to indicate that continued monitoring of people with high risk criteria should either be continuous or at 30minute intervals and people presenting with one moderate to high risk criteria, should be monitored hourly.. They agreed that a similar recommendation was appropriate for children and young people. Some scores already include measurement of mental state and these generally include either Glasgow Coma Scale (GCS) or 'AVPU' which records response to stimuli as Alert, Voice, Pressure, Unconsious. While the GDG wished to emphasise the importance of assessing mental state they were also agreed that both GCS and AVPU may not be able to pick up more subtle changes in mental state and therefore agreed that use of these tools should be considered rather than mandated.

1

14 Finding the source of infection

14.1 Introduction

Sepsis is a response to infection. The most common sites of infection include the lungs, urinary tract, abdominal organs, and pelvis. Early source identification is important if sepsis is to be treated adequately. The recommendations here aim to provide some guidance on tests that may be necessary to identify the cause or source of infection leading to sepsis.

No evidence review was performed to inform these recommendations. The GDG discussed the value of an evidence review and considered that while background information on epidemiology of causes of sepsis might be helpful the most important point for clinical practice was that investigations should be specific to the clinical presentation of the patient with suspected sepsis.

The guideline recommends immediate empirical antibiotic treatment for people with suspected sepsis at high risk of morbidity and mortality. The aim of empirical treatment is to treat likely serious infections. This treatment might require changing to more appropriate choice of antibiotic depending on bacteria causing infection. The recommendations in Section 8.2 include a recommendation to take blood cultures if possible before antibiotics are given. That recommendation is included in Section 8 because of its place on the pathway. Blood culture results will provide some information as to the bacterial cause of infection and the rationale for taking blood cultures is included here.

14.2 Recommendations and link to evidence

Recommendations	**110. Carry out a thorough clinical examination to look for sources of infection.** **111. Tailor investigations to the person's clinical history and findings on examination.** **112. Consider urine analysis and chest X-ray in all people aged over 5 years with suspected sepsis.** **113. Consider imaging of the abdomen and pelvis if no likely source is identified after clinical examination and initial tests.** **114. Involve the adult or paediatric surgical and gynaecological teams early on if intra-abdominal or pelvic infection is suspected in case surgical treatment is needed.** **115. Do not perform a lumbar puncture if any of the following contraindications are present:** • **signs suggesting raised intracranial pressure or reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)** • **relative bradycardia and hypertension**

	• **focal neurological signs** • **abnormal posture or posturing** • **unequal, dilated or poorly responsive pupils** • **papilloedema** • **abnormal 'doll's eye' movements** • **shock** • **extensive or spreading purpura** • **after convulsions until stabilised** • **coagulation abnormalities or coagulation results outside the normal range or platelet count below 100 x 10^9/litre or receiving anticoagulant therapy** • **local superficial infection at the lumbar puncture site** • **respiratory insufficiency in children.** **[This recommendation is adapted from Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE clinical guideline 102)]** **116. Perform lumbar puncture in the following children with suspected sepsis (unless contraindicated, please see contraindications in recommendation 115):** • **infants younger than 1 month** • **all infants aged 1–3 months who appear unwell** • **infants aged 1–3 months with a white blood cell count less than 5 × 10^9/litre or greater than 15 × 10^9/litre.** **[This recommendation is adapted from Fever in under 5s (NICE guideline CG160)]**
Relative values of different outcomes	No evidence review was performed for to inform these recommendations
Trade-off between clinical benefits and harms	Finding the source of infection that has led to sepsis can improve targeting of antibiotics and may enable specific treatment to be instituted. Thorought clinical assessment will allow both appropriate investigations to be planned and involvement of appropriate specialists. Harm is unlikely to come to a patient from tests such as chest x-ray and urinalysis. Tests to look for abdominal or pelvic sources of infection such as CT scans will not be necessary in all people with sepsis but if a source of infection is not found with simpler tests it will be of benefit to the patient to carry out these tests. People with abdominal or pelvic collections may require surgical drainage of these collections and will not improve unless this is carried out. Lumbar puncture is contraindicated in people with raised intracranial pressure as it can cause significant harm. It is widely accepted that taking blood cultures is beneficial for identification of organisms causing systemic infection. This is beneficial in ensuring appropriate antibiotics are used and particularly enabling de-escalation from broad spectrum to narrow spectrum antimicrobials. There are no anticipated harms from taking blood cultures.
Economic considerations	Identifying the source of the infection which has led to sepsis, and doing this in a timely way, will allow tailoring of treatment such as antibiotics which is likely to impact upon the patient's outcome. Resources likely to be involved in diagnosing the infection may include clinical assessment, blood cultures, urine samples, and imaging. The method used to diagnose the infection can very much depend upon the

	type of infection itself. Therefore although blood cultures tend to be the gold standard in identifying systemic organisms causing infection, other interventions may need to be used. The GDG noted that blood cultures are a relatively inexpensive test in the context of the total cost of care of people with sepsis/suspected sepsis. The cost increases for positive blood cultures that require additional laboratory time and analysis. The GDG considered that the costs or resources involved in diagnosing the cause of the sepsis was likely to be outweighed by the benefit that diagnosis could bring in terms of appropriate treatment. Severe sepsis can be very expensive to treat, particularly because patients are generally in ICU where continuous monitoring can take place. It is also associated with a high mortality rate. There is therefore a benefit to early identification of the cause of the sepsis in terms of downstream savings and also a likely clinical benefit to appropriate treatment taking place as soon as possible before deterioration occurs. From one of the other questions within this guideline, patients suspected of sepsis will have already been administered early broad spectrum antibiotics, as taking cultures should not delay the administration of antimicrobials. However the fast turnaround of analysis of blood cultures will allow treatment to be more tailored to the underlying cause of the sepsis which is likely to have a positive impact on the outcome of the patient. The GDG made recommendations of good practice for diagnosing sepsis based on their own clinical experiences. If blood cultures are taken these should be done to a high standard i.e. taking adequate samples. Taking blood cultures is current practice for diagnosing the cause of a systemic infection and the GDG therefore decided to refer to the antimicrobial stewardship guideline in their recommendation. Other interventions that could also be considered include urine samples (if a urinary infection is suspected) and chest x-rays (if pneumonia or a respiratory infection is suspected). Imaging of other parts of the body might also be considered. The type of imaging (x-ray, ultrasound, CT) was not specified because this may be dependent on where the patient is (which hospital, ED or ward), and so this was left to clinician judgement. The GDG also agreed it was important that there is specialist involvement depending on where the infection is located. The population that would have these additional tests is likely to be smaller than the suspected sepsis population as a thorough clinical assessment and history may already indicate the source of infection. The strength of most of these recommendations is consider, reflecting that there should be an element of clinician judgement and that the recommendations are also consensus based. The further investigations such as chest x-ray or urine test are already part of the pathway for diagnosing specific infections such as urinary infection or pneumonia, and a specialist should be involved if something falls under their clinical area or surgery is required, therefore these recommendations are not a change in practice, and there is not likely to be a large cost impact.
Quality of evidence	Not applicable
Other considerations	The GDG used epidemiology of causes of sepsis and their clinical experience and knowledge of clinical tests to inform these recommendations. Blood cultures are recommended as one of the tests to be done when people at high risk or high to moderate risk of severe illness of death are initially assessed. Blood cultures are used to identify the organism causing infection.It is current good practice is to take blood culture samples when possible and blood cultures are considered the gold standard when assessing other methods of identifying organisms that cause systemic infection such as DNA sequencing. Taking the

	cultures should not delay antimicrobial administration Yield increases with increased number of cultures taken (up to 3 or 4 samples), with the biggest difference in yield occurring between 1 and 2 samples. The GDG considered it important to emphasise that yield can be improved by ensuring valid samples are taken i.e. ensuring bottles are adequately filled and stored appropriately. The source of sepsis is important as it can help clinical consideration of antibiotic choice and may indicate whether other actions are required for example surgical intervention to drain an intra-abdominal or pelvic collection. They considered it important to remind healthcare professionals of the importance of clinical assessment which can sometimes be overlooked. Where possible the choice of additional tests should be tailored to individual patient history and examination. The source of sepsis is important as it can help clinical consideration of antibiotic choice and may indicate whether other actions are required for example surgical intervention to drain and intra-abdominal or pelvic collection. Since pneumonia and urinary tract sepsis are important cause of sepsis in UK the GDG suggested that chest x-ray and urinalysis should be considered for all patients. The GDG discussed whether they could recommend choice of imaging further investigate for sources of sepsis. They agreed however that choice more often depended on where the patient was and the availability of equipment and expertise- for example in a large centre it may be easier to perform a CT scan when a patient is in an A/E department but easier to use USS when patient is on a ward. The GDG considered it important that appropriate healthcare professionals were involved including radiologists and surgeons and gynaecologists. While lumbar puncture can be an important test to find source of infection if a patient is thought to have meningitis lumbar puncture is contraindicated in certain situations. NICE guideline CG102 did an evidence review to identify contraindications to lumbar puncture in children and young people but found no good quality evidence and made recommendations using consensus. The GDG agreed to use the existing recommendation in the meningitis guideline (CG102) to inform the recommendation on when lumbar puncture is contraindicated and adapted this by specifying that respiratory insufficiency is a contracinidcation in children only.

1

15 Information and support

Sepsis is a frightening and potentially life-threatening condition. Many patients recite the importance of receiving explanations about sepsis and available treatment options. At the same time potential serious complications and outcomes need to be discussed with patients, family members and carers. Addressing patient concerns and providing them with the knowledge to make informed choices is without doubt considered to be good clinical practice.

This section aims to provide a systematic narrative review of the relevant literature that will aid in the development of consensus recommendations.

15.1 Review question: What information, education and support would be useful for the following; people assessed for possible sepsis but discharged from medical care, people at high risk of sepsis, people who have sepsis or severe sepsis including families and carers and people who survive episodes of severe sepsis

Table 199: Characteristics of review question

Objective	To provide a systematic narrative review of the relevant literature that will aid the GDG towards consensus recommendations on providing information, education and support.
Population and setting	• People assessed for possible sepsis but discharged from medical care • People at high risk of sepsis • People who have sepsis or severe sepsis, families and carers • People who survive episodes of severe sepsis
Outcomes / themes	• Patient satisfaction, including understanding • Reduction in time to diagnosis • Themes or views based on patients'/carers'/families' experiences on what they perceived as important elements of information and support needs

15.2 Clinical evidence

15.2.1 Methods

Three qualitative studies were identified[71,84,113] one of which also undertook a survey[71]. The studies were conducted in different populations and settings. One study explored the perceptions and experiences of parents of young children that had undergone a full sepsis evaluation.[84] A second study explored the needs and aftercare of children surviving meningitis and/or septicaemia.[71] The third study explored the experiences and impact of severe sepsis from both the patients and their informal caregivers' perspectives.[113] These papers are summarised in Table 200. Key findings from these studies are summarised in the clinical evidence summary below (Table 201 to Table 206). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix L.

15.2.2 Summary of included studies

Table 200: Summary of studies included in the review

Study	Methods used	Population (n)	Research aim	Comments
Clark 2013[71]	Mixed methods Stage one: Survey Stage two: Qualitative research method: Semi-structured interviews conducted face-to-face or by telephone	Stage one: Parent or legal guardian (n=194) of children (aged <18 years at the time of illness) who had survived meningitis and/or septicaemia England; 75% Remaining UK; 22% Ireland; 3% Stage two: Parents (n=18) selected from stage one, only participants reporting permanent after-effects, and who had accessed aftercare and support were included UK	To gain understanding of parents' and children's needs and experiences of after-care for children surviving bacterial meningitis and septicaemia	Limited description of derivation and validation of survey (stage one). Limited description of analysis for stage two, the qualitative research method. Sample size for the qualitative interviews did not allow for complete data saturation (authors noted that the themes identified here were recurrent).
De 2014[84]	Semi-structured face-to-face interviews just prior to hospital discharge	Parents (n=36) of infants (n=27) aged <3 months with fever and admitted to tertiary children's hospital Australia	To explore the concerns, beliefs, attitudes and perspectives of parents of young infants who had undergone full sepsis work-up following presentation to hospital with fever	One researcher was involved in data collection and analysis and only preliminary themes were discussed with a second. Unclear how theme saturation was assessed (reported but not discussed).
Gallop	Qualitative research	Patients (n=22) ≥18 years who had	To explore and describe the subjective experiences and	

Study	Methods used	Population (n)	Research aim	Comments
2015[113]	method: Semi-structured interviews conducted face-to-face or by telephone	experienced an episode of severe sepsis in the previous 12 months Caregivers (n=17), family members or friends who had provided informal care for the patient after their episode of severe sepsis UK (n=13 patients, n=10 informal caregivers) USA (n=9 patients, n=7 informal caregivers)	long-term impact of severe sepsis on survivors of severe sepsis and their informal caregivers	

15.2.3 Summary of themes

2 **Table 201: Themes and sub-themes derived from the evidence**

Main theme	Sub-themes
Parents of infants aged <3 months who had undergone full sepsis evaluation[83,85]	
Parental attitudes at the time of presentation to hospital: Expecting reassurance and support	No sub-themes
Parental attitudes and experiences during the course of hospitalisation: Facilitators for parent empowerment	No sub-themes
Barriers to empowerment	No sub-themes
Parents of children who had survived meningitis and/or septicaemia	
Sequelae	No sub-themes
Requirement for and provision of aftercare	No sub-themes
Parents' satisfaction and aftercare provided for child	No sub-themes
Accessing appropriate support and follow-up care	Navigating the system Young age as a barrier to gaining a clear diagnosis and support Poorly appreciated link between meningitis and sequelae Appropriateness of support and aftercare
Communication	Debrief before discharge Involving parents Communication between professionals
Patients' and caregivers' experiences of severe sepsis	
Awareness and knowledge of severe sepsis	No sub-themes
Experience of hospitalisation	No sub-themes
On-going impact of severe sepsis	No sub-themes
Impact on caregivers	No sub-themes
Support after severe sepsis	No sub-themes

1 **Table 202: Summary of evidence: Parents of young infants that had been admitted to hospital and undergone full sepsis work up**

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	**Design**		**Criteria**	**Rating**	**Overall**
Theme 1: Parental attitudes at the time of presentation to hospital - Expecting reassurance and support					
1[84]	Interview	Many participants felt overwhelmed by the responsibility of caring for their infant and there was fear of the possibility of a serious underlying infection such as meningitis. Some participants believed fever by itself could cause adverse effects such as seizures. Some participants believed they had done something wrong in terms of fever management. Participants believed young infants had heightened vulnerability compared with older children. There was apprehension about missing cues of serious illness, particularly from first time parents.	Limitations of evidence	Minor limitations	LOW
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Unclear	
Theme 2: Parental attitudes and experiences during the course of hospitalisation - Facilitators for parent empowerment					
1[84]	Interview	Prompt and thorough assessment reassured participants, in particular mothers. Tests were distressing to watch but participants expressed relief the worst possibilities were being ruled out. A heightened sense of involvement and control was felt by participants when the medical team were supportive and fostered engagement. Clear explanation of the management plan, timely updates and opportunities to discuss treatment options heightened trust. Participants feared they would be dismissed as 'over protective' or 'paranoid' but felt relieved if their concerns were recognised as appropriate. Receiving a definite diagnosis was of paramount importance for most participants.	Limitations of evidence	Minor limitations	LOW
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Unclear	
Theme 3: Barriers to empowerment					

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
1[84]	Interview	The barriers to parental empowerment identified included unmet medical seriousness, unmet expectation of support, relinquished control and limited capacity. Participants experienced disbelief and shock when their infant had to be hospitalised and undergo medical tests. A sense of loss of control arose from feeling excluded from or unable to contribute meaningfully to the medical management and decision making. Unmet expectation of support stemmed from a lack of explanation of tests by medical staff, a perceived lack of empathy from staff, and explanations of tests being delivered in a manner that made them 'fear the worst'. Participants believed they were expected to rapidly comprehend a vast amount of information, and found it difficult to process all the information. Some believed they were given conflicting information or were perplexed by medical jargon. Others were hesitant about voicing their concerns fearing they may overstep their parenting role and delay medical management	Limitations of evidence	Minor limitations	LOW
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Unclear	

1 **Table 203: Survey of parents of children who had survived meningitis and/or septicaemia**

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Navigating the system					
1[71]	Survey	Most parents reported that their child had at least moderate short term after-effects (23.2% reporting no after-effects at	Limitations of evidence	Major limitations	LOW
			Coherence of findings	Not applicable	

