National Institute for Health and Care Excellence

Final version

Sepsis

Sepsis: recognition, assessment and early management

NICE guideline 51

Appendix H

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Appendices

Appendix H: Clinical evidence tables

H.1 Assessment and stratification of risk

H.1.1 Scoring systems

Table 1: ADENIJI 2011A

Study	Adeniji 2011A[4]
Study type	Retrospective cohort
Number of studies (number of participants)	n= 62 (n=43 ward-based; n=19 ICU admission)
Countries and Settings	UK, hospital
Funding	Not stated
Duration of study	July 2009 – February 2010
Age, gender, ethnicity	Age: ward-based: 35 (19-71); ICU admissions: 53 (18-71) Male: 56%, Female: 44% Ethnicity: almost entirely European Caucasian.
Patient characteristics	Adults admitted to hospital and confirmed to have contracted H1N1
Index test	STSS (Simple Triage Scoring System)
Reference standard	SOFA (Sepsis-related Organ Failure Assessment)
Target condition/ patient outcomes	ICU admission
Results: AUC for ICU admission	

Study	Adeniji 2011A[4]
STSS: 0.88 (0.78-0.98) SOFA: 0.77 (0.65-0.89) AUC for requirement for mechanical ventilation STSS: 0.91 (0.83-0.99) SOFA: 0.87 (0.72-1.00) Mortality: STSS score Fraction (percentage) 0 0/19 (0) 1 0/21 (0) 2 2/13 (15.3) ≥3 1/9 (11.1) SOFA score Fraction (percentage) 0-1 1/21 (4.8) 2-3 1/25 (4) 4-5 0-10 (0) 6-7 1/5 (20) 8-9 0/0 (0) 10-11 0/0 (0) >11 0/1 (0) General limitations according to QUADAS II Selection of patients: single centre; small sample size; patients with H1N1.	

Table 2: AKRE 2010

Study	Akre 2010[6]
Study type	Retrospective cohort

Study	Akre 2010[6]
Number of studies (number of participants)	n=186
Countries and Settings	USA, hospital
Funding	Not stated
Duration of study	October 2006 – February 2008 (follow up: 24 hours)
Age, gender, ethnicity	Age: median: 25.5 months (range: 0-252 months) Male: 60%, Female: 40% Ethnicity: 55.9% white; 17.2% Black/African American; 7.5% Asian; 7% Hispanic/Latino.
Patient characteristics	Paediatric patients who had a documented RRT (Rapid Response Team) or code blue event (PEWS calculated 24 hours before the event)
Index test	PEWS (Paediatric Early Warning Score)
Reference standard	N/A
Target condition/ patient outcomes	RRT or code blue event
Results: Sensitivity: 85.5% General limitations according to QUADAS II Selection of patients: retrospective design.	

Table 3: ALBRIGHT 2014

Study	Albright 2014[7]
Study type	Retrospective cohort
Number of studies (number of	N=850 women with suspected SIRS or sepsis.

Study	Albright 2014[7]
participants	
Countries and Settings	Women and Infants ED, USA
Funding	Not stated
Duration of study	February 2009 – May 2011
Age, gender, ethnicity	Age: S.O.S.≥6: mean (SD) = 24.0 (6.5), median (range) = 22.5 (15-42) S.O.S.<6: mean (SD) = 26.3 (6.1), median (range) = 26.0 (15-43) Gender: Female Ethnicity: S.O.S.≥6 (n=45): White = 16(35.6%), Black = 3(6.7%), Hispanic = 23(51.1%), Asian = 3(6.7%), Multiracial = 0, Other = 0 S.O.S.<6 (n=773): White = 362(46.8%), Black = 100(12.9%), Hispanic = 287(37.1%), Asian = 13(1.7%), Multiracial = 4(0.5%), Other = 7(0.9%)
Patient characteristics	Pregnant and postpartum women.
Index test	Sepsis in Obstetrics Score Temperature: +4 = >40.9 (high abnormal range) or <30 (low abnormal range) +3 = 39-40.9 (high abnormal range) or 30-31.9 (low abnormal range) +2 = 32-33.9 (low abnormal range only) +1 = 38.5-38.9 (high abnormal range) or 34-35.9 (low abnormal range) 0 = 36-38.4 (normal) Systolic blood pressure (mmHg): +4 = <70 (low abnormal range) +2 = 70-90 (low abnormal range only) 0 = >90 Normal Heart rate (bpm):

Study	Albright 2014[7]
	+4 = >179 (high abnormal range) +3 = 150-179 (high abnormal range) +2 = 130-149 (high abnormal range) +1 = 120-129 (high abnormal range) 0 = ≤119 (normal) Respiratory rate (bpm): +4 = >49 (high abnormal range) or 10-11 (low abnormal range) +3 = 35-49 (high abnormal range only) +2 = 6-9 (low abnormal range only) +1 = 25-34 (high abnormal range) or 10-11 (low abnormal range) 0 = 12-24 (normal) Sp02(%) +4 = <85% (low abnormal range only) +3 = 85-89% (low abnormal range only) +1 = 90-91% (low abnormal range only) 0 = ≥92% (normal) White blood cell count (/μL) +4 = >39.9 (high abnormal range) or <1 (low abnormal range) +2 = 25-39.9 (high abnormal range) or 1-2.9 (low abnormal range) +1 = 17-24.9 (high abnormal range) or 3-5.6 (low abnormal range) 0 = 5.7-16.9 (normal) % immature neutrophils: +2 = ≥10% (high abnormal range only) 0 = <10% (normal)

Study	Albright 2014[7]
	Lactic acid (mmol/L) +2 = ≥ 4 (high abnormal range only) 0 = >4 (normal)
Reference standard	REMS, MEWS
Target condition/ patient outcomes	Admission to ICU Telemetry unit admission Length of stay Positive blood cultures Positive influenza swabs Fetal tachycardia Composite perinatal outcome Maternal mortality
Results: Area under the curve for ICU admission: S.O.S. = 0.97 Sensitivity %: S.O.S. = 88.9 REMS = 77.8 MEWS = 100 Specificity %: S.O.S. = 99.2 REMS = 93.3 MEWS = 77.6 PPV %: S.O.S. = 16.7 REMS = 11.1	

Study	Albright 2014[7]
MEWS = 4.6 NPV %: S.O.S. = 99.9 REMS = 99.7 MEWS = 100 Admission to ICU: S.O.S.≥6: n=8/48 (16.7%) S.O.S.<6: n=1/802 (0.1%) p=<.0001 Telemetry unit admission: S.O.S.≥6: n=16/40 (33.3%) S.O.S.<6: n=16/801 (2.0%) p=<.0001 Length of stay: S.O.S.≥6 (n=42): mean (SD)=4.4(2.9), median (range)=3.5(0-14), p=.0004 S.O.S.<6 (n=192): mean (SD)=2.8(1.6) median (range)=2(0-9) Positive blood cultures: S.O.S.≥6: n=12/39 (30.8%) S.O.S.<6: n=12/141 (8.5%) P=.0003 Positive influenza swabs: S.O.S.≥6: n=4/27 (14.8%) S.O.S.<6: n=100/720 (13.9%) p=.78 Fetal tachycardia S.O.S.≥6: n=18/30 (60.0%) S.O.S.<6: n=77/598 (12.9%) p=<.0001	

Study	Albright 2014[7]
Composite perinatal outcome: S.O.S.≥6: n=2/35 (5.7%) S.O.S.<6: n=47/716 (6.6%) p=1.0 Maternal mortality: 0 Working diagnosis: Pyelonephritis: S.O.S.≥6: n=12/48 (25.0%) S.O.S.<6: n=33/796 (4.2%) ILI: S.O.S.≥6: n=12/48 (25.0%) S.O.S.<6: n=498/796 (62.6%) P=.0001 Endometritis: S.O.S.≥6: n=5/48 (10.4%) S.O.S.<6: n=33/796 (4.2%) Non-respiratory viral syndrome: S.O.S.≥6: n=3/48 (6.3%) S.O.S.<6: n= 91/796 (11.4%) Septic abortion: S.O.S.≥6: n= 2/48 (4.2%) S.O.S.<6: n= 3/796 (0.4%) Chorioamnionitis: S.O.S.≥6: n= 2/48 (4.2%) S.O.S.<6: n= 4/796 (0.5%) Pneumonia: S.O.S.≥6: n= 1/48 (2.1%) S.O.S.<6: n= 19/796 (2.4%)	

Study	Albright 2014[7]
Mastitis: S.O.S.≥6: n= 1/48 (2.1%) S.O.S.<6: n= 9/796 (1.1%) Other: S.O.S.≥6: n= 10/48 (20.8%) S.O.S.<6: n= 106/796 (13.3%) General limitations according to QUADAS II Retrospective, single centre	

Table 4: BAND 2011

Study	Band 2011[21]
Study type	Secondary analysis of prospectively collected registry data.
Number of studies (number of participants)	N=963 severe sepsis patients who presented at the ED and were admitted to hospital.
Countries and Settings	USA ED
Funding	Author's state they have no relevant financial information to declare.
Duration of study	Jan 1st 2005 – December 31 2006
Age, gender, ethnicity	>18 years Female n=449 White n=415 Black n=459 Other ethnicity n=81 Unknown ethnicity n=6
Patient characteristics	-

Study	Band 2011[21]
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results: Hospital mortality, adjusted relative risk, APACHE II: 1.05 (1.03-1.07). p=<0.001	

Table 5: BOHNEN 1988

Study	Bohnen 1988[30]
Study type	Retrospective cohort
Number of studies (number of participants)	n=100
Countries and Settings	The Wellesley University Hospital, Canada
Funding	Physicians' Services Inc Foundation
Duration of study	19-month period, 1984-1986 (Follow up: in hospital)
Age, gender, ethnicity	Age: 58.8 Male: 49%, Female: 51% Ethnicity: not stated.
Patient characteristics	Patients hospitalised for generalised peritonitis or abdominal abscess
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: Mortality: 31%	

Study	Bohnen 1988[30]
	APACHE II score and use of steroids are factors independently associated with mortality. Mean APACHE II score: 13.72 Mean APACHE II score in patients who died: 18.9 Mean APACHE II score in survivors: 11.4 General limitations according to QUADAS II Selection of patients: single centre. Retrospective (database)

Table 6: BOHNEN 1994

Study	Bohnen 1994[31]
Study type	Retrospective cohort
Number of studies (number of participants)	n=297
Countries and Settings	The Wellesley University Hospital, Canada
Funding	Not stated
Duration of study	1985-1989 (Follow up: in hospital)
Age, gender, ethnicity	Age: 58 Male/ Female: not stated Ethnicity: not stated.
Patient characteristics	Patients treated surgically or percutaneous for abdominal infection . 24% immunocompromised
Index test	APACHE II

Study	Bohnen 1994[31]
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: Mortality: 30% APACHE II score and use of steroids are independent factors for mortality. General limitations according to QUADAS II Selection of patients: single centre. Retrospective (database)	

Table 7: BUCK 2012

Study	Buck 2012[40]
Study type	Prospective cohort
Number of studies (number of participants)	N=117 consecutive patients who underwent surgical treatment for peptic ulcer perforation.
Countries and Settings	Denmark Scores taken preoperatively.
Funding	Not stated
Duration of study	1 Jan 2008 – 31 Dec 2009 30 day follow-up
Age, gender, ethnicity	Age median = 70 (25-92) Male = 57, Female = 60
Patient characteristics	ASA grade 1 = 12 ASA grade 2 = 43 ASA grade 3 = 15

Study	Buck 2012[40]
	ASA grade 4 = 2 ASA grade 5 = 59 Daily smoking = 59 Alcohol abuse = 30 BMI median = 24 (15-65) Co-morbidity = 85
Index test	APACHE II ASA score Boey score Sepsis score
Reference standard	N/A
Target condition/ patient outcomes	30 day mortality Septic shock ICU admission
Results: APACHE II score ≥ 12: 30 day mortality PPV = 24% 30 day mortality NPV = 97% 30 day mortality RR (95% CI) = 31.6 (1.8-542.2) Septic shock PPV = 35% Septic shock NPV = 94% Septic shock RR (95% CI) = 10.0 (1.4-69.4) ICU admission PPV = 49% ICU admission NPV = 75% ICU admission RR (95% CI) = 2.7 (0.8-9.5) Sepsis score ≥ 3:	

Study	Buck 2012[40]
30 day mortality PPV = 41% 30 day mortality NPV = 90% 30 day mortality R (95% CI) = 7.7 (2.1-28.0) Septic shock PPV = 72% Septic shock NPV = 88% Septic shock RR (95% CI) = 14.6 (4.2-50.2) ICU admission PPV = 80% ICU admission NPV = 69% ICU admission RR (95% CI) = 10.2 (2.6-39.7)	

Table 8: CHEN 2009

Study	Chen 2009[58]
Study type	Prospective cohort
Number of studies (number of participants)	Total n=640 with SIRS Participants with sepsis n=327
Countries and Settings	China ED
Funding	Not stated
Duration of study	Dec 2006 – Sep 2007
Age, gender, ethnicity	Age: 69.5±13.4 Male: 60.6%
Patient characteristics	Heart disease (%): 19.9 Hypertension (%): 27.5 Diabetes (%): 13.8 COPD (%): 43.7 Asthma (%): 2

Study	Chen 2009[58]
	Renal failure (%): 2 Stroke (%): 13.8 Others (%): 10.4 No basic disease (%): 9.8
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	28 day mortality
Results: Cut-off values for 28 day mortality (APACHE II), in septic patients Cut-off value: 21.5 Sensitivity (%): 35 Specificity (%): 88 PPV (%): 63 NPV (%): 69 AUC : 0.664 OR (95% CI): 3.9 (2.2-6.9) P=<.001 Study reports a significantly better predictive value of BNP compared to APACHE II in predicting 28 day mortality. Limitations: Unclear what setting APACHE II carried out (patients had confirmed SIRS and carried score was carried out within 24hours)	

Table 9: CHEN 2013

Study	Chen 2013D[59]
Study type	Prospective single-centre cohort
Number of studies (number of participants)	N=837 consecutive SIRS patients
Countries and Settings	China ED – MEDS scores calculated when patients arrived at ED.
Funding	Not stated
Duration of study	Dec 2011 – Sep 2012
Age, gender, ethnicity	Age: 71 (59-78) Male: 61.2%
Patient characteristics	-
Index test	MEDS
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results: In-hospital mortality for patients with sepsis (MEDS): OR=1.127, p=0	

Table 10: CHEN 2006

Study	Chen 2006[55]
Study type	Retrospective cohort
Number of studies (number of participants)	n=276 admitted to ED
Countries and Settings	Urban medical centre, Taiwan

Study	Chen 2006[55]
Funding	Not stated
Duration of study	January 2002 - December 2003 (28 days follow up)
Age, gender, ethnicity	Age: 72 (15.6) Male: 45%, Female: 55% Ethnicity: not stated.
Patient characteristics	Adults (≥18 years) admitted to non-surgical ICUs through the ED, with evidence of infection (tentative diagnosis of ‘sepsis’ documented by physician in the ED, or clear lab evidence, e.g. pneumonia on chest radiograph, abscess formation, bacterial cultures, etc. Exclusion: patients dead on arrival to the ED, pregnant women, those with major or multiple trauma, those with major surgery prior to ICU admission, those with terminal illness who had ‘do not attempt resuscitation ‘orders documented by treating physician in the ED. Most common site of infection: Pulmonary system: 49.2% Urinary tract: 28.9% Patients divided into 2 groups: Group A: MEDS score <12 (n=143) Group B: MEDS score 12-27 (n=133)
Index test	MEDS
Reference standard	APACHE II
Target condition/ patient outcomes	Mortality (28-day)
Results: 28-day mortality: Group A: 17.5% Group B: 48.9%	

Study	Chen 2006[55]
AUC: MEDS: 0.745 APACHE II: 0.624 General limitations according to QUADAS II Selection of patients: single centre.	

Table 11: CHEN 2013A

Study	Chen 2013A[60]
Study type	Prospective cohort
Number of studies (number of participants)	n=1691 ED patients with community acquired sepsis (CAS) (n=831 derivation cohort; n=860 validation cohort)
Countries and Settings	China ED (Beijing Chao-Yang Hospital, urban university tertiary hospital)
Funding	Not stated (no conflict of interest)
Duration of study	28 days follow up Study conducted between August 2011 and January 2013
Age, gender, ethnicity	Age: Derivation cohort 66 (55-76); validation cohort 64 (52-76) Derivation cohort Male: 63%, Female: 37%; validation cohort Male: 61%, Female: 39%; Ethnicity: not stated.
Patient characteristics	Inclusion criteria: age >18 years; no hospital admissions in the month prior to enrolment; infection was the major reason for the admission; meeting ≥2 criteria of SIRS; clinically diagnosed infection. Exclusion criteria: Age <18 years; terminal stage of disease (malignant cancer of any type, AIDS, end-stage renal or hepatic disease; chronic heart failure); refusal to participate in the study by patients or their relatives.
Index test	PIRO
Reference standard	APACHE II
Target condition/ patient outcomes	Mortality (28-day)

Study	Chen 2013A[60]
Results: 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 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 93.1 General limitations according to QUADAS II Selection of patients: single centre.	

Table 12: CHEN 2014A

Study	Chen 2014A[61]
Study type	Retrospective cohort
Number of studies (number of participants)	N=680 sepsis patients.

Study	Chen 2014A[61]
Countries and Settings	Emergency department at Beijing Chao-Yang hospital, China
Funding	Not stated
Duration of study	November 2011 - October 2012
Age, gender, ethnicity	Age: 73 (60-79) Male: 61.2% Female: 38.8% Ethnicity: not stated.
Patient characteristics	Infection site: Pneumonia: n=467 Intra-abdominal infection: n=170 Pyelonephritis: n=21 Central nervous system infection: n=18 Other infections: n=4 APACHE II score: 17.0±7.7 MEDS score: 11 (8-16) PIRO score: 11 (9-14) 28-day mortality: 26.2% ICU admission: 21.8% MOD within 3 days: 34.4%
Index test	APACHE II score MEDS score PIRO score
Reference standard	N/A
Target condition/ patient outcomes	MOD ICU admission 28 day mortality
Results: Admission to ICU:	

Study	Chen 2014A[61]
PIRO: AUC=0.889 (0.855-0.923), OR=1.758 (1.559-1.982) MEDS: AUC=0.774 (0.731-0.817) , OR=0.980 (0.919-1.044) APACHE II: AUC=0.789 (0.750-0.829) , OR=1.046 (1.002-1.092) MOD: PIRO: AUC=0.817 (0.785-0.849) , OR=1.343 (1.241-1.454) MEDS: AUC=0.758 (0.721-0.796) , OR=1.043 (0.992-1.097) APACHE II: AUC=0.764 (0.727-0.801) , OR=1.067 (1.032-1.104) 28-day mortality: PIRO: AUC=0.744 (0.701-0.786) , OR=1.119 (1.043-1.200) MEDS: AUC=0.736 (0.693-0.779) , OR=1.067 (1.015-1.122) APACHE II: AUC=0.742 (0.700-0.784) , OR=1.078 (1.043-1.114) General limitations according to QUADAS II Retrospective, single centre	

Table 13: CILDIR 2013

Study	Cildir 2013[63]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=230)
Countries and Settings	Turkey, ED
Funding	None reported.
Duration of study	August 2009 – February 2011
Age, gender, ethnicity	Mean age (SD): not reported

Study	**Cildir 2013[63]**
	Gender: 132/98 F Ethnicity: not reported
Patient characteristics	Inclusion criteria: 18 years and older, diagnosis of community-acquired sepsis Consecutive recruitment during study period Sepsis (n=64), severe sepsis (n=166)
Index test	MEWS, mMEDS
Reference standard	N/A
Target condition/ patient outcomes	28-day mortality
Results: Predictive value of MEWS in the prediction of 28-day mortality for patients with sepsis (n=64): Cut-off value: ≤5 Sensitivity: 87.5 Specificity: 30.4 PPV: 15.2 NPV: 94.4 AUC: 0.574 Predictive value of MEWS in the prediction of 28-day mortality for patients with severe sepsis (n=166): Cut-off value: >6 Sensitivity: 48.5 Specificity: 67.0 PPV: 49.2 NPV: 66.3 AUC: 0.596 Predictive value of MEWS in the prediction of 28-day mortality: Cut-off value: >6 Sensitivity: 43.24	

Study	Cildir 2013[63]
Specificity: 75 PPV: 45.1 NPV: 73.6 AUC: 0.608 Predictive value of mMEDS in the prediction of 28-day mortality for patients with sepsis (n=64): Cut-off value: >9 Sensitivity: 87.5 Specificity: 80.4 PPV: 38.9 NPV: 97.8 AUC: 0.834 Predictive value of mMEDS in the prediction of 28-day mortality for patients with severe sepsis (n=166): Cut-off value: >12 Sensitivity: 68.2 Specificity: 65.0 PPV: 56.2 NPV: 75.6 AUC: 0.712 Predictive value of mMEDS in the prediction of 28-day mortality: Cut-off value: >10 Sensitivity: 90.54 Specificity: 55.1 PPV: 48.9 NPV: 92.5 AUC: 0.772	
General limitations according to QUADAS II	

Study	Cildir 2013[63]
Selection of patients: prospective observational design; single centre; no standardised treatment; different cut-off values for sepsis and severe sepsis	

Table 14: COOKE 1999

Study	Cooke 1999[65]
Study type	Retrospective cohort
Number of studies (number of participants)	n=91
Countries and Settings	Emergency departments, UK
Funding	The Pulse Trust
Duration of study	1 month period, 10 March – 9 April 1998One month
Age, gender, ethnicity	Age, gender, and ethnicity not stated.
Patient characteristics	Computerised record of patients admitted from ED to critical care
Index test	MTS
Reference standard	N/A
Target condition/ patient outcomes	Admission to ICU
Results: 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 General limitations according to QUADAS II Retrospective; small sample size	

Table 15: CORFIELD 2014

Study	Corfield 2014[67]
Study type	Retrospective cohort
Number of studies (number of participants)	n=2003
Countries and Settings	20 emergency departments in Scotland
Funding	Not stated
Duration of study	Data collected over a 3-month period, March-May 2009
Age, gender, ethnicity	Age: Median 72 years Male: 47%, Female: 53% Ethnicity: not stated.
Patient characteristics	Patients who had (a) a suspicion or confirmation of infection within 2 days of attendance to the ED and (b) two or more of the following: temperature >30.8 or < 36; heart rate >90 bpm; respiratory rate >20/min; white cell count of >12000/microL or <4000 microL or >10% immature forms; acutely altered mental status; systolic blood pressure <90 mm Hg; blood glucose >7.7 mmol/L (in the absence of diabetes).
Index test	NEWS
Reference standard	N/A
Target condition/ patient outcomes	Mortality

Results:

Admission to ICU within 2 days:

NEWS score	% patients not admitted	% patients admitted
0-4	96.8	3.2
5-6	96.9	3.1
7-8	95.6	4.4
9-20	89.0	11.0
Total	94.4	5.6

Study	Corfield 2014[67]
AUC: 0.67 (0.61-0.72) 30 days in-hospital mortality: NEWS score % patients who not died % patients who died 0-4 94.5 5.5 5-6 88.7 11.3 7-8 86.7 13.3 9-20 72.4 27.6 Total 85.2 14.8 AUC: 0.70 (0.67-0.74) General limitations according to QUADAS II Retrospective; patients discharged and died at home within 30 days are not included; patients admitted to ICU after 2 days not included; no information on comorbidities	

Table 16: CROWE 2010

Study	Crowe 2010[68]
Study type	Secondary analysis of prospectively collected data.
Number of studies (number of participants)	N=216 treated with modified EDGT
Countries and Settings	ED USA
Funding	Not stated
Duration of study	May 2007-May 2008
Age, gender, ethnicity	Age: 22-97, median=71.5 Male: 50.2%
Patient characteristics	Pneumonia=81

Study	Crowe 2010[68]
	Urosepsis=49 Multiple aetiologies=38 Gastrointestinal=16 Bacteremia=15 Wound=4 Unidentified=13
Index test	MEDS mREMS CURB-65
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results: 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) General limitations according to QUADAS II Selection of patients: single centre.	

Table 17: DE GROOT 2014

Study	de Groot 2014A[73]
Study type	Prospective cohort

Study	de Groot 2014A[73]
Number of studies (number of participants)	N=323 high risk cohort N=485 low risk cohort
Countries and Settings	The Netherlands ED
Funding	Not stated
Duration of study	1 November 2007 – 1 April 2011
Age, gender, ethnicity	≥17 years Mean age (high risk): 66 Mean age (low risk): 57 Male (high risk) n=183 Male (low risk) n=201
Patient characteristics	High risk cohort with severe sepsis and septic shock. Low risk cohort with
Index test	PIRO MEDS
Reference standard	NA
Target condition/ patient outcomes	28 day mortality In-hospital mortality
Results: 28 day mortality AUC PIRO: 0.81 (0.72-0.91) MEDS: 0.79 (0.71-0.87) In-hospital mortality AUC 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)	

Study	de Groot 2014A[73]
Limitations: Single centre	

Table 18: EDWARDS 2015

Study	Edwards 2015[82]
Study type	Retrospective cohort
Number of studies (number of participants)	n=364 (Maternity population)
Countries and Settings	Tertiary unit, USA
Funding	The authors report no conflict of interest
Duration of study	June 2006 – November 2007
Age, gender, ethnicity	Age: not stated Male:Female 0:100 Ethnicity: not stated.
Patient characteristics	maternity population with chorioamnionitis (maternal pyrexia in labour ≥38°.associated with uterine tenderness, maternal or foetal tachycardia, or purulent/foul smelling amniotic fluid
Index test	6 different types of MOEWS (modified obstetric early warning scoring systems), representing the 2 most common methods of track-and-trigger early warning systems: colour coded trigger bands and numerical scoring triggers MEWS
Reference standard	N/A
Target condition/ patient outcomes	Severe sepsis or mortality

Results, expressed in %:

	Sensitivity	Specificity	PPV	NPV	AUC
MOEWS A	100 (47.8-100)	29 (24.3-34)	1.92 (0.63-4.43)	100 (69.5-100)	65 (62-67)
MOEWS B	100 (47.8-100)	3.9 (2.15-6.46)	1.43 (0.47-3.3)	100 (76.8-100)	52 (51-53)
MOEWS C	100 (47.8-100)	3.6 (1.94-6.11)	1.42 (0.46-3.29)	100 (75.3-100)	52 (51-53)
MOEWS D	60 (14.7-94.7)	84.4 (80.2-88)	5.08 (1.06-14.1)	99.3 (97.7-99.9)	72 (48-96)

Study	Edwards 2015[82]				
MOEWS E	40 (5.27-85.3)	96.9 (94.6-98.5)	15.4 (1.92-54.4)	99.1 (97.5-99.8)	68 (44-92)
MOEWS F	40 (5.27-85.3)	90.8 (87.3-93.6)	5.71 (0.70-19.2)	99.1 (97.4-99.8)	65 (41-89)
MEWS	100 (47.8-100)	90.4 (87.7-91.8)	5.15 (1.69-11.6)	100 (99.5-100)	95 (94-967)
General limitations according to QUADAS II Retrospective design, single centre					

Table 19: GARDNER-THORPE 2006

Study	Gardner-Thorpe 2006[106]
Study type	Prospective cohort
Number of studies (number of participants)	n=334
Countries and Settings	In-patient surgical, UK
Funding	Not stated
Duration of study	16 May -23 September 2003
Age, gender, ethnicity	Age: Mean 58.6 (19.2) years Male:Female 1:1.02 Ethnicity: not stated.
Patient characteristics	Consecutive emergency and elective patients, admitted under the colorectal team
Index test	MEWS
Reference standard	N/A
Target condition/ patient outcomes	Admission to ICU
Results: Admission to ITU or HDU: 16/334 (5%)	

Study	Gardner-Thorpe 2006[106]	
	Sensitivity (%)	Specificity (%)
MEWS ≥3	88	68
MEWS ≥4	75	83
MEWS ≥5	38	89
MEWS ≥6	19	93
MEWS ≥7	6	94
General limitations according to QUADAS II Retrospective design		

Table 20: GIANNAZZO 2006

Study	Giannazzo 2006[110]
Study type	Retrospective cohort
Number of studies (number of participants)	N=90
Countries and Settings	Italy ED from June 2004-June 2005
Funding	Not stated
Duration of study	28 day follow up
Age, gender, ethnicity	Age = 77 ± 15 (28-98) Female: 49/90 (54.4%)
Patient characteristics	Clinical suspicion of infection and 2 or more SIRS criteria and elevated lactate level (>4mmol/l) or systolic blood pressure <90mmHg.
Index test	SOFA
Reference standard	NA
Target condition/ patient outcomes	Adverse outcome at 24 hours
Results:	

Study	Giannazzo 2006[110]
Stepwise forward regression model adjusted for age >80 years, COPD, ARF, DIC, SO2, serum lactate, NNPV Adverse outcome at 24 hours: Sofa score >7 = OR 15.86 (1.40-179.32), p=0.026 Adverse outcome at 28 days: Sofa score >7 = NS p=0.157 General limitations according to QUADAS II Retrospective, single centre	

Table 21: HAMILTON 2007

Study	Hamilton 2007[118]
Study type	Retrospective cohort
Number of studies (number of participants)	n= 91, two University of Pennsylvania hospitals, USA
Countries and Settings	Two University of Pennsylvania hospitals, USA
Funding	Public Health Service grant from the National Institute of Health
Duration of study	January 1998 – June 1999
Age, gender, ethnicity	Age: 70 (67-74) Male: 44%, Female: 56% Ethnicity: 54.8% African-American, 40.5% White, 4.8% Latino.
Patient characteristics	Patients with positive culture (E.coli and K. pneumoniae) and complete APACHE II data
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: Overall mortality rate: 13.2%. Day of calculation, subject group Median APACHE II score (95% CI)	

Study	Hamilton 2007[118]
Day specimen was obtained	
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)
General limitations according to QUADAS II	
Selection of patients: single centre; small sample size; only patients hospitalised for at least 2 days prior to collection of a specimen.	

Table 22: HERMANS 2012

Study	Hermans 2012[120]
Study type	Retrospective cohort
Number of studies (number of participants	n=331
Countries and Settings	Secondary and tertiary care university hospital, Netherlands
Funding	Not stated
Duration of study	August 2009 – February 2010 (follow up: 28 days)
Age, gender, ethnicity	Mean age: 63.4 (17.3) Male: 51%, Female: 49% Ethnicity: not stated
Patient characteristics	Inclusion criteria: Age ≥18 years, examined by an internist, admitted to hospital, fulfilled the clinical criteria for sepsis, severe sepsis, or septic shock, or whose blood was cultured regardless of the sepsis criteria

Study	Hermans 2012[120]
Index test	MEDS score
Reference standard	N/A
Target condition/ patient outcomes	In hospital mortality within 28 days.
<u>Results:</u> Overall 28-day mortality: 11.5% 28-day mortality in each MEDS category: MEDS ≤4 3.1% MEDS 5-7 5.3% MEDS 8-12 17.3% MEDS 13-15 40.0% MEDS >15 77.8% AUC: 0.81 (0.73-0.88) <u>General limitations according to QUADAS II</u> Single centre	

Table 23: HILDERINK 2015

Study	Hilderink 2015[121]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=600)
Countries and Settings	Netherlands, ED
Funding	Not stated.

Study	Hilderink 2015[121]
Duration of study	August 2009 – July 2010
Age, gender, ethnicity	Mean age (SD): 64.6 years (17.6) Gender: 296/304 F Ethnicity: not reported
Patient characteristics	Inclusion criteria: 18 years and older, clinical criteria for sepsis/severe sepsis/septic shock Consecutive recruitment during study period Sepsis (57.3%), severe sepsis (36.7%), septic shock (6.0%)
Index test	APACHE II, MEDS, CURB-65, RAPS, REMS
Reference standard	N/A
Target condition/ patient outcomes	28-day mortality
Results: AUC (95% CI) for in-hospital mortality: MEDS (n=595): 0.82 (0.77-0.86) CURB-65 (n=577): 0.82 (0.77-0.87), p=0.911 CURB-65 (n=222): 0.77 (0.69-0.85), p=0.952 APACHE II (n=256): 0.76 (0.68-0.84), p=0.748 RAPS (n=596): 0.72 (0.66-0.79), p=0.003 REMS (n=594): 0.78 (0.72-0.83), p=0.127 AUC (95% CI) for total mortality: MEDS (n=595): 0.82 (0.78-0.87) CURB-65 (n=577): 0.78 (0.73-0.83), p=0.095 CURB-65 (n=222): 0.72 (0.63-0.80), p=0.125 APACHE II (n=256): 0.71 (0.64-0.79), p=0.196 RAPS (n=596): 0.70 (0.64-0.76), p<0.001 REMS (n=594): 0.74 (0.69-0.80), p=0.007	
General limitations according to QUADAS II Selection of patients: retrospective design; single centre; no standardised treatment	

Table 24: HOWELL 2007

Study	Howell 2007[129]
Study type	Prospective cohort
Number of studies (number of participants	n=2132
Countries and Settings	Urban tertiary care university hospital, USA
Funding	Not stated
Duration of study	December 2003 – September 2004 (follow up: 28 days)
Age, gender, ethnicity	Mean age: 61 (44-77) Male: 48%, Female: 52% Ethnicity: 76% White, 14% African-American, 11% other
Patient characteristics	Consecutive patients (age ≥18 years) presenting to the ED with suspected infection.
Index test	MEDS score mREMS (modified REMS: GCS is replaced with confusion, binary Y/N) CURB-65
Reference standard	N/A
Target condition/ patient outcomes	28 days mortality

Study	Howell 2007[129]
Results: Overall 28-day mortality: 3.9% CURB-65 0.788 (0.744-0.833) mREMS 0.802 (0.752-0.852) MEDS 0.849 (0.812-0.887) General limitations according to QUADAS II Single centre; misclassification bias based on missing or improperly charted data; MEDS shows the best performance but this score was developed at the same centre.	

Table 25: JO 2013

Study	Jo 2013[137]
Study type	Retrospective cohort
Number of studies (number of participants	n=151
Countries and Settings	South Korea ED (tertiary care hospital)
Funding	Not stated (no conflict of interest)
Duration of study	April 2010 – March 2011 (follow up: 28 days)
Age, gender, ethnicity	Mean age: 65.3±17.2 Male: 68%, Female: 32% Ethnicity: not stated
Patient characteristics	Critically ill patients. 65.6% had sepsis Inclusion criteria: consecutive patients (age ≥18 years) admitted to the MICU via the ED. Exclusion criteria: patients whose medical records lacked one or more elements needed to establish a modified early warning score.

Study	Jo 2013[137]
Index test	ViEWS ViEWS-L (with Lactate) APACHE II SAPS II SAPS III
Reference standard	N/A
Target condition/ patient outcomes	In hospital mortality; 28-day mortality
Results: 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) 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) General limitations according to QUADAS II Single centre; small sample size.	

Table 26: JOHNSTON 2005

Study	Johnston 2005[138]

Study	Johnston 2005[138]
Study type	Secondary analysis of prospectively collected data.
Number of studies (number of participants)	N=826 with suspected of confirmed infection, meeting criteria for modified SIRS and ≥1 dysfunctional organ system.
Countries and Settings	USA Score calculated within 24 hours of admission to trial.
Funding	Not stated
Duration of study	July 1998 - June 2000
Age, gender, ethnicity	Age: 60.6 (16.5) Male: 57.9%
Patient characteristics	Type of admission: Medical = 72.4% Emergency surgical = 21.3% Elective surgical = 6.3% Primary focus of infection Lung/pleura = 51.1% Intra-abdominal = 19.9% Urinary tract = 11.1% Other or unknown = 18.3% Time in hospital before diagnosis (days) 0-1 = 68.4% 2-5 = 14.5% ≥6 = 17.1%
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results:	

Study	Johnston 2005[138]
In-hospital mortality APACHE II acute physiology score OR 1-15: 1 16-19: 0.99 (0.61-1.62) 20-25: 1.35 (0.84-2.16) ≥26: 2.31 (1.39-3.83) APACHE II chronic health points OR 0: 1 ≥2: 2.00 (1.36-2.94) 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.	

Table 27: KOFOED 2008

Study	Kofoed 2008[153]
Study type	Prospective cohort
Number of studies (number of participants)	n=151
Countries and Settings	University Hospital, Denmark
Funding	Research Foundation at Copenhagen University Hospital, Hvidovre; and H:S Research Foundation. suPAR antibodies and suPARnostic kits were gifts from ViroGated (Copenhagen, Denmark)
Duration of study	February 2005 – February 2006. In hospital (follow up: 30 and 180 days)
Age, gender, ethnicity	Age: 56 (20-94) Male: 48%, Female: 52% Ethnicity: not stated.
Patient characteristics	Adults (≥18 years) newly admitted to ED or infectious disease services who fulfilled at least 2 criteria of SIRS.

Study	Kofoed 2008[153]
	Comorbidities (44.7%): Malignancies, HIV infection, diabetes, COPD, asthma, cardiovascular disease, drug abuse.
Index test	SAPS II, SOFA
Reference standard	N/A
Target condition/ patient outcomes	Mortality (30-day and 180-day)

Results:

30-day mortality: 6%

180-day mortality: 13%

	Sens.	Spec.	AUC
30-days			
SAPS II >22.5	100	68	0.89 (0.80-0.98)
SOFA >4.5	44	95	0.80 (0.65-0.94)
180 days			
SAPS II >22.5	100	73	0.91 (0.56-0.96)
SOFA >1.5	74	61	0.75 (0.64-0.86)

General limitations according to QUADAS II

Selection of patients: single centre; small number of outcomes (deaths).

Table 28: KOMATSU 2006[155,155]

Study	Komatsu 2006[155]
Study type	Retrospective cohort
Number of studies (number of participants)	n=26
Countries and Settings	Nagahama Red Cross Hospital, Japan
Funding	Not stated

Study	Komatsu 2006[155]
Duration of study	1996-2003. In hospital (follow up: until death or discharge from surgical ward. Mean: 42 (2-150) days)
Age, gender, ethnicity	Age: 69.0 (34-88) Male: 54%, Female: 46% Ethnicity: not stated.
Patient characteristics	Patients with signs of peritonitis who underwent emergency surgery for colorectal perforation. Exclusion: patients with colonic perforations associated with trauma or iatrogenic causes.
Index test	APACHE II, SOFA, MPI, MOF
Reference standard	N/A
Target condition/ patient outcomes	Mortality (in hospital)

Results:

Overall mortality: 26.9%

	Survivors (n=19)	Non-survivors (n=7)
APACHE II ≥19	0 (0%)	6 (85.7%)
APACHE II <19	19 (100%)	1 (14.3%)
SOFA ≥8	3 (15.9%)	7 (100%)
SOFA <8	16 (84.1%)	0 (0%)
MPI ≥30	4 (21.1%)	6 (85.7%)
MPI <30	15 (78.9%)	1 (14.3%)
MOF ≥7	3 (15.9%)	7 (100%)
MOF <7	16 (84.1%)	0 (0%)

General limitations according to QUADAS II
Selection of patients: single centre; surgical patients; small sample size.

Table 29: KUMAR 1995

Study	Kumar 1995[158]
Study type	Prospective cohort
Number of studies (number of participants)	n=86
Countries and Settings	General surgery, Kasturba Medical College, India
Funding	Not stated
Duration of study	2-year period Follow up: in hospital
Age, gender, ethnicity	Age, gender, and ethnicity not stated
Patient characteristics	Intra-abdominal sepsis after surgery
Index test	APACHE II (arterial blood gases and pH were not available and omitted from the score calculation)
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: Overall mortality: 33.7% APACHE II score / Patients, n / Deaths, n (%) 0-5 / 18 / 1 (5.6) 6-10 / 30 / 2 (6.7) 11-15 / 20 / 9(45) 16-20 / 12 / 11 (91.7) 21-25 / 5 / 5 (100) 26-30 / 1 / 1 (100) Duration of illness and source of infections are also found to be predictors of mortality.	

Study	Kumar 1995[158]
General limitations according to QUADAS II Single centre; small sample size; selected group of patients	

Table 30: LEVISON 1991

Study	Levison 1991[170]
Study type	Retrospective cohort
Number of studies (number of participants)	N=91
Countries and Settings	USA October 1980 - November 1987
Funding	Not stated
Duration of study	Unclear (in hospital)
Age, gender, ethnicity	Age: 54.8 years (21-95) 50 male, 41 female
Patient characteristics	Intra-abdominal abscess after surgery
Index test	APACHE II
Reference standard	NA
Target condition/ patient outcomes	Mortality
Results: 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)	

Study	Levison 1991[170]
P=0.24 General limitations according to QUADAS II Retrospective, single centre	

Table 31: MACDONALD 2014

Study	Macdonald 2014[179]
Study type	Subgroup analysis of data gathered in the Critical Illness and Shock Study (CISS)[14,14]
Number of studies (number of participants)	n=240 patients with sepsis (including severe sepsis and septic shock) in ED.
Countries and Settings	Australia ED (two metropolitan hospitals in Perth)
Funding	Partially funded by a grant from the Medical Research Foundation, Royal Perth Hospital
Duration of study	30 days follow up Study conducted between March 2010 and July 2013
Age, gender, ethnicity	Age (range): 67 (51-78) 36% Female/ 64% Male Ethnicity: not stated
Patient characteristics	Patients presenting to the ED with a range of critical illnesses and meeting physiologic criteria suggesting shock or organ failure Sepsis: 18%; severe sepsis: 29%; septic shock: 53%
Index test	PIRO MEDS SOFA
Reference standard	N/A
Target condition/ patient outcomes	30-day mortality

Study	Macdonald 2014[179]
Results: AUC PIRO 86 (80-92) MEDS 81 (74-88) SOFA 78 (71-85) General limitations according to QUADAS II Subgroup analysis of sepsis patients within a broader study of ED patients presenting with crucial illness; small number of participants.	

Table 32: MOSCOVITZ 1994

Study	Moscovitz 1994[200]
Study type	Prospective
Number of studies (number of participants)	n=100 admitted to ED with signs of infection or anticipated bacteraemia.
Countries and Settings	USA ED of the Hospital of the University of Pennsylvania
Funding	Not stated
Duration of study	In hospital follow up
Age, gender, ethnicity	Mean age: 51 63% Female/ 37% Male
Patient characteristics	Patients were enrolled if they had: a) the presumptive diagnosis of bacteraemia as defined by a decision by the emergency physician to perform blood cultures and b) at least one of the following: temperature >38°C or <36.5°C, hypotension (mean arterial pressure < 70 mmHg), leucocytosis (white blood cell count >12500 cells/mm3, metabolic acidosis (arterial pH<7.28), or physical findings indicative of focal infection. Patients were excluded if they were known to have neoplastic disease or acquired immunodeficiency syndrome, if they were pregnant, of it they were currently taking immunosuppressive medications, non-steroidal inflammatory drugs, or antibiotics.
Index test	APACHE II

Study	Moscovitz 1994[200]
Reference standard	N/A
Target condition/ patient outcomes	Mortality Bacteraemia
Results: 21 patients used the ICU within 72h of admission. Mean APACHDE II score 12.1±8.2 at entry. Mortality was predicted by an increase on in IL6 (p=0.009), TNF-alpha (p=0.009), and medical evaluation indicating severity (p=0.001). Bacteraemia was predicted by IL6 and APACHE II. General limitations according to QUADAS II It is not specified in which setting APACHE II was evaluated, but only 21 patients required ICU treatment in the 72h after admission.	

Table 33: MYLOTTE 2001

Study	Mylotte 2001[208]
Study type	Retrospective cohort
Number of studies (number of participants)	N=174
Countries and Settings	USA 1 teaching hospital and 1 non-teaching hospital
Funding	Not stated
Duration of study	30 days
Age, gender, ethnicity	≥18 years
Patient characteristics	Patients' ≥18 years with CAB retrospectively identified from blood cultures.
Index test	APACHE III
Reference standard	NA

Study	Mylotte 2001[208]
Target condition/ patient outcomes	30 day mortality
Results: Logistic regression model adjusted for underlying disease, age, initial combination antibiotic treatment, intravenous catheter source of CAB, S aureus bacteraemia and E coli bacteraemia. 30 day mortality: APACHE III score >35 on admission = OR 5.6 (2.6-13.1) p=<.001 General limitations according to QUADAS II Retrospective, single centre	

Table 34: OSBORN 2014

Study	Osborn 2014[225]
Study type	Retrospective cohort
Number of studies (number of participants)	n=23,428 90% (21,085) of subjects used for the development of the prediction model 10% (2343) of subjects used for the internal validation
Countries and Settings	Multicentre, SSC database with data from 218 hospitals in 18 countries ED, hospital ward, or ICU
Funding	Not stated
Duration of study	January 2005 – December 2009 (in-hospital follow up)
Age, gender, ethnicity	Not stated (patients demographics were not collected in defence to country-specific privacy laws).
Patient characteristics	All patients in the SSC database with severe sepsis or septic shock
Index test	SSS (Sepsis Severity Score)

Study	Osborn 2014[225]
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results: In-hospital mortality: 44.6% for patients presented to the ED 39.7% for patients presented to the hospital ward 15.7% for patients presented to the ICU AUC : 0.736 (development cohort); 0.748 (validation cohort) General limitations according to QUADAS II Retrospective database, demographic and comorbidities not considered; only valid for patients with severe sepsis or septic shock; SSS not tested for septic trauma patients and septic general surgery patients.	

Table 35: PRYTHERCH 2010

Study	Prytherch 2010[242]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=198,755 patient episodes) Patient episodes defined as consecutive, completed, acute medical admissions (patients who were well enough to be discharged from hospital before midnight on the day of admission were excluded).
Countries and Settings	UK, medical assessment unit
Funding	The vital signs data gathering system used was developed in collaboration with The Learning Clinic Ltd
Duration of study	May 2006 – June 2008
Age, gender, ethnicity	Mean age (SD): 67.7 years Gender: 47.5% male Ethnicity: not reported
Patient characteristics	Inclusion criteria: not reported

Study	Prytherch 2010[242]
Index test	ViEWS
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality
Results: AUC (95% CI) for in-hospital mortality within 24 hours of the observation: 0.888 (0.880-0.895)	
General limitations according to QUADAS II Selection of patients: prospective observational design; single centre; limited information on recruitment; limited information on patient characteristics; no standardised treatment Indirectness: not sepsis population	

Table 36: SANKOFF 2008

Study	Sankoff 2008[253]
Study type	Prospective cohort
Number of studies (number of participants)	n=385
Countries and Settings	Multicentre, USA
Funding	Not stated
Duration of study	August 2005 – January 2006 (28-day follow up)
Age, gender, ethnicity	Age: 56 (42-71) Male: 55%, Female: 45% Ethnicity: not stated.
Patient characteristics	Adults (≥18 years), presenting to the ED, have met criteria for SIRS, have been admitted to the hospital from the ED. Exclusion: presented to the ED as a result of trauma; already were enrolled in the study from a previous visit; were a direct admission or transfer from another institution or hospital for SIRS or sepsis; were not enrolled within 2 hours of presentation to the ED.

Study	Sankoff 2008[253]
Index test	MEDS score
Reference standard	N/A
Target condition/ patient outcomes	28-day mortality
Results: 28-day mortality: 9% AUC : 0.88 (0-83-0.92) MEDS score classification: Very low: 48% Low: 21% Moderate: 21% High: 6% Very high: 2% General limitations according to QUADAS II	

Table 37: SHAPIRO 2003

Study	Shapiro 2003[268]
Study type	Prospective cohort
Number of studies (number of participants)	n= 3179 (n=2070 for the derivation dataset and n=1109 for the validation dataset)
Countries and Settings	Emergency department (urban tertiary care university hospital), USA
Funding	Not stated

Study	Shapiro 2003[268]
Duration of study	February 2001 - February 2010 (28-day follow up)
Age, gender, ethnicity	Age: 61.4 (19.8) Male: 55%, Female: 45% Ethnicity: not stated.
Patient characteristics	Adults (≥18 years), both medical and surgical, presenting to the ED at risk of infection (as indicated by the ED physician ordering a blood culture)
Index test	MEDS score
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: AUC (derivation dataset): 0.82 AUC (validation dataset): 0.76 General limitations according to QUADAS II Selection of patients: single centre; ED physician ordering blood culture within 3 hours of admission used as surrogate for suspicion of infection. It might miss patients with infection who do not have blood culture performed; it may include patients without infection who have culture sent inappropriately.	

Table 38: SHAPIRO 2007

Study	Shapiro 2007[265]
Study type	Prospective cohort
Number of studies (number of participants)	n= 3102
Countries and Settings	Emergency department (urban tertiary care university hospital), USA
Funding	Not stated

Study	Shapiro 2007[265]
Duration of study	February 2001 - February 2010 (1 year follow up)
Age, gender, ethnicity	Age: 59.9±29.4 Male: 55%, Female: 45% Ethnicity: not stated.
Patient characteristics	Adults (≥18 years), both medical and surgical, presenting to the ED at risk of infection (as indicated by the ED physician ordering a blood culture) Suspected site of infection: lower respiratory: 23.2% skin/soft tissue: 19.0% intra-abdominal: 13.7% fever without a source: 13.4% urosepsis: 9.5% catheter infection: 3.8%
Index test	MEDS score
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: 1-year mortality: Hazard Ratio (95% CI) Low risk (5-7 points): 2.2 (1.7-2.9) Moderate risk (8-12 points): 3.5 (2.7-4.6) High risk (13-15 points): 6.7 (4.9-9.3) Very high risk (>15 points): 10.5 (7.2-15.4) MEDS was an independent predictor of mortality at 1 year. General limitations according to QUADAS II	

Study	Shapiro 2007[265]
Selection of patients: single centre; ED physician ordering blood culture within 3 hours of admission used as surrogate for suspicion of infection. It might miss patients with infection who do not have blood culture performed; it may include patients without infection who have culture sent inappropriately.	

Table 39: TALMOR 2007

Study	Talmor 2007[278]
Study type	Retrospective cohort
Number of studies (number of participants)	n=5133 Cohort 1: Derivation n=3206 Cohort 2: internal validation n=1118 Cohort 3: External validation n=809
Countries and Settings	Emergency departments, USA Cohort 1 and 2: Beth Israel Deaconess Medical Centre, an urban academic medical centre Cohort 3: Carolinas' Medical Centre, a teaching and tertiary referral hospital
Funding	Not stated
Duration of study	In hospital follow up Cohort 1: February 2000 – February 2001 Cohort 2: December 2003 – September 2004 Cohort 3: July 2004 – June 2005
Age, gender, ethnicity	Cohort 1: Age: 60±20 Male: 47%, Female: 53% Ethnicity: not stated. Cohort 2: Age: 64±19 Male: 49%, Female: 51% Ethnicity: not stated. Cohort 3: Age: 54±19 Male: 52%, Female: 48%

Study	Talmor 2007[278]
	Ethnicity: not stated.
Patient characteristics	Cohort 1: consecutive adult patients (≥18 years old) presenting with suspected infection (surrogate marker: clinical decision to obtain a blood culture). Both patients admitted to the hospital and those discharged from the ED were included in this cohort. Exclusion: intra-abdominal infection. Cohort 2: consecutive adult patients (≥18 years old) presenting to the ED with suspected infection and admitted to hospital. Exclusion: intra-abdominal infection and those sent home from the ED. Cohort 3: adult patients (≥18 years old) admitted to hospital from the ED with a principle diagnosis of an infectious pathogenesis. Exclusion: intra-abdominal infection pathogenesis that required surgical intervention. Comorbidities include: cerebrovascular disease, congestive heart failure, diabetes, HIV, malignancy, altered mental status. Common suspected site of infection: respiratory urogenital skin/soft tissue CSF suspected bacteraemia fever without a source other/unknown
Index test	STSS
Reference standard	N/A
Target condition/ patient outcomes	In-hospital mortality Intensive care admission Use of mechanical ventilation

Results:

	Cohort 1	Cohort 2	Cohort 3
In-hospital mortality (%)	5	7	6
Intensive care admission (%)	12	22	15

Study	Talmor 2007[278]

Use of mechanical ventilation (%)	4	13	4

AUC

	Cohort 1	Cohort 2	Cohort 3
In-hospital mortality	0.80	0.76	0.73
Intensive care admission	0.70	0.72	0.70
Use of mechanical ventilation	0.69	0.73	0.68

General limitations according to QUADAS II

Retrospective design; population comprising a heterogeneous set of infectious disease.

Table 40: TER AVEST 2013

Study	ter Avest 2013[279]
Study type	Retrospective cohort
Number of studies (number of participants)	N=70 ED patients with uncomplicated sepsis
Countries and Settings	The Netherlands ED
Funding	Not stated
Duration of study	1 September-December 2010
Age, gender, ethnicity	>18 years Age survivors=57, non-survivors=71
Patient characteristics	
Index test	MEDS
Reference standard	N/A

Study	ter Avest 2013[279]
Target condition/ patient outcomes	Mortality
Results: Abbrev. MEDS score, suRvivors 4.8±2.9, non-survivors=7.2±3.4, p=0.03	

Table 41: VAN VEEN 2008

Study	van Veen 2008[287]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=16,735)
Countries and Settings	Netherlands, ED, dual-centre
Funding	Academic and government funding
Duration of study	13 months (January 2006 – January 2007, university hospital) and 7 months (January – July 2006, teaching hospital)
Age, gender, ethnicity	Mean age (SD): 64.6 years (17.6) Gender: 296/304 F Ethnicity: not reported
Patient characteristics	Inclusion criteria: children under 16 attending EDs of two large inner city hospitals. Exclusion criteria: not reported
Index test	Manchester triage system (MTS)
Reference standard	Predefined independent reference classification of urgency
Target condition/ patient outcomes	Agreement with reference standard – urgency according to the MTS compared with the predefined reference standard for five urgency levels.
Results[a]: Overall: Sensitivity (95% CI): 63 (59-66)	

Study	van Veen 2008[287]
Specificity: 79 (79-80) LR+ (95% CI): 3.0 (2.8-3.2) for a high urgency result LR- (95% CI): 3.0 (2.8-3.2) for a low urgency result Very young patients: 0-2 months: Sensitivity: 50 (42-58) Specificity: 79 (76-82) LR+ (95% CI): 2.4 (1.9-2.9) LR- (95% CI): 0.63 (0.54 to 0.74) 3-11 months: Sensitivity: 65 (56-73) Specificity: 69 (67-72) LR+ (95% CI): 2.1 (1.9-2.5) LR- (95% CI): 0.50 (0.39 to 0.63) 1-3 years: Sensitivity: 67 (61-73) Specificity: 75 (74-77) LR+ (95% CI): 2.7 (2.5-3.0) LR- (95% CI): 0.43 (0.36 to 0.52) Older children: 4-7 years: Sensitivity: 66 (55-76) Specificity: 81 (80-83) LR+ (95% CI): 3.6 (3.0-4.2) LR- (95% CI): 0.41 (0.31 to 0.56)	

Study	van Veen 2008[287]
8-16 years: Sensitivity: 64 (53-73) Specificity: 88 (87-89) LR+ (95% CI): 5.4 (4.5-6.5) LR- (95% CI): 0.41 (0.31 to 0.54)	
General limitations according to QUADAS II Reference standard was based on literature and expert opinion; reference standard only an approximation of an ideal standard; nurses overruled the MTS urgency category in 10% of the patients – inclusion may have lowered the validity of the MTS; attrition – data missing for the reference standard in 9% of patients. Indirectness: population is not sepsis specific	
LR+ =likelihood ratio for high urgency triage test result LR- = likelihood ratio for low urgency triage test result Sensitivity = high urgency (immediate or very urgent) according to MTS/high urgency according to reference standard Specificity = low urgency (urgent, standard, or non-urgent) according to MTS/low urgency according to reference standard	

Table 42: VORWERK 2009

Study	Vorwerk 2009[291]
Study type	Retrospective cohort
Number of studies (number of participants)	n=307
Countries and Settings	UK, EDs of a large urban teaching hospital (Leicester Royal Infirmary) and a district general hospital (Kettering General Hospital)
Funding	None
Duration of study	January 2006 – January 2007 (follow up: 28 days)
Age, gender, ethnicity	Age: mean: 69.7 years (67.5-71.8) Male: 51%, Female: 49% Ethnicity: not stated.