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	**Design**		**Criteria**	**Rating**	**Overall**
		all). Most frequently reported problems were behavioural, psychological or emotional (40.7%).	Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Not applicable	
Sub-theme 2: Young age as a barrier to gaining a clear diagnosis and support					
1[71]	Survey	Fifty one percent of those patients with bacterial meningitis/meningococcal disease were offered a hearing assessment within 4 weeks (as recommended by NICE). Only 2% of patients with septicaemia were not offered a hearing assessment. Two thirds were offered a follow-up appointment with a paediatrician after coming home from hospital. Most parents reported that their child required aftercare and support, the greatest need was for educational support (30.4%). Most people could access the follow-up services. For hearing (n = 25), speech and language therapy (n = 36), occupational therapy (n = 49), behavioural, psychological or emotional support (n = 31) and child development centre support (n = 23). Around half of respondents (range 48% to 56% depending on service) had no difficulty accessing aftercare. A least 20% in every category of aftercare had some difficulty or could not access services at all (with the exception of plastic surgery).	Limitations of evidence	Major limitations	LOW
			Coherence of findings	Not applicable	
			Applicability of evidence	Not applicable	
			Theme saturation/sufficiency	Not applicable	
Sub-theme 3: Poorly appreciated link between meningitis and sequelae					
1[71]	Survey	About half of participants considered their children's needs were being met. The majority of parents found aftercare and support services helpful, with the exceptions of psychosocial	Limitations of evidence	Major limitations	LOW
			Coherence of findings	Not applicable	
			Applicability of evidence	Applicable	

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
		support, educational support and prosthetics. There were no parents who reported that prosthetics (i.e. the equipment provided) were useful but 40% of them were happy with the support given by staff.	Theme saturation/sufficiency	Not applicable	

1 **Table 204: Theme 1 - Parents accessing appropriate support and follow-up care for children who had survived meningitis and/or septicaemia**

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Navigating the system					
1[71]	Interview	Most parents could access the aftercare or support service their children needed, although sometimes with difficulty. Learning to navigate the support systems in place was a common issue due to language barriers and not knowing 'what to do next'. Almost all parents had experienced difficulties in gaining sufficient or timely care. In some cases, ease of navigation was attributed to having a key point of contact that had been 'proactive' and instigated further appointments.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	
Sub-theme 2: Young age as a barrier to gaining a clear diagnosis and support					
1[71]	Interview	Participants with young children felt age was a barrier to gaining a clear diagnosis and support. Gaining access to services was often difficult when the child was very young, although regular check-up appointments were mentioned in examples where young age did not present a barrier to diagnosis or access.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	
Sub-theme 3: Poorly appreciated link between meningitis and sequelae					
1[71]	Interview	Accessing support at school was difficult when the child has had less visible, psychosocial and cognitive after-effects.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	**Design**		**Criteria**	**Rating**	**Overall**
		Parents felt that the link between acute meningitis and long term complications was poorly understood and addressed by the health and social care system, as a result it was felt accessing services was harder.	Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	
Sub-theme 4: Appropriateness of support and aftercare					
1[71]	Interview	Appropriateness of services depended on how much time and attention the parent felt was paid to their child's individual needs. Some parents felt that this was adequate while others did not.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	

1 **Table 205: Theme 2- Communication and parents of children who had survived meningitis and/or septicaemia**

Study design and sample		Themes and findings	Quality assessment		
No of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Debrief before discharge					
1[71]	Interview	Some parents felt they were not 'warned' or told that there could be potential cognitive and behavioural after effects, others were told to 'wait and see'. It was felt a lot of the frustration and distress may have been reduced if there had been better, more standardised ways of communication.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	
Sub-theme 2: Involving parents					
1[71]	Interview	Parents often worried about their child being able to reach their potential. The child's care package appeared more tailored to the needs of parent and child when the parents felt listened to and	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme	Unclear	

Study design and sample		Themes and findings	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
		involved.	saturation/sufficiency		
Sub-theme 3: Communication between professionals					
1[71]	Interview	Parents felt inadequate support for the child's needs arose from poor communication between different specialists. Parents felt their child's needs were met that when professionals did communicate to produce shared plans and goals.	Limitations of evidence	Minor limitations	LOW/MODERATE /HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Unclear	

1 **Table 206: Adult patients after an episode of severe sepsis and their informal caregivers**

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
Theme 1: Awareness and knowledge of severe sepsis					
1[113]	Interview	There was wide variation in the participants' awareness of severe sepsis as a diagnosis, as was the level of understanding of severe sepsis. Some patients and caregivers were unaware of the diagnosis of severe sepsis until being invited to take part in the research. There was a general lack of understanding of severe sepsis, although all patients were aware that their illness had been life threatening. Caregivers discussed being told about the patient's chance of survival, and being warned that they may not survive.	Limitations of evidence	No limitations	HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Saturated	
Theme 2: Experience of hospitalisation					
1[113]	Interview	Patients' recollections of waking up in intensive care varied	Limitations of evidence	No limitations	HIGH

Study design and sample			Quality assessment		
No of studies	**Design**	**Descriptors of themes**	**Criteria**	**Rating**	**Overall**
		greatly. Comments included; 'having a bad or weird dream', 'feeling like being in slow motion', 'drifting in and out of consciousness', 'not knowing where they were or why they were in hospital' Others reported no recollections. Caregivers recalled the patients time in intensive care as frightening and worrying, in particular, seeing the patient dependent on life support. They recalled concerns of the patient having possible lasting brain damage or personality changes.	Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Saturated	
Theme 3: On-going impact of severe sepsis					
1[113]	Interview	The level of impact of severe sepsis varied greatly. The reported lasting impacts of the patients' severe sepsis episode included; sensory (n=2) or cognitive impairments (n=5), physical appearance (n=4), on-going symptoms from complications (n=6), medication side effects (n=9). Two patients previously independently mobile reported being unable to stand for long and unable to walk at the time of the interview. Difficulties with self-care during recovery arose due to impairments, particularly after discharge from hospital. Six patients previously independent before having severe sepsis had become completely dependent on others, while for others the impact on independence was short term. Patients described feelings helplessness, embarrassment, and angry about their loss of independence. Other emotional impacts included a fear that the severe sepsis might come back, fear of undergoing further medical tests when previously unconcerned, fear of too much activity causing a recurrence of	Limitations of evidence	No limitations	HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Applicable	
			Theme saturation/sufficiency	Saturated	

Study design and sample			Quality assessment		
No of studies	**Design**	**Descriptors of themes**	**Criteria**	**Rating**	**Overall**
		severe sepsis, and a heightened awareness and avoidance of infections to prevent recurrence.			
Theme 4: Impact on caregivers					
1[113]	Interview	The greatest impact on caregivers' time was when the patient was discharged from hospital due to the patients' self-care needs and complex medication regimes. Several caregivers reported at the time of the interview that their days still revolved around the patient's needs, in some cases caregivers were unable to leave the patient on their own. The reduced freedom and burden of caregiving along with distress related to the patient's condition had a lasting emotional impact on caregivers. They reported feelings of frustration, guilt, anxiety, and stress related to their role as a caregiver.	Limitations of evidence	No limitations	HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Saturated	
Theme 5: Support after severe sepsis					
1[113]	Interview	Participants reported a general lack of information about severe sepsis and what to expect during recovery and that the hospital should provide this information. Many patients and caregivers reported difficulties accessing follow-up community treatment (e.g. physiotherapy) after discharge or that the level of support and care available was inadequate (reported by patients and caregivers in both the UK and USA, however, accessing follow-up support and care was	Limitations of evidence	No limitations	HIGH
			Coherence of findings	Coherent	
			Applicability of evidence	Very applicable	
			Theme saturation/sufficiency	Saturated	

Study design and sample		Descriptors of themes	Quality assessment		
No of studies	Design		Criteria	Rating	Overall
		more of a challenge for UK patients (n=4) and caregivers who had received inpatient care a long way from their home)			

15.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Below are some unit costs illustrating the cost of staff time of providing information.

Table 207: Typical costs of healthcare workers' time

Healthcare professional	Cost of time – 1 hour
GP	£134
Hospital nurse	£41
Junior doctor	£40
Registrar	£59

Source: PSSRU 2014[76]

15.4 Evidence statements

Clinical

Three qualitative studies were identified. One study explored the perceptions and experiences of parents of young children that had undergone a full sepsis evaluation, a second study explored the needs and aftercare of children surviving meningitis and/or septicaemia, and the third study explored the experiences and impact of severe sepsis from both the patients and their informal caregivers' perspectives. There were common themes across all 3 three studies despite the disparately of the study populations and settings. Caregivers and patients had an expectation of support that was often not met during the acute episode and during aftercare. Information-giving during, at discharge and after the episode was often cited as being lacking. Similarly an understanding of the ongoing support needs was cited as inadequate. There was an expectation that information about sepsis and aftercare should be provided by the hospital.

Economic

No relevant economic evaluations were identified.

15.5 **Recommendations and link to evidence**

Recommendations	**People who have sepsis, and their families and carers** **117. Ensure a care team member is nominated to give information to families and carers, particularly in emergency situations such as in the emergency department. This should include:** • **an explanation that the person has sepsis, and what this means** • **an explanation of any investigations and the management plan** • **regular and timely updates on treatment, care and progress.** **118. Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given.** **119. Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed.** **120. Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis.** **Information at discharge for people assessed for possible sepsis, but not diagnosed with sepsis** **121. Give people who have been assessed for sepsis but have been discharged (and their family or carers, if appropriate) verbal and written information about:** • **what sepsis is, and why it was suspected** • **what tests and investigations have been done** • **instructions about which symptoms to monitor** • **when to get medical attention if their illness continues.** **122. Confirm that people understand the information they have been given, and what actions they should take to get help if they need it.** **Information at discharge for people at increased risk of sepsis** **123. Ensure people who are at increased risk of sepsis (for example after surgery) are told before discharge about symptoms that should prompt them to get medical attention.** **See Neutropenic sepsis (NICE guideline CG151) for information for people with neutropenic sepsis (recommendation 1.1.1.1).**

	Information at discharge for people who have had sepsis **124. Ensure people and their families and carers if appropriate have been informed that they have had sepsis.** **125. Ensure discharge notifications to GPs include the diagnosis of sepsis.** **126. Give people who have had sepsis (and their families and carers, when appropriate) opportunities to discuss their concerns. These may include:** • **why they developed sepsis** • **whether they are likely to develop sepsis again** • **if more investigations are necessary** • **details of any community care needed, for example, related to peripherally inserted central venous catheters (PICC) lines or other intravenous catheters** • **what they should expect during recovery** • **arrangements for follow-up, including specific critical care follow up if relevant** • **possible short-term and long-term problems.** **127. Give people who have had sepsis and their families and carers information about national charities and support groups that provide information about sepsis and causes of sepsis.** **128. Advise carers they have a legal right to have a carer's assessment of their needs, and give them information on how they can get this.** **See Rehabilitation after critical illness in adults (NICE guideline CG83)for recommendations on rehabilitation and follow up after critical illness.** **See Meningitis (bacterial) and meningococcal septicaemia in under 16s (NICE guideline CG102) for follow up of people who have had meningococcal septicaemia.**
Relative values of different outcomes	The GDG considered all the identified themes were critical for making recommendations for people with suspected sepsis and sepsis, and their carers.
Trade-off between clinical benefits and harm	The evidence review found three qualitative studies relevant to the question, one short term and two longer-term. Common themes were identified despite the studies being conducted in different settings (tertiary hospital, and in the community post sepsis episode) and different populations (caregivers of infants, caregivers of children, caregivers of adults and adults after a sepsis episode). Emphasis was placed on the importance of good communication (positively impacts on understanding and satisfaction) versus the damage of poor communication (potentially increases trauma, and the distress experienced). Patients and caregivers reported that

	experienced a lack of control during acute situations, but are more accepting of this when the situation is explained to them. It was noted that in acute situations such as during resuscitation too much information may be overwhelming, however, caregivers and patients reported that they would still appreciate information.
Economic considerations	No relevant economic evidence was identified. The provision of information may involve staff time of the clinicians, or resources involved in developing support materials. Some resources of information on sepsis may already exist such as from sepsis charities. Providing information to patients, families, or carers, has benefit because there is a value in knowing information and this can reduce anxiety. The clinical review identified various themes with mixed responses about what information was helpful and also what could have been improved. Good communication was highlighted as being important. The GDG recognised that explaining about the condition and providing patients with information about sepsis should be current practice. There are also existing materials that patients can be referred to. Information about next steps and on-going care should also be explained to the patient. The GDG considered that although these recommendations may have cost implications as a result of additional health care professional time and additional resource requirements (for example, where information does not already exist in a suitable format), this is an essential part of good patient care to ensure all people with sepsis and their families are adequately informed, and can have further clinical benefit not only through reduced anxiety but also through awareness of sepsis and spotting any worsening or complications of the condition.
Quality of evidence	Only one of the three studies was of low quality, primarily because the sample size did not allow for saturation of themes.
Other considerations	The GDG used the evidence review and their experience to develop recommendations. They were aware of other NICE guidance which provides principles of good communication – for example CG138: Patient experience in adult NHS services, and other guidelines that provide specific guidance in different scenarios, for example CG83: Rehabilitation after critical illness, CG102: Bacterial meningitis and meningococcal septicaemia, and CG160: Fever in under 5s. The GDG agreed that in all situations it was important to 'name' the problem and explain to the person, their families and carers, and in correspondence with the person's GP that the person had sepsis. Sepsis awareness among the general public is limited. Historically, sepsis is unlikely to be mentioned in discharge summaries to GPs which more usually states the underlying cause. The identification of sepsis can give people a name for their problem and also provides them with a diagnosis to help them get further information and support. People who were investigated for sepsis in A&E should have the nature of sepsis explained to them and be given information as to what they need to look out for when discharged. The GDG considered that it was important to clarify with people that they understood the information. The GDG were aware of several sources of written information that could be useful - an information sheet for parents and carers is available from NICE in relation to the Fever in under 5s guideline, while 'When should I worry' is information produced for parents by the University of Cardiff and supported by the RCGP (www.whenshouldiworry.com/). These sources of information are also relevant for 'safety netting' when patients are seen in primary care setting. Similar types of information should be available for people who are at higher risk of

	sepsis, for example, after childbirth or recent pregnancy following surgery or when people are immunocompromised. Information may need to be repeated several times both to the person with sepsis and to families and carers. National charities, such as the UK Sepsis Trust, can be a source of information for people and healthcare professionals. Individuals should be informed that these groups exist and may be of help. People who have had sepsis and particularly those who have required admission to the intensive care setting are likely to require follow-up. NICE has developed guidance on Rehabilitation after Critical Illness (CG83) and these recommendations on discharge and follow-up should be followed for people who have been critically ill with sepsis. The GDG were aware, however, that many intensive care centres do not do regular follow-up. National charities, such as ICU steps, provide information and support for patients and their relatives about following intensive care experiences. People who have had sepsis often need to explore why they developed sepsis and whether they might have further episodes. People should be informed about further investigations they may need, how they will be followed up and what short- and long-term problems they may face. Carers now have a legal right to a Carer's Assessment of their needs but are unlikely to be aware of this unless informed. The GDG considered a number of practices that could improve care. These included the provision of information on sepsis with discharge summaries, use of pathway co-ordinators like those in trauma centres, use of patient advocates and multi-disciplinary discharge meetings. These areas could be researched or good practice collected nationally.

1

16 Training and education

People with sepsis may present to healthcare professionals in any settings. Delays in the diagnosis of sepsis have been highlighted by the ombudsman's report. Many professionals, such as GPs, will see people with sepsis only occasionally, yet their clinical suspicion that a patient might have sepsis may be crucial in ensuring early and appropriate care. Evidence of specific education or training programmes that have successfully increased awareness of sepsis might allow such programmes to be recommended.

This guideline covers all settings and the GDG were aware that no significant studies of education or training programmes specifically about sepsis had been undertaken in the UK. They also considered that education and training is a large research area in its own right and that attempting to extrapolate from research about training in general or about programmes in similar areas such as meningitis or stroke was beyond the resources available Given these limitations the GDG agreed on a mixed methods review to capture any principles from research available on improving healthcare professionals recognition and management of sepsis.

Education and training to increase awareness of sepsis overlap with the use of protocols for the management of patients with severe sepsis. These are more common in emergency departments and hospital settings where specific standards are set, for example, for the delivery of fluids and antibiotics. Since this review is interested in education and training, studies which did not provide any information about their education and training packages and only provided results of implementation of protocols were not included in this review, but there is some inevitable overlap.

16.1 Review question: What education and training programmes improve early recognition, diagnosis and management of sepsis and severe sepsis?

16.2 For full details see review protocol in Appendix C.

Table 208: PICO characteristics of review question

Population	All healthcare professionals involved in the diagnosis, management and monitoring of sepsis (for example, doctors, nurses, ambulance staff, paramedics, physiotherapists, pharmacists and 111/999 call handlers [note: include non-UK-specific terms])
Aim	• Main objective: To examine qualitative and qualitative evidence of education for sepsis recognition and management to aid the GDG towards consensus recommendations
Review strategy	(1) Quantitative data analysis Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined). If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. For observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented. (2) Qualitative analysis Thematic analysis will be conducted, and common themes across studies will be extracted and reported. The review will be considered as complete when no new themes are found within the area (theme saturation reached). (3) Thematic synthesis from (1 and (2)

	• Search for literature to include septicaemia/septicaemia/septic.