Study	Vorwerk 2009[291]
Patient characteristics	Inclusion criteria: ED diagnosis of sepsis, 2 or more SIRS criteria, working diagnosis of infection documented in the ED notes, blood cultures taken n ED. Exclusion criteria: Missing parameters to calculate MEWS and MEDS.
Index test	MEWS MEDS (abbreviated, without neutrophil bands) Risk stratification: Abbreviated MEDS: low (0-4), moderate (5-12), high (>12) MEWS: low (<5), high (≥5)
Reference standard	N/A
Target condition/ patient outcomes	28-day mortality

Results:

28-day mortality:

Abbreviated MEDS

Low risk	Moderate risk	High risk
1/63 (1.6%)	48/205 (23.4%)	23/39 (50.9%)

For a cut off of abbreviate MEDS ≥5:
Sensitivity: 98.6 (92.5-99.9)%; Specificity: 26.5 (21.0-32.6)%
For a cut off of abbreviate MEDS >12:
Sensitivity: 31.9 (21.4-44.0)%; Specificity: 93.2 (89.2-96.1)%

AUC: 0.82 (0.78-0.87)

MEWS

Low risk	High risk
35.1%	12.6%

Study	Vorwerk 2009[291]
For a cut off of MEWS ≥5: Sensitivity: 72.2 (60.4-82.1)%; Specificity: 59.2 (52.6-65.5)% AUC: 0.72 (0.67-0.77) General limitations according to QUADAS II Selection of patients: retrospective design; death unrelated to sepsis might have occurred.	

Table 43: YILMAZLAR 2007

Study	Yilmazlar 2007[299]
Study type	Retrospective cohort
Number of studies (number of participants)	n=67
Countries and Settings	Tertiary referral centre, Uludag University Medical Faculty, Turkey
Funding	Not stated
Duration of study	January 1986-December 2002 (follow up: unclear)
Age, gender, ethnicity	Age: 54.9±1.73 Male 61%; Female: 39% Ethnicity: not stated.
Patient characteristics	Patients admitted to general surgery with necrotizing soft tissue infections (NSTI). Type of lesion: anorectal, skin, urogenital, 'other'. Common comorbidities: Diabetes mellitus type 2: 51% Atherosclerotic vascular disease: 13%

Study	Yilmazlar 2007[299]
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	Mortality
Results: 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. General limitations according to QUADAS II Selection of patients: single centre; selected group of patients (surgical, with NSTI).	

Table 44: YOO 2015A

Study	Yoo 2015A[302]
Study type	Retrospective cohort
Number of studies (number of participants)	n=100 patients with severe sepsis/septic shock
Countries and Settings	South Korea University hospital
Funding	Not stated (no conflict of interest)
Duration of study	January 2012-August 2012 (follow up: unclear)
Age, gender, ethnicity	Age: 57.9±15.9 Male 59%; Female: 41% Ethnicity: not stated.

Study	Yoo 2015A[302]
Patient characteristics	Patients with severe sepsis/septic shock who were screened or contacted by medical alert team (MAT). Inclusion criteria: age ≥18 years; had been in the general ward for ≥24 h; SBP <90 mmHg at the time at which the MAT was contacted. Exclusion criteria: MEWS could not be calculated due to omission of a measurement; patients with a do not resuscitate status; a MAT was contacted to perform cardiopulmonary resuscitation because the patient had suffered a cardiac arrest caused by septic shock.
Index test	MEWS MEWS + lactate
Reference standard	N/A
Target condition/ patient outcomes	Transfer to ICU 28-day mortality
Results: Prediction of ICU transfer ICU transfer: 38% AUC: MEWS: 81.6 MEWS + Lactate: 89.8 MEWS cut off 5.5 Sens: 81.6 Spec: 66.1 Lactate cut off 30.5 Sens: 73.7 Spec: 87.0 Prediction of 28-day mortality 28-day mortality rate: 19%	

Study	Yoo 2015A[302]
Multivariable analysis OR (95% CI) MEWS: 1.387 (1.090-1.766) Lactate: 1.058 (0.883-1.268)	
General limitations according to QUADAS II Selection of patients: retrospective design; single centre; small sample size.	

Table 45: YZERMAN 1996

Study	Yzerman 1996[304]
Study type	Prospective cohort
Number of studies (number of participants)	n=99
Countries and Settings	University Hospital Rotterdam, Netherlands
Funding	Not stated
Duration of study	3 year period (follow up: in hospital stay)
Age, gender, ethnicity	Age: 54 Male/Female: not stated. Ethnicity: not stated.
Patient characteristics	Patients with hospital acquired bacteraemia. Underlying diseases: History if cardiovascular disease: 51% Diabetes mellitus: 14% Renal disorder: 12%
Index test	APACHE II
Reference standard	N/A
Target condition/ patient outcomes	Mortality Complications

Study	Yzerman 1996[304]
Results: ΔAPACHE II score * / Patients, n / Complications, n (%) / Death, n (%) -2 to 3 / 40 / 0 / 2 (5) 4-6 / 35 / 1 (3) / 2 (6) 7-9 / 16 / 5 (31) / 7 (44) ≥10 / 8 / 1 (13) / 7 (88) *APACHE II score on the day of onset minus APACHE II score 1 day earlier Overall mortality rate: 18% In the multivariate analysis the ΔAPACHE II score was the only independent factor for mortality. General limitations according to QUADAS II Selection of patients: single centre; selected group of patients, in hospital with S. aureus bacteraemia. 40% were taken to ICU at the beginning of bacteraemia.	

ΔAPACHE II score *	Patients, n	Complications, n (%)	Death, n (%)
-2 to 3	40	0	2 (5)
4-6	35	1 (3)	2 (6)
7-9	16	5 (31)	7 (44)
≥10	8	1 (13)	7 (88)

Table 46: ZHAO 2013

Study	Zhao 2013[307]
Study type	Prospective cohort
Number of studies (number of participants)	N=501 adult ED patients with sepsis
Countries and Settings	China
Funding	Not stated
Duration of study	28 days

Study	Zhao 2013[307]
Age, gender, ethnicity	Male: 279 Age median:74
Patient characteristics	COPD: 170 Congestive heart disease = 72 Chronic liver disease = 33 Chronic renal disease = 90 Cerebrovascular disease = 63 Malignancy = 98 Diabetes mellitus = 123 PCT median = 4.3 IL-6 median = 24.3 CRP = 41.0
Index test	MEDS
Reference standard	N/A
Target condition/ patient outcomes	Severity of sepsis 28 day mortality
Results: MEDS: Severity of sepsis = OR 1.356 (1.267-1.450) p=<.001 28 day mortality = OR 1.265 (1.189-1.347) p=<.001 Limitations: single centre	

Table 47: ZHAO 2015

Study	Zhao 2015[306]
Study type	Prospective cohort
Number of studies (number of	1 (n=468: 179 with sepsis, 209 with severe sepsis, 80 with septic shock)

Study	Zhao 2015[306]
participants)	
Countries and Settings	China, high-dependency unit in ED
Funding	Authors report no conflict
Duration of study	February 2013 to July 2014
Age, gender, ethnicity	Mean age (years, SD): for sepsis, severe sepsis and septic shock groups respectively: 67.9±13.6, 68.8±14.4, 67.6±16.5 Gender: 310/468 M Ethnicity: not reported
Patient characteristics	Inclusion criteria: aged 18 years or over; met the diagnostic criteria of sepsis, severe sepsis or septic shock in ED. Exclusion criteria: aged < 18 years, accompanied by chronic renal or liver disease, immunosuppression status and refusal to take part in research by the patients or relatives.
Index test	MEDS
Reference standard	N/A
Target condition/ patient outcomes	Predicting in-hospital mortality
Results: overall in-hospital mortality 30.8% (15.1%, 38.3% and 46.2% for sepsis, severe sepsis and septic shock groups respectively) MEDS cut-off: 12.5 AUC (95% CI): 0.767 (0.721-0.814) Sensitivity: 78.5% Specificity: 59.9% PPV: 46.5% NPV: 86.2% LR+: 1.96 LR-: 0.36 OR (95% CI): 5.44 (3.45 – 8.58)	
General limitations according to QUADAS II: Single-centre study; small sample size.	

H.1.2 Signs and symptoms

Table 48: AHN 2012

Study	Ahn 2012[5]
Study type and analysis	Retrospective cohort. Multivariable logistic regression.
Number of participants and characteristics	n=285 episodes in 249 consecutive patients adults with febrile neutropenia after chemotherapy who visited ED. Single centre (Asan Medical Center, Seoul, Korea)
Prognostic variable(s)	Respiratory rate
Confounders OR stratification strategy	Multivariable analysis adjusted for age, ECOG PS≥2, respiratory rate ≥24 bpm, platelet, blood urea nitrogen, asparatate aminotransferase.
Outcomes and effect sizes	Multivariable analysis: predictors of bacteraemia. Respiratory rate ≥24/min = OR 4.1 (1.20-13.63) Univariable analysis: predictors of bacteraemia. Duration of fever prior to admission ≥24 h n(%): Bacteraemia (n=19): 8 (42.1) No bacteraemia (n=224): 104 (45.4) Respiratory rate ≥24 breaths/min: Bacteraemia (n=19): 7 (36.8) No bacteraemia (n=224): 17 (7.6) Pulse rate ≥120 bpm: Bacteraemia (n=19): 6 (31.6) No bacteraemia (n=224): 44 (19.65) Body temperature ≥39C: Bacteraemia (n=19): 7 (36.8) No bacteraemia (n=224): 45 (20.1) Systolic blood pressure <90mm Hg: Bacteraemia (n=19): 0 (0) No bacteraemia (n=224): 2 (0.9)
Comments	Bacteraemia defined as “2 positive blood cultures to diagnose coagulase-negative staphylococcal bacteraemia.” Indirectness: Bacteraemia prediction not sepsis. Population only adults after chemotherapy who visited ED.

Table 49: AMMANN 2003

Study	Ammann 2003[8]
Study type and analysis	Retrospective cohort.

Study	Ammann 2003[8]
	Univariable analysis.
Number of participants and characteristics	n=111 9285 episodes) patients under age of 18 years. Single centre, consecutive, between January 1st 1993 – December 31st 2001.
Prognostic variable(s)	Fever.
Confounders OR stratification strategy	NA (Multivariable logistic regression prediction model for SBI but not for fever (or other signs and symptoms from protocol).
Outcomes and effect sizes	Univariable association to SBI. Fever rule ≥38.5C≥2hr=67, SBI=33 Once >39C=217, SBI=38 OR=1.27 (0.58-2.89)
Comments	SBI defined as "death from bacterial infection, a positive culture of normally sterile body fluids, radiologically proven pneumonia, clinically unequivocal diagnosis of a bacterial infection, or a serum C-reactive protein level (CRP) above 150 mg/L." Indirectness: SBI prediction not sepsis.

Table 50: AMMANN 2004

Study	Ammann 2004[9]
Study type and analysis	Retrospective cohort. Univariable analysis.
Number of participants and characteristics	n=364 <17years diagnosed with malignancy screened for fever or neutropenia between January 1 1993 – December 31 2001. Single centre. Consecutive.
Prognostic variable(s)	Temperature Chills History
Confounders OR	Univariable analysis.

Study	Ammann 2004[9]
stratification strategy	
Outcomes and effect sizes	Association with bacteraemia. Univariable analysis. OR for 364 episodes (87 bacteraemia) History Induction chemotherapy: NS Bone marrow involvement malignancy: 2.4 (1.3-4.6) At least 3 past episodes of fever or neutropenia: 1.9 (1.1-3.2) At least 2 past episodes of fever or neutropenia with SBI: 2.0 (1.1-3.2) At least 2 past episodes of fever or neutropenia with bacteraemia: 3.0 (1.2-7.3) More intensive chemotherapy than pre-B cell ALL maintenance: 11 (1.7-446) Max temperature at presentation ≥39.8C: 3.2 (1.5-7.1) Chills observed at presentation: 3.5 (1.3-9.7) OR for 132 first episodes (30 bacteraemia) History Induction chemotherapy: 3.0 (1.1-8.5) Bone marrow involvement malignancy: 4.4 (1.6-12) More intensive chemotherapy than pre-B cell ALL maintenance: NS Max temperature at presentation ≥39.8C: NS Chills observed at presentation: NS
Comments	Bacteraemia defined as “1 positive blood culture using a qualitative automated culture system.” Retrospective. Univariable analysis only. Indirectness: Bacteraemia prediction not sepsis. Population those diagnosed with malignancy only.

Table 51: ANGEL 1994

Study	Angel 1994[11]
Study type and analysis	Retrospective cohort Logistic regression
Number of participants and characteristics	n=200 Children, mean age 9 years Consecutive orthopaedic admissions at Arkansas Children's Hospital. Exclusion: patients with known infections and hospitalisation <24 h. 174 were surgical patients; 26 did not have surgery (treatment of major long-bone fracture) 67% of patients had fever (temperature in triage ≥38°C) Infections occurred in <2% of patients
Prognostic variable(s)	Temperature >38°C and >39°C to predict infectious complications. (the clinical decision as to whether or not to perform a septic work-up was made at the discretion of the attending physician)
Confounders OR stratification strategy	None
Outcomes and effect sizes	Temperature >38°C: Sensitivity=67% Specificity=26% PPV=2% NPV=98% Temperature >39°C: Sensitivity=33% Specificity=91% PPV=6% NPV=99%

Study	Angel 1994[11]
Comments	Retrospective design; sepsis diagnosis not confirmed by blood test; low incidence of infections (<2%). Indirectness: prediction of infectious complications, not specifically sepsis

Table 52: BAEZ 2013

Study	Baez 2013A[18]
Study type and analysis	Retrospective cross-sectional (medical records) Chi-square used for statistical significance; OR to assess strength of association
Number of participants and characteristics	n=63 Adults (≥18 years) transported by Emergency Medical Services to a major academic centre with the diagnosis of SIRS, sepsis, severe sepsis, or septic shock, USA. Admission to ICU: 68% In-hospital mortality: 35%
Prognostic variable(s)	Mean arterial pressure, heart rate, respiratory rate to predict ICU admission and in-hospital mortality.
Confounders OR stratification strategy	None listed (also shock index as a prognostic variable, not extracted)
Outcomes and effect sizes	ICU admission: MAP (<65): OR=1.47 (0.53-4.11) Heart rate (>90): OR=1.30 (0.48-3.53) Respiratory rate (>20): OR=4.81 (1.16-21.01) In hospital mortality: MAP(<65): OR=1.68 (0.61-4.61) Heart rate (>90): OR=1.44 (0.36-5.71) Respiratory rate(>20): OR=2.87 (0.79-10.25)
Comments	Retrospective design, small sample size. Indirectness: prediction of in-hospital mortality and ICU admission in patients admitted to hospital from ED with a diagnosis of sepsis.

Table 53: BATES 1990

Study	Bates 1990[22]
Study type and analysis	Prospective cohort Multivariable analysis to develop clinical prediction model
Number of participants and characteristics	n=1516 blood culture episodes, random samples collected. Derivation set: 1007 blood culture episodes Validation set: 509 blood culture episodes Single centre. USA.
Prognostic variable(s)	Temperature
Confounders OR stratification strategy	Multivariable stepwise logistic regression adjusted for: Maximum temperature ≥38˚C, rapidly fatal disease (<1mo), ultimately fatal disease (>1mo but <5 y), presence of chills, intravenous drug abuse, acute abdomen on examination, major comorbidity.
Outcomes and effect sizes	Predictor of bacteraemia. Maximum temperature ≥38˚C = OR=2.5 (1.4 - 4.3)
Comments	Single centre. Indirect: predicting bacteraemia not sepsis.

Table 54: BENCHEKROUNE 2008

Study	Benchekroune 2008[25]
Study type and analysis	Prospective cohort Univariable analysis, multivariable analysis, and multiple logistic regression model
Number of participants and characteristics	n=68 Consecutive adults (≥18 years) admitted to ICU showing signs of septic shock, and hospitalised in ICU at least 24 h before requiring norepinephrine support. Exclusion: did not receive norepinephrine continuously for at least 72 h or were given corticosteroids during their treatment. France. Mean age: 65±17 years In-hospital mortality: 34%

Study	Benchekroune 2008[25]
Prognostic variable(s)	Diastolic arterial blood pressure, systolic arterial blood pressure to predict in-hospital mortality.
Confounders OR stratification strategy	Unclear
Outcomes and effect sizes	In hospital mortality, day 2: SAP (cut-off: 100 mm Hg): OR=5.0 (1.5-17.6) DAP (cut-off: 50 mm Hg): OR=7.6 (2.0-29.3) In hospital mortality, day 3: SAP (cut-off: 100 mm Hg): OR=6.5 (1.9-22.2) DAP (cut-off: 50 mm Hg): OR=33.0 (4.1-167.0)
Comments	Small sample size. Indirectness: prediction of in-hospital mortality in ICU patients with septic shock.

Table 55: BONADIO 1994

Study	Bonadio 1994[32]
Study type and analysis	Retrospective cohort.
Number of participants and characteristics	n=356 consecutive febrile infants 8-12 weeks who received outpatient sepsis assessment. January 1989-January 1993
Prognostic variable(s)	Body temperature
Confounders OR stratification strategy	Univariable analysis
Outcomes and	33 had SBI. Bacterial meningitis=5. Bacteraemia=8. UTI=17. Bacterial enteritis=3.

Study	Bonadio 1994[32]
effect sizes	Body temperature (<40 or >40C) sensitivity = 21% specificity = 96% PPV = 35% NPV = 93%
Comments	Serious bacterial infection defined as UTI, bacterial meningitis, salmonella enteritis or bacteraemia. Indirectness: SBI prediction not sepsis.

Table 56: BONSU 2007

Study	Bonsu 2007[35]
Study type and analysis	Retrospective cohort Logistic regression
Number of participants and characteristics	n=3765 Consecutive febrile (temperature in triage ≥38°C) infants aged 0 to 89 days in the ED at Children's Hospital Boston, USA who underwent a full sepsis workup
Prognostic variable(s)	Temperature (≥38°C) to predict invasive sepsis
Confounders OR stratification strategy	(Other prognostic variables not extracted: leucocyte in urine, age, peripheral blood leucocyte, peripheral bands)
Outcomes and effect sizes	Temperature: AUC: 0.52
Comments	Retrospective design

Table 57: BOULAIN 2014

Study	Boulain 2014[36]

Study	Boulain 2014[36]
Study type and analysis	Prospective cohort. Multivariable analysis.
Number of participants and characteristics	n=363 patients with severe sepsis or septic shock admitted to medical-surgical ICUs (multi-centre: 10 participating ICUs). Multi centre. July 2011 – June 2012. 25 patients with severe sepsis and 338 patients with septic shock at admission.
Prognostic variable(s)	Low ScvO2, initial body temperature, initial arterial partial pressure
Confounders OR stratification strategy	Adjusted for confounders (OR for initial ScvO2 <70%): SAPS II, arterial lactate, initial arterial partial pressure in CO2, McCabe class 1, McCabe class 2, male gender, initial body temperature, exposure to ACE inhibitors. Other variables adjusted for confounders using the backward method.
Outcomes and effect sizes	Each 1% increase in initial ScvO2 results in an OR 0.96 (95% CI 0.93-0.99) for 28-day mortality, p=0.004 Initial ScvO2 <70% significantly associated with an increased 28-day mortality: OR 3.60 (95% CI 1.76-7.36), p=0.0004 Initial ScvO2 <75% significantly associated with an increased 28-day mortality: OR 2.15 (95% CI 1.16-3.98), p=0.015 Initial arterial partial pressure in CO2 (for each 1 mmHg increase) for 28-day mortality: OR 1.04 (95% CI 1.01-1.06), p=0.003 Initial body temperature (for each 1C increase) for 28-day mortality: OR 0.78 (95% CI 0.62-0.98), p=0.031
Comments	Multivariable analysis.

Table 58: BRENT 2011A

Study	Brent 2011A[37]
Study type and analysis	Prospective cohort Multivariable analysis
Number of participants	N=1951 at ED, excluding neonates and children requiring resuscitation at ED. Exclusions: patients where data was insufficient to assign outcome or had missing/illegible dates of birth.

Study	Brent 2011A[37]
and characteristics	Median age = 19 months (1 month – 15 years) UK. ED. Single centre. September 2000-March 2001 and September 2001-March 2002
Prognostic variable(s)	Consciousness level Temperature Tachycardia Capillary refill time Hypotension Tachypnoea Rash
Confounders OR stratification strategy	Multivariable analysis (backwards stepwise logistic regression) for all variables significant at univariable analysis (risk factor for infection, developmental delay, consciousness level, state variation, temperature, tachycardia, capillary refill time, hydration status, hypoxia).
Outcomes and effect sizes	Consciousness level Not alert (only responding to pain or voice or unresponsive) Sensitivity: 2.8 (0.34-9.7) Specificity: 98.8 (98.2-99.3) PPV: 8.3 (1.0-27.0) NPV: 97.5 (96.7-98.1) LR+: 2.4 (1.7-3.3) LR-: 0.98 (0.7-1.4) No response to voice Sensitivity: 2.8 (0.34-9.7) Specificity: 99.8 (99.5-99.9) PPV: 33.3 (4.3-77.7) NPV: 96.4 (95.4-97.2) LR+: 13.0 (9.2-18.2) LR-: 0.97 (0.69-1.4) Unresponsive

Study	Brent 2011A[37]
	Sensitivity: 0.0 (0.0-5.0) Specificity: 99.8 (99.7-100.0) PPV: 33.3 (4.3-77.7) NPV: 96.4 (95.4-97.2) LR+: 13.0 (9.2-18.2) LR-: 0.97 (0.69-1.4) Temperature ≥37.5C Sensitivity: 60.8 (48.8-72.0) Specificity: 64.5 (62.2-66.7) PPV: 6.5 (4.8-8.6) NPV: 2.4 (1.6-3.4) LR+: 1.7 (0.65-4.5) LR-: 0.61 (0.23-1.61) ≥38.5C Sensitivity: 37.8 (26.8-49.9) Specificity: 84.8 (83.1-86.4) PPV: 9.2 (6.2-13.0) NPV: 97.1 (96.6-98.6) LR+: 2.5 (1.1-5.7) LR-: 0.73 (0.32-1.7) Tachycardia Sensitivity: 63.9 (50.6-75.8) Specificity: 60.9 (58.4-63.3) PPV: 6.0 (4.3-8.1) NPV: 97.7 (96.6-98.6) LR+: 1.6 (0.67-4.0) LR-: 0.59 (0.24-1.5)

Study	Brent 2011A[37]
	Capillary refill time ≥2s Sensitivity: 9.7 (4.0-19.0) Specificity: 98.1 (97.3-98.7) PPV: 17.5 (7.3-32.8) NPV: 96.3 (95.3-97.1) LR+: 5.1 (4.0-6.5) LR-: 0.92 (0.72-1.2) Hypotension Sensitivity: 0.0 (0.0-4.9) Specificity: 99.8 (99.5-99.9) PPV: 0.0 (0.0-60.2) NPV: 96.2 (95.3-97.0) LR+: 0.0 LR-: 1.0 Tachypnoea Sensitivity: 71.6 (59.3-82.0) Specificity: 41.9 (39.4-44.4) PPV: 5.2 (3.8-6.8) NPV: 97.1 (95.5-98.2) LR+: 1.2 (0.47-3.2) LR-: 0.68 (0.26-1.8) Rash Purpuric rash Sensitivity: 1.5 (0.04-8.0) Specificity: 99.1 (98.5-99.5) PPV: 6.3 (0.2-30.2)

Study	Brent 2011A[37]
	NPV: 96.0 (95.0-96.9) LR+: 1.6 (0.8-3.2) LR-: 0.99 (0.50-2.0) Petechial rash Sensitivity: 2.9 (0.4-10.2) Specificity: 97.6 (96.7-98.3) PPV: 4.8 (0.6-16.2) NPV: 96.0 (95.0-96.9) LR+: 1.1 (0.79-1.6) LR-: 1.0 (0.71-1.4) Macular rash Sensitivity: 5.4 (1.5-13.3) Specificity: 89.9 (88.4-91.2) PPV: 2.1 (0.6-5.2) NPV: 96.0 (95.0-96.9) LR+: 0.53 (0.53-0.54) LR-: 1.1 (1.0-1.1) Multivariable analysis (backwards stepwise logistic regression) for all variables significant at univariable analysis (risk factor for infection, developmental delay, consciousness level, state variation, temperature, tachycardia, capillary refill time, hydration status, hypoxia). Temperature category: B coefficient=0.6643 OR=1.9 (1.4-2.7) Capillary refill time: B coefficient=0.6595 OR=1.9 (0.6-5.8) Tachypnoea: B coefficient=0.1760 OR=1.2 (0.6-2.2)
Comments	Single centre.

Study	Brent 2011A[37]
	Indirect: predicting SBI.

Table 59: BRENT 2011

Study	Brent 2011[38]
Study type and analysis	Prospective cohort. X^2 tests.
Number of participants and characteristics	n=1360 First study at ED. Consecutive patients presenting at ED with suspicion of SBI. 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.
Prognostic variable(s)	Temperature-pulse centiles Age specific temperature-pulse centiles
Confounders OR stratification strategy	None.
Outcomes and effect sizes	For significant bacterial infections: Age-specific temperature-pulse centiles Above 97th centile 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) LR positive: 1.4 (0.69-2.7) LR negative: 0.96 (0.48-1.9) Above 90th centile Sensitivity: 21.6 (11.3-35.3)

Study	Brent 2011[38]
	Specificity: 80.0 (77.6-82.3) PPV: 4.5 (2.3-7.9) NPV: 95.9 (94.5-97.1) LR positive: 1.2 (0.76-1.8) LR negative: 0.96 (0.63-1.5) Above 75th centile 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) LR positive: 1.2 (0.58-2.3) LR negative: 0.90 (0.45-1.8) Above 50th centile 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) LR positive: 1.1 (0.50-2.6) LR negative: 0.75 (0.33-1.7) Age-specific pulse centiles Above 97th centile 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) LR positive: 2.7 (2.2-3.4) LR negative: 0.96 (0.76-1.2) Above 90th centile Sensitivity: 21.6 (11.3-35.3)

Study	Brent 2011[38]
	Specificity: 90.8 (89.0-92.4) PPV: 9.2 (4.7-15.9) NPV: 96.4 (95.1-97.4) LR positive: 2.4 (1.6-3.7) LR negative: 0.86 (0.57-1.3) Above 75th centile Sensitivity: 45.1 (31.1-59.7) Specificity: 75.7 (73.1-78.1) PPV: 7.2 (4.6-10.7) NPV: 96.9 (95.6-97.9) LR positive: 1.7 (0.84-3.3) LR negative: 0.78 (0.40-1.5) Above 50th centile 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) LR positive: 1.3 (0.58-3.1) LR negative: 0.64 (0.28-1.5) Tachycardia 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) LR positive: 1.5 (0.67-3.4) LR negative: 0.65 (0.29-1.46) OR for temperature-pulse data on presentation at ED with suspected SBI Age-specific temperature-pulse centiles

Study	Brent 2011[38]
	>97th centile: 1.84 (0.72-4.71) 90th-97th centile: 1.19 (0.38-3.73) 75th-90th centile: 1.67 (0.73-3.79) 50th-75th centile: 1.75 (0.83-3.69) 50th centile: 1.00 Age-specific pulse centiles >97th centile: 1.51 (0.19-12.0) >90th-97th centile: 5.04 (2.14-11.9) 75th-90th centile: 2.62 (1.19-5.79) 50th-75th centile: 1.85 (0.87-3.93) 50th centile: 1.00 Tachycardia: 2.90 (1.60-5.26) Percentage sensitivity of centile range, for identification of meningococcal sepsis >97th centile: 23.6 (18.5-29.3) >90thcentile: 37.8 (31.8-44.1) >75th centile: 55.5 (49.2-61.7) >50th centile: 70.1 (64.0-75.6) <50th centile: 29.9 (24.4-36.0) >97th centile: 11.0 (7.7-15.1) >90thcentile: 27.8 (22.8-33.2) >75th centile: 49.2 (43.4-55.0) >50th centile: 73.9 (68.5-78.8) <50th centile: 26.1 (21.2-31.5) Tachycardia: 68.9 (63.3-74.1)
Comments	SBI defined as "admission to hospital plus any of the following: positive bacterial cultures from blood or another normally sterile site in the appropriate clinical context, radiological signs of pneumonia, clinical meningitis plus a cerebrospinal fluid polymorphonuclear leucocytosis, acute febrile pupura, deep collections requiring intravenous antibiotics and surgical drainage, a white blood cell count >=20x10/1,a C reactive protein>=120mg/l, or a final diagnosis of septic arthritis, osteomyelitis, empyema or mastoiditis."

Study	Brent 2011[38]
	Note that 2 studies with different populations analysed. Indirectness: predicting SBI not sepsis.

Table 60: CARBONELL 2004

Study	Carbonell 2004[44]
Study type and analysis	Prospective cohort. Univariable analysis.
Number of participants and characteristics	n=200 patients with acute renal failure. January 1 2001 – July 2002. ICU.
Prognostic variable(s)	Hypotension Respiratory failure
Confounders OR stratification strategy	Univariable analysis.
Outcomes and effect sizes	For mortality in septic patients: Hypotension OR=1.36 (1.02-1.83) Respiratory failure OR=1.53 (1.14-2.05)
Comments	Single centre. Univariable analysis

Table 61: CASTELLANOS 2002

Study	Castellanos 2002[47]
Study type and analysis	Retrospective
Number of	n=192 in development sample from 4 PICUs (Jan 1 1983 – June 30 1995)

Study	Castellanos 2002[47]
participants and characteristics	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. Admitted to 14 PICUs in Spanish hospitals.
Prognostic variable(s)	Refractory hypotension GCS Oliguria Systolic blood pressure Heart rate (beats/min) Respiratory rate 9breaths/min) Rectal temperature (C)
Confounders OR stratification strategy	Univariable analysis and multivariable logistic regression that adjusted for cyanosis, GCS <8, refractory hypotension, oliguria, leukocytes less than 400/mm3, PTT >150% of control, base deficit >10mmol/l.
Outcomes and effect sizes	Multivariable analysis for predictors of death in development sample Refractory hypotension: OR = 3.30 (2.44-4.47) GCS: OR = 3.15 (2.41-4.12) Oliguria: OR = 5.04 (2.44-10.38) Univariable analysis for predictors of death in development sample Systolic blood pressure: RR = 2.07 (1.37-3.13) Heart rate (beats/min): RR = 1.78 (1.22-2.61) Respiratory rate (breaths/min): reported as not statistically significant Rectal temperature (C): Rectal temperature (C):
Comments	Indirect: predicting death in patients with confirmed or presumed diagnosis of meningococcal septic shock. Retrospective

Table 62: CHEN 2008

Study	Chen 2008[57]
Study type and analysis	Prospective cohort Multiple logistic regression model
Number of participants and characteristics	n=132 Consecutive adults (≥18 years) visiting the ED who met the criteria for sepsis. Exclusion: patients with persistent arrhythmia, cardiac pacing, or respiratory failure under mechanical ventilator support. Taiwan. Mean age: 66.5(10.3) years In-hospital mortality: 8%
Prognostic variable(s)	Heart rate variability to predict in-hospital mortality. SDNN: mean, standard deviation of NN (consecutive normal-to-normal intervals) nHFP: normalised high-frequency power
Confounders OR stratification strategy	Unclear
Outcomes and effect sizes	In hospital mortality: SDNN: OR=0.719 (0.537-0.962); AUC=0.700 (0.487-0.914) nHFP: OR=1.064 (1.009-1.122); AUC=0.739 (0.549-0.930)
Comments	Small sample size. Indirectness: prediction of in-hospital mortality in patients with sepsis

Study	Chen 2014[56]
Study type and analysis	Retrospective cohort Logistic regression
Number of participants and characteristics	n=331 ICU of the general hospital of Chinese People's Liberation Army, China (115 male, 216 female, median age: 56 years, range 6-91) Sepsis: n=128

Study	Chen 2014[56]
	Non-sepsis: n=203
Prognostic variable(s)	Temperature (>38°C or <36°C) Heart rate (>90 beats/min)
Confounders OR stratification strategy	(Other prognostic variables not extracted: Leptin, CRP, PCT, WBS and Platelets)
Outcomes and effect sizes	Temperature: OR=3.187 (1.655-6.139) AUC: 0.898 Heart rate: OR=1.063 (1.036-1.092)
Comments	Retrospective design

Table 63: DEULOFEU 1998

Study	Deulofeu 1998[77]
Study type and analysis	Prospective cohort Multiple logistic regression analysis
Number of participants and characteristics	n=242 Consecutive adults (≥15 years) in a community hospital with a positive blood culture for Gram-negative and Gram-positive bacilli. Spain. Mean age: 61.5 (20.3) years In-hospital mortality: 15% Definitions: Fever: T>37.5 ° C, Euthermia: T<37.5 ° C Barthel Index, functional status: the patient's activities of daily living (e.g. feeding, control of sphincters, personal toilet, dressing, walking, and others) were assesses using the Barthel Index, a simple index of independence, to score the ability of a patient to care for themselves. A Barthel score of ≤60 identifies the moderately and highly dependent patients.
Prognostic	Absence of fever; Barthel index <60, to predict bacteraemia-related mortality.

Study	Deulofeu 1998[77]
variable(s)	
Confounders OR stratification strategy	Unclear Other variables not extracted: shock, nosocomial infection, age >65 years, incorrect therapy, immunodeficiency, leucocyte count, >1 underlying disease.
Outcomes and effect sizes	Bacteraemia-related mortality: Absence of fever: OR=5.2 (1.05-26) Barthel index <60: OR=11.7 (3.2-43)
Comments	Indirectness: prediction of bacteraemia-related mortality

Table 64: DUKE 1997A

Study	Duke 1997A[79]
Study type and analysis	Prospective cohort Univariable logistic regression
Number of participants and characteristics	n=31 Children admitted to paediatric ICU with sepsis or severe sepsis. Australia. Median age: 10.2 months (interquartile range: 4.3 to 17.5 months) Overall mortality: 32%
Prognostic variable(s)	Mean arterial pressure to predict sepsis-related mortality.
Confounders OR stratification strategy	Other variables not extracted: blood lactate; DCO_2.
Outcomes and effect sizes	Mortality: MAP at 24h: AUC=0.80
Comments	Small sample size; lack of standardisation of therapy. Indirectness: prediction of mortality

Table 65: DUNSER 2009A

Study	Dunser 2009A[80]
Study type and analysis	Retrospective cohort Binary logistic regression
Number of participants and characteristics	n=274 Adults (≥18 years) in ICU with sepsis. Switzerland. Mean age: 61±16 years 28-day mortality: 28%
Prognostic variable(s)	Mean arterial pressure and Systolic arterial pressure to predict 28-day mortality.
Confounders OR stratification strategy	Adjusted for disease severity
Outcomes and effect sizes	28-day mortality: HTI of ABP drops <95 mmHg SAP: AUC=0.743 Sensitivity: 93.4 Specificity: 29 PPV: 77.4 NPV: 62.9 HTI of ABP drops <65 mmHg SAP: AUC=0.731 Sensitivity: 94.4 Specificity: 26.3 PPV: 77 NPV: 64.5

Study	Dunser 2009A[80]
	HTI of ABP drops <75 mmHg MAP: AUC=0.775 Sensitivity: 93.4 Specificity: 42.1 PPV: 80.7 NPV: 71.1 HTI of ABP drops <45 mmHg MAP: AUC=0.751 Sensitivity: 94.4 Specificity: 29 PPV: 77.5 NPV: 66.7 The hourly time integral (HTI) of arterial blood pressure (ABP) drops below certain pressure limits represents the duration and extent of blood pressure drops below the respective arterial blood pressure level per hour.
Comments	Retrospective design; lack of standardisation of therapy. Indirectness: prediction of mortality in patients with sepsis

Table 66: FONTANAROSA 1992

Study	Fontanarosa 1992[92]
Study type and analysis	Retrospective chart review Univariable and multivariable stepwise logistic regression
Number of participants and characteristics	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.
Prognostic variable(s)	Altered mental status Fever

Study	Fontanarosa 1992[92]
	Respiratory symptoms Vomiting Abdominal pain/diarrhoea Blood pressure Pulse rate > 100/min Respirations >20/min Temperature
Confounders OR stratification strategy	Multivariable analysis adjusted for vomiting and WBC ban forms of more than 6%.
Outcomes and effect sizes	Predictor of bacteraemia – multivariable analysis Altered mental status OR=2.88(1.52-5.50) Predictor of bacteraemia – univariable analysis Fever – reported as not statistically significant. Bacteraemic = 13/79. Non-bacteraemic = 19/136. Respiratory symptoms - reported as not statistically significant. Bacteraemic = 35/79. Non-bacteraemic = 75/136. Vomiting – OR=2.57(1.21-6.37) Bacteraemic = 18/79. Non-bacteraemic = 14/136. Abdominal pain/diarrhoea - reported as not statistically significant. Bacteraemic = 32/79. Non-bacteraemic = 43/136. OR=1.47 (0.83-2.62) Blood pressure - <100mm Hg OR=3.20 (1.28-8.11) Pulse rate > 100/min - reported as not statistically significant. Bacteraemic = 48/79. Non-bacteraemic = 71/136. Respirations >20/min - reported as not statistically significant. Bacteraemic = 51/79. Non-bacteraemic = 95/136. OR=0.65 (0.37-1.13) Temperature (C) - reported as not statistically significant. <36.1 Bacteraemic = 8/79. Non-bacteraemic = 8/136. OR=1.80 (0.65-5.01) 36.1-37.2 Bacteraemic = 11/79. Non-bacteraemic = 36/136. OR= 0.45 (0.21-0.94) 37.2-38.3 Bacteraemic = 31/79. Non-bacteraemic = 50/136. OR=1.11 (0.63-1.97) 38.3-39.4 Bacteraemic = 22/79. Non-bacteraemic = 31/136. OR=1.31 (0.69-2.47) >39.4 Bacteraemic = 7/79. Non-bacteraemic = 9/136. OR=1.37 (0.49-3.84)
Comments	Retrospective. Indirect – prediction of bacteraemia not sepsis.

Table 67: GLICKMAN 2010

Study	Glickman 2010[111]
Study type and analysis	Prospective cohort, multicentre Univariable and multivariable logistic regression
Number of participants and characteristics	n=472 Adults in ED with sepsis or severe sepsis (but no septic shock). n=379 had uncomplicated sepsis; n=93 had severe sepsis. USA. Median age: 52 years (interquartile range: 44-66 years) Inclusion: age ≥18 years; screened in ED; known or suspected infection; two or more SIRS criteria. Exclusion: imminently terminal comorbid condition or advanced AIDS; treated with an antibiotic; participating in an on-going clinical trial; hypotensive despite fluid resuscitation; lactate level >4 mmol/L. Progression to septic shock within 72h: 18%
Prognostic variable(s)	Hyperthermia, Respiratory rate, Heart rate to predict progression to septic shock.
Confounders OR stratification strategy	Other variables not extracted: age, gender, race, comorbidities, blood culture, organ dysfunction, infection site, causative microorganism.
Outcomes and effect sizes	Progression to septic shock (univariable model): Hyperthermia: OR=1.26 (1.02-1.55) Respiratory rate: OR=1.01 (0.98-1.05) Heart rate: OR=1.01 (1.00-1.02) Progression to septic shock (multivariable model): Hyperthermia: OR=1.34 (1.06-1.68)
Comments	Sepsis progression and patient outcomes are probably influenced by treatment. Indirectness: progression to septic shock in patients with sepsis.

Table 68: HA 2011

Study	**Ha 2011**[116]
Study type and analysis	Retrospective cohort. Multivariable analysis.
Number of participants and characteristics	Seoul, Korea. May 1995-May 2007. Patients at low-risk for febrile neutropenia, presenting at ED, after anti-cancer chemotherapy. n=802 patients and 993 episodes of low-risk febrile neutropenia. A clinical prediction model developed by the multination association for supportive care in cancer (MASCC) was used to define low-risk as MASCC score ≥21. Excluded patients <18 years, who had no history of chemotherapy for cancer treatment or no documented fever during hospital stay.
Prognostic variable(s)	Hypotension Body temperature
Confounders OR stratification strategy	Multivariable analysis adjusted for: Presence of clinical sites of infection Hypotension Presence of central line Body temperature (≥39C) Absolute neutrophil count (<50/mm) CRP (≥10 mg/dL)
Outcomes and effect sizes	Multivariable analysis for predictors for bacteraemia in low-risk febrile neutropenia. Hypotension: OR= 6.19 (2.22-17.28) Body temperature (≥39C): OR = 1.86 (1.12-3.11) Univariable analysis reported altered mental state not significant.
Comments	Bacteremia defined as ”bacterial pathogens from blood cultures with the presence of clinical signs and symptoms from infection.“ Population after anti-cancer chemotherapy. Indirectness: bacteraemia prediction not sepsis.

Table 69: HOFER 2012

Study	Hofer 2012[126]
Study type and analysis	Retrospective cohort (retrospective analysis of medical reports, case histories and electronic patient filing system). Logistic regression.
Number of participants and characteristics	n=476 Term neonates hospitalised within the first 24 hours of life. Paediatric department of the Medical University of Graz, Austria
Prognostic variable(s)	Temperature: fever (rectal temperature >38.5°C); hypothermia (rectal temperature <36°C). Tachycardia (>180/min) or bradycardia (<100/min)
Confounders OR stratification strategy	Results are diagnostic performance of risk factors in the diagnosis of culture-proven EOS (30/476 newborns). Control group: neonates with clinical suspicion of EOS who turned out to be not septic (52/476). Newborns with culture-negative clinical EOS (81/476) and EOS negative newborns without clinical suspicion (313/476) were not part of the control group.
Outcomes and effect sizes	T>38.5°C: Sensitivity: 10 (2-27) Specificity: 94 (84-99) PPV: 50 (12-88) NPV: 64 (53-75) T<36°C: Sensitivity: 10 (2-27) Specificity: 92 (81-98) PPV: 43 (10-82) NPV: 64 (52-75) Tachycardia (>180/min) or bradycardia (<100/min): Sensitivity: 27 (12-46) Specificity: 81 (67-90) PPV: 44 (22-69) NPV: 66 (53-77)

Study	Hofer 2012[126]
Comments	Retrospective analysis

Table 70: HOFER 2012A

Study	Hofer 2012A[125]
Study type and analysis	Retrospective cohort (retrospective analysis of medical reports, case histories and electronic patient filing system). Binary logistic regression.
Number of participants and characteristics	n=851, of which: N =127 with temperature symptoms (15%): 8% fever; 8% hypothermia; 6% temperature instability n=209 (25%)had diagnosis of clinical EOS n=600 (71%) were diagnosed as being EOS-negative Term neonates hospitalised within the first 24 hours of life. NICU of Paediatric department of the Medical University of Graz, Austria
Prognostic variable(s)	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. Tachycardia (>180/min) or bradycardia (<100/min)
Confounders OR stratification strategy	Results are diagnostic performance of risk factors in the diagnosis of culture-proven EOS (30/476 newborns). Control group: neonates with clinical suspicion of EOS who turned out to be not septic (52/476). Newborns with culture-negative clinical EOS (81/476) and EOS negative newborns without clinical suspicion (313/476) were not part of the control group.
Outcomes and effect sizes	Temperature symptoms: Sensitivity: 40 (16-68) Specificity: 93 (88-96) PPV: 30 (12-54) NPV: 95 (91-98) OR=6.0 (3.9-12.2) Tachycardia or bradycardia: Sensitivity: 27 (12-46)

Study	Hofer 2012A[125]
	Specificity: 81 (67-90) PPV: 44 (22-69) NPV: 66 (53-77)
Comments	Retrospective analysis of medical reports, case histories and electronic patient filing system

Table 71: KOCH 2015

Study	Koch 2015[152]
Study type and analysis	Prospective cohort Logistic regression
Number of participants and characteristics	n=50 adults with sepsis, severe sepsis or septic shock Germany. Single-centre, ICU, academic hospital Inclusion criteria: adults within the first 6 hours after onset of sepsis, severe sepsis or septic shock. Exclusion criteria: <18 years of age, history of cerebral bleeding or stroke.
Prognostic variable(s)	Mean arterial blood pressure (MAP), central venous oxygenation (ScvO2)
Confounders OR stratification strategy	(Other prognostic variables not extracted: arterial lactate, frontal rSO2)
Outcomes and effect sizes	Area under curve for mortality prediction: ScvO2 at baseline: 0.683 (0.535-0.832), p=0.026 MAP at baseline: 0.748 (0.610-0.886), p=0.003
Comments	Prospective cohort Small population size

Table 72: KREUZER 1992

Study	Kreuzer 1992[156]
Study type and analysis	Prospective cohort
Number of participants and characteristics	n=110 adults undergoing cardiac surgery at Grosshadern Hospital, University of Munich, Germany Inclusion criteria: elective operation, excluding heart transplantation and pacemaker implantation; presence of invasive perioperative hemodynamic monitoring by thermo-dilution pulmonary artery catheter; postoperative course longer than 24 h.
Prognostic variable(s)	Temperature (>39.0°C).
Confounders OR stratification strategy	(Other prognostic variables not extracted: Leucocyte count, cardiac index, left ventricular stroke work index)
Outcomes and effect sizes	Temperature to predict septic complications: Sensitivity: 44 Specificity: 89 PPV: 41 NPV: 90
Comments	

Table 73: KUPPERMAN 1998

Study	Kupperman 1998[159]
Study type and analysis	Prospective cohort. Multivariable logistic regression.
Number of participants and characteristics	n=6680 3-36 months of age, temperature ≥39C and no apparent focal infection. Multicentre (10 hospitals). Consecutive. 1987-1991.
Prognostic	Temperature

Study	Kupperman 1998[159]
variable(s)	
Confounders OR stratification strategy	Multivariable analysis adjusted for ANC, temperature, age<2 years, YOS>6, WBC count, ABC.
Outcomes and effect sizes	Prediction of occult pneumococcal bacteraemia. Temperature OR=1.77 (1.21-2.58)
Comments	Indirectness: prediction of occult pneumococcal bacteraemia sepsis.

Table 74: KUSHIMOTO 2013

Study	Kushimoto 2013[160]
Study type and analysis	Prospective cohort, multicentre Multivariable logistic regression
Number of participants and characteristics	n=624 Adults in ICU with severe sepsis with or without septic shock. n=602 had severe sepsis; n=273 had severe sepsis with septic shock. Japan. Mean age: 69 years 28-day mortality: 23%
Prognostic variable(s)	Hypothermia (T≤36.6°C).
Confounders OR stratification strategy	Age, gender, admission category of underlying medical condition, SOFA score, APACHE II score, positive blood culture, presence of comorbidity.
Outcomes and effect sizes	28-day mortality in patients with severe sepsis: Hypothermia: OR=1.952 (1.253-3.040) 28-day mortality in patients with severe sepsis with septic shock Hypothermia: OR=2.778 (1.555-4.965)

Study	Kushimoto 2013[160]
Comments	Method by which core temperature was taken was not standardises; influence of treatment. Indirectness: 28-day mortality in patients with severe sepsis ±septic shock.

Table 75: LAVRENTIEVA 2007

Study	Lavrentieva 2007[164]
Study type and analysis	Prospective cohort.
Number of participants and characteristics	n=43 ICU at Burn Unit General Hospital Tessaloniki, Greece (11 female, 32 male, mean age 45.6±20.1)
Prognostic variable(s)	Temperature
Confounders OR stratification strategy	(Other prognostic variables not extracted: PCT, CRP, Neutrophils, WBC)
Outcomes and effect sizes	Temperature to predict sepsis AUC: 0.281 (SE 0.172)
Comments	

Table 76: LEE 1998A

Study	Lee 1998A[166]
Study type and analysis	Prospective cohort. Univariable analysis on temperature.

Study	Lee 1998A[166]
Number of participants and characteristics	Single source. Paediatric ED. USA. 11911 ED visits Consecutive patients 3-36 months old, at risk of occult bacteraemia between 1993-1996. At risk was considered to be those with temperature >39.0C, source of infection not identified and discharged.
Prognostic variable(s)	Temperature.
Confounders OR stratification strategy	Multivariable analysis on other variables only.
Outcomes and effect sizes	OR bacteraemia prediction. Compared to temperature 39.0C-39.4C 40.0C-40.4C = 1.90 (1.13-3.21) 40.5C-40.9C = 2.6 (1.5-4.5) 41.0C-42.0C = 3.7 (1.9-7.3) AUC temperature: 0.62±0.03
Comments	Serious bacterial infection defined as UTI, pneumonia or bacteraemia. Univariable analysis only on temperature. Indirectness: SBI prediction not sepsis.

Table 77: LEE 2012A

Study	Lee 2012A[165]
Study type and analysis	Prospective cohort. Multivariable stepwise, backward logistic regression.
Number of participants and characteristics	n=396 Febrile adults who entered ED. August 2006 – July 2007. 96 days selected at random. Inclusion: temperature >38.0C, ≥18 years, febrile duration <1 week.

Study	Lee 2012A[165]
	Exclusion: consciousness alteration, no verbal responses, hospitalisation ≤30 days prior to presentation at ED, nursing home residents, fungemia or mycobacteremia.
Prognostic variable(s)	Temperature
Confounders OR stratification strategy	Multivariable analysis adjusted for those <0.1 in univariable: rigor, chills, thrombocytopenia, blood urea nitrogen (BUN), BUN/creatinine ratio>16, serum creatinine>1.5mg.dL, comorbidity with renal insufficiency.
Outcomes and effect sizes	Variables associated with community-onset bacteraemia, multivariable analysis. Body temperature >39.9C OR=2.68 (1.03-6.94) Univariable analysis: Heart rate >100 beats/min OR=1.44 (0.80-2.60) Respiratory rate >20 breaths/min OR=1.60 (0.90-2.86) Systolic blood pressure <90 OR=3.59 (1.71-7.54) Diastolic blood pressure <60 OR=2.47 (1.33-4.59)
Comments	Bacteraemia defined as a growth of pathogenic microorganism in at least one blood culture bottle. Indirectness: bacteraemia prediction not sepsis.

Table 78: LEIBOVICI 2007

Study	Leibovici 2007[168]
Study type and analysis	Retrospective multinational database cohort Logistic regression
Number of participants and characteristics	n=3382 Adults in hospital (department of internal medicine, gastroenterology ward, nephrology ward, ICU, infectious disease ward. Multinational: Israel, Germany and Italy. Median age: 69 years (range: 18-104) Inclusion: Age≥18 years; fulfilled the SIRS diagnostic criteria; patients with a focus of infection; patients with shock compatible with septic shock; patients with febrile neutropenia; patients prescribed antibiotics (not for prophylaxis); patients from whom blood cultures were drawn.

Study	Leibovici 2007[168]
	Exclusion: HIV-positive patients with a current (suspected or identified) opportunistic disease and/or AIDS-defining illness currently or within the past 6 months; solid-organ or bone-marrow transplant recipients; suspected travel infections or tuberculosis; pregnancy. Patients with sepsis: 91% 30-day mortality: 12%
Prognostic variable(s)	Excessive tachycardia (heart rate/temperature ratio >2.71 bpm/°C Stupor or coma Dyspnoea Diastolic blood pressure (continuous variable, increment of 10 mmHg)
Confounders OR stratification strategy	Other variables not extracted: Bacterial infection; malignancy; DIC; creatinine; endotracheal tube; functional capacity; age
Outcomes and effect sizes	30-day mortality: Excessive tachycardia (heart rate/temperature ratio >2.71 bpm/°C): OR= 1.54 (1.10-2.17) Stupor or coma: OR= 1.27 (1.01-1.60) Dyspnoea: OR= 1.83 (1.32-2.53) Diastolic blood pressure (continuous variable, increment of 10 mmHg): OR=0.67 (0.62-0.74)
Comments	Retrospective design. Indirectness: prediction of mortality in patients with sepsis.

Table 79: LINDVIG 2014

Study	Lindvig 2014[175]
Study type and analysis	Prospective cohort.
Number of participants and characteristics	n=11988 adults (>15years) presenting at medical emergency department. Consecutive. Single centre. August 1st 2009 – August 1st 2011

Study	Lindvig 2014[175]
Prognostic variable(s)	Temperature
Confounders OR stratification strategy	None
Outcomes and effect sizes	Prediction of bacteraemia – Temperature >38C 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) +LR = 3.4 (3.1-3.6) -LR = 0.1 (0.1-0.2)
Comments	Bacteraemia defined as positive blood culture within 2 days of admission. Single centre. Indirectness: prediction of bacteraemia not sepsis

Table 80: MARTIN 2010

Study	Martin 2010[190]
Study type and analysis	Retrospective cohort. Logistic regression, adjusted for age, acuity, comorbidities.
Number of participants and characteristics	n=14,262 adults undergoing isolated CAGB surgery. Three centres, Canada 6.9% developed delirium 1.6% developed sepsis Infectious complications of the people with delirium: 20% developed pneumonia

Study	Martin 2010[190]
	14% developed UTI 2% developed deep sternal wound infection 7% developed sepsis
Prognostic variable(s)	Delirium (short-term mental disturbance marked by confusion, illusion, and cerebral excitement).
Confounders OR stratification strategy	Age, acuity, comorbidities
Outcomes and effect sizes	Delirium to predict post-operative sepsis: OR=2.32 (1.59-3.39)
Comments	Retrospective design. Low percentage of patients developed sepsis.

Table 81: MURRAY 2007

Study	Murray 2007[205]
Study type and analysis	Retrospective review of records. Multivariable logistic regression.
Number of participants and characteristics	n=222 patients with burns admitted between 2001-2004. Single centre. USA. Army Institute of Surgical Research ICU.
Prognostic variable(s)	Temperature.
Confounders OR stratification strategy	WBC count Neutrophil percentage Temperature Time of collection
Outcomes and effect sizes	Temperature not significant at univariable or multivariable analysis for prediction of bacteraemia.
Comments	Bloodstream infection defined as “Gram-negative or gram-positive bacteraemia from blood cultures. “

Study	Murray 2007[205]
	Retrospective. Population: burn patients only. Indirectness: bloodstream infection prediction not sepsis.

Table 82: NIJMAN 2013

Study	Nijman 2013[216]
Study type and analysis	Prospective cohort Multivariable analysis
Number of participants and characteristics	N=1750 included children presenting with fever at ED. 1 month – 15 years Exclusions: chronic underlying disease or antibiotics 1 week prior. Derivation sample (only with analysis on individual signs and symptoms) form 2 paediatric emergency units in the Netherlands (Rotterdam and The Hague)
Prognostic variable(s)	Temperature (˚C) Tachypnoea Tachycardia Oxygen saturation Capillary refill time CRP
Confounders OR stratification strategy	Multivariable analysis with unclear variables but includes: age, gender, duration of fever, Temperature (˚C), Tachypnoea, Tachycardia Oxygen saturation, Capillary refill time, chest wall retractions, ill appearance, InCRP, C statistic.
Outcomes and effect sizes	Multivariable analysis predicting SBIs other than pneumonia. Temperature (˚C): OR=0.98 (0.75-1.26) Tachypnoea: OR=0.90 (0.48-1.69) Tachycardia: OR=0.98 (0.62-1.56)

Study	Nijman 2013[216]
	Oxygen saturation <94%: OR=0.04 (0.00-19.22) Capillary refill time >3 secs: OR=1.35 (0.53-3.42) Ill appearance: OR=1.31 (0.84-2.05) lnCRP: OR=3.11 (2.50-3.87)
Comments	Indirect: predicting SBI.

Table 83: OHLIN 2010

Study	Ohlin 2010[223]
Study type and analysis	Prospective cohort. Multivariable logistic regression.
Number of participants and characteristics	n=401 consecutive newborn infants <28 days of suspected sepsis admitted to NICU.
Prognostic variable(s)	Blood pressure/skin colour Bradycardia Tachypnea
Confounders OR stratification strategy	Logistic regression adjusted for gender and gestational age and adjusted for gender and gestational age and other signs (feeding intolerance, increased oxygen need, patent ductus arteriousus, distended abdomen, blood pressure/skin colour, bradycardia, apnoea, irritability/seizures, tachypnea)
Outcomes and effect sizes	Prediction of positive blood culture (adjusted for gender and gestational age) Blood pressure/skin colour: OR=2.68 (1.40-5.17) Bradycardia: OR=2.69 (1.40-5.17) Tachypnea: OR=1.17 (0.66-2.08) Prediction of positive blood culture (adjusted for gender and gestational age and other signs (feeding intolerance, increased oxygen need, patent ductus arteriousus, distended abdomen, blood pressure/skin colour, bradycardia, apnoea, irritability/seizures, tachypnea) Blood pressure/skin colour: OR=2.45 (1.31-4.59) Bradycardia: OR=1.19 (0.50-2.85)

Study	Ohlin 2010[223]
	Tachypnea: OR=2.00 (1.02-3.92)
Comments	Indirect: predicting positive blood culture not sepsis, in those with suspected sepsis. Single centre.

Table 84: PFITZENMEYER 1995

Study	Pfitzenmeyer 1995[236]
Study type and analysis	Prospective cohort. Odds ratios and their variances were used to estimate the relative risk of potential predictors of bacteraemia.
Number of participants and characteristics	n=438 older patients (n=558 episodes of suspected bacteraemia) University geriatric hospital of Geneva, Switzerland Median age 83.8±6.5 years Inclusion: hospitalised geriatric patients with suspected bacteraemia (blood sample was taken). Definition of bacteraemia: bacteraemia was diagnosed if a recognised pathogenic microorganism was detected in at least one blood culture.
Prognostic variable(s)	Fever ≥38.5°C; Confusion to predict bacteraemia
Confounders OR stratification strategy	N/A
Outcomes and effect sizes	Prediction of bacteraemia: Fever ≥38.5°C: Sensitivity: 87.0 Specificity: 27.0 PPV: 9.7 RR=2.46 ($p<0.05$)

Study	Pfitzenmeyer 1995[236]
	Confusion: Sensitivity: 30.4 Specificity: 79.3 PPV: 11.4 RR=1.68
Comments	Single centre. The decision to obtain blood culture was made individually, without reference to a particular standardised criteria. Indirectness: prediction of bacteraemia

Table 85: POUTSIAKA 2009

Study	Poutsiaka 2009[238]
Study type and analysis	Retrospective cohort (database). Logistic regression
Number of participants and characteristics	n=384 Immunosuppressed adults Academic Medical Centre Consortium (AMCC) cohort, USA Median age 55, IQR: 41-68 Inclusion: adults with pre-existing immunosuppression; with severe sepsis syndrome with or without septic shock. Exclusion: patients with SIRS with or without evidence of clinical infection of with blood stream infection, who did not have evidence of organ dysfunction or hypo-perfusion
Prognostic variable(s)	Maximal HR; minimal SBP; maximal temperature to predict 28-day mortality
Confounders OR stratification strategy	Age; race; presence of pre-existing liver disease; rigors; mechanical ventilation at the onset of sepsis; cardiopulmonary arrest; septic shock; vital signs at the onset of sepsis; maximal creatinine; maximal WBC; minimal haematocrit; presence of hematologic or solid cancer; presence of fungal infection.
Outcomes and effect sizes	28-day mortality (univariable analysis): Maximal HR: OR=1.02 (1.01-1.02) (OR for death every 10 beat/minute increase in maximal heart rate) Minimal SBP: OR=0.84 (0.77-0.93) (OR for death every 10 mmHg rise in minimal SBP)

Study	Poutsiaka 2009[238]
	Maximal temperature: 0.71 (0.58-0.86)
Comments	Retrospective design. Indirectness: prediction of 28-day mortality in immunosuppressed adults with severe sepsis

Table 86: SEIGEL 2012

Study	Seigel 2012[261]
Study type and analysis	Prospective cohort. Univariable analysis.
Number of participants and characteristics	n=3563 consecutive patients admitted to tertiary care centre via ED, ≥18 years, who had blood cultures taken within 3 hours of admission. 289 had positive blood cultures. Single centre. Feb 1st 2000 – Feb 1st 2001.
Prognostic variable(s)	Abnormal temperature (hypothermia or fever)
Confounders OR stratification strategy	Did not adjust for confounders.
Outcomes and effect sizes	Prediction of bacteraemia Abnormal temperature (hypothermia or fever), sensitivity = 67% Mean temperature with clinical evidence of shock in ED = 36C Mean temperature all patient in ED = 37.5C P=0.49
Comments	Bacteraemia defined as presence of a true positive blood culture. Univariable analysis. Indirectness: bacteraemia prediction not sepsis.

Table 87: SLOTMAN 1997

Study	Slotman 1997[275]

Study	Slotman 1997[275]
Study type and analysis	Retrospective analysis from 2 RCTs of recombinant human interleukin-1 receptors antagonist (IL-1ra) in severe sepsis Multivariable analysis
Number of participants and characteristics	n=59 adults with severe sepsis USA, Median age 58, range: 17-85 Inclusion: clinical evidence of a bacterial infection plus manifestations of systemic inflammation consistent with consensus definitions of severe sepsis and septic shock. 63% were alive at 72h 28-day all-cause mortality: 41%
Prognostic variable(s)	MAP ≤ 70mmHg; GCS≤11 to predict onset of organ failure in patients without end-organ dysfunction at baseline.
Confounders OR stratification strategy	Other variables not extracted: Pao2/Fio2; lung injury score; ALT; AST; PT; platelets; creatinine.
Outcomes and effect sizes	Onset of organ failure at 24h. MAP ≤ 70mmHg Sensitivity: 100% Specificity: 71% GCS≤11 Sensitivity: 60% Specificity: 100% Onset of organ failure at 48h. MAP ≤ 70mmHg Sensitivity: 92% Specificity: 100% GCS≤11 Sensitivity: 75% Specificity: 75%

Study	Slotman 1997[275]
	Onset of organ failure at 72 h. MAP ≤ 70mmHg Sensitivity: 100% Specificity: 0% GCS≤11 Sensitivity: 79% Specificity: 100%
Comments	Retrospective analysis. 34% of patients received continuous IV sedation, which may have decreased GCS variation pharmacologically. Small sample size. Patients received either placebo or IL-1ra. Indirectness: prediction of organ failure in adults with severe sepsis

Table 88: THEERAWIT 2011

Study	Theerawit 2011[281]
Study type and analysis	Retrospective cohort (database) Univariable and multivariable analysis
Number of participants and characteristics	n=183 adults with septic shock Thailand, Mean age survivor: 60.48±17.09; Mean age non-survivor: 58.80±17.41 ICU database Inclusion: all medical conditions with shock and/or multiple organ failure, severe hypoxaemic respiratory failure, coma, severe intoxication, and those requiring intensive monitoring. Exclusion: patients with post-cardiac arrest and end-stage disease 30-day mortality: 29.5%
Prognostic variable(s)	HR>130 beats/min; RR>24 breaths/min; GCS≤7 to predict mortality in patients with shock.
Confounders OR	Other variables not extracted: Chronic disease; impaired immune status; steroid usage; pH≤7.24; Cr>1.5 mmol/L; WBC ≤4.010.

Study	Theerawit 2011[281]
stratification strategy	
Outcomes and effect sizes	Mortality: HR>130 beats/min. Univariable: OR=3.679 (1.853-7.302); Multivariable: OR=4.377 (1.338-14.321) RR>24 breaths/min. Univariable: OR=2.488 (1.262-4.904); Multivariable: OR=0.636 (0.194-2.087) GCS≤7. Univariable: OR=8.044 (3.460-18.69); Multivariable: OR=3.476 (1.072-11.270)
Comments	Retrospective design. Single database. Indirectness: prediction of mortality in adults with shock

Table 89: WEINKOVE 2015

Study	Weinkove 2015[294]
Study type and analysis	Retrospective cohort (database) Multivariable analysis
Number of participants and characteristics	n=118,067 adults (over 16 years) with sepsis Australia and New Zealand, Mean age non-neutropenic sepsis: 63.6±17.1; Mean age neutropenic sepsis: 58.6±15.5 ICU database Inclusion: patients over 16 years old admitted to the ICU at one of the 157 centres in Australia and New Zealand during the study period; sepsis patients. Exclusion: not reported ICU mortality: non-neutropenic sepsis group: 10.1%; neutropenic sepsis group: 29.7%
Prognostic variable(s)	Early peak temperature to predict mortality in patients with sepsis.
Confounders OR stratification strategy	Other variables not extracted: illness severity; year of admission; site.
Outcomes and	Mortality (multivariable analysis):

Study	Weinkove 2015[294]
effect sizes	Non-neutropenic sepsis: Early peak temperature <36.5C: OR=1.57 (1.47-1.67); 36.5-37.4C: OR=1; 37.5-39.4C: OR=0.85 (0.81-0.88); >39.4C: OR=0.83 (0.74-0.91) Neutropenic sepsis: Early peak temperature <36.5C: OR=1.92 (1.34-2.75); 36.5-37.4C: OR=1; 37.5-39.4C: OR=0.91 (0.74-1.11); >39.4C: OR=1.21 (0.92-1.59)
Comments	Retrospective design. Single database. Indirectness: prediction of mortality in adults with sepsis

H.2 Managing and treating sepsis in acute hospital settings

H.2.1 Blood tests

H.2.1.1 Clinical evidence tables for adults (in alphabetical order)

Table 90: AALTO 2004

Study	Aalto 2004[1]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=92)
Country and setting	Finland. ED (Helsinki University Central Hospital). Patients with suspected systemic infection
Funding	Not stated
Duration of study	3-month period
Age, gender, ethnicity	Age: mean (range): 52 (18-88) years. Gender: 44 M/48 F. Ethnicity: not stated.
Patient characteristics	Inclusion: acutely ill patients admitted to the ED and suspected to have systemic infection, as determined by the treating clinician's request for a blood culture within 24h of admission. Exclusion: patients undergone surgery within the previous 6 weeks; patients with active haematological malignancies; patients on systemic immunosuppressive treatment at the time of blood sampling. n=13 patients with positive blood culture

Study	Aalto 2004[1]
Index test/s	CRP
Reference standard	N/A
Target condition	Bloodstream infection (BSI)
Results: CRP ≥125 mg/litre Sensitivity Specificity PPV NPV AUC	 85 (55-98) 81 (71-89) 42 (23-63) 97 (89-100) 85 (63-96)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: prediction of bloodstream infection. Risk of bias: very high.

Table 91: ADAMS 2005

Study	Adams 2005[2]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=1214)
Country and setting	Australia. ED (The Alfred Hospital, Melbourne)
Funding	Not stated
Duration of study	12-month period
Age, gender, ethnicity	Age: not stated (adults). Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: patients who had both blood cultures and CRP level taken during their assessment in ED. Exclusion: neutropenic patients
Index test/s	CRP (CRP >10mg/litre defined as elevated)
Reference standard	Positive blood culture
Target condition	ED diagnosis of bacteraemia

Study	Adams 2005[2]
Results: Sensitivity Specificity PPV NPV	 94 (86-98) 18 (16-20) 7 (6-9) 98 (94-99)
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias (convenience sample). Indirectness: none. Risk of bias: very high.

Table 92: ADAMZIK 2012

Study	Adamzik 2012[3]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=80, and n=50 control)
Country and setting	Germany. ICU (University Hospital Essen)
Funding	One author declared receiving payment for lectures, including service on speakers' bureaus from Verum Diagnostica GmbH, Munich, Germany, Instrumentation Laboratory, Kircheim, Germany, and Triolab, Copenhagen, Denmark
Duration of study	30 days follow up
Age, gender, ethnicity	Mean age: 57.5±1.1. Gender: 49/31. Ethnicity: not stated.
Patient characteristics	n=80 postoperative patients admitted to ICU with criteria for severe sepsis; n=50 control group: postoperative patients admitted to ICU without criteria for severe sepsis.
Index test/s	CRP Thrombin time Fibrinogen Platelets
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results:	

Study	Adamzik 2012[3]
Area under the curve	
CRP:	0.513 (0.412-0.614)
Thrombin time:	0.593 (0.456-0.669)
Fibrinogen:	0.563 (0.456-0.667)
Platelets:	0.736 (0.649-0.823)
Mean values, patients with sepsis	
CRP:	13.79±1.02
Thrombin time:	23.9±1.7
Fibrinogen:	479±30
Platelets:	137±12
Mean values, patients without sepsis	
CRP:	
Thrombin time:	12.18±0.81
Fibrinogen:	18.1±0.7
Platelets:	406±27
	207±14
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 93: BELL 2003

Study	Bell 2003[24]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=123)
Country and setting	Australia. ICU.
Funding	Not stated

Study	Bell 2003[24]
Duration of study	2-month period
Age, gender, ethnicity	Age: not stated. Gender: 103 M/59 F. Ethnicity: not stated.
Patient characteristics	All hospitalised patients from whom blood cultures were drawn for sepsis. Categorised into 3 groups: bacteraemic patients; patients fulfilling criteria of infection, but without positive blood cultures; patients in whom no infection was documented (non-infected patients). Exclusions: septic shock; cirrhosis or previous antimicrobial therapy within the last 2 days.
Index test/s	CRP
Reference standard	N/A
Target condition	Hospital diagnosis of bacteraemia
Results: CRP: Area under the curve **Median (range) CRP values** Bacteraemic patients: Non-bacteraemic patients: Non-infected patients:	 0.53 (SE: 0.06) 8.8 (0-30.2) 8.1 (0-34.4) 5.8 (0-20.8)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 94: BILLER 2014

Study	Biller 2014[27]
Study type	Prospective study
Number of studies (number of participants	1 (n=116)
Country and setting	Austria. Single-centre. Intensive care unit.
Funding	Not stated

Study	Biller 2014[27]
Duration of study	2007 - 2011
Age, gender, ethnicity	For patients with infection versus patients without infection: Median age (range): 69.5 (25-96) versus 58.3 (22-84); Gender M/F: 48/28 versus 29/11; Ethnicity: not stated.
Patient characteristics	Inclusion: Consecutive intensive care patients with a diagnosis of infection fulfilling criteria of the ACCP/SCCM consensus conference (infection defined according to the CDC criteria, including microbiological proof and one of the following criteria: elevated CRP or clinical signs of infection (fever, shivering, local signs)) or radiological findings. Exclusion: not reported.
Index test	Cholesterol
Reference standard	CRP, PCT
Target condition	Prediction of survival
Results: CRP Area under curve	 0.407
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 95: BOGAR 2006

Study	Bogar 2006[29]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=39) critically ill patients

Study	Bogar 2006[29]
Country and setting	Hungary. ICU.
Funding	Not stated
Duration of study	4-month period
Age, gender, ethnicity	Mean age: 56 (range: 37-78). Gender: 28 M/11 F. Ethnicity: not stated.
Patient characteristics	Febrile, critically ill patients in ICU (32 patients admitted to the ICU after major operations; 7 non-surgical patients). Exclusions: patients with haematological malignancy or previous antibiotic treatment (except for single shot surgical prophylaxis given half an hour before skin incision)
Index test/s	LAR (Leucocyte anti-sedimentation rate)
Reference standard	N/A
Target condition	Bacteraemia
Results: Bacteraemia positive patients Bacteraemia negative patients AUC, LAR	 23 16 0.80 (0.64-0.95)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: prediction of bacteraemia. Risk of bias: very high.

Table 96: CASTELLI 2004

Study	Castelli 2004[50]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=150)
Country and setting	Italy. Medicosurgical intensive care unit (Carlo Poma Hospital in Mantova)
Funding	Not stated
Duration of study	12-month period (10 days follow up)

Study	Castelli 2004[50]
Age, gender, ethnicity	Age: median (range) 59.2 (15-89). Gender: 96 M/54 F. Ethnicity: not stated.
Patient characteristics	Inclusion: consecutive patients admitted to the mixed medico-surgical ICU. Exclusion: neurosurgical and elective surgical patients without complications. The American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of sepsis was used to identify patients with sepsis, severe sepsis, septic shock, and systemic inflammatory response syndrome (SIRS). n=15 no SIRS patients n=15 SIRS patients n=49 trauma patients n=71 sepsis/severe sepsis patients
Index test/s	CRP
Reference standard	N/A
Target condition	Sepsis/ severe sepsis
Results: Area under curve CRP cut off 128 mg/litre Sensitivity Specificity PPV NPV	 0.755 (0.64-0.86) 67 82 51 90
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none Risk of bias: very high.

Table 97: CASTELLI 2006

Study	Castelli 2006[48]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=255)

Study	Castelli 2006[48]
Country and setting	Italy. Medicosurgical intensive care unit (Carlo Poma Hospital in Mantova)
Funding	Not stated
Duration of study	12-month period
Age, gender, ethnicity	Age: median (range) 59.2 (15-89). Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: consecutive patients admitted to ICU, American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) consensus definition of sepsis to identify patients with sepsis, severe sepsis, septic shock and systemic inflammatory response syndrome (SIRS). Each group split into one of four: (1) trauma; patients admitted with trauma and studied in acute phase, (2) SIRS; patients who developed clinical signs of systemic inflammatory response but no defined source of infection (2) No-SIRS; medico-surgical patients without trauma or SIRS (3) Sepsis/SIRS; patients with SIRS and known source of infection and/or positive blood cultures, further dividend into septic shock, severe sepsis and sepsis. Exclusion: neurosurgical and elective patients without complications
Index test/s	CRP, WBC
Reference standard	N/A
Target condition	ACCP/SCCM Consensus Conference definition of sepsis
Results:	
CRP to predict sepsis/SS (sepsis, severe sepsis, septic shock)	
Area under curve	0.74 (0.67-0.81)
Sensitivity	61
Specificity	87
PPV	66
NPV	87
WBC to predict sepsis/SS (sepsis, severe sepsis, septic shock)	
Area under curve	0.6 (0.5-0.69)

Study	Castelli 2006[48]
Median (lower and upper quartiles) comparisons between patient groups	
CRP (mg/litre)	No SIRS (n=50): 68 (35-109). SIRS (n=45): 74 (32-118). Sepsis/SS (n=111): 159 (71-210). Sepsis (n=68): 150 (68-209). Severe sepsis (n=28): 153 (71-202). Septic shock (n=15): 195 (75-272). Trauma (n=49): 40 (16-150).
WBC (cells/mm^3)	No SIRS (n=50): 10,300 (8,200-13,000). SIRS (n=45): 12,750 (9,325-17,800). Sepsis/SS (n=111): 12,350 (9,250-18,150). Sepsis (n=68): 11,350 (9,150-15,000). Severe sepsis (n=28): 14,500 (9,700-19,600). Septic shock (n=15): 15,200 (7,400-19,100). Trauma (n=49): 13,400 (10,225-21,100).
PNM (cells/mm^3)	No SIRS (n=50): 7,800 (6,400-10,100). SIRS (n=45): 10,450 (7,200-14,225). Sepsis/SS (n=111): 9,900 (7,600-14,700). Sepsis (n=68): 9,450 (7,600-14,700). Severe sepsis (n=28): 13,150 (8,575-19,575). Septic shock (n=15): 13,000 (6,000-16,100). Trauma (n=49): 12,050 (8,975-18,325).
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 98: CASTELLI 2009

Study	Castelli 2009[49]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=94)
Country and setting	Italy. Medicosurgical intensive care unit (Carlo Poma Hospital in Mantova)
Funding	Not stated
Duration of study	24-month period
Age, gender, ethnicity	Age: median (range) 59.2 (15-89). Gender: 62 M/32 F. Ethnicity: not stated.
Patient characteristics	Inclusion: consecutive patients admitted to ICU, consecutive trauma patients of ≥16 years admitted to ICU who survived for at least 24 hours. The American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definition of sepsis was used to identify patients with sepsis, severe sepsis, septic shock, and systemic inflammatory response syndrome (SIRS).

Study	Castelli 2009[49]
	Exclusion: neurosurgical lesions.
Index test/s	CRP
Reference standard	N/A
Target condition	ACCP/SCCM Consensus Conference definition of sepsis (sepsis defined when clinical signs of systemic inflammatory response were present and determined by definable source of infection (microbiology confirmed) and/or positive blood cultures).
Results: CRP to predict sepsis at admission AUC CRP at admission and prognostic value for organ dysfunction/failure **Median (lower and upper quartiles) comparisons between patient groups** CRP (mg/litre) Lactate (mmol/litre)	 0.489 0.787 Patients with trauma at admission who developed sepsis: 38 (11–56) Patients without septic complications: 36 (7–95) All patients: 2.9 (1.86–5.07)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: indirect (trauma patients who survived ≥24 hours) Risk of bias: very high.

Table 99: CATERINO 2004

Study	Caterino 2004[52]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=108)

Study	Caterino 2004[52]
Country and setting	USA. Urban, tertiary care, academic ED.
Funding	Not stated
Duration of study	16-month period
Age, gender, ethnicity	Age: mean 77, median 76, range 65-100. Gender: 54 M/54 F. Ethnicity: not stated.
Patient characteristics	Inclusion: ED patients ≥65 years in whom blood cultures were taken during their assessment in ED. Exclusion: Patients with antibiotic use within previous 48 hours.
Index test/s	Abnormal WBC (<4.3 or >11.4 cells/mm^3)
Reference standard	N/A
Target condition	ED diagnosis of bacteraemia (bacteria and fungus)
Results:	
Bacteraemia patients (n=14) versus all others (local infection (n=64), non-infection (n=30))	
Sensitivity	57 (31-83)
Specificity	55 (45-65)
PPV	16 (5-26)
NPV	89 (82-97)
Bacteraemia patients (n=14) versus non infected (n=30)	
Area under the curve	0.5 (95%CI 0.3 to 0.7)
Sensitivity	57 (31-83)
Specificity	66 (48-88)
PPV	44 (22-67)
NPV	81 (67-94)

Study	Caterino 2004[52]
Range WBC counts	0.4 to 38 (mean 11.28, median 9.95)
General limitations (according to QUADAS 2)	Observational design, possible selection bias (convenience sample), small sample size. Indirectness: none. Risk of bias: very high.

Table 100: CAVALLAZZI 2010

Study	Cavallazzi 2010[53]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=145) critically ill patients in ICU
Country and setting	USA. ICU (university hospital). Critically ill patients.
Funding	No financial support received.
Duration of study	6-month period.
Age, gender, ethnicity	Age, mean (SD): 59 (16). Gender: 81 M/64 F. Ethnicity: not stated.
Patient characteristics	Consecutive critically ill patients admitted to the general ICU for diseases other than infections, or patients in whom the intensivist suspected no infection. Three groups: NS: Patients in whom no sepsis developed during the study (n=31) NS-S: patients who manifested no sepsis criteria at ICU admission but experienced sepsis during the 7-day study (n=33) Control group: patients who manifested sepsis criteria confirmed within 12 hours after ICU admission (n=31)
Index test/s	Immature neutrophils (band) WBC
Reference standard	Culture-proven infection. 42 patients (29%) had an infection at ICU admission.
Target condition	Infection
Results: **Band >10%**	

Study	Cavallazzi 2010[53]
Sensitivity	43 (28-59)
Specificity	92 (28-59)
TP	18
FP	8
FN	24
TN	95
AUC	74 (64-83)
WBC >12 x10^9/litre	
Sensitivity	52 (36-68)
Specificity	59 (49-69)
TP	22
FP	42
FN	20
TN	61
WBC <4 x10^9/litre	
Sensitivity	10 (3-23)
Specificity	10 (3-23)
TP	4
FP	4
FN	38
TN	99
Band >10% & WBC >12 x10^9/litre	
Sensitivity	26 (14-42)
Specificity	97 (92-99)
TP	11
FP	3
FN	31

Study	Cavallazzi 2010[53]
TN	100
General limitations (according to QUADAS 2)	Observational design, small sample size, critically ill patients. Indirectness: prediction of infection, not sepsis. Risk of bias: very high.

Table 101: CHASE 2012

Study	Chase 2012[54]
Study type	Secondary analysis of prospective cohort.
Number of studies (number of participants)	n=5630 n=3310 had blood cultures obtained.
Country and setting	USA. ED.
Funding	None disclosed.
Duration of study	September 2005 – October 2006
Age, gender, ethnicity	All patients with suspected infection: 59.9±19.9 years Patients with bacteraemia: 63.3±18.3 years All patients = 53.7% female.
Patient characteristics	Alcohol abuse: All patients with suspected infection = 86/5630, Patients with bacteraemia = 6/409, p=1.0 Intravenous drug abuse: All patients with suspected infection = 80/5630, Patients with bacteraemia = 7/409, p=0.66 Nursing home resident: All patients with suspected infection = 298/5630, Patients with bacteraemia = 46/409, p=<0.001 Rehabilitation facility resident: All patients with suspected infection = 172/5630, Patients with bacteraemia = 20/409, p=0.06 Indwelling urinary catheter: All patients with suspected infection = 59/5630, Patients with bacteraemia = 14/409, p=<0.001 Indwelling venous catheter: All patients with suspected infection = 203/5630, Patients with bacteraemia = 44/409, p=<0.001 Diabetes: All patients with suspected infection = 1121/5630, Patients with bacteraemia = 125/409, p=<0.001 Coronary artery disease: All patients with suspected infection = 782/5630, Patients with bacteraemia = 68/409, p=0.12 ESRD: All patients with suspected infection = 194/5630, Patients with bacteraemia = 35/409, p=<0.001 Human immunodeficiency virus: All patients with suspected infection = 270/5630, Patients with bacteraemia = 18/409, p=0.90 Status after splenectomy: All patients with suspected infection = 14/5630, Patients with bacteraemia = 1/409, p=1.0 Leukaemia/lymphoma: All patients with suspected infection = 158/5630, Patients with bacteraemia = 15/409, p=0.22

Study	Chase 2012[54]
	Malignancy: All patients with suspected infection = 723/5630, Patients with bacteraemia = 64/409, p=0.20 Status after organ transplant: All patients with suspected infection = 177/5630, Patients with bacteraemia = 22/409, p=0.60 Chronic steroid use: All patients with suspected infection = 377/5630, Patients with bacteraemia = 34/409, p=0.27 Active chemotherapy: All patients with suspected infection = 173/5630, Patients with bacteraemia = 13/409, p=0.88 Died during index hospitalisation: All patients with suspected infection = 203/5630, Patients with bacteraemia = 25/409, p=0.02
Index test/s	Neutrophils Platelets WBC Lactate
Reference standard	N/A
Target condition	Bacteraemia
Results	Univariable model to predict bacteraemia (defined as a positive blood culture): Lactate >4: p=<0.001 WBC <4 or >12 = 0.435 Hypoxia, p=0.487 Tachycardia, p=<0.001 Tachypnea, p=<0.001 Abnormal temperature, p=<0.001 Hypotension, p=<0.001 Multivariable model to predict (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
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirect: predicting bacteraemia (defined as a positive blood culture) not sepsis.

Study	Chase 2012[54]
	Risk of bias: very high

Table 102: CHEVAL 2000

Study	Cheval 2000[62]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=60) patients with shock
Country and setting	France. ICU.
Funding	Supported in part by the participating institutions' departmental funds.
Duration of study	9-month period
Age, gender, ethnicity	Infected patients (n=32). Age: 61±8 years. Gender: 17 M/ 15 F. Ethnicity: not stated. Non-Infected patients (n=28). Age: 54±7 years. Gender: 17 M/ 11 F. Ethnicity: not stated.
Patient characteristics	Medical and surgical patients Exclusion: HIV-infected and immunosuppressed patients
Index test/s	CRP
Reference standard	N/A
Target condition	Bacterial infection (Prediction of infectious origin of any shock)
Results: **CRP>100 mg/ml to predict the infectious origin of any shock** Sensitivity Specificity **CRP to predict sepsis in patients with shock** AUC	 93±10 40±18 85.4 (66.9-95.7)
General limitations (according to	Observational design, small sample size, single centre.

Study	Cheval 2000[62]
QUADAS 2)	Indirectness: none. Risk of bias: very high.

Table 103: DAHABA 2006

Study	Dahaba 2006[69]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=69)
Country and setting	Austria. ICU (post-operation). Critically ill patients with severe sepsis.
Funding	Not stated.
Duration of study	2-year period.
Age, gender, ethnicity	Survivors: Age, mean (range): 57 (36-75). Gender: 23 M/28 F. Ethnicity: not stated. Non-Survivors: Age, mean (range): 61 (39-77). Gender: 10 M/8 F. Ethnicity: not stated.
Patient characteristics	Patients admitted to surgical ICU after potentially septic operations who were first diagnosed with severe sepsis within 24h preceding their operation. n=51 survivors n=18 non-survivors
Index test/s	CRP
Reference standard	N/A
Target condition	28-day mortality related to severe sepsis
Results: AUC (day 3), CRP Mean CRP values (mg/dl) Survivors Non-survivors	 0.61 18.9 (24.1) 22.9 (11.3)
General limitations (according to QUADAS 2)	Observational design, small sample size, post-op patients. Indirectness: prediction of 28-mortality from severe infection. Risk of bias: very high.

Table 104: DE KRUIF 2010

Study	de Kruif 2010[71]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=211)
Country and setting	The Netherlands. ED (patients with fever).
Funding	The authors have not disclosed any potential conflicts of interest.
Duration of study	30-month period
Age, gender, ethnicity	Median age (IQR): 64 (46-74). Gender: 115 M/96 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with fever (T≥38°C) admitted to the Department of Internal medicine of the Slotervaart Hospital in Amsterdam; age 18-85 years; non pregnant. Group 1: n=73 with confirmed infection Group 2: n=104 with possible infection Group 3: n=34 with no infection
Index test/s	CRP Leukocyte count Thrombocyte count Temperature Tachypnea Tachycardia Chills
Reference standard	N/A
Target condition	Bacterial infection
Results: **CRP** OR univ. analysis OR multiv. analysis AUC Sens. (cut off: 9 mg/litre) Spec.	 1.010 (1.005-1.015) 1.008 (1.001-1.014) 0.76 (0.67-0.85) 99 15

Study	de Kruif 2010[71]
PPV NPV **Leukocyte count** OR univ. analysis OR multiv. analysis **Thrombocyte count** OR univ. analysis OR multiv. analysis **Temperature** OR univ. analysis OR multiv. analysis **Tachypnea** OR univ. analysis OR multiv. analysis **Tachycardia** OR univ. analysis OR multiv. analysis **Chills** OR univ. analysis OR multiv. analysis	71 83 1.080 (0.996-1.172) 1.125 (0.997-1.295) 0.997 (0.993-1.001) 0.996 (0.990-1.003) 1.265 (0.692-2.314) N/A 2.855 (1.173-6.948) 3.451 (0.986-12.09) 1.302 (0.575-2.949) N/A 2.335 (0.980-5.567) 6.748 (1.452-31.37)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: prediction of bacterial infection, not sepsis. Risk of bias: very high.

Table 105: FREUND 2012

Study	Freund 2012[94]
Study type	Prospective cohort
Number of studies (number of participants)	>15years presenting to the ED with suspected infection.
Country and setting	France. ED.
Funding	None.
Duration of study	12 months.
Age, gender, ethnicity	Gender M/F=272/190 Mean age = 64±20
Patient characteristics	HIV=15 Undergoing cancer treatment=58 Multiple sclerosis=7 Systemic vasculitis on-going corticosteroid therapy=4 Temperature C = 37.3±1.1 Heart rate (bpm) = 98±23 Systolic blood pressure (mmHg) = 127±23 Pulse oximetry (median and IQR) = 95 (92-98) Temperature >38C or <36C = 130/457 Heart rate >90bpm = 283/457 Systolic blood pressure <90mmHg = 25/457 Pulse oximetry <90% = 76/457 WBC (per mm^3) = 11313±7162 Creatinine ($\mu mol.L^{-1}$) = 111±113 Lactate ($mmol.L^{-1}$) = 2.02±1.71 Lactate >2 = 140/462 Lactate >4 = 35/462 PCT ($ng.mL^{-1}$) = 0.25 (0.11-1.14) PCT >0.25 = 236/462

Study	Freund 2012[94]
	PCT >2 = 88/462 nSIRS 0 = 73/462 nSIRS 1 = 133/462 nSIRS 2 = 153/462 nSIRS 3 = 81/462 nSIRS 4 = 22/462
Index test/s	Lactate WBC count
Reference standard	NA
Target condition	Sepsis Severe sepsis Sepsis shock
Results	Multivariable analysis, backward logistic regression, only adjusting for those found significant at univariable analysis. Sepsis (multivariable analysis, including PCT≥0.25ng.mL^{-1}, temperature >38C or <36C, WBC count > 12,000mm^{-3}) • Temperature >38C or <36C: OR=2.42 (1.47-3.98) • WBC count > 12,000mm^{-3}: OR=1.83 (1.17-2.86) Severe sepsis (multivariable analysis including PCT≥0.25ng.mL^{-1}, lactate>2mmol.L^{-1}) • Lactate>2mmol.L^{-1}: OR=10.88 (6.51-18.19) Sepsis shock (multivariable analysis including PCT≥0.25ng.mL^{-1}, lactate>2mmol.L^{-1}, SAP<90mm Hg, SpO2<90%) • Lactate>2mmol.L^{-1}: OR=6.36 (1.87-21.62) Sepsis: Lactate (mmol.L^{-1}) Threshold = 1.4 AUC = 0.565 (0.508-0.616) P=0.02 Severe sepsis: Lactate (mmol.L^{-1}) Threshold = 2.0

Study	Freund 2012[94]
	AUC = 0.792 (0.736-0.838) P=<0.001 Septic shock: Lactate (mmol.L^{-1}) Threshold = 2.60 AUC = 0.840 (0.719-0.912) P=<0.001
General limitations (according to QUADAS 2)	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.

Table 106: GAINI 2006A

Study	Gaini 2006A[99]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=173)
Country and setting	Denmark. Department of internal medicine (Odense University Hospital)
Funding	University of Southern Denmark, the M.L. Jorgensen and G. Hansens Foundation, the Research Foundation of the Danish Medical Association, the H. Christensen Foundation, the K. and V. Skovgaards Foundation, and the J. and O. Madsen Foundation.
Duration of study	5-months period
Age, gender, ethnicity	Age (mean±SD): Non-infected without SIRS: 68.4±18; non-infected with SIRS: 64.4±14.6; infection without SIRS: 60.8±16.6; Sepsis: 60.4±19.9; Severe sepsis: 66.4±17.8. Gender: 79 M/94 F. Ethnicity: not stated.
Patient characteristics	Inclusion: Patients referred by a GP or admitted from the ED; suspected diagnosis of infection as judged by the referring physician and blood cultures drawn at the time of admission; age ≥18 years. Exclusion: earlier participation in the study or prior hospitalisation within 7 days before admission.

Study	Gaini 2006A[99]
	n=48 non-infected without SIRS n=19 non-infected with SIRS n=32 infections without SIRS n=47 sepsis n=27 severe sepsis or septic shock
Index test/s	CRP WBC Neutrophil
Reference standard	N/A
Target condition	Infection Sepsis/severe sepsis
Results:	
CRP to diagnose infections:	
AUC	0.83 (0.76-0.89)
cut off: 30 mg/litre	
Sensitivity	80.2
Specificity	62.7
PPV	77.3
NPV	66.7
Positive likelihood ratio	2.2
Negative likelihood ratio	0.32
cut off: 50 mg/litre	
Sensitivity	73.6
Specificity	74.6
PPV	82.1
NPV	64.1
Positive likelihood ratio	2.9
Negative likelihood ratio	0.35
cut off: 100 mg/litre	

Study	Gaini 2006A[99]
Sensitivity	62.3
Specificity	89.5
PPV	90.4
NPV	60.0
Positive likelihood ratio	5.9
Negative likelihood ratio	0.42
CRP to diagnose sepsis/ severe sepsis:	
AUC	0.84 (0.75-0.92)
cut off: 38 mg/litre	
Sensitivity	79.7
Specificity	57.9
PPV	88.1
NPV	42.3
Positive likelihood ratio	1.9
Negative likelihood ratio	0.35
cut off: 50 mg/litre	
Sensitivity	71.6
Specificity	63.2
PPV	88.3
NPV	36.4
Positive likelihood ratio	1.9
Negative likelihood ratio	0.45
cut off: 100 mg/litre	
Sensitivity	63.5
Specificity	94.7
PPV	97.9
NPV	40.0
Positive likelihood ratio	11.9

Study	Gaini 2006A[99]
Negative likelihood ratio	0.39
WBC to diagnose infection	
AUC	0.7005
WBC to diagnose sepsis/ severe sepsis	
AUC	0.6671
Neutrophil to diagnose infection	
AUC	0.6975
Neutrophil to diagnose sepsis/ severe sepsis	
AUC	0.6583
Median (IQR) CRP (mg/litre)	
non-infected without SIRS	18.0 (10.0-38.0)
non-infected with SIRS	19.0 (10.0-65.0)
infections without SIRS	122.0 (54.0-215.0)
sepsis	120.0 (41.0-190.0)
severe sepsis or septic shock	217.0 (78.0-414.0)
Median (IQR) WBC (10^9/litre)	
non-infected without SIRS	7.8 (6.7-9.2)
non-infected with SIRS	9.5 (7.8-12.1)
infections without SIRS	9.5 (7.7-11.9)
sepsis	13.0 (9.2-17.1)
severe sepsis or septic shock	12.2 (7.0-17.5)
Median (IQR) Neutrophils (10^9/litre)	

Study	Gaini 2006A[99]
non-infected without SIRS non-infected with SIRS infections without SIRS sepsis severe sepsis or septic shock	5.9 (4.6-6.9) 7.6 (4.6-6.9) 7.1 (5.1-9.7 10.1 (7.1-14.8) 10.3 (5.5-15.4)
General limitations (according to QUADAS 2)	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.

Table 107: Geppert 2003[109,109]

Study	Geppert 2003[109]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n tot=66: n=40 with cardiogenic shock; n=15 with septic shock; n=11 non-critically ill controls without infections)
Country and setting	Austria. Cardiovascular ICU.
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Cardiogenic shock: mean age (95% CI): 68 (64-72). Gender: 28 M/12 F. Ethnicity: not stated. Septic shock: mean age (95% CI): 56 (48-64). Gender: 13 M/2 F. Ethnicity: not stated. Control: mean age: 63±10 years. Gender: 5 M/6 F. Ethnicity: not stated.
Patient characteristics	Inclusion: Patients with cardiogenic shock had to be free of infection at the time of blood sapling. Exclusion: major surgery and prolonged cardiopulmonary resuscitation in the week before onset of shock; presence of mechanical assisted devices other than intra-aortic balloon pump at the time of blood sampling.
Index test/s	CRP
Reference standard	N/A

Study	Geppert 2003[109]
Target condition	Sepsis
Results: **AUC**	 0.83 (0.73-0.94)
General limitations (according to QUADAS 2)	Retrospective design, small sample size, population with cardiogenic or septic shock. Indirectness: none. Risk of bias: very high.

Table 108: GREEN 2011

Study	Green 2011[114]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=1143)
Country and setting	USA. Hospital (New York Hospital Queens)
Funding	None
Duration of study	12-month period, 28-day follow-up.
Age, gender, ethnicity	Median (interquartile range) age: 28-day survivors; 76 (62-85), 28-day non-survivors; 83 (72-91). Gender: 28-day survivors; 486 M/526 F, 28-day non-survivors; 58 M/73 F. Ethnicity: 28-day survivors versus 28-day non-survivors; White 47% versus 69%, Asian 20% versus 18%, Black 12% versus 11%, Hispanic 12% versus 9%, Other 9% versus 10%.
Patient characteristics	Inclusions: patients ≥21 years screened for severe sepsis using venous lactate and CRP testing in the ED. Patients admitted to hospital with a confirmed or suspected infection. Admitting diagnosis of infection was defined with admitting International Classification of Diseases, Ninth Revision codes. Only the index visit was used for patients with repeated visits to the ED.
Index test/s	Lactate (cut-off ≥4 mmol/dl) CRP (cut-off 10 mg/dl)
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: 28-day in-patient mortality	 Survivors: n=1012/1143 (88.5%).

Study	Green 2011[114]
	Non-survivors: n=131/1143 (11.5%; 95%CI 10.9% to 14.8%).
28-day in-patient mortality for all subjects, stratified by dichotomous lactate (4.0 mmol/litre) and CRP (10 mg/dl) level	Both a lactate level of ≥4 mmol/dl and CRP >10.0 mg/dl: 44.0% (95% CI 32.5% to 55.5%). Lactate ≥4 mmol/dl and CRP ≤10.0 mg/dl: 9.7% (95% CI 2.7% to 16.7%). All subjects lactate level ≥4.0 mmol/litre: 27.2% (95% CI 19.9% to 35.4%). All subjects lactate level <4.0 mmol/litre: 9.1% (95% CI 7.3% to 10.9%). Lactate level <4.0 mmol/litre and CRP >10.0 mg/dl: 11.9% (95% CI 8.9% to 15.0%). Lactate level <4.0 mmol/litre and CRP ≤10.0 mg/dl: 6.9% (95% CI 4.8% to 9.0%). All subjects CRP >10.0 mg/dl: 16.6% (95% CI 13.4% to 19.8%). All subjects CRP ≤10.0 mg/dl: 7.2% (95% CI 5.2% to 9.2%).
Multivariable logistic regression model for full cohort (n=1143) for 28-day inpatient mortality (adjusted for patient demographics and co-morbidities)	CRP >10.0 mg/dl and lactate level ≥4.0 mmol/litre: OR 12.34 (95%CI 6.81-22.34). CRP >10.0 mg/dl and lactate level <4.0 mmol/litre: OR 1.91 95%CI 1.22-2.98). CRP ≤10.0 mg/dl and lactate level ≥4.0 mmol/litre: OR 1.38 (95%CI 0.58-3.24). CRP ≤10.0 mg/dl and lactate level <4.0 mmol/litre: 1.00 reference.
Mean (SD) laboratory data comparisons between 28-day survivors and non-survivors	
CRP (mg/dl)	
Survivors	10.9 (10.2)
Non-survivors	16.4 (12.4)
Lactate (mmol/litre)	
Survivors	2.3 (1.8)
Non-survivors	3.5 (2.7)
Platelets 1000 cells/mm^3	
Survivors	267 (129)
Non-survivors	273 (144)

Study	Green 2011[114]
WBC (cells/mm^3) Survivors Non-survivors	 13.0 (10.9) 16.0 (11.9)
General limitations (according to QUADAS 2)	Retrospective design. Indirectness: none. Risk of bias: very high.

Table 109: HA 2011

Study	Ha 2011[115]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=87)
Country and setting	Korea. Hospital (The Samsung Medical Center, Seoul)
Funding	Not stated
Duration of study	30 days follow-up
Age, gender, ethnicity	Age: mean (range) 58 (28-81). Gender: 138/64. Ethnicity: not stated.
Patient characteristics	Inclusion: cirrhotic patients aged ≥18 years with bacteraemia (*Escherichia coli* or *Klebsiella pneumonia*), patients who had both initial and follow-up CRP levels recorded in medical histories, initial CRP level defined as level of CRP in blood samples within 24 hours after blood culture samples taken, follow-up CRP level defined as the level of CRP in the blood samples at day 4 or 5.
Index test/s	Ratio of follow-up CRP level to the initial CRP level (CRP ratio ≥0.7 defined as elevated)
Reference standard	N/A
Target condition	Hospital diagnosis of bacteraemia
Results: CRP ratio ≥0.7 **Patient factors, mean (range)** Initial CRP, mg/dl	 OR 19.12 (95%CI 1.32-276.86), p=0.043. Survivors (n=78): 5.64 (0.09-27.77). Non survivors (n=9): 2.59 (0.61-14.26). p=0.691.

Study	Ha 2011[115]
CRP ratio ≥0.7 WBC, /mm3	Survivors (n=78): 35 (0.09-27.77). Non survivors (n=9): 35 (0.09-27.77). p=0.015. Survivors (n=78): 9,000 (1,100-21,240). Non survivors (n=9): 7,820 (1,800-28,540). p=0.435.
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias (convenience sample). Indirectness: none. Risk of bias: very high.

Table 110: HAMBACH 2002

Study	Hambach 2002[117]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=214 clinical events, in a cohort of 61 patients). Immunocompromised patients
Country and setting	Germany. Hospital (bone marrow transplant unit of the Hannover Medical School)
Funding	Not stated. Conflict of interest declared: none
Duration of study	20-month period
Age, gender, ethnicity	Age: median (range) 33 (4-59). Gender: 37 M/24 F. Ethnicity: not stated.
Patient characteristics	Inclusion: allogeneic stem cell transplantation patients
Index test/s	CRP
Reference standard	N/A
Target condition	Infections (bacterial and fungal)
Results: CRP>5 mg/l CRP>50 mg/l	 Sensitivity: 100 Specificity: 4 PPV: 40 NPV: 100 Sensitivity: 94 Specificity: 41 PPV: 51 NPV: 91

Study	Hambach 2002[117]
CRP>100 mg/l	Sensitivity: 83 Specificity: 61 PPV: 58 NPV: 85
CRP>150 mg/l	Sensitivity: 68 Specificity: 74 PPV: 63 NPV: 78
Area under the curve:	AUC: 0.76 (0.69-0.93)
General limitations (according to QUADAS 2)	Observational design, small sample size Indirectness: prediction of infections, not sepsis. Risk of bias: very high.

Table 111: HILLAS 2010

Study	Hillas 2010[122]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=45) ICU patients with suspected VAP (ventilator-associated pneumonia)
Country and setting	Greece. ICU (Sotiria Chest Hospital, Athens)
Funding	Not stated
Duration of study	18-month period
Age, gender, ethnicity	Age: mean (SD) 61.5 (17.8). Gender: 34 M/11 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients admitted to ICU with suspected VAP; age ≥18 years Exclusion: patients with community-acquired pneumonia as a cause of ICU hospitalisation; patients with extra-pulmonary infection; immune-compromised patients.
Index test/s	CRP

Study	Hillas 2010[122]
Reference standard	N/A
Target condition	Severe sepsis
Results: **CRP>15.2 ng/ml, Day 1** Sensitivity Specificity PPV NPV AUC **CRP>15.75 ng/ml, Day 7** Sensitivity Specificity PPV NPV AUC **Median (IQR) CRP, day 1** Survivors Non-survivors **Median (IQR) CRP, day 7** Survivors Non-survivors	 86.4 65.2 70.4 83.3 79.4 (66.4-92.5) 93.8 73.9 71.4 94.4 78.3 (62.6-93.9) 16.5 (6.3-23.7) 19.0 (13.9-28.5) 16.8 (9.2-24.8) 16.7 (8.3-38.4)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre, patients with suspected VAP Indirectness: none. Risk of bias: very high.

Table 112: HOEBOER 2012

Study	Hoeboer 2012[124]

Study	Hoeboer 2012[124]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=101)
Country and setting	Netherlands. ICU (VU University Medical Center, Intensive Care, Amsterdam)
Funding	Not stated
Duration of study	5-year period, 28-day follow-up for mortality
Age, gender, ethnicity	Group 1 (n=44) Age median (range): 63 (22-77). Gender: 32 M/12 F. Ethnicity: not stated. Group 2 (n=45) Age median (range): 61 (19-81). Gender: 34 M/11 F. Ethnicity: not stated. Group 3 (n=12) Age median (range): 67 (19-81). Gender: 3 M/9 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients presenting with new onset fever in the 24-bed mixed medical/surgical ICU, new onset fever defined as body temperature ≥38.3°C, preceded by a period of ≥24 h in the absence of fever (<37.5°C), enrolment followed within 12 h after inclusion criteria were met. Group 1: without infection or with possible infection but negative cultures. Group 2: with probable or proven local infection without blood stream infection (BSI). Group 3 with BSI irrespective of local infection. Exclusion: pregnancy, life expectancy of less than 24 h.
Index test/s	Bloodstream infection Day 0-2 CRP mg/litre (cut-off 196 mg/litre) Lactate mmol/litre (cut-off 1.5 mmol/litre) WBC x 10^9/litre (cut-off 20.3) Septic shock Day 0-7 CRP mg/litre (cut-off 208 mg/litre) Mortality Day 0-28 Lactate mmol/litre (cut-off 1.7 mmol/litre)

Study	Hoeboer 2012[124]
Reference standard	N/A
Target condition	Hospital diagnosis of: probable or proven local infection BSI, BSI irrespective of local infection.
Results:	
Bloodstream infection Day 0-2, prediction by peak values of biomarkers	
CRP, mg/litre (cut-off 196 mg/litre)	
Area under curve	0.74
Sensitivity	92
Specificity	60
PPV	23
NPV	98
Lactate, mmol/litre (cut-off 1.5 mmol/litre)	0.75
Area under curve	83
Sensitivity	61
Specificity	23
PPV	96
NPV	
WBC, x 10^9/litre (cut-off 20.3)	0.70
Area under curve	58
Sensitivity	84
Specificity	33
PPV	94
NPV	
Septic shock Day 0-7, prediction by peak values of biomarkers	
CRP, mg/litre (cut-off 208 mg/litre)	0.75
Area under curve	71

Study	Hoeboer 2012[124]
Sensitivity Specificity PPV NPV	78 62 84
Mortality Day 0-28, prediction by peak values of biomarkers **Lactate, mmol/litre** (cut-off 1.7 mmol/litre) Area under curve Sensitivity Specificity PPV NPV	0.71 60 75 44 85
Multivariable analysis for high risk infection Peak CRP, mg/litre Peak lactate, mmol/litre	P= 0.033 P= 0.001
Peak values of biomarkers per group, median (range) **Day 0-2 infection** CRP, mg/litre Lactate, mmol/litre WBC, x 10^9	Group 1: 142 (27-440). Group 2: 153 (5-484). Group 3: 231 (71-436). Group 1: 1.3 (0.5-2.3). Group 2: 1.4 (0.5-13.1). Group 3: 1.9 (1.1-3.9). Group 1: 13.2 (5.5-38.5). Group 2: 12.8 (0.2-25.7). Group 3: 20.6 (2.5-81.7).
Peak values of biomarkers, no septic shock (n=67) versus septic shock (n=34) **Day 0-7**	No septic shock: 146 (5-440). Septic shock: 243 (5-484). p <0.001. No septic shock: 1.4 (0.5-2.5). Septic shock: 1.6 (0.8-13.1). p=0.07.