16.3 Clinical evidence

Fifteen studies[46,47,73,94,101,151,189,190,197,199,222,236,238,252,324,335] were included in this review.

- two RCTs and ten cohort studies detailing training and education programmes undertaken by healthcare workers that aimed to increase the knowledge, recognition and treatment of sepsis were included in the review. The findings were related to patients' outcomes and/or increase in knowledge of sepsis and/or compliance, or the use of sepsis protocols or an educational programme. One paper reported quantitative findings only from a mixed methods study
- one qualitative study and one survey which explored preferred ways of learning
- a systematic review which examined quantitative and qualitative evidence of nurses learning needs and effectiveness of education programmes.

The review included studies looking at different populations of health professionals and settings. Some studies examined particular groups such as doctors and nurses or students at different levels of seniority and assessed changes associated with specific methods of training. Some studies examined changes in knowledge and others examined changes in processes of care following education and training. One cohort study examined changes in mortality across six hospitals and another reported on a national campaign in Spain directed to intensive care settings. There was no consistency in education and training provided, interventions studied, how knowledge was assessed, which outcomes were measured or period of follow up. There was little evidence of any theoretical underpinnings for the methods included in the studies and few studies examined effect on systems of care which might be expected to be required to improve complex care.

No meaningful summary data or meta-analysis of quantitative data was possible and the GDG agreed that a mixed methods systematic review with synthesis of quantitative and qualitative findings was not possible. The GDG however considered it would be helpful to provide an integrated narrative report of the findings to inform discussion of education and training in recognition of sepsis.

The results of the review are presented in different ways:

- **Table 209** lists details of individual studies included in the review
- **Table 210** outlines findings from the studies Appendix L lists studies excluded from the review and the reasons for exclusion. (The studies sent by GDG members have also been added and highlighted in Appendix L)

16.4 Summary of included studies

Table 209: Summary of studies included in the review

Study	Population	Research aim	Type of training	Findings
RCTs				
Li 2012 [189]	n=98 medical postgraduates years 1-4. Emergency department in 4 hospitals in Asia (Taiwan,	To compare the effect of two education programs on sepsis.	First group: didactic lectures, then skills workshop and simulated case scenario. Second group:	The study reported significant differences in both groups in pre-test versus post-test for all postgraduate years (1-4). There was no difference between two groups.

Study	Population	Research aim	Type of training	Findings
	Singapore and India).		skills workshop and simulated case scenario, then didactic lectures.	
Muller 2012 [222]	n=61 final year medical students Completed by 59/61	To evaluate the effect of two different training interventions.	All groups received lecture on sepsis. 1 group received sepsis patient simulation (SIM group). 1 group received CRM lecture (not on sepsis), case study video presentation of a virtual sepsis case (CRM group).	The study found that participants in the SIM group had a significant difference between pre and post-test scores in the perception and anticipation components (p=0.01, p=0.07) but not in recognition (p=0.13). Participants in the CRM group had a significant difference between pre and post-test scores in recognition (p=0.06) but not in perception and anticipation (p=0.23, p=0.51). Participants in a control group (CG) had a significant difference between pre and post-test scores in recognition (p=0.015) but not in perception and anticipation (p=0.16, p=0.59).
Cohort				
Campbell 2008[46]	6 nurses 60 chart audits pre-test and 60 post-test. 16-bed ICU, USA	To determine the effect of nurse champions on compliance with Keystone: ICU Sepsis project screening and treatment (screening for sepsis at the time of admission to ICU and at regular intervals).	Information sessions. Championing of protocol by nurse champions.	Influence of nurse champions on staff nurse level of compliance with sepsis documentation: Pre-test charts: Full: 14; No: 32; Some: 14 Post-test charts: Full: 40; No: 8; Some: 5 There was a statistically significant (χ^2=30.86) difference in the pre-test/post-test compliance categories with documentation. Effect of nurse champions on physician initiation of sepsis protocol for patients with severe sepsis: no statistically significant difference (χ^2=0.563) in the pre-test/post-test initiation of sepsis protocol.
Capuzzo 2012[47]	Retrospective cohort study (discharge database) 4850 hospital	To assess the trend of the mortality rate of adults admitted to hospital for at	Lecture on sepsis. Scientific literature on	In comparison with the period before education (Dec 2003 to Oct 2007), the RR of death for the in-patients in the period Nov 2007 to Dec 2008

Study	Population	Research aim	Type of training	Findings
	beds; 164 ICU beds for adults. N. of hospital staff (physicians and nurses) = 9705 6 hospitals, Italy	least 1 night in relationship with a hospital staff education program on sepsis/septic shock.	sepsis. Electronic presentations for practice training. Scenarios of clinical cases for practice training. Booklets for practice training.	was 0.93 (0.87-0.99) and the RR for the in-patients in the period Jan-Aug 2009 was 0.89 (0.81-0.98). This study suggests that an educational programme specifically devoted to SS/SS according to the Surviving Sepsis Campaign was associated with a decrease in the hospital mortality of the patients admitted to the hospital wards/units responsible for most of the cumulative hospital mortality.
Cooper 2010 [73]	51 final year undergraduate nursing students	Processes used in a simulated environment to recognise and act on clinical cues of deterioration.	Two patient scenarios Video based reflective review and interviews	Reported a significant difference in undertaking correct observation for temperature (p=0.000 [0.57, 0.85]) and AVPU (p=0.004 [0.09, 0.42]). Reported a significant difference in undertaking correct action for Request/increase infusion rate (0.033 [-0.26, -0.01]). Sub-total for all cues was significant (p=0.000 [14.0, 24.0]).
Ferrer 2008 [101]	n=2593 patients in ICU (854 pre-intervention, 1465 post, 274 follow-up) 59 ICUs in Spain.	To investigate the effects a national education program, based on SSC, had on care and hospital mortality for severe sepsis.	Presentation on sepsis, including algorithm. SSC guideline posters. SSC pocket cards. Sepsis posters. Sepsis patient scenario.	Significant difference in pre and post intervention process –of-care measurements for; sepsis resuscitation bundle (p=<0.001), sepsis management bundle (p=<0.001), administration of low-dose steroids (p=<0.001), blood cultures obtained (p=0.03), antibiotics administered (p=0.003), mortality (hospital p=0.4, 28 day p=.009, ICU p=.03). Not significant for administration of drotrecogin alfa (activated), serum lactate measured, central venous pressure ≥8mmm HG achieved, central venous oxygen saturation ≥70% achieved, hospital stay, ICU stay.
MacRedmond 2010 [197]	86 emergency department (ED) nurses	Interventions of management protocol for recognition and initial treatment of	Lecture on sepsis. Algorithm. Championing of	The study reported that nurses significantly (p=0.002) improved in identification of septic patients (p=0.002). Early treatment including

Study	Population	Research aim	Type of training	Findings
		severe sepsis.	protocol by ED physicians.	time to antibiotics at follow-up (p=0.01), time to initiation of EGDT (p=0.004) and time to achievement of resuscitation goals (p=0.0006) were significant.
Mah 2009[199]	Cohort 74 clinicians Connecticut Simulation Center at Harford Hospital	Reinforce education of sepsis bundle through use of mannequin simulation in pre-existing teams	Sepsis patient simulation.	Participants scored significantly higher (p=<0.001) on post-test (after simulation and debriefing) then on pre-test.
Nguyen 2012[238]	Prospective observational cohort All patients at ED between 2003 and 2006 with severe sepsis or septic shock (96 included in analysis) Emergency department at 350 bed community-based teaching centre.	Utility and effectiveness of sepsis education program.	Lectures on sepsis. Educational/guideline reminders made available in ICU and in patient charts. Key physicians and nurses advocated and communicated information. Reinforced SSC guideline in daily rounds.	Control group v SSC group (P values) Appropriate initial fluid resuscitation: 0.03 Fluid resuscitation in the first 3 h of resuscitation: 0.006 Serial lactate measurements: 0.76 Blood cultures drawn before antibiotics: 0.22 Appropriate early antibiotics (within 1 h) : 0.45 Norepinephrine as initial vasopressor: 0.003 Inotropic agent (dobutamine): 0.53 Cortisol stimulation test:0.001 Corticosteroid use: 0.19 Drotrecogin alfa (Xigris) use: 0.93 Glucose control <150 mg/dl: 0.13 DVT chemoprophylaxis: 0.014 Stress ulcer prophylaxis:0.002 Limitation of support: 0.95 Days on MV: 0.3 ICU LOS: 0.6 Died: 0.006
Nguyen 2009[236]	Prospective cohort 63 medical students at all levels of training University based medical simulation centre	To increase knowledge of treatment for severe sepsis and septic shock through simulation based teaching at medical school.	Patient simulation. Didactic lecture on sepsis.	Reported significantly higher test scores post-test compared with pre-test in all participants.
Owen 2014 [252]	Prospective cohort 45 health	To explore the design, implementation,	First activity: Reflective and experiential	Reported no significant differences in pre and post test scores in first activity,

Study	Population	Research aim	Type of training	Findings
	professionals University of Virginia	and evaluation of continuing inter-professional development.	learning (reflecting on working in teams) Second activity: Role coding from SSC, videotape on roles of health professionals in SSC.	second activity had only 11 participants so no statistical analysis was performed.
Yousefi 2012 [335]	Quasi-experimental study. 64 ICU nurses (minimum 1 year experience). Shariati Hospital, Isfahan, Iran)	Effect on attitude, knowledge and practice of education program.	One day workshop on sepsis. Education pamphlets on sepsis.	Knowledge, attitude and practice reported as significantly higher in intervention group compared with control (p=<0.05).
Survey				
Jefferies 2011[151]	Survey n=92 clinicians Mount Sinai hospital, tertiary perinatal centre	The usage and preference for education tools by 92 clinicians.	Self-study module. Interactive seminars. Web-based algorithm. Written information on sepsis. Pocket card with a summary of recommendations.	The study reported no difference (p>0.05) in knowledge assessment immediately after the seminar and 3 months later. It was found that the use of pocket card distributed to staff was 76% (Nurses = 100%, Residents and fellows = 86%, 79% continued to use it after implementation period), the use of the seminars was 76%, only 1/92 participants used the web-tutorial and only 4/92 used the web-based algorithm. Compliance with recommendations post education was 83%.
Mixed methods systematic review				
Liaw 2011[190]	Literature review (2000-2010), 26 papers included Papers included that identified the educational needs of ward nurses or education programs for	Identifying educational needs and strategies for nurses who provide care to deteriorating patients.	Combinations of self-directed learning, didactic face-to-face, experiential learning, algorithm.	Educational programs identified analysed by 3 themes: Course content, teaching strategies and evaluation of learning outcomes. Study on ALERT programme found significantly higher score on knowledge of acute care following course . ALERT improved attitudes of staff,

Study	Population	Research aim	Type of training	Findings
	deteriorating patients.			confidence in recognising critically ill patients, improving mortality, improved recollection of procedures and going to senior staff for help but assessment of patient outcomes was not included. Study on MFS programme found mortality did not decrease and awareness did not increase. Study on COMPASS showed increase in vital sign monitoring, medical review prompted more in instable patients.
Qualitative				
Endacott 2010 [94]	51 final year undergraduate nursing students	Processes used in a simulated environment to recognise and act on clinical cues of deterioration.	Two patient scenarios Video based reflective review and interviews	Thematic analysis on Initial response, Differential recognition of cues, Accumulation of patient signs and Diversionary activities.

16.5 **Narrative findings**

2 **Table 210: Evidence profile: Themes**

No. of studies	Design	Sample	Educational intervention[a]	Themes[b]	Quality assessment[c]
Theme: Increase in knowledge: : Knowledge of sepsis and sepsis management is increased following different types of education and training					
4	RCT[222,189] Cohort[199,151,236,73,252,335] Systematic review[190] Qualitative [94]	122 medical students 166 clinicians Literature review including 26 studies	Lecture on sepsis. Patient simulation. Lecture (not on sepsis). Case study video presentation of a virtual sepsis case. Patient simulation. Video-based reflective review and interviews. Reflective and experiential learning (reflecting on working in teams) Role coding and videotape on roles of health professionals in SSC. Skills workshop.	Studies that assessed knowledge pre- and post-education were included in this theme. • Muller 2012[222] found that participants in the SIM group had a significant difference between pre- and post-test scores in the perception and anticipation components (p=0.01, p=0.07), but not in recognition (p=0.13). Participants in the CRM group had a significant difference between pre- and post-test scores in recognition (p=0.06) but not in perception and anticipation (p=0.23, p=0.51). Participants in the CG group had a significant difference between pre and post-test scores in recognition (p=0.015) but not in perception and anticipation (p=0.16, p=0.59). • Jefferies 2011[151] reported no difference (p>0.05) in knowledge assessment immediately after the seminar and 3 months later. • Mah 2009[199] found that participants scored significantly higher (p=<0.001) on post-test (after simulation and debriefing) then on pre-test. • Nguyen 2009[236] reported significantly higher test scores post-test compared with pre-test in all participants. • Cooper 2010[73] reported a significant difference in undertaking correct observation for temperature (p>0.0001 [0.57, 0.85]) and AVPU (p=0.004 [0.09, 0.42 and a significant difference in undertaking correct action for Request/increase infusion rate (p=0.033) (sub-total for all cues was significant [0.033 {-0.26, -0.01}]). • Owen 2014[252] reported no significant differences in pre and post test scores in first activity, second activity had only 11 participants so no	Low quality • Applicability: Population and setting in some studies not directly applicable (Medical, nursing student population/medical, nursing school setting) • Limitations/applicability: Literature review on critically ill patients not only sepsis patients and did not review studies for methodological bias

				statistical analysis was performed. • Li 2012[189] found no difference between two groups. There were significant differences in pre-test versus post-test for all postgraduate years (1-4). • Yousefi 2012[335] reported knowledge, attitude and practice reported as significantly higher in intervention group compared with control (p=<0.05). • Endacott 2010[94] performed a thematic analysis identifying a difference between pre and post intervention in Initial response, Differential recognition of cues, Accumulation of patient signs and Diversionary activities.	
Theme: Patient outcomes : Important process of care and patient outcomes may be improved by education and training					
4	Cohort[47,101,197,238] Systematic review[190]	412854 patients Literature review including 26 studies	Lecture on sepsis. Scientific literature. Electronic presentations, scenarios of clinical cases and booklets for practice training. Algorithm. Championing of protocol by key physicians and/or nurses. Educational/guide line reminders made available in ICU and in patient charts. Reinforced SSC guideline in daily	Studies that assessed patient outcomes pre- and post-education were included in this theme. • Capuzzo 2012[47] suggests that an educational programme specifically devoted to SS/SS according to the Surviving Sepsis Campaign was associated with a decrease in the hospital mortality of the patients admitted to the hospital wards/units responsible for most of the cumulative hospital mortality. • MacRedmond 2010[197] reported that nurses significantly (p=0.002) improved in identification of septic patients (p=0.002). Early treatment including time to antibiotics at follow-up (p=0.01), time to initiation of EGDT (p=0.004) and time to achievement of resuscitation goals (p=0.0006) were significant. • Nguyen 2012[238] reported a significant improvement in mortality post education (p=0.006) • Nguyen 2012[238] the study found a mixture of significant and non-significant improvements post education in the SSC recommendations. • Liaw 2011[190], a study ALERT improved staff confidence in recognising critically ill patients, improving mortality. A study on MFS programme found mortality did not decrease and awareness did not increase. A study on COMPASS showed increase in vital sign monitoring, medical	Low quality • Limitation: Populations poorly reported in some studies • Limitation/applicability: Literature review on critically ill patients not only sepsis patients and did not review studies for methodological bias Note: Sample sizes vary from small to very large samples sizes amongst studies

			rounds. Self-study module. Interactive seminars. Web-based algorithm. Written information on sepsis. Pocket card with a summary of recommendation.	review prompted more in instable patients. • Ferrer 2008 [101] reported a significant difference in administration of low-dose steroids (p=<0.001), blood cultures obtained (p=0.03), antibiotics administered (p=0.003), mortality (hospital p=0.4, 28 day p=0.009, ICU p=.03). Not significant for administration of drotrecogin alfa (activated), serum lactate measured, central venous pressure ≥8mmm HG achieved, central venous oxygen saturation ≥70% achieved, hospital stay, ICU stay.	
Theme: Compliance with protocols: There is mixed evidence for effect of education and training on adherence to protocols.					
2	Cohort[46,101] Survey[151]	6 nurse champions 92 clinicians	Information sessions. Championing of protocol by nurse champions. Presentation on sepsis, including algorithm. SSC guideline posters. SSC pocket cards. Sepsis posters.	Compliance and usage of educational materials and compliance to sepsis protocols or recommendations post-education were included in this theme. • Campbell 2008 [46] reported that the influence of nurse champions on staff nurse level of compliance with sepsis documentation and found a statistically significant (χ^2=30.86) difference in the pre-test/post-test compliance categories with documentation. However, the effect of nurse champions on physician initiation of sepsis protocol for patients with severe sepsis was not statistically significant (χ^2=0.563) in the pre-test/post-test initiation of sepsis protocol. • Jefferies 2011[151] Compliance with recommendations post education was 83%. • Jefferies 2011[151] found that the use of pocket card distributed to staff was 76% (Nurses = 100%, Residents and fellows = 86%, 79% continued to use it after implementation period), the use of the seminars was 76%, only 1/92 participants used the web-tutorial and only 4/92 used the web-based algorithm. • Ferrer 2008[101] reported a significant difference in pre and post intervention process –of-care measurements for; sepsis resuscitation	Very low quality • Limitation: Sample size small • Limitation: Survey completion optional

				bundle (p=<0.001), sepsis management bundle (p=<0.001).	