Study	Hoeboer 2012[124]
CRP, mg/litre Lactate, mmol/litre WBC, x 10^9 **Peak values of biomarkers, survivors (n=75) versus non-survivors (n=26)** **Day 0-28** CRP, mg/litre Lactate, mmol/litre WBC, x 10^9	No septic shock: 12.9 (4.8-38.5). Septic shock: 15.0 (0.2-81.7). p=0.16. Survivors: 177 (5-440). Non survivors: 201 (38-484). p=0.303. Survivors: 1.3 (0.5-3.5). Non survivors: 1.8 (0.9-13.1). p=0.002. Survivors: 12.5 (2.5-27.5). Non survivors: 16.8 (0.2-81.7). p=0.077.
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 113: JANSEN 2009A

Study	Jansen 2009[134]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=394 patients: n=140 patients with sepsis, n=123 patients with low-oxygen transport, n=131 patients with no sepsis or low-oxygen transport)
Country and setting	The Netherlands. General ICU (2 centre study: Erasmus MC University Medical Center, Rotterdam, Gelre Hospitals, Lukas site, Apeldoorn)
Funding	Not stated
Duration of study	2-year period, 24-hour survival
Age, gender, ethnicity	Sepsis group Mean (SD) age: 67 (14). Gender: 56 M/44 F. Ethnicity: not stated.
Patient characteristics	Inclusion: sepsis based on Acute Physiology and Chronic Health Evaluation (APACHE) III scoring system.

Study	Jansen 2009[134]
Lactate level mean (SD), mmol/l	At ICU admission: 2.9 (2.3) 12 hours after admission: 2.5 (2.6) 24 hours after admission: 2.2 (2.1)
Lactate level mean (SD)	At ICU admission: 44% 12 hours after admission: 31% 24 hours after admission: 26%
Hospital length of stay mean (SD), days	28 (30)
In-hospital mortality	36%
Index test/s	Lactate (hyperlactatemia ≥2.5 mmol/l)
Reference standard	N/A
Target condition	28-day mortality
Results:	At ICU admission: 0.52 for initial lactate For the initial lactate threshold of 2.5 mmol/l: TP: 18, FN: 23, FP: 42, TN: 55 (extracted from raw risk data 18/60 vs 23/78): from this sensitivity (0.44)and specificity (0.57) were calculated
General limitations	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Table 114: JEKARL 2013

Study	Jekarl 2013[136]
Study type	Prospective cohort
Number of studies (number of participants)	n=177 consecutive patients diagnosed with SIRS in the ED.
Country and setting	South Korea. ED.
Funding	Supported by Yeouido St Mary's Hospital Clinical Research Center, The Catholic University of Korea.
Duration of study	Dates the study carried out not stated. Follow up time: 96 hours.
Age, gender, ethnicity	Male: All=88/177, Sepsis=35/78 Female: All=89/177, Sepsis=43/78 Age: All=51.5±22.4, Sepsis=62±19.9
Patient characteristics	Exclusions: Immunocompromised, visited or were discharged from the hospital within 14 days of presenting at ED or had antimicrobial therapy before presenting at ED. Included: patients diagnosed with SIRS at ED. Blood samples taken at admission, prior to antimicrobial therapy. SIRS defined as: 2 or more of; temperature >38C or <36C, heart rate >90bpm, respiratory rate >20 bpm, hyperventilation ($PaCO_2$<32mmHg), WBC>12.0x10^9/litre or <4.0x10^9/litre, or >10% immature cells. Sepsis defined as: SIRS + microbial infection. Severe sepsis defined as: Sepsis + organ dysfunction, hypoperfusion or hypotension. Septic shock defined as: Sepsis + induced hypotension, despite adequate fluid resuscitation + hypoperfusion abnormities or organ dysfunction.

Study	Jekarl 2013[136]
	Final diagnosis: Acute pyelonephritis: All=20/177, Sepsis=16/78 Lower urinary tract infection: All=3/177, Sepsis=2/78 Pneumonia, lung abscess: All=35/177, Sepsis=24/78 Cardiovascular disease: All=6/177, Sepsis=2/78 Central nervous system infection: All=7/177, Sepsis=2/78 Ear nose and throat infection: All=17/177, Sepsis=3/78 Digestive tract infection: All=36/177, Sepsis=8/78 Hepatobiliary tract infection: All=14/177, Sepsis=5/78 Soft tissue and wound infection: All=12/177, Sepsis=5/78 Gynaecological infection: All=2/177, Sepsis=0/78 Pancreatitis: All=1/177, Sepsis=1/78 Malaria: All=2/177, Sepsis=2/78 Others: All=21/177, Sepsis=8/78
Index test/s	All=/177, Sepsis=/78
Reference standard	NA
Target condition	Sepsis and septic shock/severe sepsis
Results	Septic shock/severe sepsis CRP (mg/litre): AUC=0.725 Cut-off=55 Sensitivity(95% CI)=81.2 (54.4-96.0) Specificity(95% CI)=59.2 (51.0-66.7) PPV(95% CI)=16.5 (6.99-25.9) NPV(95% CI)=96.9 (93.1-100) Accuracy(95% CI)=61.0 (52.7-69.2)

Study	Jekarl 2013[136]
	WBC(x109/litre): AUC=0.536 Cut-off=11.0 Sensitivity(95% CI)=62.5 (35.4-84.8) Specificity(95% CI)=57.1 (49.1-64.9) PPV(95% CI)=12.6 (4.17-21.1) NPV(95% CI)=93.8 (88.5-99.1) Accuracy(95% CI)=57.1 (49.5-64.7)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.

Table 115: KIM 2011

Study	Kim 2011[147]
Study type	Retrospective cohort (electronic medical records)
Number of studies (number of participants)	1 (n=286)
Country and setting	Korea. ED (patients with febrile neutropenia).
Funding	Not stated
Duration of study	2-year period
Age, gender, ethnicity	Median age (range): 54 (42-64). Gender: 127 M /159 F. Ethnicity: not stated.
Patient characteristics	Adult cancer patients, age ≥16 years, with chemotherapy-associated febrile neutropenia who visited the ED of a university-affiliated tertiary referral medical centre. Bacteraemia detected in 38 patients (13.3%)
Index test/s	CRP
Reference standard	N/A
Target condition	Bacteraemia

Study	Kim 2011[147]
Results: Area under the curve (CRP) Sensitivity (CRP> 10 mg/dl) Specificity Positive likelihood ratio Negative likelihood ratio OR (multivariable analysis) CRP >10 mg/dl SBP <90 mm Hg Pulse rate >120 beats/min Respiratory rate >24 breaths/min Temperature >39 ° C Plasma concentration, median (interquartile range) CRP (mg/dl) All patients With bacteraemia Without bacteraemia	 0.655 (0.548-0.761) 57.6 67.3 1.8 0.6 0.8 (0.34-2.1) 2.4 (0.8-7.7) 1.8 (0.8-4.0) 3.4 (1.4-8.5) 1.6 (0.7-3.5) 5.8 (2.6-14.0) 15.9 (3.6-26.0) 5.6 (2.5-12.7)
General limitations (according to QUADAS 2)	Retrospective design, small sample size, heterogeneity of the cancer population. Indirectness: diagnosis of bacteraemia, not sepsis. Risk of bias: very high.

Table 116: KIM 2014A

Study	Kim 2014A[148]

Study	Kim 2014A[148]
Study type	Prospective study
Number of studies (number of participants	1 (n=128 – control group with no negative blood culture and no SIRS, n=56; bacteraemia with no SIRS symptoms: n=37; sepsis, n=25; septic shock, n=10)
Country and setting	Korea. Unclear setting – possible ED (St Mary's Hospital, Catholic University of Korea).
Funding	Not stated (authors report no conflict).
Duration of study	July 2013 – November 2013
Age, gender, ethnicity	Overall: Mean (2±SD) age: 62.0±38.4 years [For Bacteremia, Sepsis, Septic Shock, Control respectively: Mean (SD) age: 62.8±33.6, 62.4±40.2, 67.3±47.7, 60.4±39.5; Gender M/F (n): 23/14, 14/11, 3/7, 29/27; Ethnicity: not stated]
Patient characteristics	Inclusion: Four groups: Control: patients with a negative blood culture and no SIRS symptoms; Bacteremia: patients with a positive blood culture but no SIRS symptoms; Sepsis: patients in whom growth of microorganisms was detected within 48 hours after the start of SIRS symptoms; Septic shock: sepsis patients with hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities that included, but were not limited to lactic acidosis, oliguria or an acute alteration in mental status. Exclusion: Patients were excluded if their diagnosis was hematological malignancy, metastatic bone marrow infiltration by a malignancy, recovery after bone marrow hypoplasia, or acute bleeding.
Index test	Delta neutrophil index (DNI) CRP
Reference standard	N/A
Target condition	Diagnosis of sepsis and predicting mortality outcome
Results: **Prediction of sepsis/septic shock** **CRP (cut-off >6.84 mg/l)**	
Area under curve	0.819
Sensitivity	87.5
Specificity	63.5
PPV	50.9

Study	Kim 2014A[148]
NPV	92.2
DNI (cut-off >12.3%)	
Area under curve	0.932
Sensitivity	88.6
Specificity	90.3
PPV	77.5
NPV	95.5
Prediction of mortality	
CRP (cut-off >8.88 mg/l)	
Area under curve	0.723
Sensitivity	85.7
Specificity	66.7
PPV	29.3
NPV	96.7
DNI (cut-off >12.8%)	
Area under curve	0.800
Sensitivity	75.0
Specificity	81.3
PPV	37.5
NPV	95.6
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 117: KIM 2015B

Study	Kim 2015B[150]

Study	Kim 2015B[150]
Study type	Retrospective cohort study
Number of studies (number of participants	1 (n=670) Patients who had received early goal-directed therapy for severe sepsis or septic shock
Country and setting	Korea. ED, Severance Hospital at Yonsei University College of Medicine (Seoul, Korea)
Funding	The authors received no specific funding.
Duration of study	November 2007 to February 2013
Age, gender, ethnicity	Overall: Mean age (years): 65.06±14.39; Gender (number male, %): 352 (52.54); Ethnicity: not stated
Patient characteristics	Inclusion: On average, 200 patients a day were screened, and those with two or more SIRS criteria, and signs of infection, were evaluated for EGDT eligibility. One or both of the following conditions triggered initiation of the EGDT protocol: (a) an initial SBP of <90 mmHg despite IV challenge with 20 ml/kg of crystalloid fluid or (b) an initial serum lactate level of ≥4 mmol/L. Exclusion: (a) age <18 years, (b) any contraindication to CVC, (c) pregnancy, (d) acute cerebrovascular accident, (e) acute coronary syndrome, (f) active gastrointestinal bleeding, (g) trauma, (h) drug overdose, (i) requirement for immediate surgery, (j) absence of informed consent, (k) transfer to another institution, and/or (l) a do-not-resuscitate order.
Index test	CRP/Albumin CRP Lactate
Reference standard	N/A
Target condition	Prediction of 180-day mortality
Results: **Prediction of 180-day mortality** CRP/albumin ratio at admission (cut-off >5.09) Area under curve Sensitivity Specificity PPV NPV	 0.6211(0.5053-0.6166) 61.08 (54.06-68.11) 61.05 (56.67-65.44) 37.92 (32.41-43.43) 80.11 (76.00-84.22)

Study	Kim 2015B[150]
CRP alone (cut-off >67.5 mg/dl) Area under curve Sensitivity Specificity PPV NPV Multivariable analysis adjusted (for each variable) for age, gender, CRP/albumin ratio, SOFA score, lactate level and having malignancy or not. CRP/albumin at admission Lactate at admission	0.5620(0.5053-0.6166) 84.86 (79.70-90.03) 30.95 (26.79-35.10) 32.37 (28.21-36.53) 84.00 (78.56-89.43) HR=1.06 (1.03-1.10) HR=1.10 (1.05-1.14)
General limitations (according to QUADAS 2)	Observational retrospective design Indirectness: none. Risk of bias: very high.

Table 118: KOFOED 2007

Study	Kofoed 2007[154]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n tot=151; n=96 with bacterial infections; n=16 with viral infection; n=5 with parasitic infection; n= with no infection)
Country and setting	Denmark. Hospital
Funding	Competing interests: suPAR antibodies were a gift from ViroGates (Cape Town, South Africa). One author is shareholder in VoroGates and holds patents on using suPAR for diagnostic and prognostic purposes.
Duration of study	1-year period
Age, gender, ethnicity	Median (range) age: 56 (20-94). Gender: 73 M/78 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age ≥18 years; newly admitted (<24 hours) to the Department of Infectious Diseases or the infectious disease unit

Study	Kofoed 2007[154]
	in Medical Emergency Department; fulfilled at least 2 criteria for SIRS.
Index test/s	CRP Neutrophil count
Reference standard	N/A
Target condition	Bacterial infection in SIRS patients
Results: CRP (cut off: 60 mg/litre) AUC Sensitivity Specificity PPV NPV Neutrophil count (cut off: 7.5×10^9 cells/litre) AUC Sensitivity Specificity PPV NPV	 0.81 (0.73-0.86) 0.86 (0.78-0.93) 0.60 (0.46-0.73) 0.79 0.73 0.74 (0.66-0.81) 0.74 (0.64-0.82) 0.64 (0.50-0.76) 0.82 0.57
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: prediction of bacterial infection (not sepsis). Risk of bias: very high.

Table 119: LETH 2013

Study	Leth 2013[169]
Study type	Prospective cohort
Number of studies (number of participants)	n=828 consecutive patients who had blood cultures taken, at admission.

Study	Leth 2013[169]
Country and setting	Denmark <u>Department</u> Emergency: bloodstream infection=38/68, no bloodstream infection=524/828 Intensive care: bloodstream infection=1/68, no bloodstream infection=32/828 Surgery: bloodstream infection=22/68, no bloodstream infection=126/828 Internal medicine: bloodstream infection=6/68, no bloodstream infection=129/828 Other: bloodstream infection=1/68, no bloodstream infection=17/828
Funding	Not stated.
Duration of study	February 1 2010 – April 30 2010
Age, gender, ethnicity	Median age (all)=70 Median age (bloodstream infection)=73 Median age (no bloodstream infection)=70 Male: bloodstream infection=34/68, no bloodstream infection=420/828 Female: bloodstream infection=34/68, no bloodstream infection=408/828
Patient characteristics	Antibiotics before blood culture: bloodstream infection=8/68, no bloodstream infection=239/828 Body temperature >38C or <36C: bloodstream infection=54/66, no bloodstream infection=496/804 C-reactive protein >8mg/litre: bloodstream infection=67/68, no bloodstream infection=745/825 Neutrophils<2.0x10^9/litre or >7.0x10^9/litre: bloodstream infection=30/42, no bloodstream infection=423/619 p-Carbamide<3mmol/litre or >7.0mmol/litre: bloodstream infection=30/57, no bloodstream infection=330/702 Leukocyte count: bloodstream infection=41/67, no bloodstream infection=445/828 Heart rate>90 bpm: bloodstream infection=42/63, no bloodstream infection=431/781 Respiratory rate>20 bpm: bloodstream infection=11/13, no bloodstream infection=108/214
Index test/s	Leukocyte count C-reactive protein Neutrophils Body temperature Heart rate

Study	Leth 2013[169]
	Respiratory rate
Reference standard	NA
Target condition	Bloodstream infection
Results	Analysis adjusted for body temperature, leucocyte count, C-reactive protein. Body temperature ≤38C or ≥36C compared to Body temperature >38C or <36C: OR=2.55 (1.34-4.87) Leukocyte count≥4.0x10^9/litre or ≤12.0x10^9/litre compared to Leukocyte count<4.0x10^9/litre or >12.0x10^9/litre: OR=1.07 (0.63-1.80) C-reactive protein >8mg/litre compared to C-reactive protein <8mg/litre: OR=6.06 (0.82-44.6) Neutrophils≥2.0x10^9/litre or ≤7.0x10^9/litre compared to Neutrophils<2.0x10^9/litre or >7.0x10^9/litre: OR=0.88 (0.36-2.13) Heart rate≤90 bpm compared to Heart rate>90 bpm: OR=1.40 (0.80-2.46) Respiratory rate≤20 bpm compared to Respiratory rate>20 bpm: OR=5.42 (1.13-25.9)
General limitations (according to QUADAS 2)	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.

Table 120: LUZZANI 2003

Study	Luzzani 2003[178]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=70)
Country and setting	Italy. ICU (medico-surgical).
Funding	Not stated
Duration of study	3-month period
Age, gender, ethnicity	Median age: 66.5. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Consecutive patients, age ≥18 years, admitted to medicosurgical ICU of the Verona OCM Hospital, for an expected stay >24 hours.
Index test/s	CRP

Study	Luzzani 2003[178]
Reference standard	N/A
Target condition	Infection
Results: CRP: Area under the curve Plasma concentration, median (interquartile range) Negative SIRS Localised infection Sepsis group Sepsis Severe sepsis Septic shock	 0.580 (0.488-0.672) 50.4 (25.3-87.6) 79.9 (52.9-103.4) 85.5 (58.5-132.4) 115.9 (69.7-171.2) 125.6 (79.4-174.6) 73.6 (60.9-148.9) 108.0 (62.9-167.5)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 121: MAGRINI 2014

Study	Magrini 2014[181]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=513) patients presenting to the ED with signs/symptoms of local infection or sepsis
Country and setting	Italy. ED (University Hospital).
Funding	Supported in part by the participating institutions' departmental funds.
Duration of study	None declared
Age, gender, ethnicity	Age, mean (SD): 71.18 (15.90). Gender: 263 M/250 F. Ethnicity: not stated.
Patient characteristics	Patients referred to ED with symptoms of infection, and in which a diagnosis of infection or sepsis was formulated.

Study	Magrini 2014[181]
	n=221 septic patients; n=292 non-septic patients
Index test/s	CRP WBC
Reference standard	N/A
Target condition	Sepsis
Results: **AUC (diagnosis of sepsis)**: WBC CRP CRP+WBC **WBC mean (SD) value, 10^3/microlitre** Septic patients Non-septic patients **CRP mean (SD) value, mg/dl** Septic patients Non-septic patients	 0.53 0.72 0.71 15969 (8324) 11155 (5103) 20.19 (14.87) 12.34 (11.81)
General limitations (according to QUADAS 2)	Retrospective design, small sample size, single centre. Indirectness: none. Risk of bias: very high.

Table 122: MARE 2015

Study	Mare 2015[188]
Study type	Prospective cohort study (retrospective analysis)
Number of studies (number of participants	1 (n=122, SIRS; n=14, without SIRS; n=20, healthy controls) [SIRS patients further subdivided into: Definite sepsis (n=51), Possible sepsis (n=31), and Non-infectious (N-I) SIRS (n=39)]
Country and setting	UK, adults ICU (Single-centre; Guy's and St Thomas' HS Foundation Trust, St Thomas' Hospital, London)

Study	Mare 2015[188]
Funding	Not stated
Duration of study	Samples acquired every weekday for 8 weeks
Age, gender, ethnicity	For Definite sepsis, Possible sepsis, N-I SIRS, No SIRS and Control groups respectively: Mean (SD) age: 62±16, 66±13, 59±19, 54±15, 37±11; Gender (% male): 59, 63, 79, 41, 52; Ethnicity: not stated.
Patient characteristics	Inclusion: 136 consecutive patients within 48 hours of entry to adult ICU. Patients were defined as having SIRS if they satisfied at least two of the recognised criteria, but without reference to the number or distribution of WBCs. Exclusion: Number and distribution of WBCs omitted because, in the Levy definition, >10% immature neutrophils were recorded in patients with a normal WBC count, and, authors felt that if they had used a neutrophilia or a neutropenia as one of the features of SIRS, then a potentially important subgroup of patients (that is, those with normal WBC counts) would have been removed from the study.
Index test	Immature neutrophils – band cells, Total WBC counts, platelet numbers, CRP values
Reference standard	N/A
Target condition	Detection of definite sepsis, possible sepsis, N-I SIRS, no SIRS
Results: **Definite sepsis** **% Band cells (cut-off 8.5%)** Area under curve Sensitivity Specificity PPV NPV **% abnormal WBC** **% platelet count <150 x 10^9/l (thrombocytopenia)** **CRP (cut-off >5 µg/l)**	 0.80 (95% CI 0.72 – 0.88) 84.3% 71.4% 55% 23% 97%

Study	Mare 2015[188]
Possible sepsis **% Band cells (cut-off 8.5%)**	63%
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 123: MEYNAAR 2011

Study	Meynaar 2011[197]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n tot=761; n=32 with sepsis; n=44 with SIRS)
Country and setting	The Netherlands. ICU
Funding	Not stated.
Duration of study	3-month period
Age, gender, ethnicity	Median (IQR) age: 66 (56-78). Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: consecutive patients admitted to ICU; expected to be treated for >24 hours. Exclusion: patients with no SIRS or sepsis.
Index test/s	CRP
Reference standard	N/A
Target condition	Sepsis
Results: CRP (cut off: 50 mg/litre) AUC Sensitivity Specificity	 0.75 (0.63-0.86) 88 23

Study	Meynaar 2011[197]
PPV NPV	45 71
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 124: MOREIRA 2010

Study	Moreira 2010[198]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n tot=110 n=30 fever without infection or fever of unknown origin; n=26 local infection confirmed by microbiological culture; n=28 sepsis or severe sepsis; n= 26 septic shock) febrile patients
Country and setting	Spain. Hospital (ED, ward and ICU)
Funding	Obra Social y Cultura Cajastur
Duration of study	Not stated
Age, gender, ethnicity	Mean (SD) age: 44 (20). Gender: 60% M/40% F. Ethnicity: not stated.
Patient characteristics	Febrile patients.
Index test/s	CRP
Reference standard	N/A
Target condition	Sepsis
Results: CRP (cut off: 11 ng/ml) AUC Sensitivity Specificity PPV NPV	 0.79 (0.64-0.89) 87.1 (69.2-95.8) 78.4 (61.3-89.6) 77.1 87.9

Study	Moreira 2010[198]
Median (IQR) CRP values, mg/ml	
Fever without infection	10 (8.5-14)
Localised infection	9.7 (7.5-13)
Sepsis	21 (14-30)
Septic shock	20 (12-25)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.

Table 125: MULLER 2010

Study	Muller 2010[202]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=925)
Country and setting	Switzerland. Secondary and tertiary care hospitals (patients with pneumonia).
Funding	Swiss National Science Foundation
Duration of study	2-year period
Age, gender, ethnicity	Median age (IQR): 73 (59-82) years. Gender: 59% M/ 41% F. Ethnicity: not stated.
Patient characteristics	Patients with radiologic confirmed CAP (sub-study of ProHOSP: Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections) Inclusion criteria: age ≥18 years; hospital admission from the community or a nursing home for LRTI. Exclusion criteria: inability to give written informed consent; insufficient German language skills; active illegal IV drug use; previous hospitalisation for LRTI within 14 days; severe immunosuppression other than use of corticosteroids; accompanying chronic infection or endocarditis; most severe medical comorbidities where death was imminent.
Index test/s	CRP Blood urea nitrogen WBC
Reference standard	N/A

Study	Muller 2010[202]
Target condition	Bacteraemia
Results:	
CRP	
Area under the curve (CRP)	0.67 (0.59-0.74)
Sensitivity (CRP >20 mg/litre)	96
Specificity (CRP >20 mg/litre)	9
LR+ (CRP >20 mg/litre)	1.05
LR– (CRP >20 mg/litre)	0.46
Sensitivity (CRP >50 mg/litre)	89
Specificity (CRP >50 mg/litre)	18
LR+ (CRP >50 mg/litre)	1.09
LR– (CRP >50 mg/litre)	0.60
Sensitivity (CRP >100 mg/litre)	81
Specificity (CRP >100 mg/litre)	33
LR+ (CRP >100 mg/litre)	1.20
LR– (CRP >100 mg/litre)	0.59
Sensitivity (CRP >200 mg/litre)	61
Specificity (CRP >200 mg/litre)	64
LR+ (CRP >200 mg/litre)	1.70
LR– (CRP >200 mg/litre)	0.61
Blood urea nitrogen	
AUC (Blood urea nitrogen)	0.64 (0.57-0.71)
Sens (Blood urea nitrogen >11mM)	32
Spec (Blood urea nitrogen >11mM)	78
LR+ (Blood urea nitrogen >11mM)	1.44
LR– (Blood urea nitrogen >11mM)	0.87

Study	Muller 2010[202]
WBC	
AUC (WBC)	0.58 (0.50-0.65)
Sens (WBC≤5 or ≥20 $x10^9$/litre)	22
Spec (WBC≤5 or ≥20 $x10^9$/litre)	84
LR+ (WBC≤5 or ≥20 $x10^9$/litre)	1.34
LR– (WBC≤5 or ≥20 $x10^9$/litre)	0.93
SBP	
AUC (SBP)	0.61 (0.54-0.68)
Sens (SBP <90 mm Hg)	7
Spec (SBP <90 mm Hg)	97
LR+ (SBP <90 mm Hg)	2.37
LR– (SBP <90 mm Hg)	0.96
Pulse rate	
AUC (pulse rate)	0.060 (0.53-0.67)
Sens (pulse rate >125/min)	17
Spec (SBP <90 mm Hg)	93
LR+ (SBP <90 mm Hg)	2.46
LR– (SBP <90 mm Hg)	0.89
Temperature	
AUC (T)	0.59 (0.52-0.66)
Sens (T<35 or >40 ° C)	10
Spec (T<35 or >40 ° C)	96
LR+ (T<35 or >40 ° C)	2.37
LR– (T<35 or >40 ° C)	0.94
General limitations (according to QUADAS 2)	Observational design. Indirectness: prediction of bacteraemia, not sepsis.

Study	Muller 2010[202]
	Risk of bias: high.

Table 126: MURRAY 2007

Study	Murray 2007[205]
Study type	Retrospective cohort
Number of studies (number of participants)	n=223 patients with burns
Country and setting	USA. ICU (Army Institute of Surgical Research)
Funding	None
Duration of study	3.5 year duration
Age, gender, ethnicity	Patients with bacteria positive blood culture (n=73): Mean age: 43 years. Gender: 93% M/7% F. Ethnicity: not stated. Patients with bacteria negative blood culture (n=73): Mean age: 37 years. Gender: 80% M/20% F. Ethnicity: not stated.
Patient characteristics	Burn patients. Electronic medical record review of patients who underwent blood culture.
Index test/s	WBC + neutrophil percentage
Reference standard	N/A
Target condition	Bloodstream infection (Bloodstream infection defined as “Gram-negative or gram-positive bacteraemia from blood cultures“)
Results AUC	 0.624 (0.569-0.679)
General limitations (according to QUADAS 2)	Retrospective design, small sample size, single centre. Burn patients only Indirect: bloodstream infection prediction not sepsis. Risk of bias: very high.

Table 127: NAKAMURA 2009

Study	Nakamura 2009[211]
Study type	Prospective cohort

Study	Nakamura 2009[211]
Number of studies (number of participants)	n=116 suspected of having bacteraemia (≥3 days continuous fever)
Country and setting	Japan.
Funding	Supported in part by grant from Ministry of Health, Labor and Welfare of Japan, Ministry of Education, Culture, Sports, Science and Technology and the Mie University COE Project Fund.
Duration of study	1 June 2003 – 31 December 2006
Age, gender, ethnicity	Median age: 59 years Male/female: 75/41
Patient characteristics	Undergone liver transplantation = 50 Pneumonia = 13 Hematologic malignancies = 8 Heart failure = 5 Renal failure = 4 Burns = 4 Bone marrow transplant = 3 Hepatic cell carcinoma = 3 Oesophageal cancer = 3 Liver cirrhosis = 3 Pleurisy = 2 Gastric ulcer = 2 Acute myocardial infarction = 1 Diabetes = 1 Liver abscess = 1 Hemophagocytic syndrome = 1 Excluded patients with tumour or drug induced fever and fever due to an autoimmune disease.
Index test/s	CRP
Reference standard	NA
Target condition	Bacterial infection. 21 day mortality.

Study	Nakamura 2009[211]
Results	Clinical bacteraemia – CRP. Sensitivity % = 75.0 Specificity % = 40.4 PPV % = 60.8 NPV % = 56.8 OR = 2.03 (0.93-446) 21 day mortality – CRP. Sensitivity % = 10.7 Specificity % = 92.7 PPV % = 72.7 NPV % = 36.2 OR = 1.51 (0.38-6.00)
General limitations (according to QUADAS 2)	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.

Table 128: OBERHOFFER 1999A

Study	Oberhoffer 1999A[220]
Study type	Retrospective study.
Number of studies (number of participants)	1 (n=242: n=55 nil; n=117 SIRS; n=20 sepsis, n=5 severe sepsis; n=45 septic shock)
Country and setting	Germany. ICU (University Hospital) critically ill patients
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Age range: 18-86 years. Gender: 63% M/37% F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients admitted for >48 h to the interdisciplinary ICU of the university hospital Exclusion: primary fatal condition such as severe head injury resulting in cerebral death that was not combined with an infectious complication.

Study	Oberhoffer 1999A[220]
Index test/s	CRP Leukocytes
Reference standard	N/A
Target condition	Mortality
Results: Mortality **CRP >198 mg/litre** Sensitivity Specificity PPV NPV AUC **Leucocytes >15000/microlitre** Sensitivity Specificity PPV NPV AUC	 n=177 survivors n=65 non-survivors 66 80 51 88 81.1 36 80 31 83 62.0
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: prediction of mortality. Risk of bias: very high.

Table 129: O'CONNOR 2004

Study	O'Connor 2004[221]
Study type	Prospective study.

Study	O'Connor 2004[221]
Number of studies (number of participants)	1 (n=62: n=54 SIRS or sepsis, n=8 controls)
Country and setting	Australia. ICU (Royal Brisbane Hospital, Queensland)
Funding	Not stated
Duration of study	9-month study period, 7 day survival
Age, gender, ethnicity	Patients with traumatic brain injury (n=39) Mean (SEM) age: 38 (3.1). Gender: 24 M/15 F. Ethnicity: not stated. Patients with subarachnoid haemorrhage (n=23) Mean (SEM) age: 57 (3.3). Gender: 10 M/13 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with isolated head injury or acute aneurysmal subarachnoid haemorrhage with the last 48 hours. Identification of SIRS and sepsis based on guidelines developed at Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine (1992). Patient considered to have infection if all of the following criteria met: (1) documented SIRS, (2) diagnostic work-up for an infection was initiated, (3) positive culture of potentially pathogenic microorganisms, (4) statement by the medical team of a high likelihood of infection (5) antibiotics were commenced. Exclusion: existing antibiotic therapy, pre-existing febrile illness, missing patient data.
Index test/s	CRP
Reference standard	N/A
Target condition	SIRS and sepsis (combined)
Results: Mortality (%)	 Patients with traumatic brain injury: 31 Patients with subarachnoid haemorrhage: 26
CRP for prediction of mortality Area under curve	 Day 0: 0.31 Mean all days (0-7): 0.68 Peak CRP value: 0.63
Sensitivity	Day 0: 17 Mean all days (0-7): 50 Peak CRP value: 33

Study	O'Connor 2004[221]
Laboratory data, mean (SEM) **CRP, ng/ml**	No SIRS (n=13): 77 (8.2) SIRS (n=35): 116 (9.1) Sepsis (n=14): 94 (8.6)
General limitations (according to QUADAS 2)	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.

Table 130: PANCER 2011

Study	Pancer 2011[227]
Study type	Retrospectively cohort.
Number of studies (number of participants)	1 (n=168)
Country and setting	USA. Setting not stated (review oh hemogram data and electronic medical record)
Funding	No funding.
Duration of study	Not stated
Age, gender, ethnicity	Median age:65 years. Gender: 33% M/67% F. Ethnicity: not stated.
Patient characteristics	Inclusion: Blood smears with WBC count >12000 cells/mm^3 or absolute neutrophil count >10800 cells/mm^3 as well as smears with 10%immature neutrophils. n=95 non-inflammatory diagnoses n=41 SIRS or sepsis n=32 no non-inflammatory diagnoses nor sepsis Exclusion: patients with normal blood smears or abnormalities due to primary blood diseases such as leukaemia.
Index test/s	CRP

Study	Pancer 2011[227]
Reference standard	N/A
Target condition	Sepsis
Results: **CRP (cut off: 52 mg/litre)** AUC Sensitivity Specificity	 0.777 (0.569-0.800) 75 (63-84.7) 54.9 (49.2-69.1)
General limitations (according to QUADAS 2)	Retrospective design, small sample size, single-centre Indirectness: none. Risk of bias: very high.

Table 131: PATTERSON 2012

Study	Patterson 2012[230]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=200)
Country and setting	Australia. ED diagnosis of non-hospital acquired pneumonia
Funding	Not stated
Duration of study	1-year duration
Age, gender, ethnicity	Median (IQR) age: 72 (60-81). Gender: 118 M/82 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age ≥18 years; ED discharge diagnosis of non-hospital acquired pneumonia; blood culture taken within 6 hours of arrival in ED.
Index test/s	Haemoglobin WCC BP Pulse rate Temperature Respiratory rate GCS

Study	Patterson 2012[230]
Reference standard	N/A
Target condition	Bacteraemia
Results: **OR – univariable analysis** Haemoglobin ≤100 g/litre WCC <4 or >20 (*10^9/litre) BP <100 mm Hg Pulse rate >100 bpm Temperature <35 or >38.5 °C Respiratory rate >35 GCS≤13	 0.71 (0.09-5.7) 0.61 (0.3-7.17) 3.19 (0.62-16.42) 4.09 (0.89-18.81) 0.74 (0.24-2.3) 7.87 (1.86-33.3) 0.47 (0.06-3.77)
General limitations (according to QUADAS 2)	Retrospective design, small sample size Indirectness: prediction of bacteraemia. Risk of bias: very high.

Table 132: PETTILA 2002

Study	Pettilä 2002[234]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=61)
Country and setting	Finland. ICU (Helsinki University Hospital, Helsinki)
Funding	Not stated
Duration of study	48-hour survival
Age, gender, ethnicity	Survivors (n=41) Median (IQR) age: 54.9 (36.0-61.5). Gender: 31 M/10 F. Ethnicity: not stated. Non-survivors (n=20) Median (IQR) age: 54.0 (42.5-62.5). Gender: 11 M/9 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with established criteria for SIRS and obvious source of infection.

Study	Pettilä 2002[234]
Index test/s	CRP Antithrombin III WBC
Reference standard	N/A
Target condition	Sepsis
Results: Area under curve CRP	Day 1: 0.386 (0.230-0.543) Day 2: 0.533 (0.396-0.710)
Antithrombin III	Day 1: 0.598 (0.2436-0.760) Day 2: 0.628 (0.450-0.805)
WBC	Day 1: 0.551 (0.397-0.706) Day 2: 0.661 (0.522-0.799)
Multiple regression analysis for hospital mortality	Non-significant variables: antithrombin III levels, CRP, platelets, WBC counts
Laboratory data, median (IQR) CRP, mg/litre	Survivors Day 1: 176.5 (132-244) Day 2: 164.5 (119-234) Non-survivors Day 1: 156.5 (70-191) Day 2: 174 (127-251)
Antithrombin III (% of normal)	Survivors Day 1: 59.8 18.5 58, (47-70.2) Day 2: 63.5, 21.5, 62, (42.2-78.2)

Study	Pettilä 2002[234]
WBC, x 10^9	Non-survivors Day 1: 48.5 (39-68.5) Day 2: 48 (37.5-75.5) Survivors Day 1: 1.7 (0.8-2.7) Day 2: 10.7 (7.8-16.1) Non-survivors Day 1: 13.9 (8.7-16.9) Day 2: 13.3 (10.1-17.6)
General limitations (according to QUADAS 2)	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Table 133: PETTILA 2002A

Study	Pettila 2002A[235]
Study type	Prospective cohort
Number of studies (number of participants)	n=108 consecutive critically ill patients with suspected sepsis.
Country and setting	Medical-surgical ICU. Finland.
Funding	Part funded by Helsinki University Hospital.
Duration of study	12 months in 1995. In-hospital.
Age, gender, ethnicity	Age median: Survivors=44.6, Non-survivors=58.7, p=<0.001 Gender (F/M): Survivors=29/37, Non-survivors=12/30, p=0.16
Patient characteristics	Postoperative patients: Survivors=25/66, Non-survivors=9/42, p=0.09 Positive blood culture: Survivors=12/66, Non-survivors=13/42, p=0.24 SIRS criteria 2/4: Survivors=66/66, Non-survivors=42/42, p=1.0

Study	Pettila 2002A[235]
	WBC<4x10^9/litre: Survivors=1/66, Non-survivors=8/42, p=0.002 WBC<12x10^9/litre: Survivors=45/66, Non-survivors=24/42, p=0.17 Rectal temperature >38C: Survivors=37/66, Non-survivors=18/42, p=0.13 Rectal temperature <36C: Survivors=4/66, Non-survivors=8/42, p=0.06 Heart rate>90 beats/min: Survivors=46/66, Non-survivors=32/42, p=0.51 Septic shock: Survivors=36/66, Non-survivors=34/42, p=0.007 Acute renal failure: Survivors=11/66, Non-survivors=11/42, p=0.32 Admission diagnosis pneumonia: Survivors=17/66, Non-survivors=12/42 Admission diagnosis sepsis: Survivors=22/66, Non-survivors=23/42 Admission diagnosis meningitis: Survivors=9/66, Non-survivors=1/42 Admission diagnosis peritonitis: Survivors=17/66, Non-survivors=14/42 Admission diagnosis malaria: Survivors=0/66, Non-survivors=1/42 Admission diagnosis mediastinitis: Survivors=1/66, Non-survivors=1/42
Index test/s	WBC CRP Platelets Thromboplastin time (P-TT)
Reference standard	N/A
Target condition	Predicting in-hospital mortality in critically ill patients with suspected sepsis.
Results AUC for prediction of in-hospital mortality rate	Taken within 2 hours of admission to ICU. CRP: 0.60, SE=0.06 (Calculated 95%CI: 0.48-0.72) WBC: 0.53, SE=0.06 (Calculated 95%CI: 0.41-0.65) Platelets: 0.69, SE=0.05 (Calculated 95%CI: 0.59-0.79) P-TT: 0.63, SE=0.06 (Calculated 95%CI: 0.51-0.75)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirect: predicting in-hospital mortality in critically ill patients with suspected sepsis. Risk of bias: very high.

Table 134: POVOA 2005

Study	Povoa 2005[239]
Study type	Prospective cohort
Number of studies (number of participants)	n=260 consecutive patients admitted to the ICU.
Country and setting	Portugal. Medico-surgical intensive care unit.
Funding	Not stated.
Duration of study	November 2001 – December 2002
Age, gender, ethnicity	Age >18 years: infected=59.4±15.6, non-infected=52.9±20.7, p=0.068 M/F: infected=49/27, non-infected=20/16, p=0.409
Patient characteristics	APACHE II (mean±SD): infected=21.3±6.3, non-infected=19.8±10.9, p=0.349 SOFA (mean±SD): infected=7.9±3.3, non-infected=6.2±3.4, p=0.019 Mechanical ventilation: infected=60, non-infected=27, p=0.635 LOS (median, IQR): infected=19.5 (22), non-infected=5 (3) , p=<0.001 Mortality: infected=30, non-infected=6, p=0.016 Diagnosis: Cardiovascular: infected=9, non-infected=9 Respiratory: infected=26, non-infected=6 Gastrointestinal: infected=1, non-infected=0 Neurological: infected=7, non-infected=5 Endocrine: infected=2, non-infected=1 Obstetrics: infected=0, non-infected=5 Oncology: infected=4, non-infected=0 Alcoholism and drug abuse: infected=2, non-infected=3 Trauma: infected=10, non-infected=5 Surgery: infected=15, non-infected=2
Index test/s	CRP

Study	Povoa 2005[239]
Reference standard	NA
Target condition	Infection in critically ill patients.
Results	**CRP cut-off 8.7mg/dL** Sensitivity: 93.4 Specificity: 86.1 PPV: 93.4 NPV: 86
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre Indirect: predicting infection in critically ill patients. Risk of bias: very high.

Table 135: POVOA 2006

Study	Povoa 2006[240]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=63)
Country and setting	Portugal. ICU (medico-surgical ICU of the Gracia de Orta Hospital, Almada, Portugal)
Funding	The authors declare that they have no competing interests.
Duration of study	14-months period
Age, gender, ethnicity	Age (mean±SD): Non-infected: 50.6±21.9; infected: 62.2±13.3. Gender: 37 M/26 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age ≥18 years; admission to ICU for ≥72 hours. For patients with multiple ICU admissions, only the first admission was recorded. n=35 infected patients (with ICU-acquired infection according to the Centres for Disease Control definitions; with positive cultures; not receiving antibiotics for at least 5 days before infection diagnosis) n=28 non-infected patients (no bacteriological or clinical signs of infection, had never received antibiotics and were discharged alive from the ICU. Day 0 defined as the day of positive cultures in infected patients and as the day of ICU discharge in non-infected patients. Changes in CRP, WBC and T were observed from day -5 to 0.
Index test/s	CRP (maximum daily variation)

Study	Povoa 2006[240]
	WBC (maximum daily variation)
Reference standard	N/A
Target condition	Infection (ICU-acquired)
Results: **CRP (maximum daily variation):** AUC **CRP increase >4.1 mg/dl** Sensitivity Specificity Positive likelihood ratio Negative likelihood ratio **WBC (maximum daily variation):** AUC **Temperature (maximum daily variation):** AUC	 0.86 (0.752-0.933) 92.1 71.4 3.22 0.11 0.668 (0.541-0.779) 0.739 (0.616-0.839)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: prediction of ICU-acquired infections Risk of bias: very high.

Table 136: SHAABAN 2010

Study	Shaaban 2010[262]
Study type	Prospective cohort
Number of studies (number of participants)	n=68 patients admitted to the ICU
Country and setting	USA.

Study	Shaaban 2010[262]
	Admission to ICU.
Funding	Not stated
Duration of study	August 2008 – March 2009
Age, gender, ethnicity	Median age: All=68, non-infection=65, infected=68 Male gender: All=33, non-infection=19, infected=14 Hispanic = 24 African American = 30 White = 13 Asian = 1
Patient characteristics	Nursing home residents: All=28, non-infection=12, infected=16 Excluded: patients who died or were discharged within 24 hours after admission, surgical patients,
Index test/s	CRP Eosinophil cell count
Reference standard	NA
Target condition	Predicting infection in patients admitted to the ICU.
Results	<u>CRP</u> Cut-off value = >70mg/litre Sensitivity (%) = 94 Specificity (%) = 84 PPV (%) = 83 NPV (%) = 94 <u>Eosinophil cell count</u> Cut-off value = <50 cells/mm^3 Sensitivity (%) = 81 Specificity (%) = 65 PPV (%) = 66 NPV (%) = 80
General limitations (according to	Observational design, small sample, single centre.

Study	Shaaban 2010[262]
QUADAS 2)	Indirect: predicting infection. Risk of bias: very high.

Table 137: SHAPIRO 2010

Study	Shapiro 2010[264]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=699)
Country and setting	USA. ED (urban tertiary care).
Funding	Abbott Point of Care Inc.
Duration of study	11-month period (in-hospital follow up)
Age, gender, ethnicity	Age mean (SD): 60.4 (20.0). Gender: 291 M/408 F. Ethnicity: not stated.
Patient characteristics	Convenience sample of adult (age ≥18 years) ED patients with suspected infections.
Index test/s	Lactate (POC: point of care, and laboratory)
Reference standard	N/A
Target condition	In-hospital mortality
Results: **AUC** AUC, POC lactate AUC, laboratory lactate **Mean (95% CI) values, mmol/litre** POC lactate dead POC lactate survivors Laboratory lactate dead Laboratory lactate survivors	 0.72 0.70 3.2 (2.05-4.37) 1.65 (1.56-1.74) 3.83 (2.20-5.47) 1.95 (1.86-2.85)
General limitations (according to QUADAS 2)	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.

Study	Shapiro 2010[264]
	Risk of bias: very high.

Table 138: SHORR 2008

Study	Shorr 2008[271]
Study type	Post hoc analysis of 2 RCTs (PROWESS and ENHANCE).
Number of studies (number of participants)	1 (n tot=4065; n=850 intervention arm, PROWESS; n=840 placebo arm, PROWESS; n=2375 ENHANCE)
Country and setting	Multiple countries.
Funding	Eli Lilly, AstraZeneca
Duration of study	N/A
Age, gender, ethnicity	PROWESS placebo Mean (SD) age: 60.6 (16.5). Gender: 487 M/353 F. Ethnicity: not stated. PROWESS intervention (DrotAA) Mean (SD) age: 60.5 (17.2). Gender: 477 M/373 F. Ethnicity: not stated. ENHANCE (DrotAA) Mean (SD) age: 59.1 (16.9). Gender: 1383 M/995 F. Ethnicity: not stated.
Patient characteristics	Inclusion: known or suspected infection on the basis of clinical data at the time of screening and if met the following criteria within a 24-hour period: three or more signs of systemic inflammation and the sepsis-induced dysfunction of at least one organ or system that lasted no longer than 24 hours. Exclusion: treatment began 24 hours after the patient met the inclusion criteria.
Index test/s	Protein C (%) Protein S (%) Anti-thrombin III (%) Photothrombin time (seconds) D-dimer (micrograms/ml)
Reference standard	N/A
Target condition	28-day mortality
Results: Protein C (%)	

Study	Shorr 2008[271]
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)
D-dimer (micrograms/ml)	
AUC	55.1
OR	1.51 (1.11-2.05)
Laboratory data, median (IQR)	
Protein C (%)	
PROWESS placebo	50 (33-68)
PROWESS DrotAA	47 (30-63)
ENHANCE	45 (30-64)
Protein S (%)	
PROWESS placebo	38 (23-58)
PROWESS DrotAA	35 (33-57)
Anti-thrombin III (%)	

Study	Shorr 2008[271]
PROWESS placebo PROWESS DrotAA Photothrombin time (seconds) PROWESS placebo PROWESS DrotAA D-dimer (micrograms/ml) PROWESS placebo PROWESS DrotAA	60 (45-75) 58 (43-74) 18.6 (16.4-21.8) 18.7 (16.6-22.1) 4.1 (2.2-8.7) 4.2 (2.3-8.1)
General limitations (according to QUADAS 2)	Post hoc analysis. Indirectness: none Risk of bias: high.

Table 139: SIERRA 2004

Study	Sierra 2004[272]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=200)
Country and setting	Spain. ICU (critically ill patients).
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Non-infectious SIRS patients: Age median (95% CI): 53 (15-81). Gender: 45 M/10 F. Ethnicity: not stated. Sepsis patients: Age median (95% CI): 45.5 (15-76). Gender: 60 M/10 F. Ethnicity: not stated.
Patient characteristics	Critically ill adult patients admitted to the ICU. Four groups: n=70 infected patients with SIRS (sepsis); n=55 non-infected patients with SIRS; n=25 with non-complicated AMI diagnoses; n=50 healthy volunteers (used only to set normal marker values). The last two groups were designed as controls. Exclusion: Age <14 years; pregnancy; patients receiving antimicrobial therapy.
Index test/s	CRP

Study	Sierra 2004[272]
Reference standard	N/A
Target condition	Sepsis
Results: **CRP for the diagnosis of sepsis (cut off ≥8 mg/dl)** Sensitivity Specificity PPV NPV AUC **Median (95% CI) values, mg/dl** CRP non-infectious SIRS patients CRP sepsis patients	 94.3 87.3 90.4 92.3 94 (89-98) 1.7 (2.4-5.5) 18.9 (17.1-21.8)
General limitations (according to QUADAS 2)	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.

Table 140: STUCKER 2005

Study	Stucker 2005[276]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=218)
Country and setting	Switzerland. Hospital (Geneva Geriatric Hospital).
Funding	The authors did not receive financial support for this research
Duration of study	Not stated
Age, gender, ethnicity	Age, mean (SD): 85.4 (6.7) years. Gender: 44 M/174 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age ≥75 years; able to give informed consent.

Study	Stucker 2005[276]
	n=50 SIRS n=22 sepsis n=11 severe sepsis n=0 septic shock Exclusion: presence of any condition that prevented the patient from providing clear consent.
Index test/s	CRP WBC
Reference standard	N/A
Target condition	Infection
Results: **CRP (≥3 mg/ml)** AUC Sensitivity Specificity PPV NPV OR (univariable analysis) OR (multivariable analysis) **WBC (≤4000 or ≥12000 /mm^3)** Sensitivity Specificity PPV NPV OR (univariable analysis) OR (multivariable analysis) **T (≤36 or ≥38 °C)** Sensitivity	 0.63 92 36 30 94 6.4 (2.2-18.8) 3.4 (1.1-10.6) 30 89 45 81 3.5 (1.6-7.7) - 20

Study	Stucker 2005[276]
Specificity	98
PPV	71
NPV	80
OR (univariable analysis)	10.2 (3.0-34.1)
OR (multivariable analysis)	-
Pulse rate (≥90 beats/min)	
Sensitivity	34
Specificity	87
PPV	45
NPV	82
OR (univariable analysis)	3.5 (1.5-7.5)
OR (multivariable analysis)	-
Respiratory rate (≥20 breaths/min)	
Sensitivity	38
Specificity	74
PPV	32
NPV	79
OR (univariable analysis)	1.7 (0.8-3.5)
OR (multivariable analysis)	-
General limitations (according to QUADAS 2)	Observational design, small sample size, elderly population. Indirectness: prediction of infections. Risk of bias: very high.

Table 141: SVALDI 2001

Study	Svaldi 2001[277]
Study type	Prospective cohort
Number of studies (number of	1 (n=73) immunocompromised patients

Study	Svaldi 2001[277]
participants)	
Country and setting	Italy. Haematological department (Regional Hospital Bozen).
Funding	Not stated
Duration of study	17-month period
Age, gender, ethnicity	Age: not stated. Gender: 36 M/37 F. Ethnicity: not stated.
Patient characteristics	Patients admitted to the haematological department of the Regional Hospital Bozen for various reasons, such as initiation of chemotherapy and fever with or without neutropenia. n=62 SIRS n=30 sepsis n=3 severe sepsis n=3 septic shock n=280 non-systemic infected
Index test/s	WBC
Reference standard	N/A
Target condition	Sepsis (including severe sepsis and septic shock)
Results: WBC (<10^9/litre) Sensitivity Specificity WBC (>10^9/litre) Sensitivity Specificity	 63 60 94 60
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre, immune-compromises population. Indirectness: none. Risk of bias: very high.

Table 142: TSANGARIS 2009

Study	Tsangaris 2009[284]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=50) critically ill patients
Country and setting	Greece. ICU.
Funding	The authors declare that they have no competing interests.
Duration of study	6-month period
Age, gender, ethnicity	Proven infection (n=27): Age: 70±12.1. Gender: 20 M/30 F. Ethnicity: not stated. Unproven infection (n=23): Age: 56±22.1. Gender: 18 M/32 F. Ethnicity: not stated.
Patient characteristics	
Index test/s	CRP WBC
Reference standard	N/A
Target condition	Infection
Results:	
WBC (cut off: 12000x10^{9}/µ)	
Sensitivity	0.66
Specificity	0.45
PPV	0.76
NPV	0.62
AUC	0.68 (0.49-0.81)
CRP (cut off 100 mg/dL)	
Sensitivity	0.59
Specificity	0.57
PPV	0.62

Study	Tsangaris 2009[284]
NPV AUC	0.54 0.65 (0.46-0.78)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: prediction of infection. Risk of bias: very high.

Table 143: UUSITALO-SEPPLALA 2011

Study	Uusitalo-Sepplala 2011[286]
Study type	Prospective cohort
Number of studies (number of participants)	n=539 consecutive patients admitted to the ED with suspected infection, who had blood samples taken at admission.
Country and setting	Finland. ED.
Funding	Study supported by Satakunta Central Hospital Research Fund and the Turku university Hospital Research Fund.
Duration of study	14 month period 2004-2005
Age, gender, ethnicity	Age>60: all=313/539, sepsis=188/309, severe sepsis=28/49 Male: all=311/539, sepsis=177/309, severe sepsis=30/49
Patient characteristics	Obesity (BMI≥30kg/m^2): all=129/539, sepsis=77/309, severe sepsis=11/49 Alcoholism: all=25/539, sepsis=8/309, severe sepsis=8/49 Current smoker: all=126/539, sepsis=70/309, severe sepsis=11/49 Diabetes: all=82/539, sepsis=42/309, severe sepsis=11/49 Malignancy: all=95/539, sepsis=57/309, severe sepsis=4/49 Rheumatic diseases: all=50/539, sepsis=27/309, severe sepsis=6/49 Neutropenia: all=11/539, sepsis=11/309, severe sepsis=0/49 Chronic renal insufficiency: all=18/539, sepsis=7/309, severe sepsis=4/49 Cardiovascular disease: all=289/539, sepsis=168/309, severe sepsis=29/49 COPD or asthma: all=108/539, sepsis=67/309, severe sepsis=10/49 Operation 6 months previously: all=75/539, sepsis=41/309, severe sepsis=6/49 Continuous medication for chronic disease: all=390/539, sepsis=221/309, severe sepsis=42/49

Study	Uusitalo-Sepplala 2011[286]
	Continuous Antimicrobial treatment: all=32/539, sepsis=16/309, severe sepsis=6/49 Continuous Cortisone treatment: all=59/539, sepsis=27/309, severe sepsis=12/49 Continuous Acetylsalicylic acid use: all=117/539, sepsis=65/309, severe sepsis=14/49 Chemotherapy 2 months prior: all=52/539, sepsis=30/309, severe sepsis=3/49 Antimicrobial treatment 1 week prior: all=157/539, sepsis=88/309, severe sepsis=18/49
Index test/s	CRP
Reference standard	NA
Target condition	Sepsis
Results	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) Sepsis: CRP OR=1.33 (1.10-1.61) (multivariable logistic regression, unclear variables) CRP AUC: 0.70 (0.65-0.74)
General limitations (according to QUADAS 2)	Observational design, small sample size, single centre. Indirectness: none. Risk of bias: very high.

Table 144: VASSILIOU 2014

Study	Vassiliou 2014[288]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=89)
Country and setting	Greece. ICU.
Funding	Non-profit institute “Thorax” Research Centre for Intensive and Emergency Thoracic Medicine, Athens, Greece
Duration of study	24-month period (follow up: ICU stay or death)

Study	Vassiliou 2014[288]
Age, gender, ethnicity	Mean (range) age: 46 (18-89) years. Gender: 62 M/27 F. Ethnicity: not stated.
Patient characteristics	Critically ill patients admitted to the ICU of the Evangelismos Hospital, Athens. Categorised into 2 groups: sepsis-positive, including severe sepsis and septic shock (n=45), and sepsis-negative (n=44). Exclusions: sepsis on or within 24 hours of ICU admission; BMI>35Kg/m2; age <18 years; pregnancy; brain death; end-stage cancer; total ICU stay <3 days; readmission or transfer from another ICU; contagious diseases (HIV, hepatitis); oral intake of corticosteroids at an equivalent dosage of ≥1 mg/kg prednisone/day for >1 month.
Index test/s	CRP
Reference standard	N/A
Target condition	Sepsis, including severe sepsis and septic shock
Results: CRP: Area under the curve Median (Q1-Q3) CRP values (mg/dl) Sepsis-positive patients: Sepsis-negative patients:	 0.539 (0.430-0.645) 7.15 (3.28-14.58) 2.40 (0.83-6.13)
General limitations (according to QUADAS 2)	Observational design, small sample size, does not take into account sepsis severity (sepsis, severe sepsis, septic shock). Indirectness: none. Risk of bias: very high.