(a) Clarification: not all studies in theme included all types of educational interventions.

(b) Clarification: not all participants reported in the study sample contributed to the themes.

(c) Quality assessment included study limitations, indirectness (transferability) and other considerations.

16.6 **Economic evidence**

Published literature

One economic evaluation was identified with the relevant comparison and has been included in this review.[304] This is summarised in the economic evidence profile below (Table 193) and the economic evidence table in Appendix I.

See also the economic article selection flow chart in Appendix F.

Table 211: Economic evidence profile: Post education program versus pre education program

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Suarez 2011[304] ([Spain])	Partially applicable [(a)]	Potentially serious limitations [(b)]	A post education program cohort (4 months after program) was compared to a pre-education program cohort (2 months before program) in a severe sepsis cohort. Program consisted of a 2 month educational program of training physicians and nursing staff from the emergency department, medical, and surgical wards, and ICU in early recognition of severe sepsis and the treatments in the Surviving Sepsis Campaign (SSC) protocol. Unit costs applied to prospective study data up until patient discharge. Lifetime horizon for health outcomes. Multivariable regression models were used to adjust for baseline differences of costs, QALYs, and Life Years Gained.	£1,479 [(c)]	0.37	£5,476 per QALY gained [(d)]	Probabilistic analysis undertaken using non parametric bootstrapping with 2000 replications. Probability Intervention 2 cost-effective at £20K threshold was 94% (read off graph). One way sensitivity analyses: - Changing the rate for sepsis survivors. - Quality of life weight changed. - ICER calculated for different utility values. - Changing discount rate - Including the cost of the education and training program and cost of staff time spent attending the training. All sensitivity analyses generated results similar to that of the base case.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Interventions fit with the aim of the protocol. Uses EQ-5D. Not a UK study.

(b) Only includes short term costs. Data on effectiveness from a cohort study, not RCT. Base case did not include cost of the intervention itself. Methodology not always clear; particularly around where adjusted ICER comes from.

(c) The average cost of the control and intervention groups were converted to UK pounds (2006 Spanish Euros converted into GBP using the purchasing power parities [250]), and this is the incremental between those.

(d) This is the adjusted ICER from the paper converted to UK pounds. Not the incremental cost reported in the table divided by the incremental effect.

Unit costs

Costs that will be included in training staff include; the costs of the time of the staff involved in the training, the cost of resources involved in the developing the training program (which may be in an online form involving costs of setting up a website, or face to face teaching materials), the cost of the person providing the training or maintenance of the website if this is online.

The cost of staff that may be undertaking this training is provided in **Table 212** below to illustrate the opportunity cost of staff time. Costs will vary depending on the length of the training provided, which/how many healthcare workers are required to attend, and how frequently it is repeated.

Table 212: Typical costs of healthcare workers' time

Healthcare professional	Cost of time – 1 hour
GP	£134
Hospital nurse	£41
Junior doctor	£40
Registrar	£59

Source: PSSRU 2014 [76]

16.7 Evidence statements

Clinical

Fifteen studies examining different aspects of education and training for sepsis recognition and management suggest that

• knowledge of sepsis and sepsis management is increased following different types of education and training

•Important process of care and patient outcomes may be improved by education and training

•There is mixed evidence for effect of education and training on adherence to protocols.

Economic

- One cost utility analysis identified that in a population of patients with severe sepsis, the introduction of an educational program for staff was cost effective compared to before the educational program (ICER: £5,476).

16.8 Recommendations and link to evidence

Recommendations	**129. Ensure all healthcare staff and professionals are given regular appropriate training in sepsis recognition. This includes:** • **ambulance clinicians** • **allied health professionals** • **medical students and doctors of all grades** • **healthcare assistants**

	• **midwives** • **nurses** • **operating department assistants** • **receptionists in a clinical setting.** **130. Ensure all healthcare professionals are given regular appropriate training in identifying, assessing and managing sepsis. This should include:** • **risk stratification strategies** • **local protocols for early treatments, including antibiotics and fluids** • **criteria for escalation to critical care.**
Relative values of different outcomes	The most important outcomes are patient- oriented outcomes. The ideal study would be one which provides detail about educational and training programmes, and showed improved patient outcomes. No such studies were found. Other outcomes are knowledge and changed behaviour, such as improved processes of care.
Trade-off between clinical benefits and harms	The review indicated no evidence of harms and some evidence of benefits in terms of improved measures of care and of knowledge. A national study in Spain[101] indicated that using a variety of different measures to alert and train people to consider sepsis resulted in improved processes of care in intensive care settings. It is possible that if all professionals receive sepsis training, they may lose out on other training. Potential over-identification of sepsis could result in inappropriate prescribing of broad spectrum antibiotics.
Economic considerations	One economic evaluation was identified comparing a cohort after a 2 month education program with a cohort before the education program was introduced. The study found that an education program was likely to be cost effective. The program consisted of training physicians and nursing staff in early recognition of severe sepsis and the treatments in the Surviving Sepsis Campaign (SSC) protocol. The analysis was a within trial analysis based on a study included in the clinical review [101]. The study was rated as partially applicable; as the intervention fit the protocol and the health outcome was QALYs, but the study was from the Spanish healthcare perspective rather than UK NHS. The study was also rated as having potentially serious limitations as limitations include; it only included short term costs, and the base case did not include the cost of the intervention (education program) itself. The cost-effectiveness of training different healthcare professionals in sepsis identification would depend on the cost of providing the education, the time required to undertake training and the frequency at which training needs to be repeated, along with the frequency at which each professional is likely to encounter people with sepsis. For a standardised online training session the principal costs would be a one-off cost of developing the training package plus the cost of the time of those undertaking the training. If the prevalence of a condition is low but a lot of time is spent training staff, then the opportunity cost of training staff (in terms of the other work they could have

	been doing in that time) may outweigh the benefit that the training could provide. The actual prevalence of sepsis is unknown due to the underlying condition often being reported as the cause rather than the systemic condition itself. However there could be as high as over 100,000 admissions due to sepsis per year, with the mortality rate being relatively high (around 30%). It has been reported that there may be over 37,000 deaths from severe sepsis annually in the UK. The economic evaluation identified showed that educational programs are likely to be cost effective. Given the high risk of mortality of the population in question and that prevalence may be underestimated, the GDG decided that a recommendation outlining the importance of training would be appropriate.
Quality of evidence	Overall, the evidence is of low quality and covers a disparate range of educational activities and outcomes. The disparate nature of the evidence does not allow detailed conclusions about education and training to be made. Overall, however, the evidence does suggest that it is possible to increase knowledge and processes of care and the GDG considered the evidence was adequate to support general recommendations.
Other considerations	The aim of the review was to consider how to alert healthcare professionals to sepsis; to make people think 'could this be sepsis?' The GDG considered that all people working in healthcare setting should be given training in recognition of patients who may be unwell with sepsis. The receptionist in a GP surgery or a healthcare assistant should be given enough training to know when to alert nursing or medical staff in the same way as they would if a patient complained of chest pain. There is a also a need to alert people working in institutional settings, such as care homes and homes for people with learning disabilities. Many healthcare professionals now have to undergo mandatory training in areas such as basic life support and the GDG considered that sepsis could be included in such packages of training with minimal change to programmes. More specific training is training is required for example for nursing, paramedic and medical staff. The content of any educational programmes will vary according to the role of the healthcare professional and setting. Detailed training and simulation will be appropriate for people working for example in emergency departments and intensive care. The GDG recognised that education and training programmes are one part of a wider approach. Healthcare services may need to arrange services locally to have a coordinated approach to deliver appropriate care such as ensuring that antibiotics are given promptly and that senior health professional cover is available. The GDG was aware of how this has been achieved in other areas, such as stoke and chest pain services. There may be specific issues around protocol implementation and accessibility to senior staff that also affect care. The GDG considered there were a number of levers that may help raise the importance of education and training about sepsis. The GDG considered it should be included as part of existing mandatory training. It could potentially be incorporated into annual resuscitation training. The recent introduction of a CQUIN (Commissioning for Quality and Improvement) for sepsis will help improve care and the development of quality standards for sepsis following this guidance should set clear standards. The inclusion of sepsis in undergraduate curricula for all healthcare professionals would also raise awareness and might aid recognition of people who are at risk. Information for the public can help increase awareness and might result in people in the community seeking medical help more quickly. National campaigns have been run by charities in areas such as the recognition of chest pain and rash associated

	with meningococcal disease and these have been successful in raising awareness among the public.

1

2

17 Reference list

1 Aalto H, Takala A, Kautiainen H, Repo H. Laboratory markers of systemic inflammation as predictors of bloodstream infection in acutely ill patients admitted to hospital in medical emergency. European Journal of Clinical Microbiology and Infectious Diseases. 2004; 23(9):699-704

2 Adams NG. Diagnostic use of C-reactive protein in bacteraemic emergency department patients. Emergency Medicine Australasia. 2005; 17(4):371-375

3 Adamzik M, Gorlinger K, Peters J, Hartmann M. Whole blood impedance aggregometry as a biomarker for the diagnosis and prognosis of severe sepsis. Critical Care. 2012; 16(5)

4 Adeniji KA, Cusack R. The Simple Triage Scoring System (STSS) successfully predicts mortality and critical care resource utilization in H1N1 pandemic flu: A retrospective analysis. Critical Care. 2011; 15(1)

5 Ahn S, Lee YS, Chun YH, Lim KS, Kim W, Lee JL. Predictive factors of bacteraemia in low-risk patients with febrile neutropenia. Emergency Medicine Journal. 2012; 29(9):715-719

6 Akre M, Finkelstein M, Erickson M, Liu M, Vanderbilt L, Billman G. Sensitivity of the pediatric early warning score to identify patient deterioration. Pediatrics. 2010; 125(4):e763-e769

7 Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. American Journal of Obstetrics and Gynecology. 2014; 211(1):39-8

8 Ammann RA, Hirt A, Luthy AR, Aebi C. Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. Medical and Pediatric Oncology. 2003; 41(5):436-443

9 Ammann RA, Hirt A, Luthy AR, Aebi C. Predicting bacteremia in children with fever and chemotherapy-induced neutropenia. Pediatric Infectious Disease Journal. 2004; 23(1):61-67

10 Ammann RA, Hirt A, Luthy AR, Aebi C. Predicting bacteremia in children with fever and chemotherapy-induced neutropenia. Pediatric Infectious Disease Journal. 2004; 23(1):61-67

11 Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da DL. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatric Infectious Disease Journal. 2007; 26(8):672-677

12 Angel JD, Blasier RD, Allison R. Postoperative fever in pediatric orthopaedic patients. Journal of Pediatric Orthopedics. 1994; 14(6):799-801

13 Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Medicine. 2015;

14 Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet. 2007; 370(9588):676-684

15 Arendts G, Stone SF, Fatovich DM, van EP, MacDonald E, Brown SG. Critical illness in the emergency department: lessons learnt from the first 12 months of enrolments in the Critical Illness and Shock Study. Emergency Medicine Australasia : EMA. 2012; 24(1):31-36

16 Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009; 32(1):35-39

17 Aube H, Milan C, Blettery B. Risk factors for septic shock in the early management of bacteremia. American Journal of Medicine. 1992; 93(3):283-288

18 Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C et al. Comparison of dopamine and norepinephrine in the treatment of shock. New England Journal of Medicine. 2010; 362(9):779-789

19 Baez AA, Hanudel P, Wilcox SR. The Prehospital Sepsis Project: out-of-hospital physiologic predictors of sepsis outcomes. Prehospital and Disaster Medicine. 2013; 28(6):632-635

20 Baez YL, Rodriguez MAP, De Vicente Sanchez JC, Carretero PS, Martinez DAK, Ferrer AP et al. C-reactive protein in the diagnosis of postoperative infection in pediatric patients: A prospective observational study of 103 patients. Journal of Pediatric Surgery. 2011; 46(9):1726-1731

21 Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K et al. Early versus delayed administration of norepinephrine in patients with septic shock. Critical Care. 2014; 18(5)

22 Band RA, Gaieski DF, Hylton JH, Shofer FS, Goyal M, Meisel ZF. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. Academic Emergency Medicine. 2011; 18(9):934-940

23 Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. Thorax. 2007; 62(3):253-259

24 Bates DW, Cook EF, Goldman L, Lee TH. Predicting bacteremia in hospitalized patients. A prospectively validated model. Annals of Internal Medicine. 1990; 113(7):495-500

25 Beck V, Chateau D, Bryson GL, Pisipati A, Zanotti S, Parrillo JE et al. Timing of vasopressor initiation and mortality in septic shock: a cohort study. Critical Care. 2014; 18(3):R97

26 Bedside Clinical Guidelines Partnership and Partners in Paediatrics. Paediatric guidelines 2013-14. Bedside Clinical Guidelines Partnership and Partners in Paediatrics, 2013. Available from: http://www.networks.nhs.uk/nhs-networks/partners-in-paediatrics/guidelines

27 Bell K, Wattie M, Byth K, Silvestrini R, Clark P, Stachowski E et al. Procalcitonin: a marker of bacteraemia in SIRS. Anaesthesia and Intensive Care. 2003; 31(6):629-636

28 Benchekroune S, Karpati PCJ, Berton C, Nathan C, Mateo J, Chaara M et al. Diastolic arterial blood pressure: a reliable early predictor of survival in human septic shock. Journal of Trauma. 2008; 64(5):1188-1195

29 Bilavsky E, Yarden-Bilavsky H, Ashkenazi S, Amir J. C-reactive protein as a marker of serious bacterial infections in hospitalized febrile infants. Acta Paediatrica. 2009; 98(11):1776-1780

30 Biller K, Fae P, Germann R, Drexel H, Walli AK, Fraunberger P. Cholesterol rather than procalcitonin or C-reactive protein predicts mortality in patients with infection. Shock. 2014; 42(2):129-132

31 Bloos F, Thomas-Ruddel D, Ruddel H, Engel C, Schwarzkopf D, Marshall JC et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Critical Care. 2014; 18(2):R42

32 Bloos F, Reinhart K. Rapid diagnosis of sepsis. Virulence. 2014; 5(1):154-160

33 Bogar L, Molnar Z, Kenyeres P, Tarsoly P. Sedimentation characteristics of leucocytes can predict bacteraemia in critical care patients. Journal of Clinical Pathology. 2006; 59(5):523-525

34 Bohnen JM, Mustard RA, Oxholm SE, Schouten BD. APACHE II score and abdominal sepsis. A prospective study. Archives of Surgery. 1988; 123(2):225-229

35 Bohnen JM, Mustard RA, Schouten BD. Steroids, APACHE II score, and the outcome of abdominal infection. Archives of Surgery. 1994; 129(1):33-37

36 Bonadio WA, Smith DS, Sabnis S. The clinical characteristics and infectious outcomes of febrile infants aged 8 to 12 weeks. Clinical Pediatrics. 1994; 33(2):95-99

37 Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of heart and respiratory rate percentile curves for hospitalized children. Pediatrics. 2013; 131(4):e1150-e1157

38 Bonsu BK, Chb M, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Annals of Emergency Medicine. 2003; 42(2):216-225

39 Bonsu BK, Harper MB. A low peripheral blood white blood cell count in infants younger than 90 days increases the odds of acute bacterial meningitis relative to bacteremia. Academic Emergency Medicine. 2004; 11(12):1297-1301

40 Bonsu BK, Harper MB. Leukocyte counts in urine reflect the risk of concomitant sepsis in bacteriuric infants: a retrospective cohort study. BMC Pediatrics. 2007; 7:24

41 Boulain T, Garot D, Vignon P, Lascarrou JB, Desachy A, Botoc V et al. Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. Critical Care. 2014; 18(6):609

42 Brent AJ, Lakhanpaul M, Thompson M, Collier J, Ray S, Ninis N et al. Risk score to stratify children with suspected serious bacterial infection: observational cohort study. Archives of Disease in Childhood. 2011; 96(4):361-367

43 Brent AJ, Lakhanpaul M, Ninis N, Levin M, MacFaul R, Thompson M. Evaluation of temperature-pulse centile charts in identifying serious bacterial illness: observational cohort study. Archives of Disease in Childhood. 2011; 96(4):368-373

44 Bressan S, Andreola B, Cattelan F, Zangardi T, Perilongo G, Da DL. Predicting severe bacterial infections in well-appearing febrile neonates: Laboratory markers accuracy and duration of fever. Pediatric Infectious Disease Journal. 2010; 29(3):227-232

45 Buck DL, Vester-Andersen M, Moller MH. Accuracy of clinical prediction rules in peptic ulcer perforation: An observational study. Scandinavian Journal of Gastroenterology. 2012; 47(1):28-35

46 Campbell J. The effect of nurse champions on compliance with Keystone Intensive Care Unit Sepsis-screening protocol. Critical Care Nursing Quarterly. 2008; 31(3):251-269

47 Capuzzo M, Rambaldi M, Pinelli G, Campesato M, Pigna A, Zanello M et al. Hospital staff education on severe sepsis/septic shock and hospital mortality: an original hypothesis. BMC Anesthesiology. 2012; 12:28

48 Carbonell N, Blasco M, Ferreres J, Blanquer J, Garcia-Ramon R, Mesejo A et al. Sepsis and SOFA score: related outcome for critically ill renal patients. Clinical Nephrology. 2004; 62(3):185-192

49 Cartwright K, Reilly S, White D, Stuart J. Early treatment with parenteral penicillin in meningococcal disease. BMJ. 1992; 305(6846):143-147

50 Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Critical Care Medicine. 2015; 43(3):567-573

51 Castellanos-Ortega A, Delgado-Rodriguez M, Llorca J, Sanchez Buron P, Mencia Bartolome S, Soult Rubio A et al. A new prognostic scoring system for meningococcal septic shock in children. Comparison with three other scoring systems. Intensive Care Medicine. 2002; 28(3):341-351

52 Castelli GP, Pognani C, Cita M, Stuani A, Sgarbi L, Paladini R. Procalcitonin, C-reactive protein, white blood cells and SOFA score in ICU: Diagnosis and monitoring of sepsis. Minerva Anestesiologica. 2006; 72(1-2):69-80

53 Castelli GP, Pognani C, Cita M, Paladini R. Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. Critical Care Medicine. 2009; 37(6):1845-1849

54 Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Critical Care. 2004; 8(4):R234-R242

55 Caterino JM, Kulchycki LK, Fischer CM, Wolfe RE, Shapiro NI. Risk factors for death in elderly emergency department patients with suspected infection: Clinical investigations. Journal of the American Geriatrics Society. 2009; 57(7):1184-1190

56 Caterino JM, Scheatzle MD, Forbes ML, D'Antonio JA. Bacteremic elder emergency department patients: procalcitonin and white count. Academic Emergency Medicine. 2004; 11(4):393-396

57 Cavallazzi R, Bennin CL, Hirani A, Gilbert C, Marik PE. Is the band count useful in the diagnosis of infection? An accuracy study in critically ill patients. Journal of Intensive Care Medicine. 2010; 25(6):353-357

58 Chase M, Klasco RS, Joyce NR, Donnino MW, Wolfe RE, Shapiro NI. Predictors of bacteremia in emergency department patients with suspected infection. American Journal of Emergency Medicine. 2012; 30(9):1691-1697

59 Chassagne P, Perol MB, Doucet J, Trivalle C, Menard JF, Manchon ND et al. Is presentation of bacteremia in the elderly the same as in younger patients? American Journal of Medicine. 1996; 100(1):65-70

60 Chen CC, Chong CF, Liu YL, Chen KC, Wang TL. Risk stratification of severe sepsis patients in the emergency department. Emergency Medicine Journal. 2006; 23(4):281-285

61 Chen FG, Koh KF. Septic shock in a surgical intensive care--validation of multiorgan and APACHE II scores in predicting outcome. Annals of the Academy of Medicine, Singapore. 1994; 23(4):447-451

62 Chen M, Wang B, Xu Y, Deng Z, Xue H, Wang L et al. Diagnostic value of serum leptin and a promising novel diagnostic model for sepsis. Experimental and Therapeutic Medicine. 2014; 7(4):881-886

63 Chen R, Yan ZQ, Feng D, Luo YP, Wang LL, Shen DX. Nosocomial bloodstream infection in patients caused by Staphylococcus aureus: drug susceptibility, outcome, and risk factors for hospital mortality. Chinese Medical Journal. 2012; 125(2):226-229

64 Chen WL, Chen JH, Huang CC, Kuo CD, Huang CI, Lee LS. Heart rate variability measures as predictors of in-hospital mortality in ED patients with sepsis. American Journal of Emergency Medicine. 2008; 26(4):395-401

65 Chen Y, Li C. Prognostic significance of brain natriuretic peptide obtained in the ED in patients with SIRS or sepsis. American Journal of Emergency Medicine. 2009; 27(6):701-706

66 Chen Y-X, Li C-S. Prognostic value of adrenomedullin in septic patients in the ED. American Journal of Emergency Medicine. 2013; 31(7):1017-1021

67 Chen YX, Li CS. Evaluation of community-acquired sepsis by PIRO system in the emergency department. Internal and Emergency Medicine. 2013; 8(6):521-527

68 Chen YX, Li CS. Risk stratification and prognostic performance of the predisposition, infection, response, and organ dysfunction (PIRO) scoring system in septic patients in the emergency department: a cohort study. Critical Care. 2014; 18(2):R74

69 Cheval C, Timsit JF, Garrouste-Org, Assicot M, De Jonghe B, Misset B et al. Procalcitonin (PCT) is useful in predicting the bacterial origin of an acute circulatory failure in critically ill patients. Intensive Care Medicine. 2000; 26 Suppl 2:S153-S158

70 Cildir E, Bulut M, Akalin H, Kocabas E, Ocakoglu G, Aydin SA. Evaluation of the modified MEDS, MEWS score and Charlson comorbidity index in patients with community acquired sepsis in the emergency department. Internal and Emergency Medicine. 2013; 8(3):255-260

71 Clark LJ, Glennie L, Audrey S, Hickman M, Trotter CL. The health, social and educational needs of children who have survived meningitis and septicaemia: the parents' perspective. BMC Public Health. 2013; 13:954

72 Cooke MW, Jinks S. Does the Manchester triage system detect the critically ill? Journal of Accident and Emergency Medicine. 1999; 16(3):179-181

73 Cooper S, Kinsman L, Buykx P, McConnell-Henry T, Endacott R, Scholes J. Managing the deteriorating patient in a simulated environment: nursing students' knowledge, skill and situation awareness. Journal of Clinical Nursing. 2010; 19(15-16):2309-2318

74 Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K et al. Utility of a single early warning score in patients with sepsis in the emergency department. Emergency Medicine Journal. 2014; 31(6):482-487

75 Crowe CA, Kulstad EB, Mistry CD, Kulstad CE. Comparison of severity of illness scoring systems in the prediction of hospital mortality in severe sepsis and septic shock. Journal of Emergencies, Trauma, and Shock. 2010; 3(4):342-347

76 Curtis L. Unit costs of health and social care 2014. 2014. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2014/

77 Dahaba AA, Hagara B, Fall A, Rehak PH, List WF, Metzler H. Procalcitonin for early prediction of survival outcome in postoperative critically ill patients with severe sepsis. British Journal of Anaesthesia. 2006; 97(4):503-508

78 Davis J, Christie S, Fairley D, Coyle P, Tubman R, Shields MD. Performance of a Novel Molecular Method in the Diagnosis of Late-Onset Sepsis in Very Low Birth Weight Infants. PloS One. 2015; 10(8):e0136472

79 de Groot B, Ansems A, Gerling DH, Rijpsma D, van AP, Linzel D et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Critical Care (London, England). 2015; 19:194

80 de Groot B, de Deckere ERJT, Flameling R, Sandel MH, Vis A. Performance of illness severity scores to guide disposition of emergency department patients with severe sepsis or septic shock. European Journal of Emergency Medicine. 2012; 19(5):316-322

81 de Jager CPC, van Wijk PTL, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Critical Care. 2010; 14(5):R192

82 de Kruif MD, Limper M, Gerritsen H, Spek CA, Brandjes DPM, ten Cate H et al. Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. Critical Care Medicine. 2010; 38(2):457-463

83 De A, Saraswathi K, Gogate A, Raghavan K. C-reactive protein and buffy coat smear in early diagnosis of childhood septicemia. Indian Journal of Pathology and Microbiology. 1998; 41(1):23-26

84 De S, Tong A, Isaacs D, Craig JC. Parental perspectives on evaluation and management of fever in young infants: an interview study. Archives of Disease in Childhood. 2014; 99(8):717-723

85 De S, Williams GJ, Hayen A, Macaskill P, McCaskill M, Isaacs D et al. Value of white cell count in predicting serious bacterial infection in febrile children under 5 years of age. Archives of Disease in Childhood. 2014; 99(6):493-499

86 Dettmer M, Holthaus CV, Fuller BM. The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: an observational cohort study. Shock. 2015; 43(1):55-61

87 Deulofeu F, Cervello B, Capell S, Marti C, Mercade V. Predictors of mortality in patients with bacteremia: the importance of functional status. Journal of the American Geriatrics Society. 1998; 46(1):14-18

88 Dolecek M, Svoboda P, Kantorova I, Scheer P, Sas I, Bibrova J et al. Therapeutic influence of 20 % albumin versus 6% hydroxyethylstarch on extravascular lung water in septic patients: a randomized controlled trial. Hepato-Gastroenterology. 2009; 56(96):1622-1628

89 Duke TD, Butt W, South M. Predictors of mortality and multiple organ failure in children with sepsis. Intensive Care Medicine. 1997; 23(6):684-692

90 Dunser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S et al. Arterial blood pressure during early sepsis and outcome. Intensive Care Medicine. 2009; 35(7):1225-1233

91 Edgar JDM, Gabriel V, Gallimore JR, McMillan SA, Grant J. A prospective study of the sensitivity, specificity and diagnostic performance of soluble intercellular adhesion molecule 1, highly sensitive C-reactive protein, soluble E-selectin and serum amyloid A in the diagnosis of neonatal infection. BMC Pediatrics. 2010; 10

92 Edwards SE, Grobman WA, Lappen JR, Winter C, Fox R, Lenguerrand E et al. Modified obstetric early warning scoring systems (MOEWS): validating the diagnostic performance for severe sepsis in women with chorioamnionitis. American Journal of Obstetrics and Gynecology. 2015; 212(4):536-538

93 El-Solh AA, Abou Jaoude P, Porhomayon J. Bicarbonate therapy in the treatment of septic shock: a second look. Internal and Emergency Medicine. 2010; 5(4):341-347

94 Endacott R, Scholes J, Buykx P, Cooper S, Kinsman L, McConnell-Henry T. Final-year nursing students' ability to assess, detect and act on clinical cues of deterioration in a simulated environment. Journal of Advanced Nursing. 2010; 66(12):2722-2731

95 Enguix A, Rey C, Concha A, Medina A, Coto D, Dieguez MA. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. Intensive Care Medicine. 2001; 27(1):211-215

96 Falguera M, Trujillano J, Caro S, Menendez R, Carratala J, Ruiz-Gonzalez A et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. Clinical Infectious Diseases. 2009; 49(3):409-416

97 Femling J, Weiss S, Hauswald E, Tarby D. EMS patients and walk-in patients presenting with severe sepsis: differences in management and outcome. Southern Medical Journal. 2014; 107(12):751-756

98 Fernandez Lopez A, Luaces Cubells C, Garcia Garcia JJ, Fernandez Pou J, Spanish Society of Pediatric Emergencies. Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. Pediatric Infectious Disease Journal. 2003; 22(10):895-903

99 Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. American Journal of Respiratory and Critical Care Medicine. 2009; 180(9):861-866

100 Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Critical Care Medicine. 2014; 42(8):1749-1755

101 Ferrer R, Artigas A, Levy MM, Blanco J, Gonzalez-Diaz G, Garnacho-Montero J et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA. 2008; 299(19):2294-2303

102 Fischer JE, Brunner A, Janousek M, Nadal D, Blau N, Fanconi S. Diagnostic potential of neutrophil elastase inhibitor complex in the routine care of critically ill newborn infants. European Journal of Pediatrics. 2000; 159(9):659-662

103 Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet (London, England). 2011; 377(9770):1011-1018

104 Fontanarosa PB, Kaeberlein FJ, Gerson LW, Thomson RB. Difficulty in predicting bacteremia in elderly emergency patients. Annals of Emergency Medicine. 1992; 21(7):842-848

105 Fouzas S, Mantagou L, Skylogianni E, Varvarigou A. Reactive thrombocytosis in febrile young infants with serious bacterial infection. Indian Pediatrics. 2010; 47(11):937-943

106 Freund Y, Delerme S, Goulet H, Bernard M, Riou B, Hausfater P. Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. Biomarkers. 2012; 17(7):590-596

107 Freyne B, Divilley R, Kissoon-Harrison G, O'Neill MB. Field testing the utility of procalcitonin and the acute infantile observation score in febrile infants 6 to 36 months old presenting to the pediatric emergency department with no obvious focus of infection. Clinical Pediatrics. 2013; 52(6):503-506

108 Fuller BM, Gajera M, Schorr C, Gerber D, Dellinger RP, Parrillo J et al. The impact of packed red blood cell transfusion on clinical outcomes in patients with septic shock treated with early goal directed therapy. Indian Journal of Critical Care Medicine. 2010; 14(4):165-169

109 Fusco NM, Parbuoni KA, Morgan JA. Time to first antimicrobial administration after onset of sepsis in critically ill children. Journal of Pediatric Pharmacology and Therapeutics. 2015; 20(1):37-44

110 Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Critical Care Medicine. 2010; 38(4):1045-1053

111 Gaini S, Koldkjaer OG, Pedersen C, Pedersen SS. Procalcitonin, lipopolysaccharide-binding protein, interleukin-6 and C-reactive protein in community-acquired infections and sepsis: A prospective study. Critical Care. 2006; 10(2)

112 Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics. 2003; 112(5):1054-1060

113 Gallop KH, Kerr CE, Nixon A, Verdian L, Barney JB, Beale RJ. A qualitative investigation of patients' and caregivers' experiences of severe sepsis. Critical Care Medicine. 2015; 43(2):296-307

114 Gando S, Hayakawa M, Sawamura A, Hoshino H, Oshiro A, Kubota N et al. The activation of neutrophil elastase-mediated fibrinolysis is not sufficient to overcome the fibrinolytic

shutdown of disseminated intravascular coagulation associated with systemic inflammation. Thrombosis Research. 2007; 121(1):67-73

115 Gando S, Saitoh D, Ogura H, Fujishima S, Mayumi T, Araki T et al. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. Critical Care. 2013; 17(3):R111

116 Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T et al. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: Results of a multicenter, prospective survey. Critical Care Medicine. 2008; 36(1):145-150

117 Gando S, Sawamura A, Hayakawa M, Hoshino H, Kubota N, Nishihira J. High macrophage migration inhibitory factor levels in disseminated intravascular coagulation patients with systemic inflammation. Inflammation. 2007; 30(3-4):118-124

118 Gardner-Thorpe J, Love N, Wrightson J, Walsh S, Keeling N. The value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. Annals of the Royal College of Surgeons of England. 2006; 88(6):571-575

119 Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, Cayuela A, Jimenez R, Barroso S et al. Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. Critical Care. 2006; 10(4):R111

120 Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, Lepe-Jimenez JA, Iraurgi-Arcarazo P, Jimenez-Alvarez R et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. Scandinavian Journal of Infectious Diseases. 2010; 42(3):185-192

121 Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guerin S et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. Pediatric Infectious Disease Journal. 1999; 18(10):875-881

122 Geppert A, Steiner A, Delle-Karth G, Heinz G, Huber K. Usefulness of procalcitonin for diagnosing complicating sepsis in patients with cardiogenic shock. Intensive Care Medicine. 2003; 29(8):1384-1389

123 Giannazzo G, Tola F, Vanni S, Bondi E, Pepe G, Grifoni S. Prognostic indexes of septic syndrome in the emergency department. Internal and Emergency Medicine. 2006; 1(3):229-233

124 Gille-Johnson P, Hansson KE, Gardlund B. Clinical and laboratory variables identifying bacterial infection and bacteraemia in the emergency department. Scandinavian Journal of Infectious Diseases. 2012; 44(10):745-752

125 Glickman SW, Cairns CB, Otero RM, Woods CW, Tsalik EL, Langley RJ et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. Academic Emergency Medicine. 2010; 17(4):383-390

126 Gomez B, Bressan S, Mintegi S, Da Dalt L, Blazquez D, Olaciregui I et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. Pediatrics. 2012; 130(5):815-822

127 Gomez B, Mintegi S, Benito J, Egireun A, Garcia D, Astobiza E. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. Pediatric Infectious Disease Journal. 2010; 29(1):43-47