Table 145: VON LILIENFELD 2004

Study	von Lilienfeld 2004[290]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=31 neutropenic patients, n=53 febrile episodes)
Country and setting	Germany. Hospital (haematological ward).
Funding	GSK and Leukamie-Initiative Bonn, Germany
Duration of study	6-month period

Study	von Lilienfeld 2004[290]
Age, gender, ethnicity	Mean (range) age: 57 (22-77) years. Gender: 15 M/16 F. Ethnicity: not stated.
Patient characteristics	Patients with haematological malignancies after chemotherapy.
Index test/s	CRP
Reference standard	N/A
Target condition	Bacteraemia
Results: CRP: Area under the curve	 0.64
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: prediction of bacteraemia. Risk of bias: very high.

Table 146: WYLLIE 2005

Study	Wyllie 2005[297]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=6234)
Country and setting	UK. Hospital (general medical or infectious diseases).
Funding	Not stated
Duration of study	2-year period
Age, gender, ethnicity	Age range: 18-106 years. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: age ≥18 years, admitted from the community to general medical or infectious diseases services of Oxford Radcliffe Hospitals. Exclusion: patients admitted to haematology or cardiology wards. 2/3 of the cohort were used to develop the model; 1/3 to the internal validation. No external validation.
Index test/s	CRP LC (lymphocyte count) NP (neutrophil count)

Study	Wyllie 2005[297]
Reference standard	N/A
Target condition	Bacteraemia
Results: **Area under the curve** CRP+LC+NP LC+NP CRP LC NP	 0.78 0.75 0.72 0.70 0.66
General limitations (according to QUADAS 2)	Retrospective design, single centre. Indirectness: prediction of bacteraemia. Risk of bias: very high.

Table 147: YONEMORI 2001

Study	Yonemori 2001[301]
Study type	Retrospective cohort (medical records)
Number of studies (number of participants)	1 (n=97)
Country and setting	Japan. In-hospital.
Funding	Not stated
Duration of study	26-month period
Age, gender, ethnicity	Median (range) age: 56 (17-85) years. Gender: 25 M/22 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients who received chemotherapy for haematological malignancies and developed neutropenia (neutrophil <1000/microlitre) for more than 7 days Exclusions: patients who were febrile (fever >38°C)or positive CRP (CRP >10 mg/litre) on the first day of neutropenia. Categorisation: group 1: documented bacterial or fungal infections with positive blood cultures; group 2: documented or presumed bacterial or fungal infections based on clinical and/or radiographic findings with negative blood cultures; group 3: fever without an obvious source despite appropriate evaluation.
Index test/s	CRP

Study	Yonemori 2001[301]
Reference standard	N/A
Target condition	Documented infections Bacteraemia (positive blood culture)
Results: **CRP to predict documented infections**: Area under the curve **Threshold 30.8 mg/litre:** Sensitivity Specificity PPV NPV **CRP to predict Bacteraemia (positive blood culture)**: Area under the curve **Threshold 68.6 mg/litre**: Sensitivity Specificity PPV NPV	 0.61 71 50 27 88 0.55 46 73 20 91
General limitations (according to QUADAS 2)	Retrospective design, small sample size. Indirectness: prediction of bacteraemia and infections (not specific sepsis). Risk of bias: very high.

H.2.1.2 Clinical evidence tables for children and neonates (in alphabetical order)

Table 148: ANDREOLA 2007

Study	**Andreola 2007**[10]
Study type	Prospective observational
Number of studies (number of participants	1 (n=408. SBI n=94, not SBI n=314)
Country and setting	Italy. Tertiary care Emergency Department (University of Padova).
Funding	Not stated
Duration of study	18 months (May 2004-October 2005)
Age, gender, ethnicity	Age: Median age: 10 months (2.5-16.5 months)gender: 205 (50.2%) female. ethnicity: not stated
Patient characteristics	inclusion: all children younger than 3 years who were consecutively admitted to the ED with fever of unknown source, who, after a careful history and physical examination, underwent blood analysis because they were more likely to have an SBI, namely: (1) all infants aged 7 days to 3 months old with fever (rectal temperature) >38˚C; (2) children aged 3-36 months old ill/toxic appearing or with fever (rectal temperature)>39.5 ˚C. exclusion: history of (1) antibiotic use within the 48 hours before hospital admission, (2) vaccination during the previous 2 days, (3) known immunodeficiencies, (4) any chronic pathology, or (5) fever lasting longer than 5 days.
Index test	CRP, WBC, ANC
Reference standard	Culture-proven sepsis
Target condition	Serious bacterial infection (SBI)
Results: AUC CRP WBC ANC Optimal statistical cutoff for detecting SBI CRP WBC	 0.85 (95%CI 0.81-0.88) 0.71 (95%CI 0.66-0.75) 0.74 (95%CI 0.70-0.78) 32 mg/l (sensitivity 84.0%; specificity 75.5%) 10.47 x10^9/l (sensitivity 84.9%; specificity 47.4%)

Study	Andreola 2007[10]
ANC Multivariable analysis- included body temperature, Yale observation score, CRP values, pCT values, WBC and ANC. CRP Sensitivity, specificity, positive and negative likelihood ratios for SBI prediction CRP >20mg/L Sensitivity (%[95%CI]) Specificity (%[95%CI]) Likelihood ratio+ Likelihood ratio- >40mg/L Sensitivity (%[95%CI]) Specificity (%[95%CI]) Likelihood ratio+ Likelihood ratio- >80mg/L Sensitivity (%[95%CI]) Specificity (%[95%CI]) Likelihood ratio+ Likelihood ratio-	6.45 x10^9/l (sensitivity 81.8%; specificity 62.3%) OR 1.02;95%CI 1.01-1.03 p<0.001 88.3 (80.0-94.0) 60.8 (55.2-66.3) 2.25 0.19 71.3 (61.0-80.1) 81.2 (76.4-85.4) 3.79 0.35 46.0 (36.4-57.4) 94.6 (91.5-96.8) 8.65 0.56

Study	Andreola 2007[10]
WBC >15 x10^9/l Sensitivity (%[95%CI]) Specificity (%[95%CI]) Likelihood ratio+ Likelihood ratio- ANC >10 x10^9/l Sensitivity (%[95%CI]) Specificity (%[95%CI]) Likelihood ratio+ Likelihood ratio- Baseline characteristics [median (IQR)] CRP (mg/L) SBI (n=94) Non SBI (n=314) WBC (x10^9/l) SBI (n=94) Non SBI (n=314) ANC(x10^9/l) SBI (n=94) Non SBI (n=314)	 51.6 (41.0-62.1) 75.5 (70.3-80.2) 2.11 0.64 29.9 (20.5-40.6) 78.4 (73.3-82.9) 1.19 0.91 68.5 (39.0-120.0) 13 (3-31) 15,850 (12,040-20,250) 10,770 (7050-14,960) 9,522 (6830-14,154) 5,119 (3,108-8,295)
General limitations (according to QUADAS 2)	Observational design. Indirectness: none. Risk of bias: very high.

Table 149: BAEZ 2011

Study	Baez 2011[19]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=103. Infected n=41, not infected n=62)
Country and setting	Spain. ICU
Funding	No outside funding or support
Duration of study	2 years
Age, gender, ethnicity	Age: Mean age: 3.23±3.42 (infected); 4.71±4.64 (not infected) gender (M/F): 24/18 (infected); 28/34 (not infected) ethnicity: not stated
Patient characteristics	Patient characteristics inclusion: all paediatric patients that underwent programmed major surgery (abdominal, thoracic, and heart surgery; neurosurgery; orthopaedic surgery) and major burns surgery, defined as any burn that requires IV fluid resuscitation (10% body surface area or a burn to the airway), who remained in the ICU for at least 7 days according to the criteria of WIlliam about increased risk of infection in patients admitted to the ICU. Exclusion: patients with exogenous hormone therapy with clinical evidence of infection before surgery, who remained in the ICU for < 7 days, or undergoing emergency surgery.
Index test	CRP, NPV*, platelets, fibrinogen, glucose
Reference standard	N/A
Target condition	Post-operative sepsis

Study	Baez 2011[19]
Results:	
CRP	
+100 mg/l (24 hours)	
Sensitivity	84%
Specificity	74%
Efficiency	76%
+100 mg/l (48 hours)	
Sensitivity	90%
Specificity	70%
Efficiency	77%
+110 mg/l (24 hours)	
Sensitivity	92%
Specificity	61%
Efficiency	74%
+110 mg/l (48 hours)	
Sensitivity	87%
Specificity	89%
Efficiency	76%
+150 mg/l (48 hours)	
Sensitivity	88%
Specificity	72%
Efficiency	79%
+200 mg/l (48 hours)	
Sensitivity	88%
Specificity	76%

Study	Baez 2011[19]
Efficiency	81%
***NPV (undefined in paper)**	
20% (24 hours)	
Sensitivity	98%
Specificity	37%
Efficiency	62%
20% (48 hours)	
Sensitivity	95%
Specificity	45%
Efficiency	65%
Platelets	
20% increase in 24 hours	
Sensitivity	93%
Specificity	39%
Efficiency	57%
20% increase in 48 hours	
Sensitivity	95%
Specificity	19%
Efficiency	50%
Fibrinogen	
20% increase in 24 hours	
Sensitivity	71%
Specificity	63%
Efficiency	66%

Study	Baez 2011[19]
20% increase in 48 hours Sensitivity Specificity Efficiency **Glucose** 20% increase in 24 hours Sensitivity Specificity Efficiency 20% increase in 48 hours Sensitivity Specificity Efficiency	 76% 64% 69% 93% 53% 69% 90% 63% 74%
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 150: BILAVSKY 2009

Study	Bilavsky2009[26]
Study type	Prospective
Number of studies (number of participants	1 (n=892. SBI n=102, without SBI n=790)
Country and setting	Israel. Hospital
Funding	No outside funding or support
Duration of study	3 years

Study	Bilavsky2009[26]
Age, gender, ethnicity	Median age + range (days):41 (3-90) months, infants without serious bacterial infection (SBI); 40.5 (3-90) with SBI gender (M/F %): 59.7/40.3 (without SBI); 53.9/46.1 (with SBI) ethnicity: not stated
Patient characteristics	Patient characteristics inclusion: all febrile infants aged 90 days or less who were hospitalised directly from the ED to the ICU and then to the ward. exclusion: presence of a chronic disease (heart failure, lung disease or renal failure) or congenital or acquired immune deficiency, preterm birth (≤32 weeks of gestation)and receipt of antibiotics within 48 hours of presentation
Index test	CRP, WBC count
Reference standard	N/A
Target condition	Serious bacterial infection
Results: **Univariable and a backward stepwise multiple logistic regression model was used.** **Variables significantly associated with SBI in a multivariable logistic regression:** **WBC ($x10^9$/l)** OR 95%CI P value **CRP (mg/l)** OR 95%CI P value **WBC**	 1.1 1.06- 1.15 <0.001 1.21 1.13 1.29

Study	Bilavsky2009[26]
>15 x10^9/l	48 (38.6-57.6)
Sensitivity (95% CI)	84.1 (81.4-86.5)
Specificity (95% CI)	3 (2.3-3.9)
Positive likelihood ratio	0.6 (0.5-0.8)
Negative likelihood ratio	
>20 x10^9/l	21.6 (14.7-30.5)
Sensitivity (95% CI)	95.2 (93.5-96.5)
Specificity (95% CI)	4.5 (2.8-7.3)
Positive likelihood ratio	0.8 (0.7-0.9)
Negative likelihood ratio	
>15 or <5 x10^9/l	50 (40.5-59.5)
Sensitivity (95% CI)	78.1 (75-80.8)
Specificity (95% CI)	2.3 (1.8-2.9)
Positive likelihood ratio	0.6 (0.5-0.8)
Negative likelihood ratio	
>20 or <4.1 x10^9/l	21.6 (14.7-30.5)
Sensitivity (95% CI)	92.1 (90-93.8)
Specificity (95% CI)	2.7 (1.8-4.2)
Positive likelihood ratio	0.9 (0.8-0.9)
Negative likelihood ratio	
CRP	
>80mg/L	23.5 (16.4-32.6)
Sensitivity (95% CI)	98.2 (97.1-98.9)
Specificity (95% CI)	13.3 (7.1-24.8)
Positive likelihood ratio	0.8 (0.7-0.9)
Negative likelihood ratio	

Study	Bilavsky2009[26]
>40mg/L	44.1 (34.9-53.8)
Sensitivity (95% CI)	92.2 (90.1-93.8)
Specificity (95% CI)	5.6 (4.1-7.8)
Positive likelihood ratio	0.6 (0.5-0.7)
Negative likelihood ratio	
>20mg/L	55.9 (46.2-65.1)
Sensitivity (95% CI)	82.2 (79.3-84.7)
Specificity (95% CI)	3.1 (2.5-3.9)
Positive likelihood ratio	0.5 (0.4-0.7)
Negative likelihood ratio	
Patient characteristics	
WBC count ($x10^9$/l) Mean (SD)	15.3 (7.1)
Infants with SBI (n=102)	10.8 (4.6)
Infants without SBI (n=790)	
ANC ($x10^9$/l) Mean (SD)	8.1 (5)
Infants with SBI (n=102)	4.5 (2.9)
Infants without SBI (n=790)	
CRP (mg/L)	5.3 (6.3)
Infants with SBI (n=102)	1.3 (2.2)
Infants without SBI (n=790)	

Study	Bilavsky2009[26]
General limitations (according to QUADAS 2)	Indirectness: none. Risk of bias: High.

Table 151: BONSU 2003

Study	Bonsu 2003[33]
Study type	Retrospective
Number of studies (number of participants	1 (n=3810: bacteraemia n=38, no bacteraemia n=3772)
Country and setting	USA. ED
Funding	No outside funding or support
Duration of study	7 year period covered
Age, gender, ethnicity	Age: infants aged 0-89 days. Age<28 days n=950, 29-56 days n=1507, 57-89 days n=1353. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: age 0-89 days of age; temperature of at least 38˚C documented in triage. Exclusion: acute leukaemia; rectal temperatures <38˚C in ED triage (including hypothermic infants defined by a temperature <35 ˚C).
Index test	Peripheral WBC count.
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis

Study	Bonsu 2003[33]
Results:	
WBC cutoff	
≥5 x10^9/l	
Sensitivity	79 (63-90)
Specificity	5 (4-6)
≥10 x10^9/l	
Sensitivity	61 (43-76)
Specificity	42 (40-44)
≥15 x10^9/l	
Sensitivity	45 (29-62)
Specificity	78 (76-79)
≥20 x10^9/l	
Sensitivity	24 (11-40)
Specificity	93 (92-94)
≥25 x10^9/l	
Sensitivity	13 (4-28)
Specificity	98 (97-99)
≥30 x10^9/l	
Sensitivity	5 (1-2)
Specificity	99 (99-100)
<5 or ≥15 x10^9/l	
Sensitivity	66 (49-80)
Specificity	72 (71-74)
<5 or ≥20 x10^9/l	
Sensitivity	45 (29-62)
Specificity	88 (87-89)
WBC (x10^9/l)	
<5 x10^9/l	
Bacteraemia n=8	

Study	Bonsu 2003[33]
No bacteraemia n=201 Likelihood ratio 5-15 x10^9/l Bacteraemia n=13 No bacteraemia n=2727 Likelihood ratio ≥15 x10^9/l Bacteraemia n=17 No bacteraemia n=844 Likelihood ratio ≥20 x10^9/l Bacteraemia n=9 No bacteraemia n=255 Likelihood ratio **Patient characteristics** Median total peripheral WBC count Bacteraemia No bacteraemia	 3.9 (2.1-7.4) 0.4 (0.2-0.6) 2.0 (1.4-3.9) 3.5 (2.0-6.3) 13.9K (IQR 6.5-18.6K) 10.9K (IQR 8.1-14.5K)
General limitations (according to QUADAS 2)	Retrospective design. Indirectness: none. Risk of bias: very high.

Table 152: BONSU 2004

Study	Bonsu 2004[34]

Study	Bonsu 2004[34]
Study type	Retrospective
Number of studies (number of participants	1 (n=5885)
Country and setting	USA. ED
Funding	Not stated
Duration of study	7 year study periods
Age, gender, ethnicity	Age: infants aged 3-89 days. Gender: not stated. Ethnicity: 35% of patients using the ED are white, 25% African American, 20% Hispanic, .20% other races.
Patient characteristics	Inclusion: age 3-89 days of age; temperature of at least 38˚C documented in triage. Infants were included for analysis if a bacterium recognised to cause disease in young infants was isolated from blood or CSF culture. Exclusion: acute leukaemia; infants in the immediate postnatal period (first 48 hours of life).
Index test	Peripheral WBC count
Reference standard	N/A
Target condition	Bacteraemia
Results: **Peripheral WBC count (x10^9/l)** **Values are shown as % (N)** **Bacteraemia** **0-4.99 x10^9/l** PPV NPV Sensitivity **≥15 x10^9/l** PPV NPV Sensitivity	 1.2 (3/244) 99.1 (5588/5641) 6 (3) 2.0 (27/1358) 99.4 (4502/4527) 52 (27)

Study	Bonsu 2004[34]
≥20,000 x10^9/l	
PPV	3.0 (12/406)
NPV	99.3 (5421/5479)
Sensitivity	23 (12)
<5000 or ≥15,000 x10^9/l	
PPV	1.9 (30/1602)
NPV	99.5 (4261/4283)
Sensitivity	58 (30)
<5000 or ≥20,000 x10^9/l	
PPV	2.3 (15/560)
NPV	99.3 (5198/5235)
	29 (15)
SBI (acute bacterial meningitis and bacteraemia)	
0-4.99 x10^9/l	
PPV	4.5 (11/244)
NPV	98.9 (5580/5641)
Sensitivity	15 (11)
Specificity: no SBI	4 (233)
≥15 x10^9/l	
PPV	2.3 (31.1/1358)
NPV	99.1 (4486/4527)
Sensitivity	43 (31)
Specificity: no SBI	77 (4486)
≥20 x10^9/l	
PPV	3.2 (13/406)
NPV	98.9 (5420/5479)
Sensitivity	18 (13)
Specificity: no SBI	93 (5420)
<5 or ≥15 x10^9/l	

Study	Bonsu 2004[34]
PPV	2.6 (42/1602)
NPV	99. (4253/4283)
Sensitivity	58 (42)
Specificity: no SBI	73 (4253)
<5 or ≥20 x10^9/l	
PPV	3.7 (24/650)
NPV	99.1 (5187/5235
Sensitivity	33 (24)
Specificity: no SBI	89 (5187)
Differentiating acute bacterial meningitis and isolated bacteraemia	
ANC	
Area under curve	0.65 (95% CI 0.51-0.78)
WBC count	
Area under curve	0.75 (95% CI 0.63-0.88)
Median peripheral WBC count	
acute bacterial meningitis	9.5 x10^9/l (IQR 3.495-13.120)
isolated bacteraemia	15.524 x10^9/l (IQR 10.76-18.825)
Likelihood of acute bacterial meningitis relative to bacteraemia	
Peripheral WBC count (Cells/mm3)	
0-4.99 x10^9/l	
Interval LR	7 (95%CI 2,24)
≥15 x10^9/l	
Interval LR	0.39 (95%CI 0.16, 0.98)
≥20 x10^9/l	

Study	Bonsu 2004[34]
Interval LR **5 to 14.99 x10^9/l** Interval LR **5 to 19.99 x10^9/l** Interval LR	0.22 (95%CI 0.03, 1.56) 0.69 (95%CI 0.39,1.24) 0.77 (95%CI 0.50, 1.18)
General limitations (according to QUADAS 2)	Retrospective design. Indirectness: none. Risk of bias: very high.

Table 153: BRESSAN 2010

Study	Bressan 2010[39]
Study type	Prospective study
Number of studies (number of participants	1 (n=99, positive fever screening test <12hours n=37, negative fever screening test <12hours n=62)
Country and setting	Italy. Paediatric ED (Single-centre, academic Children's hospital, Padova)
Funding	Not stated
Duration of study	4-year period (1 January 2003 – 1 June 2007)
Age, gender, ethnicity	Mean (SD) age: 19.6 days (7). Gender: 56/43 F. Ethnicity: not stated.
Patient characteristics	Inclusion: previously healthy neonates 7-28 days of age hospitalised for fever without source from less than 12 hours. Exclusion: children born preterm (<37 weeks gestation), children with perinatal complications, underlying diseases or with a history of antibiotic use prior to admission to the hospital.
Index test	CRP, white blood cell count, absolute neutrophil count
Reference standard	N/A

Study	Bressan 2010[39]
Target condition	Hospital diagnosis of severe bacterial infections
Results:	
Initial determination: fever <12 hours (all patients)	
CRP (cut-off >20 mg/l)	
Area under curve	0.78 (95%CI 0.69-0.86)
Sensitivity	48 (30.3-66.5)
Specificity	93.2 (85.1-97.1)
PPV	70.6 (46.9-86.7)
NPV	84.2 (74.7-90.5)
WBC (<5 or >15 x10^9/l)	
Area under curve	0.59 (95%CI 0.49-0.69)
Sensitivity	28 (14.3-47.6)
Specificity	87.7 (78.2-93.4)
PPV	43.75 (23.1-66.8)
NPV	78.1 (68.0-85.6)
ANC (cut-off >10 x10^9/l)	
Area under curve	0.77 (95%CI 0.67-0.85)
Sensitivity	20 (8.9-39.1)
Specificity	97.3 (90.6-99.3)
PPV	71.4 (35.9-91.8)
NPV	78 (68.5-85.3)
Initial determination: fever >12 hours	

Study	Bressan 2010[39]
(58 patients)	
CRP (cut-off >20 mg/l)	
Area under curve	0.99 (95%CI 0.92-1)
Sensitivity	100 (56.6-100)
Specificity	96.2 (87.2-99)
PPV	71.4 (35.9-91.8)
NPV	100 (93-100)
WBC (<5 or >15 x10^9/l)	
Area under curve	0.79 (95%CI 0.66-0.89)
Sensitivity	80.0 (37.6-96.4)
Specificity	90.6 (79.7-95.5)
PPV	44.4 (18.9-73.3)
NPV	98.0 (89.3-99.6)
ANC (cut-off >10 x10^9/l)	
Area under curve	0.85 (95%CI 0.73-0.93)
Sensitivity	80.0 (37.6-96.4)
Specificity	100 (93.2-100)
PPV	100 (51.0-100)
NPV	98.2 (90.2-99.7)
Patient characteristics **Patients with severe bacterial infection versus non-severe bacterial infection** **(<12 hours from fever onset, 99**	

Study	Bressan 2010[39]
patients) CRP (mg/l), median (IQR) WBC (x10^9/l), median (IQR) ANC (x10^9/l), median (IQR) **(>12 hours from fever onset, 99 patients)** CRP (mg/l), median (IQR) WBC (x10^9/l), median (IQR) ANC (x10^9/l), median (IQR)	 16.1 (3.7-49.6) versus 1.8 (1.0-6.3) 11.13 (8.6-13.95) versus 9.96 (7.56-12.50) 6.70 (4.30-8.04) versus 3.67 (2.60-5.10) 55.3 (44.3-62.5) versus 3.5 (1.3-10.1) 21.52 (10.4-23.22) 9.98 (7.15-11.575) 11.58 (8.60-15.03) versus 3.04 (2.05-3.87)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 154: DE 2014

Study	De 2014[75]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=3893. Serious bacterial infection n=714, no evidence of serious bacterial infection n=3179)
Country and setting	Australia. ED
Funding	National Health and Medical Research Council of Australia.
Duration of study	Not stated
Age, gender, ethnicity	Age: 0-5 years. Age (months): <3 n=400, 3-5 n=315, 6-11 n=683, 12-23 n=1051, ≥24-60 n=1444. Gender: 2176 (55.9%) male. Ethnicity: not stated.
Patient characteristics	Inclusion: children aged 0-5 years presenting to the ED with a febrile illness, as defined by Craig 2010. Exclusion: children transferred from another hospital, those with malignancy and transplant recipients.

Study	De 2014[75]
Index test	WBC ANC
Reference standard	N/A
Target condition	Bacteraemia
Results (95% CI): **WBC** **Area under curve** **Any SBI** **Bacteraemia** **Any serious bacterial infection** **WBC count (x10^9)** **>15** **Sensitivity** **Specificity** Positive likelihood ratio Negative likelihood ratio **>20** **Sensitivity** **Specificity** Positive likelihood ratio Negative likelihood ratio **ANC** **Area under curve** **Any SBI** **Bacteraemia**	 0.653 (0.630-0.676) 0.679 (0.598-0.759) 47% (43% to 50%) 76% (74% to 77%) 1.93 (1.75 to 2.13) 0.70 (0.65 to 0.75) 26% (23% to 29%) 90% (89% to 91%) 2.59 (2.20 to 3.04) 0.83 (0.79 to 0.86) 0.638 (0.615to 0.662) 0.707 (0.631 to 0.782)

Study	De 2014[75]
Any serious bacterial infection **ANC count (x10^9)** **>10**	
Sensitivity	41% (38% to 45%)
Specificity	78% (76% to 79%)
Positive likelihood ratio	1.87 (1.68 to 2.09)
Negative likelihood ratio	0.75 (0.71 to 0.80)
>15	
Sensitivity	21% (19% to 25%)
Specificity	93% (92% to 94%)
Positive likelihood ratio	2.92 (2.42 to 3.52)
Negative likelihood ratio	0.85 (0.81 to 0.88)
General limitations (according to QUADAS 2)	Observational study. Indirectness: none. Risk of bias: High.

Table 155: EDGAR 2010

Study	Edgar 2010[81]
Study type	Prospective study
Number of studies (number of participants	1 (n=149; serum samples n=219)
Country and setting	UK. Neonatal ICU (single-centre: teaching hospital, Northern Ireland)
Funding	Support through an academic grant
Duration of study	Not reported

Study	Edgar 2010[81]
Age, gender, ethnicity	Median gestational age: infected group: 29, not infected group: 32, control group: 32. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: premature infants undergoing neonatal intensive care due to the development of acute clinical deterioration. Exclusion: not reported.
Index test	CRP
Reference standard	N/A
Target condition	Diagnosis of neonatal infection
Results: **CRP (cut-off 0.4 mg/l)** Area under curve Sensitivity Specificity PPV NPV	 0.73 69.4 70.4 59.5 78.6
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 156: ENGUIX 2001

Study	Enguix 2001[85]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=116: neonates with sepsis n=20, neonates without sepsis n=26, children with sepsis n=32, children without sepsis n=38)

Country and setting	Spain. NICU, PICU
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Age: neonates aged 3-30 days, children aged 2-12 years. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: neonates aged 3-30 days and children aged 2-12 years with and without sepsis. Bacterial sepsis defined according to Society of Critical Care Medicine and the American College of Chest Physicians criteria modified for paediatrics (SIRS due to acute bacterial infection, and/or characteristics of meningococcal rash, and/or clinical recovery with antibiotics.
Index test	CRP
Reference standard	N/A
Target condition	Hospital diagnosis of bacterial sepsis
Results:	
Neonates	
CRP, mg/l (cut-off 6.1)	
Area under curve	0.95 (0.88-1)
Sensitivity	95.8
Specificity	83.6
PPV	80.2
NPV	96.7
Children	
CRP, mg/l (cut-off 22.1)	
Area under curve	0.93 (0.89-0.97)
Sensitivity	88.6
Specificity	81.1
PPV	80.2
NPV	89.2

Patient characteristics **Neonates with sepsis versus without sepsis** CRP, ng/ml Median (range) **Children with sepsis versus without sepsis** CRP, ng/ml Median (range)	77.0 (32.4-144.0) versus 5.0 (5.0-42.1) 86.0 (11.2-248) versus 5.0 (5.0-77.6)
General limitations (according to QUADAS 2)	Observational design, possible selection bias (convenience sample), small sample size. Indirectness: none. Risk of bias: very high.

Table 157: FERNANDEZ LOPEZ 2003

Study	**Fernandez Lopez 2003[87]**
Study type	Prospective study
Number of studies (number of participants	1 (n=445, viral Infection group n=122, bacterial infection group n=230)
Country and setting	Spain. ED (Multicentre, 9 hospitals: Hospital Saint Joan de Deu, Barcelona; Hospital de Cruces, Vizcaya; Hospital Central de Asturias, Oviedo; Hospital Gregorio Maranon, Madrid; Hospital Nino Jesus, Madrid; Hospital Vall d'Hebro´, Barcelona; Hospital La Fe, Valencia; Hospital La Paz, Madrid; Hospital 9 Octubre, Valencia)
Funding	Not stated
Duration of study	12 month-study period
Age, gender, ethnicity	Mean (SD) age: 12.9 months (9.9), range 1 to 36 months. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: children between 1 and 36 months of age treated for fever in paediatric ED and required to undergo blood analysis to rule out the possibility of bacterial infection, hospital admission required. Exclusion: (1) antibiotic treatment in the 48 hours before admission to hospital; (2) vaccination in days before study, (3)

Study	Fernandez Lopez 2003[87]
	surgery performed in the 7 days before inclusion (4) any chronic pathology that could alter CRP values (rheumatic disease, intestinal inflammatory disease or other causes); and (5) history of prior urinary infection, pathology involving malformation of the kidney or of the urinary tract and vesicoureteral reflux.
Index test	CRP, Leukocytes, Total neutrophils
Reference standard	N/A
Target condition	Hospital diagnosis of viral and bacterial sepsis
Results: **CRP (cut-off 27.5% mg/l)** Area under curve Sensitivity Specificity PPV NPV **Total leukocytes (cut-off 7.1 x10^9/l)** Area under curve Sensitivity Specificity PPV NPV **Total neutrophils (cut-off >9.9 x10^9/l)** Area under curve Sensitivity Specificity PPV NPV	 0.81 (SD 0.02) 0.78 0.75 0.685 0.808 0.65 (SD 0.03) 0.54 0.76 0.69 0.695 0.65 (SD 0.03) 0.549 0.79 0.68 0.753

Study	Fernandez Lopez 2003[87]
Patient characteristics **Patients with viral infection versus bacterial infection** CRP (mg/l), mean (SD) Immature neutrophils/mm^3 Leukocytes/mm^3 Total neutrophils/mm^3	15.6 (19.8) versus 75.2 (76.9) 240 (523) versus 4373 (10,990) 12,424 (5926) versus 18,528 (9082) 6409 (4373) versus 10 990 (7383)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 158: FISCHER 2000

Study	Fischer 2000[91]
Study type	Prospective cohort study
Number of studies (number of participants	1 (n=154, samples n=632, control samples n=249, suspected infection n=383)
Country and setting	Switzerland. ICU of a tertiary referral hospital
Funding	Grant from the Alice Bucher Foundation, Lucerne, Switzerland. Merck KG, Darmstadt, Germany.
Duration of study	Not stated
Age, gender, ethnicity	Median age: 33.4 weeks (range 25-44), n=66 infants were premature. Gender: 62% male. Ethnicity: not stated.
Patient characteristics	Inclusion: not stated Exclusion: not stated
Index test	Total neutrophils Total WBC count

Study	Fischer 2000[91]
	CRP
Reference standards	N/A
Target condition	Culture-proven bloodstream infection
Results: Total neutrophils Area under curve Sensitivity Specificity Total WBC count Area under curve Sensitivity Specificity CRP Area under curve Sensitivity Specificity	 0.93 86% 85% 0.61 37% 86% 0.78 64% 85%
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: high (66/143 infants were premature). Risk of bias: very high.

Table 159: FOUZAS 2010

Study	Fouzas 2010[93]

Study	Fouzas 2010[93]
Study type	Retrospective study
Number of studies (number of participants	1 (n=408: SBI n=103, non-SBI n=305)
Country and setting	Greece. Tertiary care paediatric unit.
Funding	none
Duration of study	Not stated
Age, gender, ethnicity	Median age: 16 months (range 0.03–193), n=46 patients (26%) were <3 months, n=64 patients (37%) between 3-36 months. Gender: 665 M/447 F. Ethnicity: not stated.
Patient characteristics	Inclusion: infants aged 29 to 89 days admitted to the tertiary care paediatric unit for investigation of fever, defined as rectal temperature ≥38˚C. Exclusion: infants with fever for >72 hours, and who had received antibiotics or vaccination within 48 hours of presentation.
Index test	CRP, WBC, Platelets,
Reference standards	N/A
Target condition	Hospital diagnosis of SBI (defined as occult bacteraemia, UTI, bacterial meningitis, pneumonia, bacterial enteritis and infection of soft tissue or bones).
Results:	
Platelets (threshold x10^9/l)	
≥400 (n=253)	
Sensitivity	85.4
Specificity	45.9
PPV	34.8
NPV	90.3
Positive likelihood ratio	1.6
Negative likelihood ratio	0.32

Study	Fouzas 2010[93]
≥450 (n=175)	
Sensitivity	82.5
Specificity	70.5
PPV	48.6
NPV	92.3
Positive likelihood ratio	2.8
Negative likelihood ratio	0.25
≥500 (n=122)	
Sensitivity	52.4
Specificity	77.7
PPV	44.3
NPV	82.9
Positive likelihood ratio	2.4
Negative likelihood ratio	0.61
≥600 (n=53)	
Sensitivity	22.3
Specificity	90.2
PPV	43.4
NPV	77.5
Positive likelihood ratio	2.3
Negative likelihood ratio	0.86
Area under curve	0.74 (0.70-0.79)
WBC count	
>15x10^{9}/l	
Sensitivity	52.4

Study	Fouzas 2010[93]
Specificity PPV NPV Area under curve **CRP** **≥20mg/L** Sensitivity Specificity PPV NPV Area under curve **Patient characteristics** WBC, 10^9/l(median (range)) Non-SBI (n=305) SBI (n=103) PLT, 10^9/l (median (range)) Non-SBI (n=305) SBI (n=103) CRP, mg/L (median (range)) Non-SBI (n=305) SBI (n=103)	78.7 45.4 83.0 0.72 (0.67-0.76) 51.5 86.6 56.4 84.1 0.75 (0.71-0.80) 9.65 (7.15-14.20) 16.0 (11.1-20.2) 398 (313-463) 513 (455-598) 0.2 (0.0-1.2) 1.6 (0.1-4.2)
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias Indirectness: none.

Study	Fouzas 2010[93]
	Risk of bias: very high.

Table 160: FREYNE 2013

Study	Freyne 2013[95]
Study type	Prospective study
Number of studies (number of participants	1 (n=46)
Country and setting	Ireland. Paediatric ED (single-centre)
Funding	None received
Duration of study	Not stated
Age, gender, ethnicity	Mean age: 18.8 months. Gender: 23/23 F. Ethnicity: not stated.
Patient characteristics	Inclusion: infants aged 6 to 36 months with a confirmed axillary temperature of >38.1C who presented to the ED between the hours of 8am and 12 midnight were considered for enrolment Exclusion: underlying chronic illness, vaccination within 2 days or antipyretic use within 2 hours.
Index test	CRP, white cell count
Reference standard	N/A
Target condition	Hospital diagnosis of evolving illness and confirmed bacterial sepsis
Results: **CRP (>20 mg/l)** Sensitivity Specificity PPV NPV	 83.5 84.3 27.7 96.4

Study	Freyne 2013[95]
WCC (<5 or >15 x10^9/l) Sensitivity Specificity PPV NPV	 83.3 56.6 27.8 94.4
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 161: GALETTO-LACOUR 2003

Study	Galetto-Lacour 2003[100]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=99: benign infection n=70, lower UTI n=11, acute otitis media diagnosed at follow-up visit n=4, aseptic meningitis n=3)
Country and setting	Switzerland. Emergency Department (University Hospital of Geneva).
Funding	None stated
Duration of study	Not stated
Age, gender, ethnicity	Median (range) age in months: benign infection 7.2 (0.4-31.1); SBI 9.7 (0.7-34). Gender (M/F): benign infection 39/31; SBI 14/15 Ethnicity: not stated
Patient characteristics	Inclusion: children aged from 7 days to 36 months, body temperature >38.˚C, no localising signs of infection in history or physical examination. Exclusion: fever lasting longer than 7 days, children treated with antibiotics during the previous 2 days, and those with known immunodeficiencies.
Index test	CRP, leukocytes, band

Study	Galetto-Lacour 2003[100]
Reference standards	Culture-proven sepsis
Target condition	Hospital diagnosis of SBI
Results: CRP Cut-off 40mg/L Sensitivity (%[95%CI]) Specificity (%[95%CI]) PPV (%) NPV (%) Leucocytes ≥15 x10^9/l Sensitivity (%[95%CI]) Specificity (%[95%CI]) PPV (%) NPV (%) Band ≥1.5 x10^9/l Sensitivity (%[95%CI]) Specificity (%[95%CI]) PPV (%) NPV (%) Leucocytes ≥15 or Band ≥1.5 x10^9/l Sensitivity (%[95%CI]) Specificity (%[95%CI]) PPV (%) NPV (%)	 79 (60-92) 79 (67-88) 90 61 52 (33-71) 74 (62-84) 78 45 11 (2-28) 93 (84-98) 72 38 55 (36-74) 72 (61-83) 80 46

Study	Galetto-Lacour 2003[100]
Patient characteristics	
CRP (mg/L)	Benign infection (median [range]) 16 (10-200) SBI (median [range]) 100 (10-200)
Leucocytes (x10^9/l)	Benign infection (median [range]) 10.2 (3-29.3) SBI (median [range]) 15.1 (3.8-46.4)
Band (x10^9/l)	Benign infection (median [range]) 0.2 (0-2.7) SBI (median [range]) 0.7 (0-13)
General limitations (according to QUADAS 2)	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Table 162: GENDREL 1999

Study	Gendrel 1999[108]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=360: bacterial septicaemia/meningitis n=46, bacterial localised infections n=78, viral infections n=236)
Country and setting	France. 2 Hospitals (Hospital Saint Vincent de Paul and Hospital Cochin, Paris).
Funding	Grant CRC 97044 from AP-Hopitaux de Paris
Duration of study	2 years 3 months
Age, gender, ethnicity	Mean age (range) (invasive bacterial infections): 2.1 years (1 month-17 years), localised bacterial infections: 4.2 years (2 months to 15 years), viral infections: 2.2 years (1 month to 15 years) Gender: not stated. Ethnicity: not stated.

Study	Gendrel 1999[108]
Patient characteristics	Inclusion: children aged from 1 month to 15 years, body temperature >38.5˚C, responsible pathogen identified. Exclusion: known chronic disease.
Index test	CRP
Reference standards	N/A
Target condition	Hospital diagnosis of invasive bacterial infection localised bacterial infection, viral infection.
Results: **CRP** **<20mg/l** **Discrimination between groups (1+2) and 3** **>10mg/l** Sensitivity Specificity PPV NPV **>20mg/l** Sensitivity Specificity PPV NPV **>40mg/l** Sensitivity Specificity	 5/46 bacterial septicaemia/meningitis (group 1) 15/78 bacterial localised infections (group 2) 111/236 viral infections (group 3) 0.98 0.50 0.50 0.98 0.83 0.71 0.60 0.89 0.73 0.88

Study	Gendrel 1999[108]
PPV	0.76
NPV	0.86
Discrimination between groups 1 and (2+3)	
CRP	
>10mg/l	
Sensitivity	0.98
Specificity	0.38
PPV	0.19
NPV	0.992
>20mg/l	
Sensitivity	0.89
Specificity	0.58
PPV	0.24
NPV	0.972
>40mg/l	
Sensitivity	0.87
Specificity	0.75
PPV	0.34
NPV	0.975
Patient characteristics	
CRP median/ mean/ range	
Group 1: bacterial septicaemia/ meningitis	143.50/ 148.4/ 9-400
Group 2: bacterial localised infections	65.50/ 82.8/ 0-400

Study	Gendrel 1999[108]
Group 3: viral infections	10.00/ 19.5/ 4-220
General limitations (according to QUADAS 2)	Observational design, small sample size, possible selection bias Indirectness: none. Risk of bias: very high.

Table 163: GOMEZ 2010

Study	Gomez 2010[113]
Study type	Retrospective cross-sectional study
Number of studies (number of participants	1 (n=1018)
Country and setting	Spain. Paediatric ED (single-centre, tertiary teaching hospital)
Funding	Not stated
Duration of study	5-year period (September 2003 through August 2008)
Age, gender, ethnicity	Age: under 31 days (n=243), 31-60 days (n=417), 61-90 days (n=358). Gender: 585/433 F. Ethnicity: not stated.
Patient characteristics	Inclusion: all infants younger than 90 days of age with fever without source admitted to the Paediatric ED during the 5-year study period Exclusion: if origin of fever could be determined, patients with a diarrheal process or certain respiratory symptoms/signs (such as tachypnea, breathing difficulties, wheezing, grunting, nasal flaring, retractions, rhonchi, rales, focal areas of decreased breath sounds)
Index test	CRP
Reference standard	N/A
Target condition	Diagnosis of severe bacterial infection or invasive bacterial infection

Study	Gomez 2010[113]
Results:	
CRP (cut-off 70 mg/l)	
Area under curve	0.847 (0.754-0.940)
Sensitivity	69.6
Specificity	93.8
PPV	Not reported
NPV	99.3
CRP (cut-off 20 mg/l)	
Area under curve	Not reported
Sensitivity	73.9
Specificity	74.8
PPV	Not reported
NPV	Not reported
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 164: GOMEZ 2012

Study	Gomez 2012[112]
Study type	Retrospective study
Number of studies (number of participants	1 (n=1112: definite SBI n=289, invasive bacterial infection (IBI) n=23
Country and setting	5 Spanish and 2 Italian Paediatric EDs (Cruces University Hospital, University of Padova Hospital Ca'Foncello Hospital, 12 de Octubre University Hospital, Donostia University Hospital, Nino Jesus University Hospital, Navarra Hospital Complex).

Study	Gomez 2012[112]
Funding	No external funding
Duration of study	3 year study period
Age, gender, ethnicity	Age: ≤28 days: 277, 29-60 days: 506, 61-90 days: 329 Gender: 665 M/447 F. Ethnicity: not stated.
Patient characteristics	Inclusion: well-appearing infants <3 months with fever without source, defined as axillary or rectal temperature at home or rectal temperature in the ED of ≥38˚C, without catarrhal or other respiratory signs or symptoms or a diarrhoeal process, in patients who had a normal physical examination. Well-appearing was defined by a normal paediatric assessment triangle (Diekmann et al, 2010) in those departments where these data are recorded. For the other departments, infants were considered to not be well appearing if the findings of the physical examination documented in the patients' medical record indicated any clinical suspicion of sepsis; these included, but where not limited to 'poor/bad general appearance', 'irritable', 'cyanosis', 'hypotonic' and 'cutis marmorata'. Exclusion: (1) patients in whom the anamnesis and/ or the physical examination performed on arrival in the ED allowed the origin of fever to be identified. (2) patients classified as not well appearing on arrival to the ED; patients initially classified as well appearing but whose clinical situation subsequently worsened were included. (3) patients who were afebrile in the ED and has been judged to have fever at home without the use of a thermometer. Patients who were afebrile in the ED but in whom fever was confirmed by measurement of the infant's temperature at home were included. (4) Patients in whom PCT was not measured or its value was not recorded in the patient's medical record and those in whom a blood culture was not performed.
Index test	CRP, ANC, WBC
Reference standards	N/A
Target condition	Hospital diagnosis of SBI or IBI. SBI defined as the isolation of a bacterial pathogen from the blood, CSF, urine or stools. IBI defined as isolation of a bacterial pathogen from the blood or CSF.
Results: **CRP≥20mg/L, WBC count ≥15 x10^9/l and ANC ≥10 x10^9/l were not found to be independent risk factors for IBI on multivariable analysis (data not shown).** CRP	

Study	Gomez 2012[112]
Area under curve: SBI Area under curve: IBI ANC Area under curve: SBI Area under curve: IBI WBC Area under curve: SBI Area under curve: IBI **Patient characteristics** CRP, mg/l (median (range)) IBI (n=266) No IBI (n=23) WBC count, **x10^9/l** IBI (n=266) No IBI (n=23) ANC count, **x10^9/l** IBI (n=266) No IBI (n=23)	0.776 (0.741-0.811) 0.747 (0.629-0.865) 0.711 (0.674-0.748) 0.629 (0.506-0.752) 0.692 (0.655-0.729) 0.583 (0.460-0.706) 33 (9-112) 6 (2-21) 13.38 ±5.84 12.09 ±8.39 7.19 ±4.56 5.23 ±3.69
General limitations (according to QUADAS 2)	Retrospective design. Indirectness: none. Risk of bias: very high.

Table 165: HATHERILL 1999

Study	Hatherill 1999[119]

Study	Hatherill 1999[119]
Study type	Prospective study
Number of studies (number of participants	1 (n=175: non-infected controls n=43; viral infection n=14; localised bacterial infection without shock n= 25; bacterial meningitis/encephalitis n=10; septic shock n=77; presumed septic shock n=6)
Country and setting	UK. PICU (Guy's Hospital)
Funding	No funding stated
Duration of study	18 month-study period
Age, gender, ethnicity	Median age: 16 months (range 0.03–193), n=46 patients (26%) were <3 months, n=64 patients (37%) between 3-36 months. Gender: 665 M/447 F. Ethnicity: not stated.
Patient characteristics	Inclusion: children admitted to PICU. Septic shock defined as evidence of infection, hypotension or poor capillary refill responding to fluid or pharmacological intervention, in the presence of hyperthermia or hypothermia, tachycardia, and tachypnoea, in addition to at least one of the following: acute mental changes, hypoxaemia, hyperlactataemia, or oliguria. Exclusion: parenteral antibiotics in past 7 days (except within preceding 24 hours).
Index test	CRP, Leukocytes
Reference standards	N/A
Target condition	Hospital diagnosis of septic shock
Results:	
CRP	
Area under curve	0.83 (0.76-0.90)
CRP >20 mg/l	91
Sensitivity	62
Specificity	66
PPV	89
NPV	
CRP >30 mg/l	81

Study	Hatherill 1999[119]
Sensitivity	70
Specificity	69
PPV	82
NPV	
CRP >40 mg/l	79
Sensitivity	77
Specificity	74
PPV	82
NPV	
CRP >50 mg/l	
Sensitivity	76
Specificity	80
PPV	76
NPV	80
WBC	
Area under curve	0.51 (0.41-0.60)
Patient characteristics	
CRP, mg/l (median (range))	
Septic shock (n=77)	101 (3–335)
Bacterial meningitis (n=10)	110.5 (32–353)
Localised bacterial infection (n=25)	20 (7–213)
Viral infection (n =14)	12 (7–76)
Non-infected controls (n =43)	8 (2–47)
WBC, x10^9/l (median (range))	
Septic shock (n=77)	12.1 (0.4–83.8)

Study	Hatherill 1999[119]
Bacterial meningitis (n=10) Localised bacterial infection (n=25) Viral infection (n =14) Non-infected controls (n =43)	18.2 (2–33.5) 9.7 (1.4–30.4) 5.75 (2.5–32) 13.7 (2.4–25.3)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 166: HORNIK 2012

Study	Hornik 2012[128]
Study type	Retrospective cohort
Number of studies (number of participants	1 (n=37 826: 9656 (13.8%) positive cultures in 7951 infants (21.0%)).
Country and setting	USA. 293 NICUs
Funding	One author received support from: United States government, Thrasher Research Foundation, Astellas Pharma US, AstraZeneca, Johnson & Johnson, Pfizer, Biosynexus, and UCB Pharma, Cerexa, Astellas Pharma US. One author received support from: the NIH, U.S. Department of Health and Human Services One author received support from NICHD.
Duration of study	13 year-study period
Age, gender, ethnicity	Age: days of life 4-120. Gender: not stated. Ethnicity: White: 52%. Black 20%. Hispanic 23%. Other 5%.
Patient characteristics	Inclusion: patients with late onset sepsis defined as a positive culture (blood, urine collected by catheterization or suprapubic tap, or cerebrospinal fluid) between 4 and 120 days of life. Exclusion: incomplete record of laboratory tests and/or culture results.
Index test	ANC, I/T, Platelets, WBC
Reference standard	N/A
Target condition	Hospital diagnosis of bacterial sepsis

Study	Hornik 2012[128]
Results:	
ANC, $x10^9$/l (cut-off <1)	
Sensitivity	2.4
Specificity	98.0
Positive likelihood ratio	1.2
Negative likelihood ratio	1.00
ANC, $x10^9$/l (cut-off <1.5)	
Sensitivity	5.0
Specificity	95.5
Positive likelihood ratio	1.1
Negative likelihood ratio	1.00
I/T ratio (cut-off >0.20)	
Sensitivity	54.2
Specificity	61.9
Positive likelihood ratio	1.4
Negative likelihood ratio	0.7
I/T ratio (cut-off >0.25)	
Sensitivity	43.2
Specificity	71.1
Positive likelihood ratio	1.5
Negative likelihood ratio	0.8
I/T ratio (cut-off >0.50)	
Sensitivity	13.1
Specificity	92.6
Positive likelihood ratio	1.8
Negative likelihood ratio	0.9

Study	Hornik 2012[128]
Platelets, $x10^9$/l cut-off <50)	
Sensitivity	7.7
Specificity	97.8
Positive likelihood ratio	3.5
Negative likelihood ratio	0.9
Platelets, $x10^9$/l (cut-off <100)	
Sensitivity	22.9
Specificity	89.0
Positive likelihood ratio	2.1
Negative likelihood ratio	0.9
WBC, $x10^9$/l (cut-off <1)	
Sensitivity	1.0
Specificity	>99.99
Positive likelihood ratio	4.1
Negative likelihood ratio	1.00
WBC, $x10^9$/l (cut-off <5)	
Sensitivity	7.0
Specificity	96.1
Positive likelihood ratio	1.8
Negative likelihood ratio	0.97
WBC, $x10^9$/l (cut-off >20)	
Sensitivity	22.6
Specificity	79.8
Positive likelihood ratio	1.1
Negative likelihood ratio	0.97

Study	Hornik 2012[128]
WBC, x10^9/l (cut-off >50) Sensitivity Specificity Positive likelihood ratio Negative likelihood ratio **Patient characteristics** **Culture positive patients (n=9834) versus culture negative patients (n=62,702)** Mean ANC Mean I/T Mean Platelets Mean WBC count	 1.0 99.1 1.2 1.00 15,287/mm^3 (5th, 95th percentile: 4200/mm^3, 33,800/mm^3) versus 15,214/mm^3 (5400/mm^3, 32,400/mm^3 9420/mm^3 (1504/mm^3, 24,510/mm^3) versus 8582/mm^3 (1584/mm^3, 24,510/mm^3) 0.26 (0.03, 0.67) versus 0.20 (0.02, 0.57) for negative cultures (*P*<0.01). 222,510/mm^3 (40,000/mm^3, 504,000/mm^3) versus 273,700/mm^3 (70,000/mm^3, 550,000/mm^3)
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias (convenience sample). Indirectness: none. Risk of bias: very high.