128 Green JP, Berger T, Garg N, Shapiro NI. Serum lactate is a better predictor of short-term mortality when stratified by C-reactive protein in adult emergency department patients hospitalized for a suspected infection. Annals of Emergency Medicine. 2011; 57(3):291-295

129 Guidet B, Mosqueda GJ, Priol G, Aegerter P. The COASST study: cost-effectiveness of albumin in severe sepsis and septic shock. Journal of Critical Care. France 2007; 22(3):197-203

130 Ha YE, Kang CI, Joo EJ, Joung MK, Chung DR, Peck KR et al. Usefulness of C-reactive protein for evaluating clinical outcomes in cirrhotic patients with bacteremia. Korean Journal of Internal Medicine. 2011; 26(2):195-200

131 Ha YE, Song JH, Kang WK, Peck KR, Chung DR, Kang CI et al. Clinical factors predicting bacteremia in low-risk febrile neutropenia after anti-cancer chemotherapy. Supportive Care in Cancer. 2011; 19(11):1761-1767

132 Hambach L, Eder M, Dammann E, Schrauder A, Sykora KW, Dieterich C et al. Diagnostic value of procalcitonin serum levels in comparison with C-reactive protein in allogeneic stem cell transplantation. Haematologica. 2002; 87(6):643-651

133 Hamilton KW, Bilker WB, Lautenbach E. Controlling for severity of illness in assessment of the association between antimicrobial-resistant infection and mortality: impact of calculation of Acute Physiology and Chronic Health Evaluation (APACHE) II scores at different time points. Infection Control and Hospital Epidemiology : the Official Journal of the Society of Hospital Epidemiologists of America. 2007; 28(7):832-836

134 Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. Archives of Disease in Childhood. 1999; 81(5):417-421

135 Hermans MAW, Leffers P, Jansen LM, Keulemans YC, Stassen PM. The value of the Mortality in Emergency Department Sepsis (MEDS) score, C reactive protein and lactate in predicting 28-day mortality of sepsis in a Dutch emergency department. Emergency Medicine Journal. 2012; 29(4):295-300

136 Hilderink MJM, Roest AA, Hermans M, Keulemans YC, Stehouwer CDA, Stassen PM. Predictive accuracy and feasibility of risk stratification scores for 28-day mortality of patients with sepsis in an emergency department. European Journal of Emergency Medicine. 2015; 22(5):331-337

137 Hillas G, Vassilakopoulos T, Plantza P, Rasidakis A, Bakakos P. C-reactive protein and procalcitonin as predictors of survival and septic shock in ventilator-associated pneumonia. European Respiratory Journal. 2010; 35(4):805-811

138 Hjortrup PB, Haase N, Treschow F, Moller MH, Perner A. Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. Acta Anaesthesiologica Scandinavica. 2015; 59(1):25-34

139 Hoeboer SH, Alberts E, van den Hul I, Tacx AN, Debets-Ossenkopp YJ, Groeneveld ABJ. Old and new biomarkers for predicting high and low risk microbial infection in critically ill patients with new onset fever: a case for procalcitonin. Journal of Infection. 2012; 64(5):484-493

140 Hofer N, Muller W, Resch B. Neonates presenting with temperature symptoms: role in the diagnosis of early onset sepsis. Pediatrics International. 2012; 54(4):486-490

141 Hofer N, Zacharias E, Muller W, Resch B. Performance of the definitions of the systemic inflammatory response syndrome and sepsis in neonates. Journal of Perinatal Medicine. 2012; 0(0):1-4

142 Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. New England Journal of Medicine. 2014; 371:1381-1391

143 Hornik CP, Benjamin DK, Becker KC, Benjamin DKJ, Li J, Clark RH et al. Use of the complete blood cell count in late-onset neonatal sepsis. Pediatric Infectious Disease Journal. 2012; 31(8):803-807

144 Howell MD, Donnino MW, Talmor D, Clardy P, Ngo L, Shapiro NI. Performance of severity of illness scoring systems in emergency department patients with infection. Academic Emergency Medicine. 2007; 14(8):709-714

145 Hsiao AL, Chen L, Baker MD. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. Pediatrics. 2006; 117(5):1695-1701

146 Isaacman DJ, Burke BL. Utility of the serum C-reactive protein for detection of occult bacterial infection in children. Archives of Pediatrics and Adolescent Medicine. 2002; 156(9):905-909

147 Jacquot A, Labaune J-M, Baum T-P, Putet G, Picaud J-C. Rapid quantitative procalcitonin measurement to diagnose nosocomial infections in newborn infants. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2009; 94(5):F345-F348

148 Jalili M, Barzegari H, Pourtabatabaei N, Honarmand AR, Boreiri M, Mehrvarz A et al. Effect of door-to-antibiotic time on mortality of patients with sepsis in emergency department: a prospective cohort study. Acta Medica Iranica. 2013; 51(7):454-460

149 Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. Critical Care Medicine. 2009; 37(10):2827-2839

150 Jansen TC, van Bommel J, Mulder PG, Lima AP, van der Hoven B, Rommes JH et al. Prognostic value of blood lactate levels: does the clinical diagnosis at admission matter? Journal of Trauma. 2009; 66(2):377-385

151 Jefferies A, Shah V. Clinicians prefer simple educational tools for implementing practice change. Medical Teacher. 2011; 33(11):e602-e606

152 Jekarl DW, Lee SY, Lee J, Park YJ, Kim Y, Park JH et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. Diagnostic Microbiology and Infectious Disease. 2013; 75(4):342-347

153 Jo S, Lee JB, Jin YH, Jeong TO, Yoon JC, Jun YK et al. Modified early warning score with rapid lactate level in critically ill medical patients: the ViEWS-L score. Emergency Medicine Journal. 2013; 30(2):123-129

154 Johnston JA. Determinants of mortality in patients with Severe Sepsis. Medical Decision Making. 2005; 25(4):374-386

155 Joint Formulary Committee. British National Formulary (BNF). 66th edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2013. Available from: http://www.bnf.org.uk

156 Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010; 303(8):739-746

157 Jones AE, Saak K, Kline JA. Performance of the Mortality in Emergency Department Sepsis score for predicting hospital mortality among patients with severe sepsis and septic shock. American Journal of Emergency Medicine. 2008; 26(6):689-692

158 Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010; 303(8):739-746

159 Karvellas CJ, Abraldes JG, Arabi YM, Kumar A, Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Appropriate and timely antimicrobial therapy in cirrhotic patients with spontaneous bacterial peritonitis-associated septic shock: a retrospective cohort study. Alimentary Pharmacology and Therapeutics. 2015; 41(8):747-757

160 Kellett J, Murray A, Woodworth S, Huang W. Trends in weighted vital signs and the clinical course of 44,531 acutely ill medical patients while in hospital. Acute Medicine. 2015; 14(1):3-9

161 Kellett J, Woodworth S, Wang F, Huang W. Changes and their prognostic implications in the abbreviated Vitalpac early warning score (ViEWS) after admission to hospital of 18,853 acutely ill medical patients. Resuscitation. 2013; 84(1):13-20

162 Kellett J, Wang F, Woodworth S, Huang W. Changes and their prognostic implications in the abbreviated VitalPACTM Early Warning Score (ViEWS) after admission to hospital of 18,827 surgical patients. Resuscitation. 2013; 84(4):471-476

163 Kim CS, Kristopaitis RJ, Stone E, Pelter M, Sandhu M, Weingarten SR. Physician education and report cards: Do they make the grade? Results from a randomized controlled trial. American Journal of Medicine. 1999; 107(6):556-560

164 Kim DY, Lee YS, Ahn S, Chun YH, Lim KS. The usefulness of procalcitonin and C-reactive protein as early diagnostic markers of bacteremia in cancer patients with febrile neutropenia. Cancer Research and Treatment. 2011; 43(3):176-180

165 Kim H, Kim Y, Lee HK, Kim KH, Yeo CD. Comparison of the delta neutrophil index with procalcitonin and C-reactive protein in sepsis. Clinical Laboratory. 2014; 60(12):2015-2021

166 Kim JY, Yoon J, Lim CS, Choi BM, Yoon S-Y. Clinical significance of platelet-associated hematological parameters as an early supplementary diagnostic tool for sepsis in thrombocytopenic very-low-birth-weight infants. Platelets. 2015; 26(7):620-626

167 Kim MH, Ahn JY, Song JE, Choi H, Ann HW, Kim JK et al. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. PloS One. 2015; 10(7)

168 Kim YA, Ha EJ, Jhang WK, Park SJ. Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Medicine. 2013; 39(10):1818-1823

169 Koch C, Rohrig R, Monz T, Hecker A, Uhle F, Schneck E et al. Prospective evaluation of regional oxygen saturation to estimate central venous saturation in sepsis. Journal of Clinical Monitoring and Computing. 2015; 29(4):443-453

170 Kofoed K, Eugen-Olsen J, Petersen J, Larsen K, Andersen O. Predicting mortality in patients with systemic inflammatory response syndrome: an evaluation of two prognostic models, two soluble receptors, and a macrophage migration inhibitory factor. European Journal of Clinical Microbiology and Infectious Diseases : Official Publication of the European Society of Clinical Microbiology. 2008; 27(5):375-383

171 Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J et al. Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study. Critical Care. 2007; 11(2):R38

172 Komatsu S, Shimomatsuya T, Nakajima M, Ono S, Maruhashi K. Severity scoring systems for prognosis and efficacy of polymyxin B-immobilized fiber treatment for colonic perforation. Surgery Today. 2006; 36(9):807-810

173 Kreuzer E, Kaab S, Pilz G, Werdan K. Early prediction of septic complications after cardiac surgery by APACHE II score. European Journal of Cardio-Thoracic Surgery. 1992; 6(10):524-529

174 Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical Care Medicine. 2006; 34(6):1589-1596

175 Kumar PS, Rao CS. Prognosis in intra-abdominal sepsis. Indian Journal of Gastroenterology. 1995; 14(1):8-10

176 Kuppermann N, Fleisher GR, Jaffe DM. Predictors of occult pneumococcal bacteremia in young febrile children. Annals of Emergency Medicine. 1998; 31(6):679-687

177 Kushimoto S, Gando S, Saitoh D, Mayumi T, Ogura H, Fujishima S et al. The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. Critical Care. 2013; 17(6):R271

178 Lacour AG, Gervaix A, Zamora SA, Vadas L, Lombard PR, Dayer JM et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. European Journal of Pediatrics. 2001; 160(2):95-100

179 Larche J, Azoulay E, Fieux F, Mesnard L, Moreau D, Thiery G et al. Improved survival of critically ill cancer patients with septic shock. Intensive Care Medicine. 2003; 29(10):1688-1695

180 Lauzier F, LéVy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Medicine. 2006; 32(11):1782-1789

181 Lavrentieva A, Kontakiotis T, Lazaridis L, Tsotsolis N, Koumis J, Kyriazis G et al. Inflammatory markers in patients with severe burn injury. What is the best indicator of sepsis? Burns. 2007; 33(2):189-194

182 Lee CC, Wu CJ, Chi CH, Lee NY, Chen PL, Lee HC et al. Prediction of community-onset bacteremia among febrile adults visiting an emergency department: rigor matters. Diagnostic Microbiology and Infectious Disease. 2012; 73(2):168-173

183 Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post-Haemophilus influenzae type b era. Archives of Pediatrics and Adolescent Medicine. 1998; 152(7):624-628

184 Leedahl DD, Frazee EN, Schramm GE, Dierkhising RA, Bergstralh EJ, Chawla LS et al. Derivation of urine output thresholds that identify a very high risk of AKI in patients with septic shock. Clinical Journal of the American Society of Nephrology. 2014; 9(7):1168-1174

185 Leibovici L, Gafter-Gvili A, Paul M, Almanasreh N, Tacconelli E, Andreassen S et al. Relative tachycardia in patients with sepsis: an independent risk factor for mortality. QJM. 2007; 100(10):629-634

186 Leth RA, Forman BE, Kristensen B. Predicting bloodstream infection via systemic inflammatory response syndrome or biochemistry. Journal of Emergency Medicine. 2013; 44(2):550-557

187 Levison MA, Zeigler D. Correlation of APACHE II score, drainage technique and outcome in postoperative intra-abdominal abscess. Surgery, Gynecology and Obstetrics. 1991; 172(2):89-94

188 Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Medicine. 1997; 23(3):282-287

189 Li CH, Kuan WS, Mahadevan M, Daniel-Underwood L, Chiu TF, Nguyen HB et al. A multinational randomised study comparing didactic lectures with case scenario in a severe sepsis medical simulation course. Emergency Medicine Journal. 2012; 29(7):559-564

190 Liaw SY, Scherpbier A, Klainin-Yobas P, Rethans JJ. A review of educational strategies to improve nurses' roles in recognizing and responding to deteriorating patients. International Nursing Review. 2011; 58(3):296-303

191 Linder A, Christensson B, Herwald H, Bjorck L, Akesson P. Heparin-binding protein: an early marker of circulatory failure in sepsis. Clinical Infectious Diseases. 2009; 49(7):1044-1050

192 Lindvig KP, Henriksen DP, Nielsen SL, Jensen TG, Kolmos HJ, Pedersen C et al. How do bacteraemic patients present to the emergency department and what is the diagnostic validity of the clinical parameters; temperature, C-reactive protein and systemic inflammatory response syndrome? Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2014; 22:39

193 Lorente L, Martin MM, Labarta L, Diaz C, Sole-Violan J, Blanquer J et al. Matrix metalloproteinase-9, -10, and tissue inhibitor of matrix metalloproteinases-1 blood levels as biomarkers of severity and mortality in sepsis. Critical Care. 2009; 13(5):R158

194 Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. Interdisciplinary Perspectives on Infectious Diseases. 2012; 2012:765205

195 Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. Critical Care Medicine. 2003; 31(6):1737-1741

196 Macdonald SPJ, Arendts G, Fatovich DM, Brown SGA. Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock. Academic Emergency Medicine. 2014; 21(11):1257-1263

197 MacRedmond R, Hollohan K, Stenstrom R, Nebre R, Jaswal D, Dodek P. Introduction of a comprehensive management protocol for severe sepsis is associated with sustained improvements in timeliness of care and survival. Quality and Safety in Health Care. 2010; 19(5):e46

198 Magrini L, Gagliano G, Travaglino F, Vetrone F, Marino R, Cardelli P et al. Comparison between white blood cell count, procalcitonin and C reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department. Clinical Chemistry and Laboratory Medicine. 2014; 52(10):1465-1472

199 Mah JW, Bingham K, Dobkin ED, Malchiodi L, Russell A, Donahue S et al. Mannequin simulation identifies common surgical intensive care unit teamwork errors long after introduction of sepsis guidelines. Simulation in Healthcare. 2009; 4(4):193-199

200 Mahajan P, Grzybowski M, Chen X, Kannikeswaran N, Stanley R, Singal B et al. Procalcitonin as a marker of serious bacterial infections in febrile children younger than 3 years old. Academic Emergency Medicine. 2014; 21(2):171-179

201 Mahmoud KM, Ammar AS. Norepinephrine supplemented with dobutamine or epinephrine for the cardiovascular support of patients with septic shock. Indian Journal of Critical Care Medicine. 2012; 16(2):75-80

202 Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO et al. Mortality after fluid bolus in African children with severe infection. New England Journal of Medicine. 2011; 364(26):2483-2495

203 Makhoul IR, Yacoub A, Smolkin T, Sujov P, Kassis I, Sprecher H. Values of C-reactive protein, procalcitonin, and Staphylococcus-specific PCR in neonatal late-onset sepsis. Acta Paediatrica. 2006; 95(10):1218-1223

204 Maniaci V, Dauber A, Weiss S, Nylen E, Becker KL, Bachur R. Procalcitonin in young febrile infants for the detection of serious bacterial infections. Pediatrics. 2008; 122(4):701-710

205 Manzano S, Bailey B, Gervaix A, Cousineau J, Delvin E, Girodias JB. Markers for bacterial infection in children with fever without source. Archives of Disease in Childhood. 2011; 96(5):440-446

206 Mare TA, Treacher DF, Shankar-Hari M, Beale R, Lewis SM, Chambers DJ et al. The diagnostic and prognostic significance of monitoring blood levels of immature neutrophils in patients with systemic inflammation. Critical Care. 2015; 19:57

207 Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA. 1994; 272(17):1354-1357

208 Martin BJ, Buth KJ, Arora RC, Baskett RJF. Delirium as a predictor of sepsis in post-coronary artery bypass grafting patients: a retrospective cohort study. Critical Care. 2010; 14(5):R171

209 Martin C, Medam S, Antonini F, Alingrin J, Haddam M, Hammad E et al. Norepinephrine: Not too much, too long. Shock. 2015; 44(4):305-309

210 Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest. 1993; 103(6):1826-1831

211 Marty P, Roquilly A, Vallee F, Luzi A, Ferre F, Fourcade O et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in Intensive Care Unit: an observational study. Annals of Intensive Care. 2013; 3(1):3

212 Mathur S, Dhunna R, Chakraborty A. Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography. Indian Journal of Critical Care Medicine. 2007; 11(4):186-191

213 McIntyre LA, Fergusson D, Cook DJ, Nair RC, Bell D, Dhingra V et al. Resuscitating patients with early severe sepsis: a Canadian multicentre observational study. Canadian Journal of Anaesthesia. 2007; 54(10):790-798

214 Menendez R, Torres A, Reyes S, Zalacain R, Capelastegui A, Aspa J et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. European Respiratory Journal. 2012; 39(1):156-162

215 Meynaar IA, Droog W, Batstra M, Vreede R, Herbrink P. In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, Il-6, or LBP. Critical Care Research and Practice. 2011; 2011:594645

216 Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. British Journal of Anaesthesia. 2005; 94(6):767-773

217 Moreira VG, Prieto B, Rodriguez JSM, Alvarez FV. Usefulness of cell-free plasma DNA, procalcitonin and C-reactive protein as markers of infection in febrile patients. Annals of Clinical Biochemistry. 2010; 47(Pt 3):253-258

218 Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Critical Care. 2009; 13(4):R130

219 Moscovitz H, Shofer F, Mignott H, Behrman A, Kilpatrick L. Plasma cytokine determinations in emergency department patients as a predictor of bacteremia and infectious disease severity. Critical Care Medicine. 1994; 22(7):1102-1107

220 Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD et al. Trial of early, goal-directed resuscitation for septic shock. New England Journal of Medicine. 2015; 372(14):1301-1311

221 Muller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B et al. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest. 2010; 138(1):121-129

222 Muller MP, Hansel M, Winkelmann AM, Hardt F, Gijselaers W, Hacker W et al. Impact of simulator training and crew resource management training on final-year medical students' performance in sepsis resuscitation: A randomized trial. Minerva Anestesiologica. 2012; 78(8):901-909

223 Murray A, Kellett J, Huang W, Woodworth S, Wang F. Trajectories of the averaged abbreviated Vitalpac early warning score (AbEWS) and clinical course of 44,531 consecutive admissions hospitalized for acute medical illness. Resuscitation. 2014; 85(4):544-548

224 Murray CK, Hoffmaster RM, Schmit DR, Hospenthal DR, Ward JA, Cancio LC et al. Evaluation of white blood cell count, neutrophil percentage, and elevated temperature as predictors of bloodstream infection in burn patients. Archives of Surgery. 2007; 142(7):639-642

225 Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. New England Journal of Medicine. 2012; 367(20):1901-1911

226 Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Medicine. 2008; 34(12):2226-2234

227 Mylotte JM, Kahler L, McCann C. Community-acquired bacteremia at a teaching versus a nonteaching hospital: impact of acute severity of illness on 30-day mortality. American Journal of Infection Control. 2001; 29(1):13-19

228 Nademi Z, Clark J, Richards CG, Walshaw D, Cant AJ. The causes of fever in children attending hospital in the north of England. Journal of Infection. 2001; 43(4):221-225

229 Nahum E, Livni G, Schiller O, Bitan S, Ashkenazi S, Dagan O. Role of C-reactive protein velocity in the diagnosis of early bacterial infections in children after cardiac surgery. Journal of Intensive Care Medicine. 2012; 27(3):191-196

230 Nakamura A, Wada H, Ikejiri M, Hatada T, Sakurai H, Matsushima Y et al. Efficacy of procalcitonin in the early diagnosis of bacterial infections in a critical care unit. Shock. 2009; 31(6):586-591

231 National Clinical Guideline Centre. Intravenous fluid therapy in adults in hospital. NICE clinical guideline 174. London. National Clinical Guideline Centre, 2013. Available from: http://guidance.nice.org.uk/CG174

232 National Collaborating Centre for Women's and Children's Health. Feverish illness in children: assessment and management in children younger than 5 years. NICE clinical guideline 160. London. RCOG Press, 2013. Available from: http://guidance.nice.org.uk/CG160

233 National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

234 National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. 2nd edition. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf

235 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/

236 Nguyen HB, Daniel-Underwood L, Van Ginkel C, Wong M, Lee D, Lucas AS et al. An educational course including medical simulation for early goal-directed therapy and the severe sepsis resuscitation bundle: an evaluation for medical student training. Resuscitation. 2009; 80(6):674-679

237 Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Critical Care Medicine. 2004; 32(8):1637-1642

238 Nguyen HM, Schiavoni A, Scott KD, Tanios MA. Implementation of sepsis management guideline in a community-based teaching hospital - can education be potentially beneficial for septic patients? International Journal of Clinical Practice. 2012; 66(7):705-710

239 Nijman RG, Vergouwe Y, Thompson M, van VM, van Meurs AH, van der Lei J et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ (Clinical Research Ed). 2013; 346:f1706

240 Ninis N, Phillips C, Bailey L, Pollock JI, Nadel S, Britto J et al. The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. BMJ. 2005; 330(7506):1475

241 Nosrati A, Ben TA, Reif S. Diagnostic markers of serious bacterial infections in febrile infants younger than 90 days old. Pediatrics International. 2014; 56(1):47-52

242 Nygard ST, Langeland N, Flaatten HK, Fanebust R, Haugen O, Skrede S. Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital. BMC Infectious Diseases. 2014; 14:121

243 O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008; 63 Suppl 6:vi1-68

244 O'Leary F, Hayen A, Lockie F, Peat J. Defining normal ranges and centiles for heart and respiratory rates in infants and children: a cross-sectional study of patients attending an Australian tertiary hospital paediatric emergency department. Archives of Disease in Childhood. 2015;

245 Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. Clinical Chemistry and Laboratory Medicine. 1999; 37(3):363-368

246 Oconnor E, Venkatesh B, Mashongonyika C, Lipman J, Hall J, Thomas P. Serum procalcitonin and C-reactive protein as markers of sepsis and outcome in patients with neurotrauma and subarachnoid haemorrhage. Anaesthesia and Intensive Care. 2004; 32(4):465-470

247 Ogura H, Gando S, Saitoh D, Takeyama N, Kushimoto S, Fujishima S et al. Epidemiology of severe sepsis in Japanese intensive care units: A prospective multicenter study. Journal of Infection and Chemotherapy. 2014; 20(3):157-162

248 Ohlin A, Bjorkqvist M, Montgomery SM, Schollin J. Clinical signs and CRP values associated with blood culture results in neonates evaluated for suspected sepsis. Acta Paediatrica. 2010; 99(11):1635-1640

249 Olaciregui I, Hernandez U, Munoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Archives of Disease in Childhood. 2009; 94(7):501-505

250 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2012. Available from: http://www.oecd.org/std/ppp [Last accessed: 10 November 2015]

251 Osborn TM, Phillips G, Lemeshow S, Townsend S, Schorr CA, Levy MM et al. Sepsis severity score: an internationally derived scoring system from the surviving sepsis campaign database*. Critical Care Medicine. 2014; 42(9):1969-1976

252 Owen JA, Brashers VL, Littlewood KE, Wright E, Childress RM, Thomas S. Designing and evaluating an effective theory-based continuing interprofessional education program to improve sepsis care by enhancing healthcare team collaboration. Journal of Interprofessional Care. 2014; 28(3):212-217

253 Pancer G, Engelman E, Hoque F, Alam M, Rucinski J, Bernstein LH. C-reactive protein for the enhanced evaluation of the systemic inflammatory response syndrome (SIRS). Open Clinical Chemistry Journal. 2011; 4(1):1-9

254 Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ. 2014; 349:g4561

255 Patel GP, Grahe JS, Sperry M, Singla S, Elpern E, Lateef O et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock. 2010; 33(4):375-380

256 Patterson M, Kelly AM, Klim S. Predictors of bacteraemia in emergency department patients with pneumonia. Hong Kong Journal of Emergency Medicine. 2012; 19(3):177-182

257 Pavcnik-Arnol M, Hojker S, Derganc M. Lipopolysaccharide-binding protein in critically ill neonates and children with suspected infection: comparison with procalcitonin, interleukin-6, and C-reactive protein. Intensive Care Medicine. 2004; 30(7):1454-1460

258 Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ et al. Goal-directed resuscitation for patients with early septic shock. New England Journal of Medicine. 2014; 371(16):1496-1506

259 Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. New England Journal of Medicine. 2012; 367(2):124-134

260 Pettila V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Medicine. 2002; 28(9):1220-1225

261 Pettila V, Pentti J, Pettila M, Takkunen O, Jousela I. Predictive value of antithrombin III and serum C-reactive protein concentration in critically ill patients with suspected sepsis. Critical Care Medicine. 2002; 30(2):271-275

262 Pfitzenmeyer P, Decrey H, Auckenthaler R, Michel JP. Predicting bacteremia in older patients. Journal of the American Geriatrics Society. 1995; 43(3):230-235

263 Phua J, Koay ESC, Lee KH. Lactate, procalcitonin, and amino-terminal pro-B-type natriuretic peptide versus cytokine measurements and clinical severity scores for prognostication in septic shock. Shock. 2008; 29(3):328-333

264 Poutsiaka DD, Davidson LE, Kahn KL, Bates DW, Snydman DR, Hibberd PL. Risk factors for death after sepsis in patients immunosuppressed before the onset of sepsis. Scandinavian Journal of Infectious Diseases. 2009; 41(6-7):469-479

265 Povoa P, Almeida E, Moreira P, Fernandes A, Mealha R, Aragao A et al. C-reactive protein as an indicator of sepsis. Intensive Care Medicine. 1998; 24(10):1052-1056

266 Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P et al. C-reactive protein as a marker of infection in critically ill patients. Clinical Microbiology and Infection. 2005; 11(2):101-108

267 Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P et al. Pilot study evaluating C-reactive protein levels in the assessment of response to treatment of severe bloodstream infection. Clinical Infectious Diseases. 2005; 40(12):1855-1857

268 Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P et al. Early identification of intensive care unit-acquired infections with daily monitoring of C-reactive protein: a prospective observational study. Critical Care. 2006; 10(2):R63

269 Pratt A, Attia MW. Duration of fever and markers of serious bacterial infection in young febrile children. Pediatrics International. 2007; 49(1):31-35

270 Prytherch DR, Smith GB, Schmidt PE, Featherstone PI. ViEWS--Towards a national early warning score for detecting adult inpatient deterioration. Resuscitation. 2010; 81(8):932-937

271 Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics. 2001; 108(6):1275-1279

272 Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Horton JM, Studnek JR et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Critical Care Medicine. 2011; 39(9):2066-2071

273 Puskarich MA, Trzeciak S, Shapiro NI, Albers AB, Heffner AC, Kline JA et al. Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest. 2013; 143(6):1548-1553

274 Rey C, Los Arcos M, Concha A, Medina A, Prieto S, Martinez P et al. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. Intensive Care Medicine. 2007; 33(3):477-484

275 Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New England Journal of Medicine. 2001; 345(19):1368-1377

276 Rudinsky SL, Carstairs KL, Reardon JM, Simon LV, Riffenburgh RH, Tanen DA. Serious bacterial infections in febrile infants in the post-pneumococcal conjugate vaccine era. Academic Emergency Medicine. 2009; 16(7):585-590

277 Ruokonen E, Takala J, Kari A, Saxén H, Mertsola J, Hansen EJ. Regional blood flow and oxygen transport in septic shock. Critical Care Medicine. 1993; 21(9):1296-1303

278 Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ et al. Vasopressin versus norepinephrine infusion in patients with septic shock. New England Journal of Medicine. 2008; 358(9):877-887

279 SAFE S, I, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Medicine. 2011; 37(1):86-96

280 Sankoff JD, Goyal M, Gaieski DF, Deitch K, Davis CB, Sabel AL et al. Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS). Critical Care Medicine. 2008; 36(2):421-426

281 Santhanam I, Sangareddi S, Venkataraman S, Kissoon N, Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. Pediatric Emergency Care. 2008; 24(10):647-655

282 Schmoelz M, Schelling G, Dunker M, Irlbeck M. Comparison of systemic and renal effects of dopexamine and dopamine in norepinephrine-treated septic shock. Journal of Cardiothoracic and Vascular Anesthesia. 2006; 20(2):173-178

283 Schramm GE, Kashyap R, Mullon JJ, Gajic O, Afessa B. Septic shock: a multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality. Critical Care Medicine. 2011; 39(2):252-258

284 Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. Academic Emergency Medicine. 2012; 19(11):1276-1280

285 Segal I, Ehrlichman M, Urbach J, Bar-Meir M. Use of time from fever onset improves the diagnostic accuracy of C-reactive protein in identifying bacterial infections. Archives of Disease in Childhood: Education and Practice Edition. 2014; 99(11):974-978

286 Seguin P, Bellissant E, Tulzo Y, Laviolle B, Lessard Y, Thomas R et al. Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock. Clinical Pharmacology and Therapeutics. 2002; 71(5):381-388

287 Seguin P, Laviolle B, Guinet P, Morel I, Mallédant Y, Bellissant E. Dopexamine and norepinephrine versus epinephrine on gastric perfusion in patients with septic shock: a randomized study [NCT00134212]. Critical Care. 2006; 10(1):R32

288 Seigel TA, Cocchi MN, Salciccioli J, Shapiro NI, Howell M, Tang A et al. Inadequacy of temperature and white blood cell count in predicting bacteremia in patients with suspected infection. Journal of Emergency Medicine. 2012; 42(3):254-259

289 Shaaban H, Daniel S, Sison R, Slim J, Perez G. Eosinopenia: Is it a good marker of sepsis in comparison to procalcitonin and C-reactive protein levels for patients admitted to a critical care unit in an urban hospital? Journal of Critical Care. 2010; 25(4):570-575

290 Shaoul R, Lahad A, Tamir A, Lanir A, Srugo I. C reactive protein (CRP) as a predictor for true bacteremia in children. Medical Science Monitor. 2008; 14(5):CR255-CR261

291 Shapiro NI, Fisher C, Donnino M, Cataldo L, Tang A, Trzeciak S et al. The feasibility and accuracy of point-of-care lactate measurement in emergency department patients with suspected infection. Journal of Emergency Medicine. 2010; 39(1):89-94

292 Shapiro NI, Howell MD, Talmor D, Donnino M, Ngo L, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score predicts 1-year mortality. Critical Care Medicine. 2007; 35(1):192-198

293 Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM et al. The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney

injury in emergency department patients with suspected sepsis. Annals of Emergency Medicine. 2010; 56(1):52-59

294 Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Critical Care Medicine. 2009; 37(1):96-104

295 Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. Critical Care Medicine. 2003; 31(3):670-675

296 Sherwin C, Broadbent R, Young S, Worth J, McCaffrey F, Medlicott NJ et al. Utility of interleukin-12 and interleukin-10 in comparison with other cytokines and acute-phase reactants in the diagnosis of neonatal sepsis. American Journal of Perinatology. 2008; 25(10):629-636

297 Shmuely H, Pitlik S, Drucker M, Samra Z, Konisberger H, Leibovici L. Prediction of mortality in patients with bacteremia: the importance of pre-existing renal insufficiency. Renal Failure. 2000; 22(1):99-108

298 Shorr AF, Nelson DR, Wyncoll DLA, Reinhart K, Brunkhorst F, Vail GM et al. Protein C: a potential biomarker in severe sepsis and a possible tool for monitoring treatment with drotrecogin alfa (activated). Critical Care. 2008; 12(2):R45

299 Sierra R, Rello J, Bailen MA, Benitez E, Gordillo A, Leon C et al. C-reactive protein used as an early indicator of infection in patients with systemic inflammatory response syndrome. Intensive Care Medicine. 2004; 30(11):2038-2045

300 Silverman LZ, Hoesel LM, Desai A, Posa P, Purtill MA, Brandt MM. It takes an intensivist. American Journal of Surgery. United States 2011; 201(3):320-323

301 Simon L, Saint-Louis P, Amre DK, Lacroix J, Gauvin F. Procalcitonin and C-reactive protein as markers of bacterial infection in critically ill children at onset of systemic inflammatory response syndrome. Pediatric Critical Care Medicine. 2008; 9(4):407-413

302 Slotman GJ, Quinn JV. Multivariate regression modeling for the prediction of inflammation, systemic pressure, and end-organ function in severe sepsis. Shock. 1997; 8(3):225-231

303 Stucker F, Herrmann F, Graf JD, Michel JP, Krause KH, Gavazzi G. Procalcitonin and infection in elderly patients. Journal of the American Geriatrics Society. 2005; 53(8):1392-1395

304 Suarez D, Ferrer R, Artigas A, Azkarate I, Garnacho-Montero J, Goma G et al. Cost-effectiveness of the surviving sepsis campaign protocol for severe sepsis: a prospective nation-wide study in Spain. Intensive Care Medicine. Spain 2011; 37(3):444-452

305 Svaldi M, Hirber J, Lanthaler AI, Mayr O, Faes S, Peer E et al. Procalcitonin-reduced sensitivity and specificity in heavily leucopenic and immunosuppressed patients. British Journal of Haematology. 2001; 115(1):53-57