Table 167: HSIAO 2006A

Study	Hsiao 2006A[130]
Study type	Prospective study
Number of studies (number of participants	1 (n=429)
Country and setting	USA. Paediatric ED (single-centre, academic hospital, New Haven, Connecticut)
Funding	None declared

Study	Hsiao 2006A[130]
Duration of study	12 month-study period (February 2003 to February 2004)
Age, gender, ethnicity	Mean (SD) age: SBI 117.8 days (33.7), Non-SBI 112.7 days (36.2). Gender: 218/211 F. Ethnicity: 41.3% White, 34.2% Hispanic, 20.0% Black, 1.4% Asian, 3.0% self-described 'other'
Patient characteristics	Inclusion: infants 57-180 days of age with rectal temperatures >37.9C who consecutively presented to the emergency department of Yale-New Haven Children's Hospital. Exclusion: children whose families chose not to participate.
Index test	CRP, white blood cell count, absolute neutrophil count
Reference standard	N/A
Target condition	Not reported
Results: **CRP** Area under curve **WBC** Area under curve **ANC** Area under curve **Patient characteristics** **Patients with severe bacterial infection versus non-severe bacterial infection** CRP (mg/dl), mean (SD) White blood cell count, K/mm^3 Absolute neutrophil count	 0.78 0.72 0.70 2.7 (3.7) versus 0.9 (1.4) 17.4 (8.1) versus 12.4 (5.5) 11,662 (9,234) versus 6,972 (6,097)

Study	Hsiao 2006A[130]
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 168: ISAACMAN 2002

Study	Isaacman 2002[131]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=256, occult bacterial infection n=29, pneumonia n=17, UTI n=9, bacteraemia n=3)
Country and setting	USA. ED (Children's Hospital of The King's Daughters , Norfolk, VA)
Funding	Grant 872090 from the Department of Paediatrics, Eastern Virginia Medical School, Norfolk
Duration of study	15 months
Age, gender, ethnicity	Median (range) age at study entry: 15.3 (3.1-35.2) months. Gender: not reported. Ethnicity: not stated.
Patient characteristics	Inclusion: children aged between 3 and 36 months with fever who required a complete blood cell count and blood culture as part of their evaluation. Exclusion: patients were excluded if they had taken any oral or parenteral antibiotics within 48 hours of the visit, or had a known case of bacteraemia during the previous 48 hours. Immuno-deficient patients were enrolled, but analysed separately.
Index test	WBC, CRP, ANC
Reference standard	N/A
Target condition	Hospital diagnosis of occult bacterial infection

Study	Isaacman 2002[131]
Results:	
WBC (cut-off 17.1x10^9/L)	
Area under curve	0.69 (0.61-0.77
Sensitivity	0.69 (0.51-0.89)
Specificity	0.80 (0.75-0.85)
PPV	0.31 (0.20-0.43)
NPV	0.95 (0.92-0.98)
CRP (cut-off 44mg/L)	
Area under curve	0.71 (0.62-0.79)
Sensitivity	0.63 (0.43-0.82)
Specificity	0.81 (0.76-0.87)
PPV	0.30 (0.18-0.43)
NPV	0.94 (0.91-0.98)
ANC (cut-off 10.6x10^9/L)	
Area under curve	0.73 (0.65-0.81)
Sensitivity	0.69 (0.51-0.87)
Specificity	0.79 (0.73-0.84)
PPV	0.32 (0.20-0.44)
NPV	0.95 (0.91-0.98)
WBC (cut-off 17.1x10^9/L) or CRP≥31mg/L	
Area under curve	0.63 (0.53-0.71)
Sensitivity	0.76 (0.59-0.92)
Specificity	0.58 (0.51-0.64)
PPV	0.19 (0.12-0.27)
NPV	0.95 (0.91-0.99)

Study	Isaacman 2002[131]
ANC (cut-off 10.5x10^9/L) or CRP ≥36mg/L Area under curve Sensitivity Specificity PPV NPV	 0.66 (0.57-0.74) 0.79 (0.64-0.95) 0.50 (0.43-0.56) 0.17 (0.10-0.23) 0.95 (0.91-0.99)
Multiple logistic regression model 1 (included age, temperature, length of illness CRP and ANC)	Each cell increase of 1000x10^9 in the ANC resulted in a risk increase of 1.15 for OBI (OR 1.15, 95%CI1.07-1.24, p<0.001)after adjusting for CRP and length of illness. Each 10mg/L increase in CRP resulted in a risk increase of 1.12 for OBI (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 1000x10^9 in the ANC resulted in a risk increase of 1.15 for OBI (OR 1.15, 95%CI1.07-1.23, p<0.001)after adjusting for CRP and length of illness. Each 10mg/L increase in CRP resulted in a risk increase of 1.12 for OBI (OR 1.12, 95%CI1.04-1.21, p0.003)after adjusting for WBC and length of illness.
Patient characteristics	
WBC (thousands) Patients with OBI (n=29) Patients without OBI (n=227) Excluded patients (n=10)	 19.7 (6.4-39.1) 11.4 (3.6-33.9) 9.0 (4.8-26.2)
CRP Patients with OBI (n=29) Patients without OBI (n=227) Excluded patients (n=10)	 5.6 (0.7-43.3) 1.5 (0.2-31.1) 2.7 (1.2-7.8)

Study	Isaacman 2002[131]
ANC Patients with OBI (n=29) Patients without OBI (n=227) Excluded patients (n=10)	 13.8 (2.6-26.4) 6.6 (0.6-28.2) 4.9 (1.3-17.6)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 169: JACQUOT 2009

Study	Jacquot 2009[132]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=73, infected group n=30, non-infected group n=43)
Country and setting	France. NICU (Croix-Rousse Hospital, Lyon)
Funding	Not reported
Duration of study	12 month-study period
Age, gender, ethnicity	Mean (range) age at study entry: 11 (8-18) days. Gender: 56% male. Ethnicity: not stated.
Patient characteristics	Neonates >72 hours old with clinically suspected late onset sepsis (LOS). Newborn infants only included once.
Index test	CRP (cut-off 10 mg/l)
Reference standard	N/A

Study	Jacquot 2009[132]
Target condition	Hospital diagnosis of sepsis
Results: CRP (cut-off 10 mg/l) Area under curve Sensitivity Specificity PPV NPV Positive likelihood ratio Negative likelihood ratio	 0.77 58 (47-69) 86 (78-94) 74 (64-84) 75 (65-85) 4.18 0.48
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 170: KIM 2015A

Study	Kim 2015A[149]
Study type	Retrospective cohort study
Number of studies (number of participants	1 (n=2336 neonates; 6716 blood samples)
Country and setting	Korea; Korea University Hospital
Funding	National Research Foundation of Korea grant funded by the Korea government (MSIP) and also by a Korea University Grant
Duration of study	October 2006 to July 2010
Age, gender, ethnicity	3 groups of neonates in study: Healthy full-terms (n=225); very low birth weight (VLBW without sepsis (n=35); VLBW with sepsis (n=32). Gender M/F (n): 166:126; Ethnicity: not reported
Patient characteristics	Inclusion: all babies born between 37 and 42 weeks of pregnancy as being full-term (n=656 (1065 samples); all pre-term babies were defined as babies born alive between 37 weeks of pregnancy, which includes VLBW infants (405 samples of non-septic VLBW (n=32) and 263 samples of VLBW infants (n=35). VLBW neonates defined as babies whose birth weight was <1500g.

Study	Kim 2015A[149]
	Exclusion: 1)maternal of infant haemorrhage, 2) documented or clinical sepsis at birth, 3) blood group incompatibility with hemolysis, 4) small for gestational age infants (birth weight below the 10th percentile for gestational age), 5)multiple gestations, 6)congenital anomalies,7)maternal pregnancy induced hypertension
Index test	Platelets
Reference standard	N/A
Target condition	Diagnosis of sepsis
Results: Diagnosis of sepsis Platelets (cut-off 68.0 x10^9/l) Area under curve Sensitivity Specificity PPV NPV	 0.692 0.593 0.765 0.667 0.703
General limitations (according to QUADAS 2)	Observational design, retrospective Indirectness: none. Risk of bias: very high.

Table 171: LACOUR 2001

Study	Lacour 2001[161]
Study type	Prospective cohort
Number of studies (number of participants	1 (n=124, benign infection n=96, SBI n=28)
Country and setting	Switzerland. ED (University Children's Hospital, Geneva)
Funding	Not reported

Study	Lacour 2001[161]
Duration of study	17 months
Age, gender, ethnicity	Mean (SD) age at study entry (months): 10.9±0.9 (benign infection group), 11.2±1.8 . Gender: not reported. Ethnicity: not stated.
Patient characteristics	Inclusion: children aged 7 days to 36 months, with a rectal temperature above 38˚C and without localising signs of infection. Exclusion: not reported
Index test	CRP, leucocytes
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: CRP (cut-off 40 mg/l) Sensitivity Specificity PPV NPV Leucocytes (>15 x10^9/l) Sensitivity Specificity PPV NPV Patient characteristics CRP (mg/l) Benign infection (n=96) SBI (n=28)	 89 (72-98) 75 (65-83) 51 96 68 (48-84) 77 (67-85) 46 89 20 (10-200) 108 (10-200)

Study	Lacour 2001[161]
General limitations (according to QUADAS 2)	Small sample size, possible selection bias. Indirectness: none. Risk of bias: very high.

Table 172: MAHAJAN 2014

Study	Mahajan 2014[183]
Study type	Prospective study
Number of studies (number of participants	1 (n=226)
Country and setting	USA. ED (Multicentre, 4 participating EDs)
Funding	Some authors supported by government/academic grants
Duration of study	20 month-study period (May 2004 to December 2005)
Age, gender, ethnicity	Mean (SD) age: 10.5 months (8.4). Gender: 95/131 F. Ethnicity: 88.5% Non-White.
Patient characteristics	Inclusion: convenience sample of well-appearing febrile children without obvious source 36 months old or younger who presented to one of the four participating EDs during the study period. All such children with documented fever (defined as rectal temperature measured in the ED or at home of ≥38C if ≤3 months of age and ≥39C if >3 months of age) and who were otherwise being evaluated for serious bacterial infections, and were documented to be well-appearing, were eligible. Exclusion: if child had received antibiotics within 48 hours of ED presentation, obvious source of fever, known immunologic or

Study	Mahajan 2014[183]
	systemic diseases, history of prematurity in febrile infants younger than 3 months, immunisation during the previous 2 days, if guardians/parents did not provide informed consent
Index test	White blood cell count, absolute neutrophil count, absolute band count
Reference standard	N/A
Target condition	Diagnosis of severe bacterial infection
Results:	
WBC (cut-off >15 x 10^9 cells/l)	
Sensitivity	56.7
Specificity	76.3
PPV	27
NPV	92
WBC (cut-off >19 x 10^9 cells/l)	
Area under curve	0.76 (95%CI 0.66-0.86)
Sensitivity	46.7
Specificity	90.2
PPV	15
NPV	85
ANC (cut-off >10 x 10^9 cells/l)	
Sensitivity	46.7
Specificity	88.1
PPV	38
NPV	91
ANC (cut-off >13 x 10^9 cells/l)	
Area under curve	0.73 (95%%CI 0.63-0.84)
Sensitivity	30.0

Study	Mahajan 2014[183]
Specificity PPV NPV **Absolute band count (cut-off >1.5 x 10^9 cells/l)** Sensitivity Specificity PPV NPV **Absolute band count (cut-off >1.8 x 10^9 cells/l)** Area under curve Sensitivity Specificity PPV NPV **Patient characteristics** **Patients with severe bacterial infection versus non-severe bacterial infection** WBC (x10^9 cells/l), mean (SD) ANC (x10^9 cells/l), mean (SD) Absolute band count (x10^9 cells/l), Mean (SD)	94.3 45 90 20.0 93.3 32 88 0.67 (95%CI 0.55-0.78) 20.0 96.4 6 94 18.6 (8.6) versus 11.5 (5.3) 10.6 (6.7) versus 5.6 (3.8) 0.90 (1.10) versus 0.35 (0.60)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none.

Study	Mahajan 2014[183]
	Risk of bias: very high.

Table 173: MAKHOUL 2006

Study	Makhoul 2006[185]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=111)
Country and setting	Israel. NICU (Meyer Children's Hospital and Rambam Medical Center, Haifa)
Funding	A. and E. Blum Medical Research Fund
Duration of study	13.5 month-study period
Age, gender, ethnicity	Mean (SD) age at onset of septic event: 17.3 (18.7) days, range 4-105 days. Gender: not stated. Ethnicity: not stated.
Patient characteristics	N=111 neonates >3 days with clinically suspected late onset sepsis (LOS). LOS defined as clinical features of sepsis with positive blood culture. Suspected LOS defined as clinical features of sepsis pending positive blood culture.
Index test/s	CRP Immature neutrophil to total neutrophil (I/T) ratio
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: **Positive blood culture** **Univariable analysis for variables associated with proven LOS (at onset of sepsis)**	 26/148 events (17.6%)

Study	Makhoul 2006[185]
CRP >10 mg/l I/T >2 WBC <5 x10^9/l WBC >20 x10^9/l Platelet count <150 x10^9/l **Multivariable analysis for variables associated with proven LOS (at onset of sepsis)** I/T >2 **Mean (SD) CRP values (mg/dl), culture positive patients versus culture negative patients**	RR 2.85 (1.13-6.15) RR 5.13 (2.54-10.31) No association No association No association RR 4.89 (2.48-9.66) Culture positive: 1.7 (1.58). Culture negative: 0.63 (1.21).
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 174: MANIACI 2006

Study	Maniaci 2006[186]
Study type	Prospective observational study
Number of studies (number of participants)	1 (n=234: definite SBI n=30, possible SBI n=12, no SBI n=192)
Country and setting	USA. ED (urban paediatric ED)
Funding	Frederick H Lovejoy, Jr, MD, Resident Research Fund American Academy of Paediatrics resident research grant
Duration of study	18 month study period
Age, gender, ethnicity	Median(IQR) age in days: 51 (31-70) Gender: not stated. Ethnicity: not stated.

Study	Maniaci 2006[186]
Patient characteristics	Inclusion: Infants aged ≤90 days with a temperature ≥38.0˚C seen in the ED. Exclusion: infants with a previously identified immunodeficiency or chronic disease, focal bacterial infection (other than otitis media) on physical examination, vesicoureteral relux requiring antibiotic prophylaxis, surgery in the previous 7 days (excluding neonatal circumcision), immunisations in the 48 hours preceding the visit. Definitions: Definite SBI: (1) bacteraemia, as a positive blood culture result with a pathogen; (2) UTI, as a urine culture (from catheterisation) with ≥50,000 colony forming units per mL with positive urinalysis results; (3) bacterial meningitis, as a positive CSF culture; (4) bacterial pneumonia, as a positive pleural fluid culture results with a pathogen or a chest radiograph interpreted by an attending radiologist as indicating pneumonia with a positive blood or sputum culture result with a respiratory pathogen or (5) bacterial gastroenteritis. Possible SBI (1) UTI, as a urine culture with 10,000 to 49,000 colony forming units per mL of a single pathogen with a negative urinalysis result or (2) bacterial pneumonia as indicating pneumonia or possible pneumonia in the absence of a positive pleural fluid, sputum or blood culture result. All other patients were considered not to have a SBI.
Index test/s	WBC ANC
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: **WBC count** ROC curve for definite SBI v no SBI Area under curve ROC curve for definite and possible SBI v no SBI Area under curve ANC ROC curve for definite SBI v no SBI Area under curve	 0.66 0.61 0.74

Study	Maniaci 2006[186]
ROC curve for definite and possible SBI v no SBI Area under curve Baseline characteristics WBC count, mean (SD), cells x 1000 per mm^3 Definite SBI (n=30) Definite and possible SBI (n=42) No SBI (n=192) ANC, mean (SD), cells x 1000 per mm^3 Definite SBI (n=30) Definite and possible SBI (n=42) No SBI (n=192)	0.66 15.9 (8.7) 14.4 (7.9) 11.2 (4.2) 9.6 (8.7) 8.1 (6.4) 4.7 (2.8)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 175: MANZANO 2011

Study	Manzano 2011[187]
Study type	Prospective cohort study, which was part of an RCT
Number of studies (number of participants)	1 (n=328, n=54 SBI, n=274 no SBI)
Country and setting	Canada. Paediatric emergency department of a tertiary care hospital

Study	Manzano 2011[187]
Funding	The investigators received 200 PCT-Q kits from Brahms (Germany). Reagents for the kryptor PCT measurements were provided by Brahms (Switzerland).
Duration of study	Not stated
Age, gender, ethnicity	Median age in months (IQR): 11 (6-17). Gender: M 50.0% (n=165). Ethnicity: not stated.
Patient characteristics	Inclusion: age 1-36 months with a recorded rectal temperature of ≥38˚C and no identified source of infection. Exclusion: acquired/ congenital immunodeficiency, already treated with antibiotics.
Results:	
AUC	
Clinical evaluation (VAS)	0.59 (0.54 to 0.65)
ANC	0.80 (0.75 to 0.84)
WBC	0.81 (0.76 to 0.85)
CRP	0.88 (0.84 to 0.91)
Diagnostic accuracy for detecting SBI in fever without source	
CRP>17.7mg/l	
Sensitivity (95%CI)	94.4 (85.5 to 98.1)
Specificity (95%CI)	68.6 (66.9 to 69.3)
PPV (95%CI)	37.2 (33.7 to 38.7)
NPV (95%CI)	98.4 (95.9 to 99.5)
WBC>14.1 x10^{9}/l	81.5 (70.3 to 89.3)
Sensitivity (95%CI)	70.8 (68.6 to 72.4)
Specificity (95%CI)	35.5 (30.6 to 38.9)
PPV (95%CI)	95.1 (92.1 to 97.2)
NPV (95%CI)	
	87.0 (76.5 to 93.5)
ANC>5.2 x10^{9}/l	59.9 (57.8 to 61.1)
Sensitivity (95%CI)	29.9 (26.3 to 32.1)

Study	Manzano 2011[187]
Specificity (95%CI)	95.9 (92.1 to 97.2)
PPV (95%CI)	
NPV (95%CI)	
VAS>14.8%	68.5 (56.5 to 78.8)
Sensitivity (95%CI)	38.7 (36.3 to 40.7)
Specificity (95%CI)	18.0 (14.9 to 20.7)
PPV (95%CI)	86.2 (80.9 to 90.7)
NPV (95%CI)	
Diagnostic accuracy for detecting SBI when urinalysis was normal	
CRP>17.7mg/l	
Sensitivity (95%CI)	87.5 (53.6 to 97.8)
Specificity (95%CI)	69.7 (68.6 to 70.0)
PPV (95%CI)	8.3 (5.1 to 9.3)
NPV (95%CI)	99.4 (97.9 to 99.9)
WBC>14.1 x10^9/l	
Sensitivity (95%CI)	75.0 (41.5 to 92.8)
Specificity (95%CI)	71.7 (70.6 to 72.2)
PPV (95%CI)	7.7 (4.3 to 9.5)
NPV (95%CI)	98.9 (97.5 to 99.7)
ANC>5.2 x10^9/l	
Sensitivity (95%CI)	75.0 (41.4 to 92.8)
Specificity (95%CI)	59.8 (41.5 to 92.8)
PPV (95%CI)	5.6 (3.1 to 6.9)
NPV (95%CI)	98.7 (97.0 to 99.6)

Study	Manzano 2011[187]
VAS>14.8% Sensitivity (95%CI) Specificity (95%CI) PPV (95%CI) NPV (95%CI)	 75.0 (41.4 to 92.8) 39.4 (38.3 to 39.9) 3.8 (2.1 to 4.6) 98.0 (95.4 to 99.4)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: low.

Table 176: NADEMI 2001

Study	Nademi 2001[209]
Study type	Prospective study
Number of studies (number of participants	1 (n=141)
Country and setting	UK. Paediatric assessment units (Dual-centre: Newcastle General Hospital, Royal Victoria Infirmary in Newcastle)
Funding	Not stated
Duration of study	3-month study period (August 1999 to November 1999)
Age, gender, ethnicity	Mean age: 3.3 years, range 8 days to 16 years. Gender: 90/51 F. Ethnicity: not stated.
Patient characteristics	Inclusion: all children with a temperature of ≥38C seen in the two hospitals during the study period. Exclusion: temperature less than 38C
Index test	White blood cell count
Reference standard	N/A

Study	Nademi 2001[209]
Target condition	Cause of fever
Results: **WBC (cut-off >15 x10^9/l)** Sensitivity Specificity PPV NPV **WBC (cut-off >20 x10^9/l)** Sensitivity Specificity PPV NPV	 10 (0.6-18) 95 (90-99) 44 (11-76) 72 (64-79) 29 (15-43) 93 (87-98) 63 (41-84) 76 (68-83)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 177: NAHUM 2012

Study	Nahum 2012[210]
Study type	Prospective case-control study
Number of studies (number of participants	1 (n=121)
Country and setting	Israel. Cardiac ICU (Single-centre: tertiary paediatric medical centre, Tel Aviv)
Funding	None declared

Study	Nahum 2012[210]
Duration of study	2-year study period
Age, gender, ethnicity	Mean (SD) age: 46 months (56), range 4 days to 17.8 years. Gender: 68/38 F. Ethnicity: not stated.
Patient characteristics	Inclusion: all consecutive children aged 1 to 18 years who underwent cardiac surgery with bypass were eligible Exclusion: patients who had fever during the 72 hours prior to surgery or were under treatment course with antibiotic at the time of surgery
Index test	CRP
Reference standard	N/A
Target condition	Differential diagnosis of early bacterial infection
Results: **CRP velocity (0 mg/l per day)** Sensitivity Specificity PPV NPV **CRP velocity (10 mg/l per day)** Sensitivity Specificity PPV NPV **CRP velocity (20 mg/l per day)** Sensitivity Specificity PPV NPV	 86.7 42.9 52.0 81.8 80.0 73.8 68.6 83.8 60.0 81.0 69.2 73.9

Study	Nahum 2012[210]
CRP velocity (30 mg/l per day)	
Sensitivity	50.0
Specificity	90.5
PPV	78.9
NPV	71.7
CRP velocity (40 mg/l per day)	
Sensitivity	40.0
Specificity	95.2
PPV	85.7
NPV	69.0
CRP velocity (50 mg/l per day)	
Sensitivity	26.7
Specificity	97.6
PPV	88.9
NPV	65.1
Patient characteristics	
Patients with bacteriaemia versus pneumonia	
CRP velocity (mg/dl per day), mean (SD)	4.0 (4.8) versus 3.2 (2.8)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 178: NOSRATI 2014

Study	Nosrati 2014[218]
Study type	Retrospective
Number of studies (number of participants)	1 (n=401, n=48 SBI, n=353 no SBI)
Country and setting	Israel. Tertiary care (Dana-Dwek Children's Hospital, Tel-aviv)
Funding	Not stated
Duration of study	2 year study period
Age, gender, ethnicity	Mean age (SD): 49.6 (18.6) days. 9.9% were ≤29 days old, 69.5% were 30-60 days old and 20.4% were 61-90 days old. Gender: M 55.8% (n=224). Ethnicity: not stated.
Patient characteristics	Inclusion: febrile infants aged <3 months with a recorded rectal temperature of ≥38˚C Exclusion: preterm birth (<35 weeks of gestation), presence of a chronic disease (heart failure, lung disease or renal failure), congenital or acquired immune deficiency, current antibiotic use and/or incomplete records.
Index test/s	CRP, ANC, leucocyte count
Reference standard	N/A
Target condition	Hospital diagnosis of SBI (UTI, meningitis, bacteraemia or bacterial enteritis).
Results: **Univariable logistic regression model:** **CRP** (multivariable analysis) OR (95% CI) Threshold (mg/L) **2** Sensitivity Specificity PPV NPV	 Significant independent laboratory predictors were ANC, platelets, blood urea nitrogen (BUN) and CRP. WBC showed no superiority in identifying SBI (see 'patient characteristics'). These risk factors were further assessed using logistic regression analysis: only CRP was found to be significantly associated with SBI (see CRP- multivariable analysis). 1.042 (1.028-1.056), p<0.001 90 30 15 96

Study	Nosrati 2014[218]
Positive likelihood ratio	1.28
Negative likelihood ratio	0.3
4	
Sensitivity	88
Specificity	38
PPV	16
NPV	96
Positive likelihood ratio	1.41
Negative likelihood ratio	0.31
6	
Sensitivity	86
Specificity	47
PPV	18
NPV	96
Positive likelihood ratio	1.62
Negative likelihood ratio	0.29
10	
Sensitivity	83
Specificity	61
PPV	22
NPV	96
Positive likelihood ratio	2.1
Negative likelihood ratio	0.27
20	
Sensitivity	79
Specificity	84
PPV	40
NPV	97
Positive likelihood ratio	4.9
Negative likelihood ratio	0.25

Study	Nosrati 2014[218]
30	
Sensitivity	67
Specificity	92
PPV	53
NPV	95
Positive likelihood ratio	8.3
Negative likelihood ratio	0.35
40	
Sensitivity	56
Specificity	94
PPV	56
NPV	94
Positive likelihood ratio	9.3
Negative likelihood ratio	0.46
Area under curve	0.819 (0.731-0.906)
ANC	
Area under curve	0.588 (0.489-0.686)
Leukocyte count	
Area under curve	0.574 (0.477-0671)
Patient characteristics (mean±SD)	
WBC count ($x10^9$/l)	
Infants without SBI (n=353)	12.20 ±6.096
Infants with SBI (n=48)	14.07 ±6.944
Absolute neutrophil count ($x10^9$/l)	
Infants without SBI (n=353)	5.0662 ±4.0005

Study	Nosrati 2014[218]
Infants with SBI (n=48) Platelets (10^9/L) Infants without SBI (n=353) Infants with SBI (n=48) Blood urea nitrogen (mg/dL) Infants without SBI (n=353) Infants with SBI (n=48) CRP (mg/L) Infants without SBI (n=353) Infants with SBI (n=48)	6.5516 ±4.52 446.5 ±161.9 499.7 ±77 8.1 ±3.5 9.3 ±2.7 12.6 ±19.8 48.5 ±36.08
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias Indirectness: none. Risk of bias: very high.

Table 179: OLACIREGUI 2009

Study	Olaciregui 2009[224]
Study type	Retrospective
Number of studies (number of participants)	1 (n=347, n=82 SBI, n=265 minor infection)
Country and setting	Spain. ED (Division of emergency department, Donostia Hospital, San Sebastian)
Funding	Not stated
Duration of study	2 year study period

Study	Olaciregui 2009[224]
Age, gender, ethnicity	Mean age (SD): 47 (24) days. Gender: 196 M/151 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age 4-90 days seen in the ED for fever (rectal temperature>38˚C), in whom a detailed history and physical examination did not reveal a focus of infection, and in whom a blood test was performed. Exclusion: lack of blood test, fever of >7 days' duration antibiotic therapy in the 48 hours prior to diagnosis, and the presence of any type of immunodeficiency.
Index test/s	CRP, leucocyte count
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: **SBI** Leucocyte count ($x10^9/l$) Area under curve >10 $x10^9/l$ Sensitivity Specificity PPV NPV Positive likelihood ratio Negative likelihood ratio >15 $x10^9/l$ Sensitivity Specificity PPV NPV Positive likelihood ratio Negative likelihood ratio	 0.67 (0.63-0.73 73 (4-82) 58 (52-64) 35 (28-42) 87 (82-92) 1.7 0.46 38 (28-48) 84 (80-88) 43 (32-54) 81 (77-85) 2.4 0.74

Study	Olaciregui 2009[224]
CRP (mg/l)	
Area under curve	0.79 (0.75-0.84)
≥20	
Sensitivity	64 (54-74)
Specificity	84 (80-88)
PPV	55 (45-65)
NPV	88 (84-92)
Positive likelihood ratio	4
Negative likelihood ratio	0.43
≥30	
Sensitivity	59 (48-70)
Specificity	89 (85-93)
PPV	63 (52-74)
NPV	87 (83-91)
Positive likelihood ratio	5.4
Negative likelihood ratio	0.46
Bacteraemia/sepsis	
CRP>30mg/l	
Sensitivity	56 (32-80)
Specificity	74 (69-79)
PPV	9.6 (4-16)
NPV	97 (95-99)
Positive likelihood ratio	2.15
Negative likelihood ratio	0.59
Multivariable analysis was performed with the variables that were significant on univariable analysis (leucocytes,	

Study	Olaciregui 2009[224]
neutrophils, CRP and PCT) WCC ($x10^9/l$) Trend estimate SE t-ratio p value OR (95% CI) CRP (≥30mg/l) Trend estimate SE t-ratio p value OR (95% CI) **Patient characteristics** Leucocyte count $x10^9/l$ l) SBI (N=82) Minor infection (n=265) Neutrophil count (/µl) SBI (N=82) Minor infection (n=265) CRP (mg/l) SBI (N=82) Minor infection (n=265)	 0.09 0.03 3.08 <0.001 1.1 (1.03 to 1.16) 1.84 0.35 5.37 <0.001 6.3 (3.1 to 12.8) 14.635 (7.596) 10.084 (4.689) 7.738 (5.823) 4.341 (6.714) 59.3 (55.9) 14.7 (18.8)

Study	Olaciregui 2009[224]
General limitations (according to QUADAS 2)	Retrospective design, possible selection bias. Indirectness: none. Risk of bias: very high.

Table 180: PAVCNICK 2004

Study	Pavcnick 2004[231]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=60, n=37 SIRS/sepsis, n=27 SIRS/no sepsis)
Country and setting	Slovenia. NICU/PICU (University Medical Center, Ljubljana)
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Median age (range): 2.8 (13 hours–13 years) days. Neonates aged 0-28 days: 41 (68%). Neonates aged <48 hours: 12 (10%). Children aged >28 days: 19 (32%). Gender: 68 M/49 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with SIRS and suspected infection. SIRS defined as at least 2 of the following: hypothermia, hyperthermia, tachycardia, tachycardia/hyperventilation, leucocytosis/leukopenia, or more than 10% immature (band) form. Exclusion: premature neonates, surgery in late 7 days, antibiotic therapy for >24 hours prior to PICU admission.
Index test/s	CRP
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis

Study	Pavcnick 2004[231]
Results: CRP (cut-off 23 mg/l) Area under curve Sensitivity Specificity PPV NPV **Patient characteristics** SIRS/sepsis (n=33) CRP (mg/l), median (range) SIRS/no infection (n=33) CRP (mg/l), median (range)	 0.84 (0.57-0.89) 70 89 53 94 33 (3-468) 9 (0-158)
General limitations (according to QUADAS 2)	Observational design, possible selection bias (possible convenience sample), small study size. Indirectness: none. Risk of bias: very high.

Table 181: PRATT 2007

Study	Pratt 2007[241]
Study type	Prospective study
Number of studies (number of participants	1 (n=119)
Country and setting	USA. Paediatric ED (single-centre, tertiary care children's hospital)
Funding	Not stated
Duration of study	18-month study period (January 2002 to July 2003)

Study	Pratt 2007[241]
Age, gender, ethnicity	Median age: 10 months, range 1 to 34 months. Gender: 55% female. Ethnicity: not stated.
Patient characteristics	Inclusion: a sample of children aged 1-36 months who presented to the duPont Hospital for Children ED with reported or documented fever ≥39C and who after careful history and physical exam by house staff and attending paediatric emergency medicine physicians were found to have no localising source of fever, were eligible to be enrolled Exclusion: explainable cause of fever such as acute otitis media, acute pharyngitis, acute respiratory tract infection, acute gastroenteritis and those who had a positive viral study, history of antibiotic use during the past 10 days, known underlying immunologic disease, vaccination during the previous 2 days
Index test	CRP, white blood cell count, absolute neutrophil count
Reference standard	N/A
Target condition	Hospital diagnosis of severe bacterial sepsis
Results: **CRP (≤12 hours, cut-off 30 mg/l)** Sensitivity Specificity **CRP (≤12 hours, cut-off 50 mg/l)** Sensitivity Specificity **CRP (≤12 hours, cut-off 70 mg/l)** Sensitivity Specificity **WBC (≤12 hours, cut-off 10 x10^9/l)** Sensitivity Specificity	 67 (24-94) 74 (58-86) 50 (14-86) 92 (78-98) 33 (6-76) 97 (85-100) 50 (14-86) 33 (20-50)

Study	Pratt 2007[241]
WBC (≤12 hours, cut-off 15 x10^9/l)	
Sensitivity	17 (1-63)
Specificity	67 (50-80)
WBC (≤12 hours, cut-off 17.5 x10^9/l)	
Sensitivity	17 (1-63)
Specificity	74 (58-86)
ANC (≤12 hours, cut-off 10 x10^9/l)	
Sensitivity	17 (1-63)
Specificity	77 (60-88)
ANC (≤12 hours, cut-off 11 x10^9/l)	
Sensitivity	17 (1-63)
Specificity	82 (66-92)
ANC (≤12 hours, cut-off 12 x10^9/l)	
Sensitivity	17 (1-63)
Specificity	85 (69-94)
CRP (>12 hours, cut-off 30 mg/l)	
Sensitivity	100 (72-100)
Specificity	63 (50-75)
CRP (>12 hours, cut-off 50 mg/l)	

Study	Pratt 2007[241]
Sensitivity	82 (48-97)
Specificity	79 (67-88)
CRP (>12 hours, cut-off 70 mg/l)	
Sensitivity	73 (40-93)
Specificity	81 (69-89)
WBC (>12 hours, cut-off 10 x10^9/l)	
Sensitivity	100 (72-100)
Specificity	47 (34-60)
WBC (>12 hours, cut-off 15 x10^9/l)	
Sensitivity	82 (48-97)
Specificity	69 (56-80)
WBC (>12 hours, cut-off 17.5 x10^9/l)	
Sensitivity	73 (40-93)
Specificity	79 (67-88)
ANC (>12 hours, cut-off 10 x10^9/l)	
Sensitivity	64 (32-88)
Specificity	81 (68-89)
ANC (>12 hours, cut-off 11 x10^9/l)	
Sensitivity	55 (25-82)

Study	Pratt 2007[241]
Specificity **ANC (>12 hours, cut-off 10 x10^9/l)** Sensitivity Specificity **CRP (≤12 hours)** Are under curve **CRP (>12 hours)** Are under curve **WBC (≤12 hours)** Are under curve **WBC (>12 hours)** Are under curve **ANC (≤12 hours)** Are under curve **ANC (>12 hours)** Are under curve	81 (68-89) 55 (25-82) 84 (72-92) 0.68 (95%CI 0.39-0.97) 0.92 (95%CI 0.85-0.99) 0.37 (95%CI 0.11-0.64) 0.85 (95%CI 0.75-0.94) 0.42 (95%CI 0.15-0.69) 0.83 (95%CI 0.72-0.94)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 182: PULLIAM 2001

Study	Pulliam 2001[243]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=77: SBI=14, no SBI n=63)
Country and setting	USA. ED (DuPont Hospital for Children)
Funding	Research grant W20-8619 from the Nemours Research Programs, Wilmington, Delaware.
Duration of study	10 months
Age, gender, ethnicity	Mean age (range): 9.7 (1–35) months. Gender: SBI: 71.4%F n=14, without SBI: 52.4%F n=63. Ethnicity: not stated.
Patient characteristics	Inclusion: ages 1-36 months, temperature ≥39˚C; clinically undetectable source of fever. Exclusion: acute otitis media, acute pharyngitis, clinical pneumonia, acute respiratory tract infection, acute gastroenteritis, history of antibiotic use during the past 7 days, known underlying immunologic disease, vaccination during the previous 2 days.
Index test/s	ANC, CRP, WBC
Reference standard	N/A
Target condition	Hospital diagnosis of SBI (bacteraemia, meningitis, UTI, pneumonia, septic arthritis, osteomyelitis)
Results:	
CRP	
Area under curve	0.905 (SE 0.05, 95% CI 0.808, 1.002)
ANC	
Area under curve	0.805 (SE 0.051, 95% CI 0.705, 0.905)
WBC	
Area under curve	0.761 (SE 0.068, 95% CI 0.628, 0.895)

Study	Pulliam 2001[243]
WBC (15x10^9/l)	
Sensitivity	64 (35.8-85.9)
Specificity	67 (53.6-77.7)
PPV	30 (14.7-49.4)
NPV	89 (76.9-96.5)
ANC (10.2 x10^9/l)	
Sensitivity	71 (42.2-90.3)
Specificity	76 (63.6-85.6)
PPV	40 (21.2-61.3)
NPV	92(81.5-99.0)
CRP (70mg/l)	
Sensitivity	79 (49.0-94.2)
Specificity	91 (79.8-96.0)
PPV	65 (38.3-85.8)
NPV	95 (86.1-99.0)
Patient characteristics (mean+SD)	
WBC (x10^9/l)	
Patients with SBI (n=14)	22.3 (9.8)
Patients without SBI (n=63)	12.5 (7.0)
Polymorphonuclear cells (%)	
Patients with SBI (n=14)	56.3 (7.6)
Patients without SBI (n=63)	52.5 (15.3)
Band count (%)	
Patients with SBI (n=14)	5.7 (5.8)
Patients without SBI (n=63)	3.6 (4.2)

Study	Pulliam 2001[243]
ANC ($x10^9$/l) Patients with SBI (n=14) Patients without SBI (n=63) CRP concentration, median (range) mg/L Patients with SBI (n=14) Patients without SBI (n=63)	 13.9 (6.1) 7.3 (5.4) 97 (2, 372) 10 (2, 207)
General limitations (according to QUADAS 2)	Observational design, small sample size, convenience sample. Indirectness: none. Risk of bias: very high.

Table 183: REY 2007

Study	Rey 2007[246]
Study type	Prospective observational cohort
Number of studies (number of participants)	1 (n=94, n (samples)= 359, negative n=85, SIRS n=92, localised infection n=57, sepsis 43, severe sepsis n=39, septic shock n=43)
Country and setting	Spain. PICU (Hospital Universitario Central de Asturias)
Funding	Not stated
Duration of study	2 years
Age, gender, ethnicity	Mean age (range): 62 (1–203) months. Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: not stated Exclusion: not stated

Study	Rey 2007[246]
Index test/s	Leucocyte count, CRP
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: Leucocyte count Area under curve CRP Area under curve CRP>56.5mg/l Sensitivity Specificity CRP >65.5mg/l Sensitivity Specificity CRP according to diagnosis CRP≤2 CRP 2-6.5 CRP 6.5-27.9 CRP >27.9	 0.532 (0.462-0.602) 0.750 (0.699-0.802) 72% 66% 64% 73% Negative n=52, SIRS n=36, localised infection n=9, sepsis n=6, severe sepsis n=3, septic shock n=1 Negative n=26, SIRS n=25, localised infection n=20, sepsis n=19, severe sepsis n=10, septic shock n=6 Negative n=6, SIRS n=26, localised infection n=21, sepsis n=13, severe sepsis n=17, septic shock n=23 Negative n=0, SIRS n=2, localised infection n=6, sepsis n=5, severe sepsis n=9, septic shock n=13
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 184: RUDINSKY 2009

Study	Rudinsky 2009[248]
Study type	Retrospective cohort with nested case controls

Study	Rudinsky 2009[248]
Number of studies (number of participants)	1 (n=985 of which n=132 with SBI)
Country and setting	USA. ED (tertiary care military hospital, California)
Funding	Not stated
Duration of study	1 year
Age, gender, ethnicity	Median age (range): 12 (8–17). Gender: 55% male. Ethnicity: not stated.
Patient characteristics	Inclusion: 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 Exclusion: not stated
Index test/s	WBC
Reference standard	N/A
Target condition	Hospital diagnosis of SBI
Results: WBC $x10^9$/l cutoff <5 Sensitivity Specificity LR+ LR- <5 or >15 Sensitivity Specificity LR+ LR- >10 Sensitivity Specificity	 0.05 (0.02-0.11) 0.92 (0.90-0.94) 0.60 (0.25-1.48) 1.0 (0.99-1.07) 0.47 (0.37-0.57) 0.66 (0.63-0.70) 1.41 (1.11-1.78) 0.79 (0.66-0.95) 0.72 (0.62-0.80) 0.47 (0.43-0.51)

Study	Rudinsky 2009[248]
LR+ LR- >15 Sensitivity Specificity LR+ LR- >20 Sensitivity Specificity LR+ LR- >25 Sensitivity Specificity LR+ LR-	1.34 (1.17-1.55) 0.61 (0.45-0.82) 0.42 (0.33-0.52) 0.74 (0.71-0.78) 1.66 (1.28-2.15) 0.77 (0.66-0.91) 0.16 (0.10-0.25) 0.93 (0.91-0.95) 2.3 (1.36-3.90) 0.9 (0.83-0.98) 0.02 (0.00-0.07) 0.98 (0.96-0.99) 0.79 (0.18-3.44) 1.01 (0.98-1.03)
General limitations (according to QUADAS 2)	Retrospective design Indirectness: none. Risk of bias: very high.

Table 185: SEGAL 2014

Study	Segal 2014[258]
Study type	Prospective observational

Study	Segal 2014[258]
Number of studies (number of participants)	1 (n=373 of which n=103 had bacterial infection)
Country and setting	Israel. ED of an urban academic hospital.
Funding	Not stated
Duration of study	3 months
Age, gender, ethnicity	Median age (range): 3 (1–91). Gender: 68 M/49 F. Ethnicity: not stated.
Patient characteristics	Inclusion: age 0-16 years with a rectal or oral temperature of ≥38˚C documented in the ED. Exclusion: no objective documentation of fever at home (e.g. tactile temperature) or those who used fever measurement methods other than rectal or oral readings, treatment with antibiotics in the past 2 days, known immunodeficiency.
Index test/s	CRP
Reference standard	N/A
Target condition	Hospital diagnosis of bacteraemia
Results: ≤ 12 hours (n=74, cut off 21mg/L) Area under curve (%[95%CI]) Sensitivity (%[95%CI]) Specificity (%[95%CI]) LR+ (%[95%CI]) Post-test probability (%[95%CI]) > 12-24 hours (n=67, cut off 60mg/L) Area under curve (%[95%CI]) Sensitivity (%[95%CI]) Specificity (%[95%CI]) LR+ (%[95%CI]) Post-test probability (%[95%CI]) > 24-48 hours (n=51, cut off 107mg/L) Area under curve (%[95%CI])	 76 (63 to 88) 72 (52 to 87) 77 (64 to 86) 3.1 (1.8 to 5.5) 76 (62-89) 81 (69 to 92) 68 (48 to 83) 83 (69 to 92) 4.2 (2 to 8.4) 80 (63-96) 87 (77 to 96)

Study	Segal 2014[258]
Sensitivity (%[95%CI])	68 (47 to 84)
Specificity (%[95%CI])	90 (73 to 96)
LR+ (%[95%CI])	6.8 (2.1 to 20)
Post-test probability (%[95%CI])	87 (62-99)
> 48 hours (n=98, cut off 126mg/L)	
Area under curve (%[95%CI])	90 (84 to 97)
Sensitivity (%[95%CI])	80 (64 to 90)
Specificity (%[95%CI])	94 (85 to 97.5)
LR+ (%[95%CI])	13.3 (4.8 to 33)
Post-test probability (%[95%CI])	93 (82-99)
Pre-test probability 27%	
Patient characteristics: median (range)	
ANC (x103 x10^9/l)	
Bacterial (n=103)	
Viral (n=189)	11.9 (0.8-40.9)
Acute otitis media (n=30)	4.7 (0.8-21.8)
	6.2 (1.6-16.3)
CRP (md/L)	
Bacterial (n=103)	
Viral (n=189)	147 (5-670)
Acute otitis media (n=30)	18 (3-283)
	32 (5-163)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 186: SHAOUL 2008

Study	**Shaoul 2008**[263]
Study type	Retrospective data collection
Number of studies (number of participants)	1 (n=425 of which n=50 had a positive blood culture)
Country and setting	Israel. NICU (Dunedin Hospital)
Funding	Not stated
Duration of study	Not stated
Age, gender, ethnicity	Median age in months (IQR): positive blood culture: 9 (4, 22.2), contaminated blood culture: 17 (8,32), negative blood culture: 20 (10.2, 36.8). Gender: not stated. Ethnicity: not stated.
Patient characteristics	Inclusion: admission or discharge from paediatric ward with an infectious disease e.g. pneumonia, acute gastroenteritis, UTI or acute otitis media. Exclusion: chronic disease, immunodeficiency
Index test/s	ANC, CRP, WBC
Reference standard	Blood culture
Target condition	Hospital diagnosis of bacteraemia
Results: CRP >85mg/L Sensitivity Specificity PPV CRP and ANC >10 x10^9/l or WBC >15 x10^9/l Sensitivity Specificity PPV CRP and ANC >10 x10^9/l and WBC >15 x10^9/l	 70% 67.6% 60.3% 84% 27% 48.8%

Study	Shaoul 2008[263]
Sensitivity	36%
Specificity	84.5%
PPV	62.1%
Patient characteristics	
CRP (mg/L)	
Positive blood culture	101.0 (34.1-200.0)
Contaminated blood culture	30.9 (9.5-86.4)
Negative blood culture	34.3 (9.6-88.6)
WBC ($x10^9$/l)	
Positive blood culture	177750 (11300-23725)
Contaminated blood culture	14200 (10300-18300)
Negative blood culture	16000 (11000-20675)
ANC ($x10^9$/l)	
Positive blood culture	10008 (6248-16475)
Contaminated blood culture	8210 (5720-13157)
Negative blood culture	9325 (5546-14517)
General limitations (according to QUADAS 2)	Retrospective design, small sample size. Indirectness: none. Risk of bias: very high.

Table 187: SHERWIN 2008

Study	Sherwin 2008[269]
Study type	Prospective cohort

Study	Sherwin 2008[269]
Number of studies (number of participants)	1 (n=164 of which n=52 with late onset sepsis)
Country and setting	New Zealand. NICU (Dunedin Hospital)
Funding	Not stated
Duration of study	52 month-study period
Age, gender, ethnicity	Median age (range): 3 (1–91). Gender: 68 M/49 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with suspected sepsis and commenced on antibiotics Exclusion: no informed consent, difficulty finding laboratory data
Index test/s	ANC, CRP, Platelet count, WBC
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: ANC (10 x10^9/l)	 AUC 0.63 (0.46-0.81) Sensitivity 33 (20-47) Specificity 93 (86-100) PPV 75 (63-87) NPV 69 (56-82)
CRP (cut-off 18mb/l)	AUC 0.72 (0.55-0.90) Sensitivity 41 (25-57) Specificity 94 (87-100) PPV 88 (77-98) NPV 63 (45-79)

Study	Sherwin 2008[269]
Platelets (100 x10^9/l)	AUC 0.70 (0.55-0.86) Sensitivity 18 (7-29) Specificity 93 (86-100) PPV 60 (46-74) NPV 66 (52-80)
WBC (<4 or >20 x10^9/l)	AUC 0.50 (0.33-0.68) Sensitivity 22 (10-34) Specificity 75 (62-88) PPV 36 (22-50) NPV 60 (46-74)
General limitations (according to QUADAS 2)	Observational design, possible selection bias (possible convenience sample). Indirectness: none. Risk of bias: very high.

Table 188: SIMON 2008

Study	Simon 2008[274]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=64: bacterial SIRS n=25, non-bacterial SIRS n=39)
Country and setting	Canada. PICU (Sainte-Justine Hospital)
Funding	Not stated
Duration of study	6 month-study period
Age, gender, ethnicity	Mean age (SD): 80 (71.1) months. Gender: M 47%. Ethnicity: not stated.

Study	Simon 2008[274]
Patient characteristics	Inclusion: SIRS criteria were defined as (1)a) temperature ≥38˚C or <36 ˚C rectal; b) abnormal white blood cell count:> 12 x 10^9/L or <4x 10^9/L or >10% bands; c) heart rate greater than mean for age+2SD (4) respiratory rate greater than mean for age +2SD (4) or PCO2<32mmHg. Patients meeting at least two of the four criteria, including either abnormal temperature or abnormal white blood cell count, were considered for inclusion. Exclusion: never been discharged home from a neonatology unit, post conception age <40 weeks, younger than 3 days of age or older than 18 years, already been enrolled in this study, enrolled in another study that could interfere with this study, refusal of consent by parent/guardian or physician, suspected or confirmed brain death, anticipated discharged from PICU in the following 24 hours, allowed time for inclusion exceeded, parents not available, patient out of the unit, screening done >24 hours after beginning of SIRS.
Index test/s	CRP
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: CRP Area under curve CRP threshold 20 mg/L Sensitivity Specificity PPV NPV CRP threshold 40 mg/L Sensitivity Specificity PPV NPV CRP threshold 60 mg/L Sensitivity	 0.65 95% 24% 44% 90% 95% 42% 51% 94% 59%

Study	Simon 2008[274]
Specificity PPV NPV Patient characteristics: mean (SD) CRP level (mg/L) Bacterial SIRS (n=25) Non-bacterial SIRS (n=39)	55% 46% 68% 85.5 (55.8) 61.8 (50.1)
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 189: THAYYIL 2005

Study	Thayyil 2005[280]
Study type	Prospective observational
Number of studies (number of participants)	1 (n=72: SBI n=8, possible bacterial infection n=19, viral/ possible viral infection n=45)
Country and setting	UK. Paediatric units of 2 university hospitals (University hospital of North Tees and Hartlepool)
Funding	North Tees and Hartlepool R&D Department
Duration of study	Not stated
Age, gender, ethnicity	Median age (SD): 18.5 months (1-36 months). Gender: not stated Ethnicity: not stated.
Patient characteristics	Inclusion: age 1 to 36 months with fever >39˚C without localising signs. Exclusion: children who had taken antibiotics in the past 72 hours, immune deficiency, fever >7 days.
Index test/s	CRP, ANC, WBC
Reference standard	N/A
Target condition	Hospital diagnosis of SBI
Results:	

Study	Thayyil 2005[280]
ANC	
Area under curve	0.52 (95%CI 0.36-0.71)
WBC	
Area under curve	0.56 (95%CI 0.38-0.74)
WBC >15x10^9/l	
Sensitivity	50
Specificity	53.1
NPV	89.5
PPV	11.8
LR-	0.94 (8% post-test probability)
LR+	1.1 (10% post-test probability)
CRP	
Area under curve	0.66 (95%CI 0.42-0.91)
CRP >50mg/l	
Sensitivity	75
Specificity	68.7
NPV	95.6
PPV	23
LR-	0.36 (3% post-test probability)
LR+	2.4 (20% post-test probability)
Pretest probability of SBI=11%	
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 190: TRAUTNER 2006

Study	Trautner 2006[282]
Study type	Cross-sectional observational
Number of studies (number of participants)	1 (n=103: SBI n=20, laboratory-proven viral illness n=22, febrile illness with negative cultures n=62)
Country and setting	USA. ED (The Texas Children's Hospital)
Funding	US Public Health Service grant HD42014
Duration of study	2 years
Age, gender, ethnicity	Median age (IQR): 17 months (11-25 months). Gender: 57M/46F. Ethnicity: black n=49, Hispanic n=38, White n=12, Asian n=4.
Patient characteristics	Inclusion: all children <18 years of age presenting to paediatric ED with rectal temperature ≥106˚F Exclusion: none
Index test/s	ANC, WBC
Reference standard	N/A
Target condition	Hospital diagnosis of SBI
Results: Predictors of bacterial illness n=20 WBC count, x10^9/l <15 Frequency, n (%) ≥15 Frequency, n (%) OR (95%CI) ANC, x10^9/l <10 Frequency, n (%) ≥10 Frequency, n (%) OR (95%CI)	 11 (55) 9 (45) 0.78 (0.29-2.08) 9 (45) 11 (55) 1.11 (0.41-2.96)

Study	Trautner 2006[282]
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

H.2.1.3 Lactate

Table 191: CASSERLY 2015

Study	Casserly 2015[46]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (19,945)
Country and setting	USA; 218 hospitals
Funding	Academic grant; no financial conflicts of interest
Duration of study	5 years
Age, gender, ethnicity	unclear
Patient characteristics	Inclusion: suspected infection, 2 or more systemic inflammation criteria; one or more organ dysfunction criteria Exclusion: not reported
Prognostic variable	Initial lactate (with or without hypotension)
Target condition	In-hospital mortality

Study	Casserly 2015[46]
Results:	**Unadjusted** OR (95% CI) for in-hospital mortality was 1.34(1.14-1.58) for high lactate(>4 mmol/l) combined with being non-hypotensive compared to low/moderate lactate(≤4 mmol/l) combined with being non-hypotensive OR (95% CI) for in-hospital mortality was 1.36(1.24-1.50) for low/moderate lactate(≤4 mmol/l) combined with being hypotensive compared to low/moderate lactate(≤4 mmol/l) combined with being non-hypotensive OR (95% CI) for in-hospital mortality was 2.63(2.38-2.91) for high lactate(>4 mmol/l) combined with being hypotensive compared to low/moderate lactate(≤4 mmol/l) combined with being non-hypotensive **Diagnostic accuracy** From risk data, at a threshold of 4, the diagnostic accuracy was calculated from the following raw data: TP: 2635, FN: 3827, FP: 3633, TN: 9850.
General limitations	Lack of evidence that physicians treating patients were blinded to the lactate status.

Table 192: CATERINO 2009

Study	Caterino 2009[51]
Study type and analysis	Prospective cohort study – split-cohort study with derivation arm involving a logistic regression to inform a diagnostic algorithm (risk tool) and the validation arm to assess the accuracy of that derived risk tool.
Number of studies (number of participants)	1(935 in derivation cohort; 2015 in validation cohort)
Country and setting	USA; ED patients
Funding	No financial conflicts of interest
Duration of study	2 years for derivation and 1 year for validation
Age, gender, ethnicity	Derivation; 28.8% > 85; validation 27.3% > 85; 57% female in derivation cohort and 55.6% in validation cohort;
Patient characteristics	Most common co-morbid conditions in both cohorts were CAD, CHF, COPD, Diabetes mellitus, malignancy, immune-compromise and dementia; 34% had temperature on admission > 100.4F; WBC count was >15000/iL in 29.8% of derivation cohort and 23.7% of validation cohort; 28.9% of the derivation cohort and 16.2% of the validation cohort had 2 or more organ

Study	Caterino 2009[51]
	failures. Inclusion: age >65; admitted to hospital and presenting at ED with suspected infection;
Prognostic variable	Lactate levels
Target condition	Mortality within 30-days
Results:	**Derivation cohort** **Lactate was not included in the final model as it did not have a significant association with mortality after adjustment for other predictors** (ethnicity, co-morbidities, vital signs, laboratory values (for example of lactate, platelets, creatinine) respiratory failure, cardiac failure). The unadjusted data for lactate was: risk of death if lactate >4 mmol/l was 16/56, risk of death if lactate was <4 mmol/l was 40/879. RR= 6.21; From above the diagnostic accuracy data were extracted: TP:16, FN: 40, FP: 40, TN: 839; sensitivity: 0.29, specificity 0.95 **Validation cohort** The risk tool was created from the final logistic regression, involving 5 predictors: respiratory failure, tachycardia, cardiac failure, pre-existing terminal illness and platelets <150,000/uL. The weightings and exact details of the algorithm are not reported. In the separate validation cohort the risk tool had a C statistic of 0.74
General limitations	Outcome data collected blind.