306 Talmor D, Jones AE, Rubinson L, Howell MD, Shapiro NI. Simple triage scoring system predicting death and the need for critical care resources for use during epidemics. Critical Care Medicine. 2007; 35(5):1251-1256

307 Ter Avest E, de Jong M, Brummer I, Wietasch GJ, Ter Maaten JC. Outcome predictors of uncomplicated sepsis. International Journal of Emergency Medicine. 2013; 6(1):9

308 Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, Verber IG. Is procalcitonin useful in early diagnosis of serious bacterial infections in children? Acta Paediatrica (Oslo, Norway : 1992). 2005; 94(2):155-158

309 The College of Emergency Medicine. Severe sepsis and septic shock: report of the clinical audit 2013-14. UK. The College of Emergency Medicine, 2014. Available from: http://www.rcem.ac.uk/Shop-Floor/Clinical%20Standards/Sepsis

310 Theerawit P, Kiastboonsri S, Ingsathit A, Tanwattanathavorn K. Prognostic indicators related to risk of death in shock patients: A new simplified score. Singapore Medical Journal. 2011; 52(2):81-85

311 Trautner BW, Caviness AC, Gerlacher GR, Demmler G, Macias CG. Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher). Pediatrics. 2006; 118(1):34-40

312 Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Medicine. 2007; 33(6):970-977

313 Tsalik EL, Jaggers LB, Glickman SW, Langley RJ, van Velkinburgh JC, Park LP et al. Discriminative value of inflammatory biomarkers for suspected sepsis. Journal of Emergency Medicine. 2012; 43(1):97-106

314 Tsangaris I, Plachouras D, Kavatha D, Gourgoulis GM, Tsantes A, Kopterides P et al. Diagnostic and prognostic value of procalcitonin among febrile critically ill patients with prolonged ICU stay. BMC Infectious Diseases. 2009; 9:213

315 Umscheid CA, Betesh J, VanZandbergen C, Hanish A, Tait G, Mikkelsen ME et al. Development, implementation, and impact of an automated early warning and response system for sepsis. Journal of Hospital Medicine. 2015; 10(1):26-31

316 Uusitalo-Sepplala R, Koskinen P, Leino A, Peuravuori H, Vahlberg T, Rintala EM. Early detection of severe sepsis in the emergency room: Diagnostic value of plasma C-reactive protein, procalcitonin, and interleukin-6. Scandinavian Journal of Infectious Diseases. 2011; 43(11-12):883-890

317 Van Veen M, Steyerberg EW, Ruige M, van Meurs AH, Roukema J, van der Lei J et al. Manchester triage system in paediatric emergency care: prospective observational study. BMJ (Clinical Research Ed). 2008; 337:a1501

318 Vassiliou AG, Mastora Z, Orfanos SE, Jahaj E, Maniatis NA, Koutsoukou A et al. Elevated biomarkers of endothelial dysfunction/activation at ICU admission are associated with sepsis development. Cytokine. 2014; 69(2):240-247

319 Ventura AM, Shieh HH, Bousso A, Goes PF, Fernandes IC, de Souza DC et al. Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock. Critical Care Medicine. 2015;

320 von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann L, Breig P, Hahn C et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and

IL-6 are more reliable than C-reactive protein. European Journal of Clinical Microbiology and Infectious Diseases. 2004; 23(7):539-544

321 Vorwerk C, Loryman B, Coats TJ, Stephenson JA, Gray LD, Reddy G et al. Prediction of mortality in adult emergency department patients with sepsis. Emergency Medicine Journal. 2009; 26(4):254-258

322 Wacharasint P, Nakada Ta, Boyd JH, Russell JA, Walley KR. Normal-range blood lactate concentration in septic shock is prognostic and predictive. Shock. 2012; 38(1):4-10

323 Walker CA, Griffith DM, Gray AJ, Datta D, Hay AW. Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: time to aim higher? Journal of Critical Care. 2013; 28(5):832-837

324 Warren DK, Zack JE, Cox MJ, Cohen MM, Fraser VJ. An educational intervention to prevent catheter-associated bloodstream infections in a nonteaching, community medical center. Critical Care Medicine. 2003; 31(7):1959-1963

325 Weinkove R, Bailey M, Bellomo R, Saxena MK, Tam CS, Pilcher DV et al. Association between early peak temperature and mortality in neutropenic sepsis. Annals of Hematology. 2015; 94(5):857-864

326 Weinkove R, Bailey M, Bellomo R, Saxena MK, Tam CS, Pilcher DV et al. Association between early peak temperature and mortality in neutropenic sepsis. Annals of Hematology. 2015; 94(5):857-864

327 Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Critical Care Medicine. 2014; 42(11):2409-2417

328 Wisdom A, Eaton V, Gordon D, Daniel S, Woodman R, Phillips C. INITIAT-E.D.: Impact of timing of INITIation of Antibiotic Therapy on mortality of patients presenting to an Emergency Department with sepsis. Emergency Medicine Australasia. 2015; 27(3):196-201

329 Wyllie DH, Bowler ICJW, Peto TEA. Bacteraemia prediction in emergency medical admissions: role of C reactive protein. Journal of Clinical Pathology. 2005; 58(4):352-356

330 Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F et al. A randomized trial of protocol-based care for early septic shock. New England Journal of Medicine. 2014; 370(18):1683-1693

331 Yilmazlar T, Ozturk E, Alsoy A, Ozguc H. Necrotizing soft tissue infections: APACHE II score, dissemination, and survival. World Journal of Surgery. 2007; 31(9):1858-1862

332 Yokota PK, Marra AR, Martino MD, Victor ES, Durao MS, Edmond MB et al. Impact of appropriate antimicrobial therapy for patients with severe sepsis and septic shock--a quality improvement study. PLoS ONE [Electronic Resource]. 2014; 9(11):e104475

333 Yonemori K, Kanda Y, Yamamoto R, Hamaki T, Suguro M, Chizuka A et al. Clinical value of serial measurement of serum C-reactive protein level in neutropenic patients. Leukemia and Lymphoma. 2001; 41(5-6):607-614

334 Yoo JW, Lee JR, Jung YK, Choi SH, Son JS, Kang BJ et al. A combination of early warning score and lactate to predict intensive care unit transfer of inpatients with severe sepsis/septic shock. Korean Journal of Internal Medicine. 2015; 30(4):471-477

335 Yousefi H, Nahidian M, Sabouhi F. Reviewing the effects of an educational program about sepsis care on knowledge, attitude, and practice of nurses in intensive care units. Iranian Journal of Nursing and Midwifery Research. 2012; 17(2 Suppl 1):S91-S95

336 Yzerman EP, Boelens HA, Tjhie JH, Kluytmans JA, Mouton JW, Verbrugh HA. Delta APACHE II for predicting course and outcome of nosocomial Staphylococcus aureus bacteremia and its relation to host defense. Journal of Infectious Diseases. 1996; 173(4):914-919

337 Zant R, Melter M, Knoppke B, Ameres M, Kunkel J. Kinetics of interleukin-6, procalcitonin, and C-reactive protein after pediatric liver transplantation. Transplantation Proceedings. 2014; 46(10):3507-3510

338 Zhang D, Micek ST, Kollef MH. Time to Appropriate Antibiotic Therapy Is an Independent Determinant of Postinfection ICU and Hospital Lengths of Stay in Patients With Sepsis. Critical Care Medicine. 2015; 43(10):2133-2140

339 Zhao X, Chen YX, Li CS. The prognostic performance of the complement system in septic patients in emergency department: a cohort study. Biomarkers in Medicine. 2015; 9(7):661-668

340 Zhao Y, Li C, Jia Y. Evaluation of the mortality in emergency department sepsis score combined with procalcitonin in septic patients. American Journal of Emergency Medicine. 2013; 31(7):1086-1091

18 Acronyms and abbreviations

Acronym or abbreviation	Description
A/E	Accident and emergency
ABC	Automated blood count
AbEWS	Abbreviated VitalPac Early Warning Score
ABP	Arterial blood pressure
AKI	Acute kidney injury
AMS	Altered mental state
ANC	Absolute neutrophil count
APACHE	Acute Physiology and Chronic Health Evaluation
APLS	Advanced paediatric life support
aPTR	Activated partial thromboplastin time ratio
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
AT	Antimicrobial treatment
AUC	Area under curve
AVPU	Alert, voice, pain, unresponsive
BNF	British National Formulary
BNP	Brain natriuretic peptide
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CAB	Community acquired bacteraemia
CABSI	Catheter-Associated Blood Stream Infection
CAP	Community acquired pneumonia
CAS	Community acquired sepsis
CEA	Cost-effectiveness analysis
CG	Clinical guideline
CI	Confidence interval
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRM	Crew resource management
CRP	C-reactive protein
CRT	Capillary refill time
CT 3/4	Core medical trainee year 3/4
CUA	Cost-utility analysis
CURB-65	Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years and older
CV	Central venous
CVC	Central venous catheter
CVP	Central venous pressure

Acronym or abbreviation	Description
DAP	Diastolic arterial pressure
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DNI	Delta neutrophil index
ED	Emergency department
EGDT	Early goal-directed therapy
EOS	Eosinophil count
ESRD	End-stage renal disease
EWRS	Early warning response system
FBC	Full blood count
FDP	Fibrin degradation products
FiO_2	Fraction of inspired oxygen
FN	False negative
FP	False positive
GCS	Glasgow Coma Scale
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	Haemoglobin
HES	Hydroxyethyl starch
HR	Hazard ratio
HTA	Health technology assessment
HTI	Hourly time integral
I/T ratio	Immature to total neutrophil ratio
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IM	Intramuscular
INR	International normalized ratio
IPF	Immature platelet function
IQR	Interquartile range
IV	Intravenous
K	Potassium
LAR	Leukocyte anti-sedimentation rate
LOS	Length of stay
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
LVSV	Left ventricular stroke volume
MAP	Mean arterial pressure
MBFFP	Methylene blue fresh frozen plasma
MEDS	Mortality in Emergency Department Sepsis
MEWS	Modified Early Warning Score
MICU	Medical intensive care unit
MID	Minimally important difference

Acronym or abbreviation	Description
MODS	Multi organ dysfunction syndrome
MOEWS	Modified obstetric early warning score
MOF	Multiple organ failure
MPI	Mannheim Peritonitis Index
MTS	Manchester Triage System
MV	Mechanical ventilation
N	Number
N/A	Not applicable
Na	Sodium
NEWS	National Early Warning Score
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NPV	Negative predictive value
NSTI	Necrotizing soft tissue infections
NYHA	New York Heart Association
O_2	Oxygen
OBI	Occult bacterial infection
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
PaO_2	Partial pressure of oxygen in arterial blood
PAOP	Pulmonary artery occlusion pressure
PCT	Procalcitonin
PEWS	Paediatric Early Warning Score
PiCCO	Pulse Contour Cardiac Output
PICO	Population, intervention, comparison, outcome
PICU	Paediatric intensive care unit
PIRO	Predisposing factors, infection/insult, response, and organ dysfunction
POPS	Paediatric Observation Priority Score
PPV	Positive predictive value
PRBC	Packed red blood cells
PSC	Protocolised standard care
PT	Prothrombin time
PTT	Thromboplastin time
QALY	Quality adjusted life year
QUADAS II	Quality Assessment of Diagnostic Accuracy Studies II
RAPS	Rapid Acute Physiology Score
RCT	Randomised controlled trial
REMS	Rapid Emergency Medicine Score
ROC	Receiver operating characteristic
RR	Relative risk / risk ratio
RRT	Renal replacement therapy
SAP	Systolic arterial pressure
SAPS	Simplified Acute Physiology Score

Acronym or abbreviation	Description
SBI	Severe bacterial infection
SBP	Systolic blood pressure
SCBU	Special Care Baby Unit
$ScvO_2$	Central venous oxygen saturation
SD	Standard deviation
SDNN	Standard deviation of NN intervals (N=peak in an electrocardiogram)
SE	Standard error
Sens	Sensitivity
SF-36	Short Form (36) Quality of Life
SHR	Sub-distribution hazard ratio
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SOS	Sepsis in Obstetrics Score
Spec	Specificity
SpO2	Oxygen saturation
SRT	Sepsis response team
SSC	Surviving Sepsis Campaign
SSS	Sepsis severity score
ST 3/4	Specialty trainee year 3/4
STSS	Simple Triage Scoring System
T	Temperature
TLC	Total leucocyte count
TN	True negative
TNFα	Tumour necrosis factor alpha
TP	True positive
TT	Thrombin time
ULN	Upper level of normal
UO	Urine output
UTI	Urinary tract infection
ViEWS	VitalPac Early Warning Score
WBC	White blood cell count
WCC	White cell count
YOS	Yale Observation Scale

1

19 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

19.1 Guideline-specific terms

Term	Definition
Acute kidney injury (AKI)	Or acute renal failure, abrupt decline in renal function, often due to an underlying serious illness
Acute Physiology and Chronic Health Evaluation (APACHE) II score	Severity of illness classification system for patients in intensive care with a score ranging from 0 to 71
Antimicrobials	Medicines which kill microorganisms or inhibit their growth. They are grouped according to the microorganism they primarily act against (e.g. antibiotics, antifungals, antivirals)
Bacteraemia	Presence of bacteria in the blood, which can lead to sepsis or the spread to other parts of the body (haematogenous spread)
Beta coefficient	Standardised estimates resulting from a regression analysis showing the effect of an independent variable on the dependent variable
Bicarbonate	Or hydrogen carbonate, is an intermediate form of carbonic acid through deprotonation (the removal of a proton from a molecule)
Comparative costing (CC)	A type of analysis where costs are compared without the consideration of health benefits
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs)
Disseminated intravascular coagulation (DIC)	Widespread activation of the clotting cascade which results in the formation of blood clots in the small blood vessels throughout the body. The following reduced tissue blood flow and the consumption of platelets and clotting factors results in both multiple organ damage and severe bleeding.
Early goal-directed therapy (EGDT)	Protocolised treatment technique used in intensive care medicine involving aggressive management and intensive monitoring
Escalation of care	Access and provision of additional health care staff support for patients whose medical condition is deteriorating
Inotropic agents	Medicines which either positively or negatively alter heart muscle contractions
Meningitis	Acute infection of the protective membranes covering the brain and spinal cord (meninges)
Multiple organ dysfunction syndrome (MODS)	Medical condition of potentially reversible physiologic derangement involving at least two organ systems that were not involved in the disorder

Term	Definition
	that resulted in intensive care admission
Senior clinical decision maker	For people over 18 years old: someone authorised to prescribe antibiotics, such as a CT3 (core trainee year 3) or ST3 (speciality trainee year 3) or above, or an advanced nurse practitioner, depending on local arrangements. For people 12-17 years old: a paediatric qualified doctor of grade ST4 or above.
Sepsis	Presence of infection together with systemic manifestations of infection
Septic shock	Severe sepsis plus persistently low blood pressure despite the adequate administration of intravenous fluids
Septicaemia	See 'sepsis'
Sequelae	Often chronic condition which is a complication of an acute condition, such as an infection or trauma
Sequential Organ Failure Assessment (SOFA) score	Scoring system for patients in intensive care to measure the extent and rate of the organ failure
Severe sepsis	Sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion
Simplified Acute Physiology Score (SAPS) II score	Severity of illness classification system for patients in intensive care with a score ranging from 0 to 163
Systemic inflammatory response syndrome (SIRS)	Inflammatory state affecting the entire body often but not necessarily as a response of the immune system to an infection; two or more of the following criteria: abnormal body temperature, heart rate, respiratory rate or blood gas, and white blood cell count
Triangulation	Use of multiple measurements or methods within a study to validate results and reduce potential bias
Vasopressors	Antihypotensive medicines which cause the constriction of blood vessels

19.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Area under curve	The area under curve is the area under the receiver operated characteristic curve. The shape of a curve and the area under the curve helps us estimate how high the discriminative power of a test is. The area under the curve can have any value between 0 and 1 and it is a good indicator of the goodness of the test. A perfect diagnostic test has an area under curve of 1.0, whereas a non-discriminating test has an area of 0.5.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other

Term	Definition
	variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.

Term	Definition
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any

Term	Definition
	effects due to the treatment.
Cost-benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost-consequences analysis (CCA)	Cost-consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support

Term	Definition
	the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Egger's statistic	A graphical test used to test for funnel plot asymmetry
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost-effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Funnel plot	A funnel plot is a scatter plot of the intervention effect estimates from individual studies against a measure of each study's size or precision. Precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias the plot should approximately resemble a symmetrical (inverted) funnel.
Generalisability	The extent to which the results of a study hold true for groups that did not

Term	Definition
	participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the

Term	Definition
	agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with negative test results who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN / (FN + TN)
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.

Term	Definition
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).

Term	Definition
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP / (TP + FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For

Term	Definition
	example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months

Term	Definition
	pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.

Term	Definition
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).