Table 193: FEMLING 2014

Study	Femling, 2014[86]
Study type and analysis	Prospective cohort study
Number of studies (number of participants)	1(378)
Country and setting	New Mexico, USA; ICU patients referred from level 1 trauma centre ED
Funding	No financial conflicts of interest

Study	Femling, 2014[86]
Duration of study	2.5 years
Age, gender, ethnicity	Age: 305; male 53.5%; ethnicity unreported
Patient characteristics	Inclusion: admission to MICU with an admission diagnosis of sepsis or severe sepsis; Exclusion: inadequate arrival information in electronic medical record
Prognostic variable	Lactate
Target condition	28-day mortality
Results:	**Unadjusted** Survivors lactate 5.6 mmol/l (IQR: 3.1-8.3)[n=266]; non-survivors 4.0 (2.3-5.9)[n=112], p<0.01 72/112 people dying had lactate >4 and 127/266 surviving had with lactate >4 **Diagnostic accuracy** From raw risk data above, at threshold of 4, TP: 72, FN: 60, FP: 127, TN: 139; sens: 0.54; spec: 0.52
General limitations	

Table 194: FREUND 2012

Study	Freund 2012[94]
Study type	Prospective cohort
Number of studies (number of participants)	>15 years presenting to the ED with suspected infection.
Country and setting	France. ED.
Funding	None.
Duration of study	12 months.
Age, gender, ethnicity	Gender M/F=272/190 Mean age = 64±20

Study	Freund 2012[94]
Patient characteristics	HIV=15 Undergoing cancer treatment=58 Multiple sclerosis=7 Systemic vasculitis on-going corticosteroid therapy=4 Temperature C = 37.3±1.1 Heart rate (bpm) = 98±23 Systolic blood pressure (mmHg) = 127±23 Pulse oximetry (median and IQR) = 95 (92-98) Temperature >38C or <36C = 130/457 Heart rate >90bpm = 283/457 Systolic blood pressure <90mmHg = 25/457 Pulse oximetry <90% = 76/457 WBC (per mm^3) = 11313±7162 Creatinine (µmol.L^{-1}) = 111±113 Lactate (mmol.L^{-1}) = 2.02±1.71 Lactate >2 = 140/462 Lactate >4 = 35/462 PCT (ng.mL^{-1}) = 0.25 (0.11-1.14) PCT >0.25 = 236/462 PCT >2 = 88/462 nSIRS 0 = 73/462 nSIRS 1 = 133/462 nSIRS 2 = 153/462 nSIRS 3 = 81/462 nSIRS 4 = 22/462
Index test/s	Lactate WBC count
Reference standard	NA
Target condition	Death or ICU admission

Study	Freund 2012[94]
Results	At threshold of 2 mmol/l for initial lactate sensitivity was 0.54(0.45-0.64) and specificity was 0.76(0.72-0.81)

Table 195: HOEBOER 2012

Study	Hoeboer 2012[124]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=101)
Country and setting	Netherlands. ICU (VU University Medical Center, Intensive Care, Amsterdam)
Funding	Not stated
Duration of study	5-year period, 28-day follow-up for mortality
Age, gender, ethnicity	Group 1 (n=44) Age median (range): 63 (22-77). Gender: 32 M/12 F. Ethnicity: not stated. Group 2 (n=45) Age median (range): 61 (19-81). Gender: 34 M/11 F. Ethnicity: not stated. Group 3 (n=12) Age median (range): 67 (19-81). Gender: 3 M/9 F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients presenting with new onset fever in the 24-bed mixed medical/surgical ICU, new onset fever defined as body temperature ≥38.3ºC, preceded by a period of ≥24 h in the absence of fever (<37.5ºC), enrolment followed within 12 h after inclusion criteria were met. Group 1: without infection or with possible infection but negative cultures. Group 2: with probable or proven local infection without blood stream infection (BSI). Group 3 with BSI irrespective of local infection. Exclusion: pregnancy, life expectancy of less than 24 h.
Index test/s	Bloodstream infection Day 0-2 CRP mg/l (cut-off 196 mg/l) Lactate mmol/l (cut-off 1.5 mmol/l) WBC x 10^9/l (cut-off 20.3)

Study	Hoeboer 2012[124]
	Septic shock Day 0-7 CRP mg/l (cut-off 208 mg/l) Mortality Day 0-28 Lactate mmol/l (cut-off 1.7 mmol/l)
Reference standard	N/A
Target condition	Hospital diagnosis of: probable or proven local infection BSI, BSI irrespective of local infection.
Results: Bloodstream infection Day 0-2, prediction by peak values of biomarkers	
CRP, mg/l (cut-off 196 mg/l)	
Area under curve	0.74
Sensitivity	92
Specificity	60
PPV	23
NPV	98
Lactate, mmol/l (cut-off 1.5 mmol/l)	
Area under curve	0.75
Sensitivity	83
Specificity	61
PPV	23
NPV	96
WBC, x 10^9/l (cut-off 20.3)	
Area under curve	0.70
Sensitivity	58
Specificity	84
PPV	33
NPV	94

Study	Hoeboer 2012[124]
Septic shock Day 0-7, prediction by peak values of biomarkers	
CRP, mg/l (cut-off 208 mg/l)	
Area under curve	0.75
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)	
Area under curve	0.71
Sensitivity	60
Specificity	75
PPV	44
NPV	85
Multivariable analysis for high risk infection	
Peak CRP, mg/l	P= 0.033
Peak lactate, mmol/l	P= 0.001
Peak values of biomarkers per group, median (range)	
Day 0-2 infection	
CRP, mg/l	Group 1: 142 (27-440). Group 2: 153 (5-484). Group 3: 231 (71-436).
Lactate, mmol/l	Group 1: 1.3 (0.5-2.3). Group 2: 1.4 (0.5-13.1). Group 3: 1.9 (1.1-3.9).
WBC, x 10^9	Group 1: 13.2 (5.5-38.5). Group 2: 12.8 (0.2-25.7). Group 3: 20.6 (2.5-81.7).

Study	Hoeboer 2012[124]
Peak values of biomarkers, no septic shock (n=67) versus septic shock (n=34) **Day 0-7** CRP, mg/l Lactate, mmol/l WBC, x 10^9	No septic shock: 146 (5-440). Septic shock: 243 (5-484). p <0.001. No septic shock: 1.4 (0.5-2.5). Septic shock: 1.6 (0.8-13.1). p=0.07. No septic shock: 12.9 (4.8-38.5). Septic shock: 15.0 (0.2-81.7). p=0.16.
Peak values of biomarkers, survivors (n=75) versus non-survivors (n=26) **Day 0-28** CRP, mg/l Lactate, mmol/l WBC, x 10^9	Survivors: 177 (5-440). Non survivors: 201 (38-484). p=0.303. Survivors: 1.3 (0.5-3.5). Non survivors: 1.8 (0.9-13.1). p=0.002. Survivors: 12.5 (2.5-27.5). Non survivors: 16.8 (0.2-81.7). p=0.077.

Table 196: JANSEN 2009A

Study	Jansen 2009A[134]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=394 patients: n=140 patients with sepsis, n=123 patients with low-oxygen transport, n=131 patients with no sepsis or low-oxygen transport)
Country and setting	The Netherlands. General ICU (2 centre study: Erasmus MC University Medical Center, Rotterdam, Gelre Hospitals, Lukas site, Apeldoorn)
Funding	Not stated
Duration of study	2-year period, 24-hour survival
Age, gender, ethnicity	Sepsis group Mean (SD) age: 67 (14). Gender: 56 M/44 F. Ethnicity: not stated.
Patient characteristics	Inclusion: sepsis based on Acute Physiology and Chronic Health Evaluation (APACHE) III scoring system.

Study	Jansen 2009A[134]
Lactate level mean (SD), mmol/l	At ICU admission: 2.9 (2.3) 12 hours after admission: 2.5 (2.6) 24 hours after admission: 2.2 (2.1)
Lactate level mean (SD)	At ICU admission: 44% 12 hours after admission: 31% 24 hours after admission: 26%
Hospital length of stay mean (SD), days	28 (30)
In-hospital mortality	36%
Index test/s	Lactate (hyperlactatemia ≥2.5 mmol/l)
Reference standard	N/A
Target condition	28-day mortality
Results:	At ICU admission: 0.52 for initial lactate For the initial lactate threshold of 2.5 mmol/l: TP: 18, FN: 23, FP: 42, TN: 55 (extracted from raw risk data 18/60 vs 23/78): from this sensitivity (0.44)and specificity (0.57) were calculated
General limitations	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Table 197: KIM 2013A

Study	Kim 2013A[151]
Study type and analysis	Retrospective cohort
Number of studies (number of participants)	1 (65)

Study	**Kim 2013A[151]**
Country and setting	South Korea; paediatric ICU
Funding	None reported
Duration of study	4.5 years
Age, gender, ethnicity	Age: 119.9 months (1month to 19 years) 58 % male Ethnicity not reported
Patient characteristics	100% required inotropic or vasopressor support; 93.8% had underlying disease (47.5% hemato-oncological, 14.8% neurological, 9.8% cardiac, 9.8% chronic kidney disease, 6.6% GI disease, 6.6% post liver transplantation). Inclusion: admitted to PICU with septic shock, as defined by IPSCC; Exclusion: not reported
Index tests	Initial lactate Lactate clearance
Target condition	28-day mortality
Results:	Unadjusted Non-survivors (n=17) lactate 6.16(4.87) mmol/l; survivors(n=48) lactate 3.13(2.79) mmol/l Patients with initial lactate levels >5mmol/l showed a significantly higher 28-day mortality rate (compared to $\leq$5 mmol/l) with an OR of 3.38(1.04-10.9) [raw risk data 8/17 vs 10/48] Diagnostic accuracy analysis Initial lactate AUC (95% CI): 0.699(0.549-0.849) for predicting 28-day mortality For the threshold of 5 mmol/l: TP: 8, FN: 10, FP: 9, TN: 38 (extracted from raw risk data 8/17 vs 10/48): from this sensitivity (0.44)and specificity (0.81) were calculated lactate clearance AUC (95% CI): 0.719(0.558-0.881) for predicting 28-day mortality
General limitations	Observational design, small sample size Indirectness: none. Risk of bias: very high.

Table 198: LINDER 2009

Study	**Linder 2009[174]**
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=233)
Country and setting	Sweden. Hospital (Clinic for Infectious Diseases at Lund University Hospital). Patients with fever and suspected infection
Funding	Swedish Research Council (projects 7480 and 13413), the Royal Physiographic Society, Lund, the Swedish Government Funds for Clinical Research (ALF), the University Hospital in Lund, Hansa Medical AB, and the Foundations of Greta and Johan Kock, Alfred Osterlund, and Torsten and Ragnar Soderberg.
Duration of study	1-year period
Age, gender, ethnicity	Severe sepsis with septic shock (n=26). Age: median (range): 65 (32-90) years. Gender: 50% M/50% F. Ethnicity: not stated. Severe sepsis without septic shock (n=44). Age: median (range): 64 (18-91) years. Gender: 55% M/45% F. Ethnicity: not stated. Sepsis (n=100). Age: median (range): 57 (20-90) years. Gender: 45% M/55% F. Ethnicity: not stated. Infection without SIRS (n=43). Age: median (range): 44 (18-92) years. Gender: 35% M/65% F. Ethnicity: not stated. SIRS without infection (n=20). Age: median (range): 74 (33-90) years. Gender: 90% M/10% F. Ethnicity: not stated.
Patient characteristics	Inclusion criteria: body temperature of 38°C and a suspected infection as judged by the attending physician, 3 signs of the systemic inflammatory response syndrome (SIRS; body temperature≥38°C; WBC count >12x10^9 cells/L or <4 x10^9 cells/L; pulse rate >90 beats/min; and respiratory rate >20 breaths/min) or a significant hypotension (systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline). Exclusion criteria: antibiotic treatment for >24 h, neutropenia because of hematological malignancy, immunosuppressive therapy, and age <18 years.
Index test/s	Lactate
Reference standard	N/A
Target condition	Diagnosis of severe sepsis with or without septic shock
Results: Lactate >2.5 mmol/litre	

Study	Linder 2009[174]
Sensitivity	25.0
Specificity	97.5
PPV	81.0
NPV	88.4
AUC	79 (73-85)
CRP >100 mg/litre	
Sensitivity	75.7
Specificity	56.2
PPV	37.0
NPV	89.2
AUC	68.5 (61.1-75.9)
WBC >14 x10^9 cells/L	
Sensitivity	34.3
Specificity	75.6
PPV	35.4
NPV	72.0
AUC	51.6 (42.9-60.3)

Table 199: LORENTE 2009

Study	Lorente 2009[176]
Study type and analysis	Prospective multicentre cohort study
Number of studies (number of participants)	1(192)
Country and setting	Spain; six different intensive care units
Funding	Academic grants – no apparent industry sponsorship

Study	Lorente 2009[176]
Duration of study	unclear
Age, gender, ethnicity	Age (IQR) 60 (49-70); 33.3% female; ethnicity not reported
Patient characteristics	Inclusion: severe sepsis, as evidenced by suspected infection and 'some' of the following – fever/tachypnea/altered mental status/alterations in fluid balance of blood sugar; inflammatory parameters; hemodynamic parameters; organ dysfunction; tissue perfusion parameters. Exclusion: age <18; pregnancy; lactation; HIV; WBC count < 1000/microL; tumours; immunosuppressive therapy.
Index test	Lactic acid
Target condition	ICU mortality
Results:	Unadjusted Lactic acid (mmol/l) in Survivors: 2.0(IQR 1.2 to 3.7)[125]; non survivors: 3.95 (IQR: 1.47-6.55)[67] Diagnostic analysis AUC for lactic acid: 0.67 (95% CI: 0.58 to 0.75). The optimal cut-off for lactic acid for predicting ICU mortality was >3.1 mmol/l; at this threshold sensitivity was 0.55 and specificity was 0.75 RR also reported: RR of 2.13 (95% CI: 1.44-3.16) for ICU death for lactic acid >3.1 mmol/l compared to <3.1 mmol/l. Unclear if adjusted for confounders.
General limitations	Observational design, poor reporting of method. Indirectness: none. Risk of bias: very high.

Table 200: MARTY 2013

Study	Marty 2013[193]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (94)
Country and setting	France; university hospital ICU

Study	Marty 2013[193]
Funding	No financial conflicts of interest
Duration of study	1 year
Age, gender, ethnicity	Age 58 (16) years 56% male Ethnicity not reported
Patient characteristics	Sepsis origin from pulmonary (29%), digestive (28%), urinary (4%) and other (39%); SAPS 2 60(17); MAP at admission: 66.5(10.3) mmHg; Scv02 73.3(9.4) Inclusion: severe sepsis or septic shock, from the ED. Exclusion: Age <19 years, pregnancy, ICU acquired severe sepsis
Prognostic variable	Initial lactate Lactate clearance
Target condition	28-day mortality
Results:	**Unadjusted** Survivors (n=52) had an initial lactate of 5 (3.1) and non-survivors (n=42) had an initial lactate of 6.9 (4.3) [p=0.049]. Survivors (n=52) had lactate clearance from baseline to 6 hours of 13% (381) and non-survivors (n=42) had lactate clearance of -13 (67) [p=0.021]. **Diagnostic accuracy** Initial lactate at a threshold of 5.4 mmol/l: sens: 0.77 (0.63-0.87); spec: 0.55(.39-0.70) Lactate clearance at a threshold of 7.7%: sens: 0.63(0.49-0.76); spec: 0.56(0.40-0.72)
General limitations	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 201: PHUA 2008

Study	Phua 2008[237]

Study	Phua 2008[237]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (77 consecutive patients)
Country and setting	Singapore. ICU (Singapore, National University Hospital)
Funding	National Medical Research Council, Ministry of Health, Singapore.
Duration of study	10 month study period (recruited between February 2004 to April 2005), 28-day patient follow-up
Age, gender, ethnicity	Age (years), mean (SD): survivors (n = 42) versus non-survivors (n = 30): (6) versus 54 (17). Gender (male/female): survivors 27/15 versus non survivors 19/11. Ethnicity: not stated.
Patient characteristics	Inclusion: patients with septic shock early within 24 h of admission to the ICU, septic shock defined according to 2001 International Sepsis Definitions Conference (sepsis with hypotension despite adequate volume resuscitation) diagnosis of sepsis required the presence of systemic inflammation in response to known/suspected infection (demonstrated by white cells in normally sterile body fluid, perforated viscus, radiographic evidence of pneumonia in association with production of purulent sputum, and a syndrome associated with a high risk of infection (for example ascending cholangitis). Exclusions: patients presenting with acute coronary syndromes and acute heart failure with cardiogenic pulmonary oedema, and patients for whom withdrawal of intensive life support was considered early upon admission.
Index test	Lactate
Target condition	Septic shock
Results: **Day 1 lactate levels as predictive of 28-day mortality**	p=0.002 (repeat measures ANCOVA, shown as box and whisker plot)
Rise in lactate levels between days 1 and 2 as a predictor of 28-day mortality Sensitivity	58.3

Study	Phua 2008[237]
Specificity	88.1
PPV	73.7 (refers to the chance of dying if lactate rose or did not change between days 1 and 2)
NPV	78.7 (refers to the chance of dying if biomarker level fell or remained within the normal reference range between days 1 and 2)
Admission lactate level as predictor of 28-day mortality	
AUC	
Lactate threshold	0.66 (0.52-0.79)
Sensitivity	3.5
Specificity	53
PPV	71
NPV	57
	67
Multivariable analysis (logistic regression model, factors entered; APACHE II and SOFA scores, IL-1, IL-6, IL-10, lactate levels)	Not significant for lactate
Baseline characteristic	
Survivors (n = 42) versus non-survivors (n = 30)	
Survival refers to survival at 28-days from admission to the ICU	
APACHE II score	23.1 (7.5) versus 32.3 (8.7), p<0.001
SOFA score	10.1 (3.0) versus 12.7 (4.4), p<0.003
General limitations	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 202: PUSKARICH 2013

Study	Puskarich 2013[245]
Study type and analysis	Prospective cohort (based on patients from one arm in an RCT)
Number of studies (number of participants)	1 (187)
Country and setting	USA; large urban tertiary care hospitals
Funding	Academic grant; no financial conflicts of interest
Duration of study	2 years
Age, gender, ethnicity	Age survivors 60, non survivors 67; survivors 53.8% male, non survivors 56.8% male; survivors 52.4% white, 37.8% black American, 9% Hispanic and 0.7% other. Non-survivors 61.4% white, 36.4% black American, 0% Hispanic and 2.2% other.
Patient characteristics	Inclusion: age >17; suspected infection, 2 or more systemic inflammation criteria; systolic bp <90 mmHg OR lactate >4 mmol/l; 2 serial lactate measurements; initial lactate >2 mmol/l Exclusion:
Index test	Initial lactate Lactate clearance
Target condition	In–hospital Survival (note this is the opposite of mortality)
Results:	**Unadjusted** Non-survivors lactate 5.9(IQR:3.4-8.3)[n=44] mmol/l; survivors lactate 4.3 (IQR: 3-6.1)[n=143] mmol/l Lactate clearance of 50% or more (compared to <50%) lead to an OR of 4.3(1.8-10.2) of survival. Thus is equivalent to an OR of 0.23(0.09-0.56) for mortality Initial lactate of >4 (compared to 2-4) led to an OR of 1.5(0.8-3.3) for mortality **Diagnostic accuracy analysis** Initial lactate AUC (95% CI): 0.64 for predicting 28-day mortality lactate clearance AUC (95% CI): 0.67 for predicting 28-day mortality The paper did not originally provide details on the actual diagnostic accuracy at specific thresholds. However the authors kindly provided the following information after we contacted them: Patient with initial lactate >2 mmol/l (n = 187)

Study	Puskarich 2013[245]
	Accuracy in detecting SURVIVAL: Initial lactate < 4 mmol/l 46.8 63.6 ≥ 10% Relative lactate clearance 86.7 20.5 ≥50% Relative lactate clearance 44.8 84.1 Note that to detect mortality it can easily be shown that you reverse the direction of the threshold (ie > to <) and also switch the sensitivity and specificity
General limitations	Observational design. Indirectness: none. Risk of bias: very high.

Table 203: SCOTT 2012

Study	Scott 2012[257]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (239)
Country and setting	USA; paediatric ED
Funding	Academic grant; no financial conflicts of interest
Duration of study	1 year
Age, gender, ethnicity	Age: 55% aged 2-12, 28% 3 months to 2 years and 17% 13-18 years or <3 months; 54% male 50% African American, 30% white
Patient characteristics	CHILDREN; 28% chronic illnesses (inc. 8% immunocompromised); SBI present in 22% - pneumonia, UTI, blood; antibiotics given to 62% and IV fluids 49%; 7% sepsis resuscitation; 5% organ dysfunction within 24 hrs of triage Inclusion: age <19; paediatric SIRS criteria with temperature >38.5 or <36C; HR>2 SDs above age normal; underwent phlebotomy or CV catheter Exclusion: Patients transferred after care at another facility or with inborn errors of metabolism; no lactate measured within

Study	Scott 2012[257]
	15 minutes of IV therapy initiation
Prognostic variable	Initial lactate
Target condition	ICU admission
Results:	**Unadjusted** 5/18 (28%) of those with lactate of ≥4 mmol/l were admitted to ICU, compared to 14/221 (6%) with lactate <4 mmol/l. This gave an unadjusted RR of 4.4 (1.8 – 10.8). **Diagnostic accuracy analysis** For threshold of >4, raw data extracted from other data: TP: 5, FN: 14, FP: 13, TN: 207; sens: 0.26 and spec: 0.94
General limitations	Observational design. Indirectness: none. Risk of bias: very high.

Table 204: TRZECIAK 2007

Study	Trzeciak 2007[283]
Study type	Post-hoc analysis of a prospectively compiled registry
Number of studies (number of participants)	1 (n=1177) patients with infection
Country and setting	USA. Urban academic medical centre: ED (60%), ICU (22%), non-ICU ward (18%)
Funding	No outside source of funding
Duration of study	18-month period
Age, gender, ethnicity	Age: ≤49 years: 23%; 50-65 years: 28%; 66-75 years: 20%; ≥75 years: 29%. Gender: 50% M/ 50% F. Ethnicity: not stated.
Patient characteristics	Age ≥18 years; primary or secondary diagnosis of infection.
Index test/s	Lactate
Reference standard	N/A
Target condition	In-hospital mortality

Study	Trzeciak 2007[283]
Results: Lactate ≥4.0 mmol/l Sensitivity Specificity LR+ LR- AUC OR RR	 19 (15-23) 93 (91-94) 2.6 (1.9-3.7) 0.87 (0.82-0.92) 56 (53-59) 3.0 (2.0-4.6) 2.3 (1.7-2.9)
General limitations	Observational design. Indirectness: none. Risk of bias: very high.

Table 205: VORWERK 2009

Study	Vorwerk 2009[291]
Study type and analysis	Retrospective cohort
Number of studies (number of participants)	1 (307).
Country and setting	UK; 2 large urban teaching hospitals in Leicester and Kettering
Funding	No financial conflicts of interest
Duration of study	12 months
Age, gender, ethnicity	Age 79.7 (non-survivors), 66.6 (survivors) 53 % male (non survivors), 51% male (survivors) Ethnicity not reported
Patient characteristics	MEDS score 11.7 (non-survivors) and 6.7(survivors); MEW score 6.3 (non-survivors) and 4.2(survivors) Inclusion: ED diagnosis of sepsis, 2 or more SIRS criteria and a working diagnosis of infection documented in ED notes;

Study	Vorwerk 2009[291]
	Exclusion: parameters to calculate MEW or MEDS score were missing
Index test	Initial lactate
Target condition	28-day mortality
Results:	**Unadjusted** Patients with initial lactate level >4mmol/l had a significantly (p=0.006) higher 28-day mortality rate (49.1%) than people with initial lactate <4 mmol/l (25.7%): OR: 2.8(95% CI: 1.39-5.57). Non-survivors had an initial lactate of 5 mmol/l and survivors 3.6mmol/l (p=0.0054) **Diagnostic accuracy** An initial lactate of >4 mmol/l predicted 28-day mortality with 0.49 (95% CI: 0.35-0.63) sensitivity and 0.74 (95% CI: 0.65-0.82) specificity
General limitations	Observational design. Indirectness: none. Risk of bias: very high.

Table 206: WACHARASINT 2012

Study	Wacharasint 2012[292]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (665)
Country and setting	Canada; ICU
Funding	No financial conflicts of interest
Duration of study	4 years

Study	Wacharasint 2012[292]
Age, gender, ethnicity	Age ranged from 46 to 76 60% male Ethnicity not reported
Patient characteristics	Inclusion: septic shock, defined by presence of 2 or more SIRS criteria; proven or suspected infection; at least one new organ dysfunction by Brussels criteria; hypotension despite adequate fluid resuscitation. Exclusion: not reported
Index test	Initial lactate
Target condition	28-day mortality
Results:	**Diagnostic analysis** AUC for capillary lactate was 0.63. The ROC curve identified the ideal threshold as 1.4 mmol/l. The sensitivity and specificity at this threshold were 86% and 27%. At a threshold of 23 mmol/l sensitivity and specificity were 60% and 55%. At a threshold of 4.4 mmol/l sensitivity and specificity were 36% and 82%.
General limitations	Observational design. Indirectness: none. Risk of bias: very high.

Table 207: WALKER 2013

Study	Walker 2013[293]
Study type and analysis	Retrospective observational study
Number of studies (number of participants)	1 (78)
Country and setting	UK; tertiary hospital with ICU admitting >1000 level 3 patients/year
Funding	None; no conflicts of interest

Study	Walker 2013[293]
Duration of study	Three year retrospective study
Age, gender, ethnicity	Median (IQR) age 56(40-66); 43% female; ethnicity not defined
Patient characteristics	Consecutive adults (age $\geq$16) with sepsis admitted directly from the ED to the ICU of a tertiary UK hospital. Mean (95% CI) APACHE II score: 24.6 (22.5-26.7); initial lactate median (IQR): 4.9(2.1-7.8), LC median (IQR): 26.9% (-0.1% to 50.6%). Inclusion: primary diagnosis of infection or sepsis Exclusion: no record of arterial lactate measurement in ED; confirmed diagnosis was not sepsis or infection; unobtainable written notes
Prognostic variable	Lactate Lactate clearance
Confounders / stratification strategy	In addition to the above, age and APACHE II score (applied to logistic regression and Cox models only)
Target condition	30-day mortality
Results:	**Unadjusted** Survivors: median initial lactate 3.4 mmol/l (IQR: 1.8-6.4)[n=53]; Non-survivors: 6.0 mmol/l (IQR: 4.2-13.3)[n=25] Survivors: lactate clearance 37.2% (IQR: 1.4%-55%)[n=53]; Non-survivors: 10.5% (IQR: -0.7% to 29.5%)[n=25] **Diagnostic accuracy analysis [for those with abnormal admission lactate (>2 mmol/l), n=64]** AUC for initial lactate level as predictor of 30-day mortality: 0.57(95% CI: 0.43-0.71) *(AUC for initial lactate level as predictor of 30-day mortality in all (n=78) patients: 0.68(95% CI: 0.57-0.80)* AUC for lactate *non*-clearance as predictor of 30-day mortality: 0.79(95% CI: 0.68-0.90) Based on the ROC curve for lactate *non*-clearance, the optimal clearance threshold was chosen as 36%. Using this threshold, lactate clearance at 6 hours of 36% or less predicted 28-day mortality with sensitivity of 88%, specificity of 64.1%, PPV of 61.1% and NPV of 89.3% The following additional supplementary data were received from the authors after we contacted them requesting further information:

Study	Walker 2013[293]
	Please find attached the ROC curve coordinates for our lactate clearance study. Note that these are for patients in our study that had abnormal lactate (>2) at presentation. *1. Lactate non-clearance. NB to derive lactate clearance, the values in the first column need to be subtracted from 100.*

Coordinates of the Curve

Test Result Variable(s): lactate non-clearance

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
10.3978	1.000	1.000
13.0204	1.000	.974
18.1641	1.000	.949
22.1552	1.000	.923
27.4063	1.000	.897
32.8604	1.000	.872
34.0247	1.000	.846
34.7157	.960	.846
35.2576	.960	.821
35.6846	.960	.795
37.8846	.960	.769
41.9444	.960	.744
44.3071	.960	.718
44.8626	.960	.692
45.1515	.960	.667
45.5682	.920	.667
46.1063	.920	.641

Study	Walker 2013[293]			
	46.4773	.920	.615	
	47.9846	.920	.590	
	49.4192	.920	.564	
	49.4841	.920	.538	
	50.2031	.920	.513	
	51.4896	.920	.487	
	54.3060	.920	.462	
	58.1918	.920	.436	
	60.7936	.880	.436	
	62.1094	.880	.410	
	62.6705	.880	.385	
	63.4205	.880	.359	
	64.4818	.840	.359	
	67.0101	.800	.359	
	69.5283	.760	.359	
	70.2190	.760	.333	
	70.4445	.760	.308	
	70.9398	.720	.308	
	72.0557	.680	.308	
	72.7821	.680	.282	
	73.7380	.680	.256	
	75.2005	.680	.231	
	77.8089	.680	.205	
	81.1321	.680	.179	
	83.0619	.640	.179	
	84.1082	.600	.179	
	84.7195	.600	.154	
	86.4468	.560	.154	

Study	Walker 2013[293]

88.5000	.560	.128
89.2368	.520	.128
90.5508	.480	.128
91.7755	.440	.128
92.6282	.400	.128
94.2857	.400	.103
95.4451	.360	.103
96.6667	.320	.103
99.1739	.280	.103
105.4848	.240	.103
110.3515	.240	.077
112.5684	.240	.051
118.9813	.200	.051
123.5462	.200	.026
124.1882	.160	.026
131.0049	.120	.026
163.7500	.080	.026
195.6757	.040	.026
213.7299	.040	.000
227.1084	.000	.000

2. Initial Lactate

Coordinates of the Curve

Test Result Variable(s): lac0

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity

Study	Walker 2013[293]		
	1.0000	1.000	1.000
	2.0150	.960	.923
	2.0650	.920	.923
	2.1500	.920	.897
	2.2500	.920	.872
	2.4000	.880	.872
	2.5500	.840	.872
	2.6700	.840	.846
	2.7700	.840	.821
	2.9500	.800	.821
	3.1500	.760	.769
	3.2500	.760	.744
	3.3500	.760	.692
	3.5500	.760	.667
	3.9000	.760	.641
	4.1500	.760	.615
	4.2500	.720	.615
	4.5000	.680	.615
	4.7500	.640	.615
	4.9000	.640	.590
	5.0500	.640	.564
	5.2000	.600	.564
	5.3500	.520	.538
	5.6000	.520	.462
	5.8500	.520	.436
	5.9500	.520	.385
	6.1000	.480	.385
	6.3000	.480	.359

Study	Walker 2013[293]		
	6.5000	.480	.333
	6.9500	.440	.308
	7.3500	.440	.282
	7.5000	.440	.256
	7.7000	.400	.256
	7.8500	.360	.256
	7.9500	.320	.256
	8.2000	.320	.231
	8.6000	.320	.205
	8.8500	.320	.179
	9.0000	.320	.154
	9.2000	.320	.128
	9.4000	.320	.103
	11.2500	.280	.103
	13.1500	.280	.077
	13.5000	.240	.077
	13.7500	.200	.077
	13.9000	.160	.077
	14.5000	.120	.077
	17.0000	.040	.000
	20.0000	.000	.000

From these data we used the following thresholds and sensitivity/specificity values for the review. These were chosen on the basis that they approximated to the thresholds measured by other studies and represented reasonably high resolution increments without 'dominating' the review data.

Lactate clearance:

Study	Walker 2013[293]
	Threshold sens spec <9.4% 0.48 0.87 <18.9% 0.68 0.82 <29.8% 0.76 0.67 <39.2% 0.88 0.56 <49.8% 0.92 0.49 <58.1% 0.96 0.23 Initial lactate: 1 mmol/l 1.0 0 2.01 mmol/l 0.96 0.08 2.4 mmol/l 0.88 0.13 2.95 mmol/l 0.8 0.18 3.55 mmol/l 0.76 0.33 4.15 mmol/l 0.76 0.38 4.5 mmol/l 0.68 0.39 5.05 mmol/l 0.64 0.44 5.6 mmol/l 0.52 0.54
General limitations	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

H.2.1.4 Serum creatinine

Table 208: HJORTRU 2015

Study	Hjortru 2015[123]
Study type	Prospective cohort study as a sub-study from Scandinavian Starch for Severe Sepsis and Septic Shock (6S) RCT[233,233]

Study	Hjortru 2015[123]
Number of studies (number of participants)	1 (n=222)
Country and setting	Denmark. Multicentre: 3 ICUs (Copenhagen).
Funding	BioPorto diagnostics A/S (Gentofte, Denmark). The 6S trial was funded by the Danish Strategic Research Council, Rigshospitalet and the ACTA foundation. B Braun Medical AG delivered trial fluid to all sites.
Duration of study	18-month period (March 2010 through November 2011)
Age, gender, ethnicity	Median (IQR) age: 66 (57–75). Gender: 126 M/96 F. Ethnicity: Not stated.
Patient characteristics	Inclusion criteria: Patients meeting criteria for severe sepsis within the previous 24 hours, need of fluid resuscitation in the ICU, and the consent from patient or proxy. Exclusion criteria: Aged >18 years; previous randomised into the 6S trial, allergy towards HES or malic acid, treatment with >1000 ml of any synthetic colloid within the last 24 h prior to randomisation, any form of RRT, acute burn injury >10% of body surface area, severe hyperkalaemia (p-K >6 mmol/l) within the last 6 hours, liver or kidney transplantation or intracranial bleeding during current hospital admission, withdrawal of active therapy and enrolment into another ICU trial of drugs with potential action on circulation, renal function or coagulation.
Index test/s	Serum creatinine (cut-off ≥1.7 mg/dl)
Reference standard	N/A
Target condition	90-day mortality
Results:	
90-day mortality	
Serum creatinine (cut-off ≥1.7 mg/dl)	
AUC	0.50 (0.42–0.58)
Sensitivity	0.38
Specificity	0.70
PPV	0.62
NPV	0.48
90-day mortality, n (%)	123 (55)
ICU mortality, n (%)	84 (39)

Study	Hjortru 2015[123]
ICU length of stay (days), median (IQR)	7 (3-6)
Baseline characteristics	
SAPS, median (IQR)	54 (39–66)
SOFA score excluding GCS score, median (IQR)	8 (6-10)
Enrolment plasma creatinine (µmol/l)	101 (66–185)
Missing patient pre-admission creatinine, n(%)	20 (9)
Hours from ICU admission to enrolment, median (IQR)	4 (1–13)
General limitations (according to QUADAS 2)	Observational design. Convenience sample. Indirectness: none. Risk of bias: very high.

Table 209: LEEDAHL 2014

Study	Leedahl 2014[167]
Study type	Retrospective cohort study of prospectively collected data
Number of studies (number of participants)	1 (n=390)
Country and setting	USA. ICU (urban tertiary, academic medical centre at Mayo Clinic, Rochester).
Funding	Discretionary funds for statistical efforts were provided by Mayo Clinic Pharmacy Services.
Duration of study	24-month period (January 2008 and December 2010)
Age, gender, ethnicity	Median (IQR) age: 71 (56–81). Gender: 191 M/199 F. Ethnicity: 92.6% White.
Patient characteristics	Inclusion criteria: Aged >18 years; patients with septic shock with a systolic BP <90 mm Hg despite a fluid challenge of 20 ml/kg body weight of crystalloid or equivalent colloid, based on recommendations from the 2008 Surviving Sepsis Campaign. Exclusion criteria:

Study	Leedahl 2014[167]
	Patients having severe sepsis without shock, those with a history of ESRD, and those lacking research authorization.
Index test/s	Serum creatinine
Reference standard	N/A
Target condition	28-day mortality
Results: **28-day mortality** Serum creatinine increase, per 0.1 mg/dl (n=333 patients with measured serum creatinine available) AUC Univariate OR (95% CI) Multivariate OR (95%CI) **Baseline characteristics** APACHE III score, median (IQR) Baseline serum creatinine (mg/dl), median (IQR) Baseline measured serum creatinine unavailable, n (%) Number of baseline serum creatinine measurements available in first 12 h, median (IQR)	 0.54 (0.47-0.61) 0.95 (0.87-1.05), p=3.10 0.88 (0.79-0.98), p=0.02 57 (43-73) 1.0 (0.7–1.5) 52 (13.3) 2 (1-2)
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

Table 210: SHAPIRO 2010A

Study	Shapiro 2010A[266]

Study	Shapiro 2010A[266]
Study type	Secondary analysis of a prospective observational study[267,268] of a convenience sample of patients
Number of studies (number of participants)	1 (n=661)
Country and setting	USA. ED. Multicentre: 10 academic medical centres.
Funding	Blosite Diagnostics.
Duration of study	18-month period
Age, gender, ethnicity	Mean (SD) age: 59 (19). Gender: 48% M/52% F. Ethnicity, n (%): White 346 (52), Black 242 (37), Hispanic 51 (8), Asian 11 (2), Native American 1 (0), Other 10 (2).
Patient characteristics	Inclusion criteria: Aged ≥18 with suspected infection or a serum lactate level greater than 2.5 mmol/l, 2 or more systemic inflammatory response syndrome criteria (temperature >38°C, or >36°C, respiration >20 breaths/ min or partial pressure of carbon dioxide <32 mmHg, pulse>90 beats/min, WBC > 12,000 cells/mm^3 or less than 4000 cells/mm^3, a subsequent serum creatinine level obtained within 12 to 72 hours of enrolment. Exclusion criteria: pregnancy, do-not-resuscitate status, cardiac arrest, dialysis dependency, no ED presentation value for serum creatinine.
Index test/s	Serum creatinine
Reference standard	N/A
Target condition	In-hospital mortality
Results: **In-hospital mortality** Serum creatinine AUC cut-off >0.7 mg/dl Sensitivity Specificity OR (95% CI) cut-off >1.7 mg/dl Sensitivity	 0.73 0.83 (0.75-0.94) 0.17 (0.14-0.20) 1.27 (0.58-2.80) 0.41 (0.28-0.54)

Study	Shapiro 2010A[266]
Specificity OR (95% CI) In-hospital mortality, n (%) **Baseline characteristics** Baseline serum creatinine (mg/dl), mean (SD) WBC count, 1000 mm^3, mean (SD) Platelet count/mm^3, mean (SD)	0.81 (0.78-0.84) 2.94 (1.7-5.1) 59 (8.9) 1.4 (1.1) 14.4 (8.9) 278 (282)
General limitations (according to QUADAS 2)	Secondary analysis of observational cohort. Convenience sample. Indirectness: none. Risk of bias: very high.

Table 211: SHMUELY 2000

Study	Shmuely 2000[270]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=2722)
Country and setting	Israel. ED (Rabin Medical Center, Beilinson university campus).
Funding	Not stated.
Duration of study	5-year and 9-month period (March 1998 and December 1994)
Age, gender, ethnicity	Age: median according to admission serum creatinine ≤1 mg/dl: 65.5. 1.1 to 3 mg/dl: 74.0. >3 mg/dl: 65.5. Gender: percentage male according to admission serum creatinine ≤1 mg/dl: 36.1. 1.1 to 3 mg/dl: 59.5 >3 mg/dl: 76.0 Ethnicity: not stated.
Patient characteristics	Inclusion criteria: Patients aged ≥18 with bacteraemia or fungaemia defined as positive blood cultures and uncontaminated in

Study	Shmuely 2000[270]
	the presence of clinical and laboratory evidence of infection >38°C or >35°C septic shock, leucocytosis ≥12.0 x 109/l, metabolic acidosis (ph <7.3) or laboratory findings of disseminated intravascular coagulopathy. Exclusion criteria: not stated.
Index test/s	Serum creatinine
Reference standard	N/A
Target condition	In-hospital mortality
Results: **In-hospital mortality** Initial creatinine >3.0 mg/dl (265.2 µmol/L) Multivariate OR (95%CI) **Outcome** **In-hospital mortality according to 3 study groups** Creatinine ≤1 mg/dl (88.4 µmol/L) Percentage Median (range) time since hospital admission, days Creatinine 1.1 to 3 mg/dl (97.2 to 265.2 µmol/L) Percentage Median (range) time since hospital admission, days Creatinine >3 mg/dl (265.2 µmol/L) Percentage Median (range) time since hospital	1.7 (1.0-2.7) 20.8 11 (1-83) 25.5 6 (1-320) 50.2 3 (0-119)

Study	Shmuely 2000[270]
admission, days **Baseline characteristics** **Median (range) admission serum creatinine according to 3 study groups** Creatinine ≤1 mg/dl (88.4 µmol/L) Creatinine 1.1 to 3 mg/dl (97.2 to 265.2 µmol/L) Creatinine >3 mg/dl (265.2 µmol/L)	 0.8 (0.1-1) 1.1 (1.5-3.0) 4.0 (3.1-11.9)
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

H.2.1.5 Disseminated intravascular coagulation

Table 212: GANDO 2007

Study	Gando 2007[102]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=45)
Country and setting	Japan. ICU (urban university hospital, Sapporo).
Funding	Partly supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan
Duration of study	Not reported
Age, gender, ethnicity	DIC group (n=11) Mean (SD) age: 47.8 (8). Gender: 3/8 F. Ethnicity: not reported. Non-DIC group (n=34)

Study	Gando 2007[102]
	Mean (SD) age: 58 (3). Gender: 20/14 F. Ethnicity: not reported.
Patient characteristics	Patients with SIRS or sepsis Inclusion criteria: patients with SIRS or sepsis who were admitted to the ICU. Exclusion criteria: aged <12 years or >90 years, people receiving anticoagulant therapy, trauma patients. Blood samples were collected within24 hours of diagnosis.
Index test/s	Soluble fibrin, antithrombin, protein C
Reference standard	N/A
Target condition	Mortality
Definition of DIC	ISTH
Results: **Serial changes in markers (DIC group versus non-DIC group):** Soluble fibrin (mcg/ml), mean (SD) Antithrombin (%), mean (SD) Protein C (%), mean (SD) **Mortality** DIC score (n=45 patients with measured serum creatinine available) Multivariable OR (95%CI) **Baseline characteristics** APACHE II score, mean (SD) Baseline DIC score, mean (SD) Baseline MODS (yes/no)	Day 0: 44.6 (10.6) v 15.3 (3.1); Day 2: 45.8 (11.7) v 15.7 (5.0); Day 4: 42.2 (9.4) v 13.9 (2.0) Day 0: 57 (6) v 72 (4); Day 2: 60 (4) v 78 (3); Day 4: 71 (5) v 78 (4) Day 0: 32 (6) v 49 (3); Day 2: 39 (6) v 57 (5); Day 4: 39 (9) v 71 (9) 4.225 (1.418-12.584), p=0.0097 DIC group: 29 (2); non-DIC group: 19 (2) DIC group: 5.0 (0.1); non-DIC group: 2.3 (0.2) DIC group: 11/0; non-DIC group: 21/13 DIC group: 3.7 (0.4); non-DIC group: 1.8 (0.2)

Study	Gando 2007[102]
Baseline MODS number	
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

Table 213: GANDO 2007A

Study	Gando 2007A[105]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=48)
Country and setting	Japan. ICU (urban university hospital, Sapporo).
Funding	Partly supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan
Duration of study	Not reported
Age, gender, ethnicity	DIC group (n=20) Mean (SD) age: 51 (5). Gender: 8/12 F. Ethnicity: not reported. Non-DIC group (n=28) Mean (SD) age: 56 (3). Gender: 17/11 F. Ethnicity: not reported.
Patient characteristics	Patients with SIRS or sepsis Inclusion criteria: not reported. Exclusion criteria: <12 or >90 years old, individuals receiving anticoagulant therapy, trauma patients Blood samples were collected within 24 hours of diagnosis based on SIRS/sepsis criteria.
Index test/s	TNFalpha, soluble fibrin, protein C, PAI-1
Reference standard	N/A
Target condition	Mortality
Definition of DIC	ISTH (>5), Japanese Ministry of Health and Welfare (>7)
Results:	

Study	Gando 2007A[105]
Mortality DIC as a risk factor for death (n=48) Univariable OR (95% CI)	 40.5 (4.544-360.9), p=0.0009
Baseline characteristics APACHE II score, mean (SD) Baseline MODS (yes/no) Baseline MODS number	DIC group: 27.4 (2.1); non-DIC group: 16.9 (1.2) DIC group: 20/0; non-DIC group: 15/13 DIC group: 3.5 (0.2); non-DIC group: 1.5 (0.2)
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

Table 214: GANDO 2008

Study	Gando 2008[104]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=329)
Country and setting	Japan. Multi-centre study at 14 ICUs (urban tertiary care hospitals).
Funding	Supported in part by the Japanese Association for Acute Medicine, Tokyo, Japan.
Duration of study	4-month period (in 2005)
Age, gender, ethnicity	Mean (SD) age: 58.4 (18.5). Gender: 222/107 F. Ethnicity: not reported.
Patient characteristics	Patients with DIC (34.7% had sepsis or severe infection) Inclusion criteria: all patients diagnosed with DIC Exclusion criteria: <15 years old, haematopoietic malignancy, liver cirrhosis classified as Child-Pugh grade C, concomitant treatment with carcinostatics or irradiation, known clotting disorders or receiving anticoagulant therapy

Study	Gando 2008[104]
	Blood samples were taken on admission to critical care centres and daily thereafter.
Index test/s	N/A
Reference standard	N/A
Target condition	28-day all-cause mortality
Definition of DIC	JAAM DIC, ISTH
Results: **28-day all-cause mortality** SIRS criteria (n=329 patients) Multivariable OR (95%CI) JAAM DIC score (n=329) Stepwise method OR (95%CI) **Baseline characteristics** APACHE II score, mean (SD) SOFA score, mean (SD) ISTH DIC score, mean (SD) ISTH DIC, yes/no	 2.289 (0.964-5.434), p=0.060 1.223 (1.004-1.489), p=0.046 19.2 (9.2) 8.7 (4.1) 3.4 (1.4) 65/264
General limitations (according to QUADAS 2)	Observational design Indirectness: very serious (34.7% of the study population had sepsis). Risk of bias: very high.

Table 215: GANDO 2013

Study	Gando 2013[103]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=624)

Study	Gando 2013[103]
Country and setting	Japan. Multi-centre study at 15 ICUs (urban tertiary hospitals).
Funding	Discretionary funds for statistical efforts were provided by Mayo Clinic Pharmacy Services.
Duration of study	12-month period (1 June 2010 – 31 May 2011)
Age, gender, ethnicity	JAAM DIC group: Mean (SD) age: 69 (18). Gender: 181/111 F. Ethnicity: not reported. Non-DIC group: Mean (SD) age: 69 (15). Gender: 210/122 F. Ethnicity: not reported.
Patient characteristics	Patients with severe sepsis Inclusion criteria: all patients diagnosed with severe sepsis and admitted to the ICU. Exclusion criteria: not reported. Blood samples were taken on admission to the ICU and daily thereafter.
Index test/s	DIC score
Reference standard	N/A
Target condition	28-day mortality
Definition of DIC	JAAM DIC
Results: **28-day mortality** DIC score (n=624 at time of inclusion) Stepwise regression OR (95%CI) **Baseline characteristics (DIC group versus non-DIC group)** APACHE II score, mean (SD) SOFA score, mean (SD) MODS, %	 1.282 (1.141-1.439), p<0.001 25.2 (8.5) versus 21.9 (7.9) 10.6 (3.8) versus 6.7 (3.3) 65.4% versus 40.4%

Study	Gando 2013[103]
DIC score	5.6 (1.3) versus 1.9 (0.9)
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

Table 216: OGURA 2014

Study	Ogura 2014[222]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=624)
Country and setting	Japan. Multi-centre study at 15 ICUs (urban tertiary hospitals).
Funding	Discretionary funds for statistical efforts were provided by Mayo Clinic Pharmacy Services.
Duration of study	12-month period (1 June 2010 – 31 May 2011)
Age, gender, ethnicity	Mean (SD) age: 69 (17). Gender: 391/233 F. Ethnicity: not reported.
Patient characteristics	Patients with severe sepsis Inclusion criteria: all patients diagnosed with severe sepsis and admitted to the ICU. Exclusion criteria: not reported. Blood samples were taken on admission to the ICU and daily thereafter.
Index test/s	DIC score
Reference standard	N/A
Target condition	28-day mortality, hospital all-cause mortality
Definition of DIC	JAAM DIC
Results: **28-day mortality** DIC score	

Study	Ogura 2014[222]
(n=624 at time of inclusion) Multivariable OR (95%CI) **Hospital all-cause mortality:** DIC score (n=624 at time of inclusion) Stepwise method OR (95%CI) **Baseline characteristics** APACHE II score, mean (SD) SOFA score, mean (SD) MODS, number (%) DIC score	 1.733 (1.094-2.747), p=0.019 1.546 (1.008-2.370), p=0.046 23.4 (8.3) 8.6 (4.0) 144 (23.1%) 3.6 (2.2)
General limitations (according to QUADAS 2)	Observational design Indirectness: none. Risk of bias: very high.

H.2.2 Empiric antimicrobials

Table 217: BLOOS 2014

Study	Bloos 2014[28]
Study type	Prospective observational cohort
Number of studies (number of participants)	1 (n= 1011)
Countries and setting	Conducted in Germany. 44 ICUs
Line of therapy	Mixed
Duration of study	Follow up: 5 months
Method of assessment of guideline condition	Adequate

Study	Bloos 2014[28]
Stratum	Patients treated in the ICU for proven or suspected infection with at least one new organ dysfunction related to the infection.
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients treated in the ICU for proven or suspected infection with at least one new organ dysfunction related to the infection were eligible for inclusion. Organ dysfunctions were defined as follows: acute encephalopathy, thrombocytopenia defined as a platelet count <100,000/microlitres or a drop in platelet count >30% within 24 hours, arterial oxygen partial pressure <10 kPa (75 mmHg) when breathing room air or partial pressure of arterial oxygen/fraction of inspired oxygen ratio <33 kPa (<250 mmHg), renal dysfunction defined as oliguria (diuresis ≤0.5 ml/kg body weight/hour) despite adequate fluid resuscitation or an increase of serum creatinine more than twice the local reference value, metabolic acidosis with a base excess < −5 mmol/litre or a serum lactate >1.5 times the local reference value, and arterial hypotension defined as systolic arterial blood pressure <90 mmHg or mean arterial blood pressure <70 mmHg for >1 hour despite adequate fluid loading or vasopressor therapy at any dosage to maintain higher blood pressures.
Exclusion criteria	Patients who received initial infection control measures for sepsis in another hospital and patients who did not receive full life-sustaining treatment were excluded.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 69 (58 to 77). Gender (M:F): 634M (62.7%). Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Onset of severe sepsis or septic shock was defined as the time of first infection-related organ dysfunction as documented in the patient file. Patient location at time of onset of severe sepsis was defined as the patient location where the first infection-related organ dysfunction was documented. For patients who developed severe sepsis outside the ICU, this could be the pre-hospital setting, the emergency department, the hospital ward, or the operating room. Time and type of first AT as well as pre-existing AT were also recorded from the medical records. Any AT prescribed up to 24 hours before the onset of organ dysfunction but for the current infectious episode was considered previous AT. Perioperative antimicrobial prophylaxis was not regarded as specific AT for sepsis. Change of empirical AT was assessed on day 5. Initial AT was defined as inadequate if escalation had occurred within the first 5 days. For each patient, a blinded arbitrator assessed whether the initial AT complied with German guideline recommendations. Source control was defined as removal of an anatomic source of infection either by surgery or intervention (that is, computed tomography-guided drainage). Source control was defined as inadequate if the technical procedure was unsuccessful. Time to source control was obtained from the medical record. Other factors included serum lactate and procalcitonin at the time of onset of severe sepsis, number of blood culture sets taken,

Study	Bloos 2014[28]
	and ICU and hospital mortality. Severity of disease was assessed by the Simplified AcutePhysiology Score II and the Sequential Organ Failure Assessment score on the day of sepsis diagnosis.
Funding	Financial support was received from the German Federal Ministry of Education and Research via the integrated research and treatment Center for Sepsis Control and Care (FKZ 01EO1002).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: [28-day mortality]
- Actual outcome: [28-day mortality. Multivariable analysis for time to antimicrobial therapy >1 hour (against previous antimicrobial therapy and antimicrobials within 1 hour after infection-related onset of organ dysfunction, n=725)]; OR 0.81, 95%CI 0.54-1.23, p= 0.323. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [28-day mortality. Multivariable analysis for time to antimicrobial therapy >1 hour (against previous antimicrobial therapy and antimicrobials within 1 hour after infection-related onset of organ dysfunction in patients where surgical site control was required, n=234)]; OR 0.80, 95%CI 0.38-1.72, p= 0.552. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [28-day mortality. Multivariable analysis for time to antimicrobial therapy >1 hour (against previous antimicrobial therapy and antimicrobials within 1 hour after infection-related onset of organ dysfunction in patients where no surgical site control was required, n=424)]; OR 0.69, 95%CI 0.39-1.21, p= 0.189. Risk of bias: low; Indirectness of outcome: No indirectness

Multivariable logistic regression analysis to calculate adjusted ORs included initial Sequential Organ Failure Assessment score, age, and serum lactate.

Protocol outcome 1: [28-day mortality]
- Actual outcome: [28-day mortality-administration of AT more than 1 hour after onset of organ dysfunction- multivariable analysis]; OR 0.96, 95% CI 0.69- 1.33 . Risk of bias: low; Indirectness of outcome: No indirectness

Adjusted for inadequate empirical antimicrobial therapy, age, initial SOFA score and maximum serum lactate levels and further covariates.

Protocol outcome 1: [28-day mortality]
- Actual outcome: [28-day mortality]; Group 1 (antimicrobial therapy within 1 hour after onset of first sepsis related organ dysfunction): n= 186, 34.9%, Group 2 (antimicrobial therapy >1 hour after onset of first sepsis related organ dysfunction): n= 641, 36.2% p=0.76. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [. 28-day mortality]

Study	Bloos 2014[28]
- Actual outcome: [e.g. 28-day mortality]; Group 1 (antimicrobial therapy within 1 hour after onset of first sepsis related organ dysfunction, including 186 who received antimicrobials in the first hour and 184 who received antimicrobials prior to onset of organ dysfunction): n= 370, 32.4%, Group 2 (antimicrobial therapy >1 hour after onset of first sepsis related organ dysfunction): n= 641, 36.2% p=0.227. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: . 28-day mortality] For the subgroup of 370 patients who received AT within 1 hour - Actual outcome: [time to antimicrobial therapy and risk of death within 28 days]; (OR per hour increase of time to AT: 1.0 (95% CI: 1.0 to 1.0), P = 0.482) in those 849 patients that received their AT after the first organ dysfunction. Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 218: CARTWRIGHT 1992

Study	Cartwright 1992[45]
Study type	Retrospective review of hospital notes
Number of studies (number of participants)	1 (n= 360)
Countries and setting	Conducted in UK. General practice and hospital
Line of therapy	Unclear
Duration of study	Follow up: Not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with meningococcal disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were accepted as having meningococcal disease of (a) a meningococcus had been isolated from blood or CSF (b) clinical evidence of meningitis had been accompanied by the presence of Gram negative diplococci in cerebrospinal fluid; (c) signs and symptoms of meningitis or septicaemia had been accompanied by a haemorrhagic rash; or (d) a haemorrhagic rash or clinical evidence of meningitis, or both, had been accompanied by isolation of a meningococcus from a nasopharyngeal swab,20 by a rise in meningococcal antibody, or the presence of IgM specific to meningococcus.
Exclusion criteria	Cases were excluded from analysis if the patient had been transferred from another hospital, if the patient had been

Study	Cartwright 1992[45]
	admitted to hospital as a result of self-referral or developed meningococcal disease while in hospital, or if the final diagnosis was chronic meningococcal sepsis.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): not stated (includes children and adults). Gender (M:F): 205: 155. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Parenteral antibiotics prior to admission to hospital Concurrent medication/care: not stated
Funding	The information and alerting campaign in Darlington was supported by the Dawn Craggs Meningitis Appeal Fund.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: 28-day mortality - Actual outcome: mortality; Group 1 (antibiotic given): n= 88 (95%) survived, n=5 (5%) died, Group 2 (antibiotic not given): n= 224 (91%) survived, n= 22 (9%) died. Not known n=1 (died). RR 0.60 (95% CI 0.23-1.54) Risk of bias: High; Indirectness of outcome: Indirect: time to mortality not stated.	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 219: DE GROOT 2015

Study	De Groot 2015[70]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n= 1168)
Countries and setting	Conducted in The Netherlands. ED
Line of therapy	Unclear
Duration of study	Follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Not applicable

Study	De Groot 2015[70]
Subgroup analysis within study	Not applicable
Inclusion criteria	All consecutive patients, age ≥17 years, with suspected infection and triage category (Manchester triage system) yellow, orange or red, treated with intravenous antibiotics.
Exclusion criteria	Triage category blue and green
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 62 (17). Gender (M:F): 56%M/44%F. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Antibiotic administration. Concurrent medication/care: not stated
Funding	The authors declare that they have no competing interests.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS 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) Risk of bias: High; Indirectness of outcome: Direct.	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 220: FERRER 2009

Study	Ferrer 2009[88]
Study type	Prospective observational

Study	Ferrer 2009[88]
Number of studies (number of participants)	1 (n= 2796)
Countries and setting	Conducted in Spain. ICU
Line of therapy	Mixed
Duration of study	Follow up: not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with severe sepsis or septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with severe sepsis Or septic shock from the 77 intensive care units participating in the Edusepsis study. All ICU admissions from the emergency department or from wards and all ICU patients were actively screened daily for the presence of severe sepsis or septic shock. Severe sepsis was defined as sepsis associated with organ dysfunction unexplained by other causes. A diagnosis of sepsis was made based on the following findings: respiratory dysfunction (bilateral pulmonary infiltrates with Pao/Froa <3()()), renal dysfunction (urine output <0.5 ml/kg/hour for at least 2 hours or creatinine >2.0 mg/dl), coagulation abnormalities (International Normalized Ratio [INRI >1.5 or a partial thromboplastic time (PIT] >60 seconds), thrombocytopenia (platelet count < 100,000 pi -I), hyperbilirubincmia (total plasma bilirubin >2.0 mg/dl), hypoperfusion (lactate >18 mg/dl), or hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or a reduction in systolic blood pressure >40 mm H from baseline measurements). Septic shock was defined as acute circulatory failure (systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Ilg, or a reduction in systolic blood pressure >40 mm Hg from baseline) despite adequate volume resuscitation.
Exclusion criteria	Patients in whom the onset of severe sepsis could not be determined.
Recruitment/selection of patients	All patients
Age, gender and ethnicity	Age - Mean (SD): 62.2 years (16.3). Gender (M:F): n=1717 M (61,4%). Ethnicity: Not stated
Indirectness of population	No indirectness
Interventions	The following clinical variables were recorded: age, sex, Acute Physiology and Chronic Health Evaluation Il (APACHE Il) score, patient location at sepsis diagnosis, origin of infection, baseline lactate level, organ dysfunction at sepsis diagnosis, and hospital mortality. During the first 24 hours after sepsis, we recorded the four therapeutic goals and the four treatments included in the SSC care bundles. Therapeutic goals were (I) central venous pressure (CVP) at least 8 mm Hg in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, (2) central venous oxygen saturation (Scvo,) at least 70% in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, (3) blood glucose greater than or equal to the lower limit of normal but less than 150 mg/dl, and (4) inspiratory plateau pressure less than 30 cm H20 for mechanically ventilated patients.

Study	Ferrer 2009[88]
	Treatments were (1) early administration of broad-spectrum antibiotics (time from severe sepsis presentation to antibiotic administration: first hour, 1 to 3 hours, 3 to 6 hours, previous antibiotic, or no antibiotic administered in the first 6 hours), (2) fluid challenge of a minimum of 20 ml/kg of crystalloid (or colloid equivalent) in the event of hypotension and/or lactate greater than 36 mg/dl, (3) low-dose steroids in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, and (4) drotrecogin alfa (activated) for multiorgan failure.
Funding	None stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: 28-day mortality
- Actual outcome: PROPENSITY-ADJUSTED LOGISTIC REGRESSION MODELS FOR THE IMPACT OF THERAPEUTIC INTERVENTIONS FOR SEVERE SEPSIS ON HOSPITAL MORTALITY

Broad-spectrum antibiotics (Propensity-adjusted logistic regression model)

Hours (n=510) OR 0.67 95%CI 0.50-0.90 p= 0.008

1-3 hours (n=572)OR 0.80 95%CI 0.60-1.06 p= 0.127

3-6 hours (n=290) OR 0.87 95%CI 0.62-1.22 p= 0.419

Previous antibiotic (n=989) OR 0.89 95%CI 0.69-1.15 p=0.383

No antibiotic I the first 6 hours (n=415)OR 1

(treatment within 1 hour vs. no treatment within first 6 hours of diagnosis; odds ratio, 0.67; 95% confidence interval, 0.50-0.90; P = 0.008)

Risk of bias: low; Indirectness of outcome: No indirectness

The effectiveness of each treatment was estimated using propensity scores in the subsample where it was Indicated. Propensity scores were estimated by fitting a multinomial logistic regression for time-to-administration of broad-spectrum antibiotics. The covariates included in the propensity score models were all clinical variables (diagnosis on ICU admission, patient location on sepsis diagnosis, origin of infection, APACHE, organ dysfunction at sepsis presentation, number of organ failure)and the therapeutic goals that showed a statistically significant association with mortality (central venous oxygen saturation ≥70% for persistent hypotension despite fluid resuscitation and/or lactate >36 mg/di, blood glucose lower limit of normal but <150mg/dl, inspiratory plateau pressure <30cm /H2O for mechanically ventilated patients). We derived propensity score quintiles and assessed the validity of the propensity scores in three ways. First, to assess the balancing of covariates between treated and untreated groups in each propensity score quintile, we compared all the covariates for the treated and untreated groups within each quintile. Second, we drew box plots of the estimated propensity scores for treated and untreated patients within each quintile of the propensity scores. Third, the area under the curve for the propensity score models was derived. For each assessed treatment, to take into account potential residual imbalances in the final model in addition to treatment and the propensity score quintiles, we included all the covariates that showed a statistically significant difference between treated and untreated groups in any quintile and APACHE Il scores in the logistic regression model for mortality.

Study	Ferrer 2009[88]
Protocol outcome 1: 28-day mortality - Actual outcome: bivariate analysis: survivors and non-survivors Broad-spectrum antibiotics, n (%)all patients n=2776, non-survivors n=1164, survivors n=1632 hours all patients 510 (18.4) non-survivors 175 (15.1) survivors 335 (20.7) 1-3 hours all patients 572 (20.6) non-survivors 228 (19.7) survivors 344 (21.2) 3-6 hours all patients 290 (10.4) non-survivors 123 (10.6) survivors 167 (10.3) previous antibiotic all patients 989 (35.6) non-survivors 441 (38.1) survivors 548 (33.8) no antibiotic in the first 6 hours all patients 415 (14.9) non-survivors 189 (16.3) survivors 226 (14.0)	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a

Study	Ferrer 2009[88]
	proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 221: FERRER 2014

Study	Ferrer 2014[89]
Study type	Retrospective analysis of a large dataset collected prospectively for the Surviving Sepsis Campaign
Number of studies (number of participants)	1 (n= 17,990)
Countries and setting	Conducted in Europe, the United States and South America. ICU
Line of therapy	Unclear
Duration of study	Follow up: Not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with severe sepsis and septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible subjects were those admitted to an ICU having a suspected site of infection, two or more systemic inflammatory response syndrome criteria, and one or more organ dysfunction criteria (International Sepsis Definitions). The patient was considered to have a nosocomial infection if severe sepsis or septic shock was discovered in the ICU more than 72 hours after admission or if severe sepsis or septic shock was discovered in the ward and the patient had been in the ward more than 72 hours prior to sepsis identification. Otherwise, the patient was considered to have a community infection.
Exclusion criteria	Subjects who did not receive any antibiotics in the first 6 hours, those with missing time of antibiotic administration, or subjects who were receiving antibiotics prior to presentation of severe sepsis were excluded from the data analysis.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	Once severe sepsis or septic shock was identified using the screening criteria established in the Surviving Sepsis Campaign (SSC) initiative, patients were eligible for antibiotics. All dates and times in the SSC database are based on the time of presentation. Time to first antibiotic administration was reported as the difference between time of

Study	Ferrer 2014[89]
	presentation and first antibiotic administration. For each antibiotic given to a particular patient, the name of the antibiotic and time of administration were recorded in the database. Patients could receive none, one or multiple antibiotics.
Funding	No funding stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: 28-day mortality
- Actual outcome: hospital mortality- logistic regression model

hours: OR 1.00, probability of mortality 24.6% 95% CI 23.2-26.0

1-2 hours: OR 1.07 95%CI 0.97-1.18 p 0.165, probability of mortality 25.9% 95%CI 24.5-27.2

2-3 hours: OR 1.14 95%CI 1.02-1.26 p 0.021, probability of mortality 27.0% 95%CI 25.3-28.7

3-4 hours: OR 1.19 95%CI 1.04-1.35 p 0.009, probability of mortality 27.9% 95%CI 25.6-30.1

4-5 hours: OR 1.24 95%CI 1.06-1.45 p 0.006, probability of mortality 28.8% 95%CI 25.9-31.7

5-6 hours: OR 1.47 95%CI 1.22-1.76 p <0.001, probability of mortality 32.3% 95%CI 28.5-36.2

>6 hours: OR 1.52 95%CI 1.36-1.70 p <0.001, probability of mortality 33.1% 95%CI 30.9-35.3

Risk of bias: high; Indirectness of outcome: Indirect: time to mortality not reported

Hospital mortality odds ratio referent group is 0-1 hour for the time to antibiotics and is adjusted by the sepsis severity score (SSS), ICU admission source (ED, ward, vs. ICU), and geographic region (Europe, United States, and South America).

Probability Of hospital mortality is estimated using the generalized estimating equation population averaged logistic regression model and is based on the subject having the following characteristics: from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

Antibiotics administered in the first hour are the referent group and thus the odds ratio by definition is 1.00 while the 95% Cl and the p value are not generated

Logistic regression was used to analyse hospital mortality since the database has complete information on the time to antibiotic administration on all subjects and their mortality status (no censoring). Time to only the patient's first antibiotics was entered into the model as a categorical variable, and only covariates that acted as either a confounder or an effect modifier were included. A confounder was identified when its addition to the model changed the odds ratio associated with the time to antibiotic administration by more than 10% in either direction, without considering statistical significance. A covariate that had a statistically significant interaction (p < 0.05) with antibiotic administration was considered to be an effect modifier. Table Sl (Supplemental Digital Content 1, http://links.lww.com/CCM/A900) in the online appendix lists the 51 covariates that were considered possible confounders and effect modifiers. GEE population averaged logistic regression was used since patients are nested within a particular ICU. This method takes into account the variability within and between ICUs and uses this inherent correlation when estimating the SES

Study	Ferrer 2014[89]
that are used to test model coefficients. Protocol outcome 1: 28-day mortality - Actual outcome: hospital mortality; 0-1 hours: 1512/4728 (32%), 1-2 hours: 1292/4595 (28.1%), 2-3 hours: 863/3020 (28.6%), 3-4 hours: 517/1734 (29.8%), 4-5 hours 337/1037 (32.5%), 5-6 hours: 234/640 (36.6%), >6 hours: 885/2239 (39.6%) Risk of bias: high; Indirectness of outcome: Indirect: time to mortality not reported Protocol outcome 4: Duration of hospital stay - Actual outcome: hospital length of stay- median (IQR). 0-1 hours: 13 (6.4-25), 1-2 hours: 10 (5.6-19), 2-3 hours: 10 (5.6-19), 3-4 hours: 11 (5.9-20), 4-5 hours: 12 (5.9-23), 5-6 hours: 12 (6.3-22) ,>6 hours: 14 (7.3-29) Risk of bias: high; Indirectness of outcome: No indirectness Protocol outcome 5: Duration of critical care stay - Actual outcome: [ICU length of stay- median (IQR)]. 0-1 hours: 5.1 (2.4-11), 1-2 hours: 4.1 (2.1-8.9), 2-3 hours: 4.2 (2.1-8.8), 3-4 hours: 4.3 (2.0-9.5), 4-5 hours: 4.9 (2.4-11), 5-6 hours: 4.6 (2.1-10) ,>6 hours: 6.7 (2.8-15) Risk of bias: high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 222: FUSCO 2015

Study	Fusco 2015[97]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in the USA. 1 PICU
Line of therapy	Mixed
Duration of study	January 2011 – December 2012
Method of assessment of guideline condition	Adequate
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years or younger admitted to the PICU with a diagnosis of sepsis (based on ICD-9 codes for septicaemia, severe sepsis and septic shock).

Study	Fusco 2015[97]
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): 5 years (0.9-16.2). Gender (M:F): 47M (65.3%). Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Time to first antimicrobial administration from sepsis onset was calculated as the time from the first fluid bolus order to the time that the first antimicrobial was administered. Time to appropriate antimicrobial administration was calculated as the time from first fluid bolus order to the time that the first appropriate antimicrobial, as defined below, was administered. Appropriate empiric antimicrobial treatment was defined as the microbiological documentation of an infection that was being effectively treated based on in vitro susceptibility results at the time of its identification.
Funding	Not stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 4: [Duration of hospital stay]: 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

Protocol outcome 4: [Duration of ICU stay]: 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

Risk of bias: very high; Indirectness of outcome: No indirectness

Study	Fusco 2015[97]
Protocol outcomes not reported by the study	Critical: 1. 28-day mortality 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 223: GAIESKI 2010

Study	Gaieski 2010[98]
Study type	Retrospective analysis of a Cohort study
Number of studies (number of participants)	1 (n= 261)
Countries and setting	Conducted in USA. ED of an academic tertiary care centre.
Line of therapy	Unclear
Duration of study	Follow up: N/A
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients undergoing early goal-directed therapy for severe sepsis or septic shock
Subgroup analysis within study	N/A
Inclusion criteria	Inclusion criteria included1) inclusion in the severe sepsis and septic shock database; 2) initiation of EGDT (defined as algorithmic volume resuscitation, placement of central venous catheter, and measurement of central venous pressure, mean arterial pressure, and ScvO2) during the patient's ED stay.
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 59 (16) years. Gender: 41%F. Ethnicity: 48% black, 43% white
Indirectness of population	No indirectness
Interventions	Antibiotic therapy in the ED Concurrent medication/care: not stated
Funding	None stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS	

Study	Gaieski 2010[98]

Protocol outcome 1: 28-day mortality
- Actual outcome: In-hospital mortality: Triage to ED antibiotics

≤1 hour n=46 mortality 26.1%

>1 hour n=215 mortality 32.1% difference (%) 6.0 OR 0.51 95%CI 0.21–1.22 p value 0.13 probability of death 0.20 vs. 0.28

≤2hrs n=136 mortality 30.9%

>2 hours n=125 mortality 31.2% difference (%) 0.3 OR 0.72 95%CI 0.38–1.37 p value 0.30 probability of death 0.25 vs. 0.28

≤3hrs n=187 mortality 29.4%

>3 hours n=74 mortality 35.1% difference (%) 5.7 OR 0.64 95%CI 0.32–1.29 p value 0.21 probability of death 0.25 vs. 0.31

≤4hrs n=217 mortality 30.0%

>4 hours n=44 mortality 36.4% difference (%) 6.4 OR 0.80 95%CI 0.35–1.84 p value 0.59 probability of death 0.27 vs. 0.29

≤5hrs n= 237 mortality 32.1%

>5 hours n=24 mortality 20.8% difference (%) -11.2 OR 0.86 95%CI 0.56–6.15 p value 0.31 probability of death 0.28 vs. 0.16

- Actual outcome: In-hospital mortality: Qualified for EGDT to ED antibiotics

≤1 hour n=154 mortality 26.6%

>1 hour n=107 mortality 37.4% difference (%) 10.8 OR 0.58 95%CI 0.31–1.08 p value 0.09 probability of death 0.22 vs. 0.34

≤2hrs n=218 mortality 29.8%

>2 hours n=43 mortality 37.2% difference (%) 7.4 OR 0.77 95%CI 0.34–1.70 p value 0.51 probability of death 0.26 vs. 0.34

≤3hrs n=239 mortality 30.1%

>3 hours n=22 mortality 40.9% difference (%) 10.8 OR 0.62 95%CI 0.23–1.69 p value 0.36 probability of death 0.26 vs. 0.39

≤4hrs n=252 mortality 30.6%

>4 hours n=9 mortality 44.4% difference (%) 13.9 OR 0.77 95%CI 0.17–3.59 p value 0.74 probability of death 0.27 vs. 0.37

Study	Gaieski 2010[98]
≤5hrs n=257 mortality 31.1% >5 hours n=4 mortality 25.0% difference (%) -6.1 OR 1.33 95%CI 0.12–14.20 p value 0.82 probability of death 0.27 vs. 0.24 - Actual outcome: In-hospital mortality: Time from Triage to appropriate antibiotics ≤1 hour n=41 mortality 19.5% >1 hour n=220 mortality 33.2% difference (%) 13.7 OR 0.30 95%CI 0.11–0.83 p value 0.02 probability of death 0.13 vs. 0.29 ≤2hrs n=124 mortality 28.2% >2 hours n=137 mortality 33.6% difference (%) 5.4 OR 0.54 95%CI 0.29–1.03 p value 0.06 probability of death 0.22 vs. 0.31 ≤3hrs n=172 mortality 27.9% >3 hours n=89 mortality 37.1% difference (%) 9.2 OR 0.53 95%CI 0.27–1.01 p value 0.05 probability of death 0.23 vs. 0.34 ≤4hrs n=200 mortality 28.5% >4 hours n=61 mortality 39.3% difference (%) 10.8 OR 0.62 95%CI 0.31–1.24 p value 0.18 probability of death 0.25 vs. 0.34 ≤5hrs n= 218 mortality 30.7% >5 hours n=43 mortality 32.6% difference (%) 1.8OR 0.82 95%CI 0.37–1.79 p value 0.62 probability of death 0.27 vs. 0.29 - Actual outcome: In-hospital mortality: Time from qualification for EGDT to appropriate antibiotics ≤1 hour n=144 mortality 25.0% >1 hour n=117 mortality 38.5% difference (%) 13.5 OR 0.50 95%CI 0.27–0.92 p value 0.03 probability of death 0.20 vs. 0.35 ≤2hrs n=201 mortality 28.4% >2 hours n=60 mortality 40.0% difference (%) 11.6 OR 0.57 95%CI 0.27–1.15 p value 0.12 probability of death 0.24 vs. 0.38 ≤3hrs n=220 mortality 28.6% >3 hours n=41 mortality 43.9% difference (%) 15.3 OR 0.47 95%CI 0.22–1.01 p value 0.05 probability of death 0.24 vs. 0.43 ≤4hrs n=232 mortality 29.3%	

Study	Gaieski 2010[98]
>4 hours n=29 mortality 44.8% difference (%) 15.5 OR 0.49 95%CI 0.20–1.18 p value 0.11 probability of death 0.25 vs. 0.42 ≤5hrs n= 238 mortality 29.8% >5 hours n=23 mortality 43.5% difference (%) 13.7OR 0.48 95%CI 0.18–1.25 p value 0.13 probability of death 0.25 vs. 0.43 Multivariable logistic regression was used to adjust for potential confounding in the association between time to antibiotics and in-hospital mortality. Age, Acute Physiology and Chronic Health Evaluation II score, initial lactate, initial systolic blood pressure, initial temperature, and amount of intravenous fluid given during the first 6 hours and over the total ED stay were considered to be potential confounders.	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 224: GARNACHO-MONTERO 2010

Study	Garnacho-Montero 2010[107]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n= 125)
Countries and setting	Conducted in Spain. Tertiary care centre
Line of therapy	Mixed
Duration of study	Follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with bacteraemic pneumococcal community-acquired pneumonia
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients with at least 1 positive blood culture for S. pneumoniae
Exclusion criteria	Patients with severe neutropenia (<500 neutrophils/mm3)
Recruitment/selection of patients	All patients
Age, gender and ethnicity	Age - Mean (SD): 55 (30). Gender (M:F): Not reported. Ethnicity: Not reported

Study	Garnacho-Montero 2010[107]
Indirectness of population	No indirectness
Interventions	The following variables were prospectively collected: age, gender, chronic organ insufficiencies, recorded as defined by the acute physiology and chronic health evaluation Il (APACHE Il) score , and other comorbidities (alcoholism, smoking habit and diabetes mellitus) as defined by Pittet et al. (11]. The impact of comorbidities was also evaluated by the Charlson comorbidity index . At hospital admission, severity of illness was measured on the basis of the APACHE IJ score and the pneumonia severity index (PSI). In addition, clinical presentation (sepsis, severe sepsis or septic shock) was defined following American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria. The APACHE Il score of the first 24 h in the intensive care unit (ICU) was recorded in all patients who required ICU admission. Time to first antibiotic dose was defined as the period elapsed between the recorded time of hospital admission (i.e. when the patient first presented to the emergency department) and the time of the first dose of antibiotic. Time to first adequate antibiotic dose was defined as the period elapsed between the recorded time of hospital admission and the time of the first dose of appropriate antibiotics based on susceptibilities provided by the Microbiology Service.
Funding	This study was supported by Consejería de Salud de la Junta de Andalucía. Exp. Num. 0185 (2006), and Ministerio de Sanidad y Consumo, Instituto de Salud Carlos Ill, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: 28-day mortality
- Actual outcome: in-hospital mortality- bivariate analysis (1st antibiotic dose]; Survivors: 3h (15min-64h), Non-survivors: 5h (40 min-14h) p value 0.563. Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcome 1: 28-day mortality
- Actual outcome: in-hospital mortality- bivariate analysis (1st antibiotic dose ≥4 hours)]; Survivors: 44/104 (42%), Non-survivors: 12/21 (57%) p value 0.212. Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcome 1: 28-day mortality
- Actual outcome: in-hospital mortality- Cox proportional hazard model (1st antibiotic dose ≥4 hours)]; HR 1.909 (0.797-4.570) p value 0.147. Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcome 1: 28-day mortality
- Actual outcome: in-hospital mortality- Cox proportional hazard model- unadjusted (1st adequate antibiotic dose ≥4 hours)]; HR 2.101(0.860-5.130) p value 0.103. Risk

Study	Garnacho-Montero 2010[107]
of bias: high; Indirectness of outcome: No indirectness Protocol outcome 1: 28-day mortality - Actual outcome: in-hospital mortality- Cox proportional regression analysis (1st adequate antibiotic dose ≥4 hours)]; aHR 2.62 (1.06-6.45) p value 0.037. Risk of bias: high; Indirectness of outcome: No indirectness Protocol outcome 1: 28-day mortality - Actual outcome: 90 day mortality- Cox proportional regression analysis (1st adequate antibiotic dose ≥4 hours)]; aHR 2.21 (1.01-4.86) p value 0.048. Risk of bias: high; Indirectness of outcome: No indirectness To determine the independent effect of the variables on survival, the corresponding unadjusted and multivariable adjusted hazard ratio of death using the Cox proportional hazard regression analysis were calculated. All covariates with p < 0.1 in the unadjusted model were entered into the multivariable model (age, Charlson index, chronic renal failure, APACHE II, severe sepsis/ septic shock). Co-linearity was assessed via correlation matrices. Adjusted hazard ratios (aHR) and their 95% confidence intervals (CI) were calculated for each variable	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 225: JALILI 2013

Study	Jalili 2013[133]
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=145)
Countries and setting	Conducted in Iran. ED
Line of therapy	Unclear
Duration of study	Follow up: Hospital stay (mean 211.9 hours)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with sepsis: severity of sepsis determined using APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system
Subgroup analysis within study	Not applicable

Study	Jalili 2013[133]
Inclusion criteria	Patients with at least 2 out of 4 criteria for SIRS combined with high levels of serum procalcitonin (above 2µg/l).
Exclusion criteria	Age below 12 years, mechanical trauma, surgical trauma, heat stroke, thyroid tumours, squamous cell carcinoma, and severe burns.
Recruitment/selection of patients	APACHE score ≤10: n=55 (38%), APACHE score 11-20: n=62 (43%), APACHE score >20: n=27 (19%)
Age, gender and ethnicity	Age - Mean (SD): 60.4 (14.4) years. Gender: 82 male / 63 female. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Empiric antimicrobial treatment: prompt initiation of appropriate antibiotic therapy based on clinical diagnosis (at least one effective antibiotic (as confirmed by specialist in infectious diseases department) administered within 24 hours of patient entry to ED, administered according to the standard dose and pattern). The door-to antibiotic time was defined as the interval between patient`s arrival to ED and administration of first dose of antibiotic. Concurrent medication/care: not stated
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: Hospital mortality
- Actual outcome: Hospital mortality: overall population
Group 1 (door-to-antibiotic time <60 min): n=1/26 (4%)
Group 2 (door-to-antibiotic time 60-120 min): n= 16/80 (20%)
Group 3: (door-to-antibiotic time >120 min): n= 14/38 (37%), p=0.005
Risk of bias: very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Hospital mortality
Protocol outcome 2: Hospital mortality
- Actual outcome: Hospital mortality: overall population according to APACHE score
Door-to-antibiotic time <60 min
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 60-120 min

Study	Jalili 2013[133]
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 >120 min APACHE score ≤10: n=0/12 (0%) APACHE score 11-20: n=1/13 (8%) APACHE score >20: n=13/13 (100%) Risk of bias: very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health-related quality of life (for example, as assessed by SF-12 or EQ-5D), admission to critical care, duration of hospital stay. duration of critical care stay, number of organs supported (change is SOFA score), adverse events (inability to tolerate drugs).

Table 226: Joo 2014[141]

Study	Joo 2014
Study type	Retrospective observational cohort (prospective data collection)
Number of studies (number of participants)	1 (n= 591)
Countries and setting	Conducted in Korea ED
Line of therapy	Mixed
Duration of study	Follow up: 5 months
Method of assessment of guideline condition	Adequate
Stratum	Patients treated in the ED for septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 18 years of age with severe sepsis who had initial blood lactate concentrations of over 4 mmol/L and septic shock diagnosed at the time of ED arrival between August 2008 and March 2012.
Exclusion criteria	Patients with terminal malignancies or a previously signed “Do Not Attempt Resuscitation (DNAR)” order, as well as patients who refused early goal-directed therapy.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (interquartile range): 66 (55-73). Gender (%): 330 Male (55.8). Ethnicity: not stated

Study	Joo 2014
Indirectness of population	No indirectness
Interventions	Sepsis was defined as suspected or confirmed infection in the presence of two or more systemic inflammatory response syndrome. criteria. The systemic inflammatory response syndrome is defined by two or more of the following conditions: (1) body temperature greater than 38°C or less than 36°C; (2) heart rate greater than 90 beats per minute; (3) respiratory rate greater than 20 breaths per minute or PaCO2 of less than 32 mmHg; and (4) white blood cell count greater than 12,000/mm3, less than 4,000/mm3, or the presence of more than 10% immature neutrophils ("bands").1 Severe sepsis was defined as sepsis associated with acute organ dysfunction. Septic shock was defined as sepsis that presented with hypotension (systolic blood pressure <90 mmHg, mean arterial pressure [MAP] <60 mmHg, or a reduction in systolic blood pressure of >40 mmHg from baseline) despite adequate fluid resuscitation, in the absence of other causes for hypotension. Early antibiotic use was defined as administration of a broad-spectrum antibiotic within three hours from the time of ED arrival.11 All patients were classified into either the early administration group or delayed administration group for comparison. The sepsis registry was analysed, which had been prospectively collected since August of 2008, for relevant patients presenting to the ED. During the study period the resuscitation bundle was recommended for patients with severe sepsis or septic shock based on the protocol by Rivers et al. and the 2008 SSC guidelines.
Funding	None stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: [28-day mortality] - Actual outcome: [28-day mortality. Multivariable analysis for time to antimicrobial therapy (early administration median time 1.9 hours (IQR, 1.4 to 2.4 h) OR 0.54, 95%CI 0.34 - 0.87, p = 0.01 Multivariable logistic regression analysis to calculate adjusted ORs adjusted for potential cofounders including demographic factors (age, comorbidities, sites of infection), severity factors (APACHE II score, initial blood lactate concentration), and treatment factors (achievement of early resuscitation targets).	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 227: KARVELLAS 2015

Study	Karvellas 2015[142]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in the USA, Saudi-Arabia, and Canada. 28 medical centres
Line of therapy	Mixed
Duration of study	1996-2011
Method of assessment of guideline condition	Adequate
Stratum	Adult cirrhotic patients with spontaneous bacterial peritonitis-associated septic shock.
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with persistent hypotension requiring vasopressors and two of the following: heart rate of >90 beats/min, respiratory rate of >20 breaths/min or PaCO2 of <32 mmHg, core temperature of <36C or >38C, WBC count of <4000/mcl or >12000/mcl or bands >10%.
Exclusion criteria	Not stated
Recruitment/selection of patients	Retrospective database analysis (CATSS database)
Age, gender and ethnicity	Age – Mean (SD): 55 years (13). Gender (M:F): 60% male. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	For culture-positive septic shock, initial antimicrobial therapy was considered appropriate if an antimicrobial with in vitro activity appropriate for the isolated pathogen or pathogens was the first new antimicrobial agent given after the onset of recurrent or persistent hypotension or was initiated within 6 h of the administration of the first new antimicrobial agent. Otherwise, the initial therapy was considered inappropriate. For culture-negative septic shock, initial therapy was considered appropriate when an antimicrobial agent consistent with broadly accepted norms for empiric management of the typical pathogens for the clinical syndrome was the new antimicrobial agent given after the onset of recurrent or persistent hypotension or was initiated within 6 h of administration of the first new antimicrobial agent.
Funding	None declared.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS	

Study	Karvellas 2015[142]
Protocol outcome 1: [28-day mortality]: - Actual outcome: Multivariable analysis of in-hospital mortality due to hourly time delay to appropriate antimicrobial therapy: OR 1.86 (95% CI 1.10-3.14), p=0.02. Risk of bias: very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of ICU stay 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 228: KUMAR 2006

Study	Kumar 2006[157]
Study type	Retrospective observational cohort
Number of studies (number of participants)	1 (n= 2731)
Countries and setting	Conducted in Canada First cohort: adult ICUs (2 medical, 2 general surgical, five mixed) of all hospitals (2 tertiary, 5 community) in province of Manitoba, Canada, from May 1999 to June 2004. Second cohort: all cases of septic shock occurring between June 1989 and April 1999 at a single adult academic tertiary care institution (1 medical and 1 general surgical) in Winnipeg, Manitoba. Third cohort: consecutive adult septic shock patients (approximately 150 each from July 1999 to June 2004) at 3 academic American institutions.
Line of therapy	Mixed
Duration of study	Total recruitment period: 5 years
Method of assessment of guideline condition	Adequate
Stratum	Patients treated in the ICU for proven or suspected infection with at least one new organ dysfunction related to the infection.
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients identified according to 1991 Society of Critical Care Medicine/American College of Chest Physicians Consensus Statement on Sepsis Definitions.
Exclusion criteria	No other obvious cause of shock.

Study	Kumar 2006[157]
Recruitment/selection of patients	First and second cohort: use of a locally developed ICU database in which ICU admission and acquired diagnoses are prospectively encoded by the attending physician and confirmed by specially trained research nurses. Third cohort: use of a combination of internal ICU registries and/or International Classification of Diseases Revision 9 coding strategies dependant on specific institutions coding practices.
Age, gender and ethnicity	Age - Mean (SD): 62.7 (16.4) years. Gender (M:F): 54.3% M, 45.7% F. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Antimicrobial therapy
Funding	Eli-Lilly, Pfizer, Merck, and Astra-Zeneca, Health Sciences Centre Department of Research and Health Sciences Centre Foundation.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: Survival to hospital discharge
- Actual outcome: Survival to hospital discharge

Overall mortality rate (n=2731): 56.2%. Survival similar for: documented or suspected infection, a plausible pathogen identified or not, bacteraemia present or absent. Of n=2731 patients with septic shock, n=19 did not receive effective antimicrobials before death, n=558 were on antimicrobial therapy that was either proven (defined pathogen) or adjudicated (undefined pathogen) effective for the infection thought to underlie septic shock before the onset of hypotension. Of the remaining

Mortality rate of remaining n=2154 patients who received effective antimicrobials only after onset of hypotension: 58.0%.

Risk of bias: high; Indirectness of outcome: No indirectness

- Actual outcome: Mean decrease in survival over first 6 hours after onset recurrent or persistent hypotension

Each hour of delay in initiation of effective antimicrobial therapy was associated with mean decrease in survival of 7.6% (range 3.6 –9.9)

Risk of bias: high; Indirectness of outcome: No indirectness

- Actual outcome: Survival to ICU and hospital discharge:

Univariable analysis (adjusted): delay from initial recurrent or persistent hypotension to administration of effective antimicrobial therapy associated with survival to ICU (p<0.001) and hospital discharge (p<0.001)

Risk of bias: high; Indirectness of outcome: No indirectness

- Actual outcome: In-hospital mortality 1st versus 2nd hour delay in antimicrobial therapy

Study	Kumar 2006[157]
Univariable analysis (adjusted): odds ratio 1.67 (1.12-2.48) Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: In-hospital mortality as continuous variable Univariable analysis (adjusted): odds ratio 1.119 (per hour delay) (1.103–1.136, p<0.0001 Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: Survival to hospital discharge Multivariable analysis (adjusted for; effectiveness of initial antimicrobial therapy, choice and magnitude of early fluid resuscitation, single vs. multiple drug class, antimicrobial therapy, and choice and rapidity of initiation of initial vasopressor/inotropic support): time to effective anti- microbial therapy was most strongly associated with outcome (p<0.0001). Delay from onset of persistent/ recurrent hypotension to initiation of effective antimicrobial therapy accounted for 28.1% of the variance in outcome APACHE II score at ICU admission accounted for 24.6% of the variance. Volume of fluids infused in the first hour of hypotension accounted for 2% of the variance (p=0.038) Risk of bias: high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 229: LARCHE 2003

Study	Larche 2003[162]
Study type	Retrospective observational cohort
Number of studies (number of participants)	1 (n= 88)
Countries and setting	Conducted in France. ICU (St Louis Teaching hospital, Paris)
Line of therapy	Mixed
Duration of study	Study period: 6 years
Method of assessment of guideline condition	Adequate
Stratum	Critically ill cancer patients with septic shock

Study	Larche 2003[162]
Subgroup analysis within study	Not applicable
Inclusion criteria	Septic shock defined on the basis of the 5 following: (1) clinical evidence of infection, (2)tachycardia (>90 beats/min, (3) tachypnea (>20 breaths/min) or need for mechanical ventilation, (4) refractory hypotension defined as the sustained decrease in systolic blood pressure <90 min mmHg despite fluid replacement (500 ml), or use of vasopressor to maintain blood pressure >90 beats/min, (5)evidence of inadequate organ function or perfusion within 12 h of enrolment, as manifested by at least one of the following syndromes; acute alteration of mental status, arterial hypoxemia, plasma lactate concentrations above normal range or metallic acidosis, oliguria defined by urine output <0.5 ml/kg per hour, and disseminated intravascular coagulation. Comorbidities
Exclusion criteria	Patients who were recipients of allogenic bone marrow transplantation.
Recruitment/selection of patients	Patients admitted to ICU between Jan 1995-Dec 2000.
Age, gender and ethnicity	Age - Mean (range): 55 (43.5-63) years. Gender (M:F): 55M, 33 F. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Antimicrobial therapy
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: 30-day mortality - Actual outcome: 30-day mortality Univariable analysis: time to antibiotic administration 2 h: OR 6.5 (1.386-30.492) (p<0.0176) Multivariable analysis (adjusted for severity of illness); antibiotic administration <2 h vs. >2 h OR 7.04 (1.17-42.21) (p=0.03) Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: ICU mortality, n (%): 57 (65.5)	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 230: LUENANGARUN 2012

Study	Lueangarun 2012[177]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=229)
Countries and setting	Conducted in Thailand. Hospital (medical wards)
Line of therapy	Unclear
Duration of study	Follow up: unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis (All cases with positive hemoculture result were determined to meet the specific criteria for sepsis, severe sepsis, and septic shock according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference definition)
Stratum	Patients with sepsis (13.5%), severe sepsis (25.3%) and septic shock (61.1%)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed as sepsis, severe sepsis, or septic shock, with positive hemoculture on the day of diagnosis.
Exclusion criteria	Patients with second episode of sepsis or more likely with bacteraemia in the same admission, polymicrobial infection, and organisms other than bacteria (e.g., fungus).
Recruitment/selection of patients	A retrospective cohort study was conducted during January–December 2009 at the medical wards of the Siriraj Hospital. Comorbidities: diabetes mellitus (31.0%), immunosuppressive therapy (29.3%), reduced mobility (29.7%), liver failure (21.8%), congestive heart failure (21.8%), chronic kidney disease (18.3%), and hematologic malignancy (18.2%)
Age, gender and ethnicity	Age - Mean (SD): 63.5 (17.2). Gender (M:F): 49.8% M/ 50.2% F. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Empiric antimicrobial treatment: about 63.3% of septic patients received single antimicrobial therapy. Antimicrobials frequently administered were cephalosporin (57.6%), carbapenem (23.1%), beta-lactam/beta-lactamase inhibitor (12.2%), vancomycin (11.4%), aminoglycosides (7.4%), fluoroquinolones (8.3%), and colistin (4.8%). Group 1: antimicrobial <1 hour Group 2: antimicrobial 1-6 hour Group 3: antimicrobial >6 hours Concurrent medication/care: not stated
Funding	The authors have no conflict of interests to declare
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS	

Study	Lueangarun 2012[177]
Protocol outcome 1: 28-day mortality - Actual outcome: 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%) Risk of bias: high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	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. Duration of hospital stay. Duration of critical care stay. Number of organs supported (change is SOFA score). Adverse events (inability to tolerate drugs).

Table 231: MENENDEZ 2012

Study	Menendez 2012[196]
Study type	Prospective observational
Number of studies (number of participants)	1 (n= 4137, 2966 (72%) with sepsis or with severe sepsis)
Countries and setting	Conducted in Spain. Hospital
Line of therapy	Mixed
Duration of study	Follow up: 30 days
Method of assessment of guideline condition	Adequate
Stratum	Patients with community-acquired pneumonia (CAP)
Subgroup analysis within study	Not applicable
Inclusion criteria	A new radiographic infiltrate compatible with the presence of acute pneumonia and at least 2 signs or symptoms of CAP
Exclusion criteria	Exclusion criteria were admission within the previous 15 days, nursing-home patients, immunosuppressive treatment and/or steroids (>15 mg/day) and do not resuscitate orders.
Recruitment/selection of patients	Not reported 1394 sepsis (33.7%) 1572 severe sepsis (38.0%) Sepsis and severe sepsis were defined according to previously accepted criteria [International Sepsis Definition)) Sepsis was defined as the presence of pneumonia and SIRS. Severe sepsis was considered if the criteria for sepsis were met, together with acute organ dysfunction: arterial hypoxaemia, creatinine >2 mg/dL, acute confusion, thrombocytopenia or hyperbilirubinaemia

Study	Menendez 2012[196]
Age, gender and ethnicity	Age - Mean (SD): Non-severe sepsis (n=1394): 61.5 (19.3). Severe sepsis (n=1572): 68.7 (16.5). Gender (M:F): Non- severe sepsis: 909/485. Severe sepsis: 1091/481 Ethnicity: Nor reported
Indirectness of population	No indirectness
Interventions	The most frequent non-adherent (53% in the non-sepsis group, 46% in the sepsis group and 37% in the severe sepsis group) and fluorquinolone plus ß-lactams (27% in the non-sepsis group, 32% in the sepsis group and 36% in the severe sepsis group). The combination of two processes of care was observed in 53.4% of patients and three processes of care in 48.4% of patients . The following processes of care in accordance with Spanish guidelines were recorded: 1) assessment of arterial oxygenation on presentation (by pulse oximetry or arterial blood gas analysis); 2) time until first antibiotic dose (<6 h); and 3) antibiotic adherence to the Spanish guidelines. Antibiotic adherence was considered as follows: in hospitalised CAP patients, either third-generation cephalosporin, amoxicillin-clavulanate combined with a macrolide, or third- or fourth-generation fluoroquinolone in monotherapy and, in intensive care unit patients, a combination of third-generation cephalosporin or amoxicillin-clavulanate plus macrolides or fluoroquinolone. All other regimens were considered non-adherent.
Funding	The study was supported by CIBERES, an initiative of ISCIII, FIS grant PI041150, SEPAR grant 2007 and PII (SEPAR Research Programme) in respiratory infections, and a grant from the Ministry of Health of the Autonomous Community of Valencia Conselleria Sanitat Comunidad Valenciana 2007.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Multivariable analyses Protocol outcome 1: 28-day mortality - Actual outcome: mortality at 30 days- multivariable analysis for whole population; OR 0.67 (0.50-0.89) p 0.007. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: 28-day mortality - Actual outcome: [mortality at 30 days- multivariable analysis for non-severe sepsis]; OR 0.44 (0.24-0.82) p 0.009. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: 28-day mortality - Actual outcome: mortality at 30 days- multivariable analysis for severe sepsis; OR 0.69 (0.48-1.015) p 0.06. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 2: Duration of hospital stay	

Study	Menendez 2012[196]
- Actual outcome: length of hospital stay- multivariable analysis for whole population; OR 0.80 (0.71-0.91) p 0.001. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: Duration of hospital stay - Actual outcome: length of hospital stay - multivariable analysis for non-severe sepsis; OR 0.73 (0.58-0.92) p 0.007. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: Duration of hospital stay - Actual outcome: length of hospital stay - multivariable analysis for non-severe sepsis; OR 0.94 (0.77-1.16) p 0.6. Risk of bias: low; Indirectness of outcome: No indirectness Several logistic regression analyses were performed for each outcome: 30-day mortality, and LOS. For each dependent outcome variable, several logistic regression analyses were performed for the whole cohort and stratified by sepsis criteria using processes of care in one to three combinations as independent variables. We included the prognostic scale PSI and the hospital as independent variables in order to adjust for the independent effect of processes of care. The Hosmer and Lemeshow goodness-of-fit test was used to evaluate the adequacy of the models. The areas under the receiver operating characteristic curves were also calculated. Protocol outcome 1: 28-day mortality - Actual outcome: 30 day mortality- non-severe sepsis; Group 1 (antibiotics within 6 hours): n= 18 (2.4%), Group 2 (antibiotics >6 hours): n= 5 (2.3%) p value 0.9. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: 28-day mortality - Actual outcome: 30 day mortality- severe sepsis; Group 1 (antibiotics within 6 hours): n= 58 (6.9%), Group 2 (antibiotics >6 hours): n= 20 (10.2%). p value 0.1 Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 2: Duration of hospital stay. Median and IQR - Actual outcome: length of hospital stay in days- non-severe sepsis; Group 1 (antibiotics within 6 hours, n=753): 6 (4-9), Group 2 (antibiotics >6 hours, n=1394-753= 641): 7 (5-9). p value 0.04 Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 2: Duration of hospital stay. Median and IQR - Actual outcome: length of hospital stay in days- severe sepsis; Group 1 (antibiotics within 6 hours, n=856): 8 (5-13), Group 2 (antibiotics >6 hours, n=1572-856=716): 7 (5-11). p value 0.2 Risk of bias: low; Indirectness of outcome: No indirectness	

Study	Menendez 2012[196]
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 232: NYGARD 2014

Study	Nygard 2014[219]
Study type	Prospective case-defined observational study
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in Norway. University hospital in western Norway.
Line of therapy	Empirical antimicrobial regimen based on suspected or confirmed focus of infection
Duration of study	Follow up: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalisation due to community acquired infection with the development of sepsis within 24 hours of admission to primary institution.
Exclusion criteria	≤15 years of age
Recruitment/selection of patients	All patients transferred to ICUs from emergency department were screened for sepsis based on international criteria. Selection of patients based on consensus meetings within the group of co-authors.
Age, gender and ethnicity	Age - Median: 67. Gender (M:F): 117:103. Ethnicity: not reported
Indirectness of population	No indirectness
Interventions	Empirical antimicrobial treatment: time of initial dose administered Group 1: <6 hours after admission Group 2: ≥6 hours after admission Concurrent medication/care: not reported
Funding	This study was funded by the Department of Medicine, Haukeland University Hospital.

Study	Nygard 2014[219]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality]; Group 1: n=157, 19.1%, Group 2: n=54, 40.7%. Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	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, duration of hospital stay, duration of critical care stay, number of organs supported (change is SOFA score), adverse events (inability to tolerate drugs).

Table 233: PUSKARICH 2011

Study	Puskarich 2011[244]
Study type	Pre-planned analysis of RCT
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in the USA. Multicentre study at the emergency departments of three large, urban, tertiary care hospitals.
Line of therapy	Unclear
Duration of study	Follow up: unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with confirmed or suspected infection, two or more systemic inflammatory response criteria, hypoperfusion evidenced by hypotension after fluid challenge or blood lactate concentration of at least 4 mmol/L
Exclusion criteria	<18 years old
Recruitment/selection of patients	Consecutive patients presenting to one of the emergency departments
Age, gender and ethnicity	Age - Mean (IQR): 62 (50, 73). Gender (M:F): 156:135. Ethnicity: 54% Caucasian, 34% Black American, 9% Hispanic, 2% other
Indirectness of population	No indirectness
Interventions	Antibiotic treatment: hourly increment up to a maximum of 6 hours after ED triage Group 1: ≤1 hour

Study	Puskarich 2011[244]
	Group 2: >1 hour Group 3: ≤2 hours Group 4: >2 hours Group 5: ≤3 hours Group 6: >3 hours Group 7: ≤4 hours Group 8: >4 hours Group 9: ≤5 hours Group 10: >5 hours Group 11: ≤6 hours Group 12: ≤6 hours Antibiotic treatment: hourly increment up to a maximum of 3 hours after shock recognition Group 1: prior to shock recognition Group 2: after shock recognition Group 3: ≤1 hour Group 4: >1 hour Group 5: ≤2 hours Group 6: >2 hours Group 7: ≤3 hours Group 8: >3 hours Concurrent medication/care: not reported
Funding	The study was supported by national grants and grants from research bodies. Two authors had received industry support in the past or were holding company stock ownership.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 1 hour]; Group 1: n=65, 16.9%, Group 2: n=226, 19.5%. Risk of bias: low; Indirectness of outcome: No	

Study	Puskarich 2011[244]
indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 2 hours]; Group 3: n=155, 21.3%, Group 4: n=136, 16.2%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 3 hours]; Group 5: n=223, 20.6%, Group 6: n=68, 13.2%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 4 hours]; Group 7: n=255, 20.4%, Group 8: n=36, 8.3%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 5 hours]; Group 9: n=274, 19.7%, Group 10: n=17, 5.9%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 6 hours]; Group 11: n=281, 19.6%, Group 12: n=10, 0%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after shock recognition]; Group 1: n=119, 11.8%, Group 2: n=172, 23.8%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 1 hour after shock recognition]; Group 3: n=101, 25.8%, Group 4: n=71, 21.1%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 2 hours after shock recognition]; Group 5: n=145, 24.1%, Group 6: n=27, 22.2%. Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality] - Actual outcome: [in-hospital mortality; before and after 3 hours after shock recognition]; Group 7: n=164, 23.8%, Group 8: n=8, 25.0%. Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	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, duration of hospital stay, duration of critical care stay, number of organs supported (change is SOFA score), adverse events (inability to tolerate drugs).

Table 234: Ryoo 2015[251]

Study	Ryoo 2015
Study type	Retrospective observational cohort (prospective data collection)
Number of studies (number of participants)	1 (n= 426)
Countries and setting	Conducted in Korea ED
Line of therapy	Mixed
Duration of study	Follow up: 1 month
Method of assessment of guideline condition	Adequate
Stratum	Patients treated in the ED for septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Septic shock adult patients (≥18 years old) who fulfilled the septic shock criteria were prospectively added to the septic shock registry from January 2010 to December 2012. From this registry, we retrospectively identified patients who developed shock at or after initial assessment and 1st received antibiotics after shock recognition.
Exclusion criteria	39 patients who received antibiotics before shock recognition and 38 patients who had a "do not attempt resuscitation" status
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean: 62.9 Gender (%): 260 Male (61). Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Diagnosis of septic shock was defined as refractory hypotension, specifically, systolic blood pressure ,90 mm Hg or mean arterial pressure ,70 mm Hg requiring vasopressors despite adequate fluid therapy, or a blood lactate concentration of at least 4 mmol/L.4 All consecutive patients with septic shock received protocol-driven resuscitation bundle therapy, including early quantitative resuscitation, according to the Surviving Sepsis Campaign. The achievement of early resuscitation goals was defined as the accomplishment of all 3 bundle elements within 6 hours as follows: (1) mean arterial pressure >65 mm Hg, (2) central venous pressure >8 mm Hg and (3) central venous oxygenation ≥70%. There was guidance on initial empiric antibiotic selection to minimize the percentage of patients who received inappropriate antibiotics in the ED. Recommendations were based on the presumed source of infection: ceftriaxone with azithromycin or piperacillin-tazobactam with levofloxacin for pneumonia, cefotaxime with metronidazole for intra-abdominal infections, piperacillin-tazobactam with vancomycin for neutropenia, carbapenem for recent infection of extended spectrum betalactamase releasing pathogen and piperacillin-tazobactam with ciprofloxacin for unknown infection sources

Study	Ryoo 2015
	Antibiotic treatment: hourly increment up to a maximum of 5 hours after ED triage Group 1: ≤1 hour Group 2: ≤2 hour Group 3: ≤3 hours Group 4: ≤4 hours Group 5: ≤5 hours
Funding	The authors have no financial or other conflicts of interest to disclose.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: [28-day mortality] - Actual outcome: [28-day mortality. Multivariable analysis for time to antimicrobial therapy (early administration median time 1.9 hours (IQR, 1.4 to 2.4 h) Group 1: OR 0.81 (0.45 - 1.45) Risk of bias: low; Indirectness of outcome: No indirectness Group 2: OR 0.72 (0.4 - 1.29) Risk of bias: low; Indirectness of outcome: No indirectness Group 3: OR 0.61 (0.30 - 1.25) Risk of bias: low; Indirectness of outcome: No indirectness Group 4: OR 0.66 (0.27 - 1.66) Risk of bias: low; Indirectness of outcome: No indirectness Group 5: OR 0.48 (0.15 - 1.52) Risk of bias: low; Indirectness of outcome: No indirectness Adjusted for achievement of early resuscitation goals, initial respiratory rate, lactic acid concentration and sequential organ failure assessment score.	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 235: WEISS 2014

Study	Weiss 2014[295]
Study type	Retrospective observational study
Number of studies (number of participants)	1 (n=130)

Study	Weiss 2014[295]
Countries and setting	Conducted in the USA. Single-centre study at one PICU of an academic medical centre.
Line of therapy	Unclear
Duration of study	Follow up: unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with
Subgroup analysis within study	Not applicable
Inclusion criteria	Entry into the sepsis registry; recognition and initial therapy for sepsis on the PICO, inpatient ward or operating theatre of the participating hospital; treatment for severe sepsis or septic shock on the PICU
Exclusion criteria	Patients transferred from other facilities with sepsis
Recruitment/selection of patients	All patients with severe sepsis and septic shock treated at the PICU from January 2012 through January 2013.
Age, gender and ethnicity	Age - Median (IQR): 7.7 (1.7-15.1). Gender (M:F): 73:57. Ethnicity: 49% white, 32% black, 3% other, 16% unknown
Indirectness of population	No indirectness
Interventions	Antibiotic treatment: time from sepsis recognition to initial antimicrobial administration Group: ≤1 hour Group: >1 hour Group 3: ≤2 hours Group 4: >2 hours Group 5: ≤3 hours Group 6: >3 hours Group: 7: ≤4 hours Group 8: >4 hours Antibiotic treatment: time from sepsis recognition to first appropriate antimicrobial administration Group: ≤1 hour Group: >1 hour Group 3: ≤2 hours Group 4: >2 hours Group 5: ≤3 hours Group 6: >3 hours

Study	Weiss 2014[295]
	Group: 7: ≤4 hours Group 8: >4 hours Concurrent medication/care: vasoactive infusion (74%), mechanical ventilation (62%), IV fluids
Funding	This study was supported by academic and public research funds. Some of the authors received industry support.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 1 hour of sepsis recognition]; Group 1: n=24, 8%, Group 2: n=106, 13%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 2 hours of sepsis recognition]; Group 3: n=55, 7%, Group 4: n=75, 17%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 3 hours of sepsis recognition]; Group 5: n=78, 6%, Group 6: n=52, 23%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 4 hours of sepsis recognition]; Group 7: n=91, 8%, Group 8: n=39, 23%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, appropriate treatment before and after 1 hour of sepsis recognition]; Group 1: n=16, 13%, Group 2: n=114, 12%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 2 hours of sepsis recognition]; Group 3: n=43, 7%, Group 4: n=87, 15%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 3 hours of sepsis recognition]; Group 5: n=66, 6%, Group 6: n=64, 19%. Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 1: [28-day mortality]
- Actual outcome: [PICU mortality, initial treatment before and after 4 hours of sepsis recognition]; Group 7: n=78, 8%, Group 8: n=52, 19%. Risk of bias: low; Indirectness of outcome: No indirectness

Study	Weiss 2014[295]
Protocol outcomes not reported by the study	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, duration of hospital stay, duration of critical care stay, number of organs supported (change is SOFA score), adverse events (inability to tolerate drugs).

Table 236: WISDOM 2015

Study	Wisdom 2015[296]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in Australia. 1 tertiary hospital
Line of therapy	Mixed
Duration of study	January 2012 – December 2012
Method of assessment of guideline condition	Adequate
Stratum	Uncomplicated sepsis (n=102) and severe sepsis (n=118)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not stated
Exclusion criteria	<18 years old, transferred to the medical centre from another hospital, received IV antibiotics within 24 hours before ED presentation.
Recruitment/selection of patients	Patients assessed for inclusion if they presented with clinical evidence of sepsis at the ED.
Age, gender and ethnicity	Age – Median (IQR): 74.5 (61.8-85.0). Gender (M:F): 51.8% male. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	Initial empirical antibiotic regimens were assessed to determine appropriateness according to presumed source of infection, immune function, antibiotic hypersensitivities and multi-resistant organism colonisation. Prescribed empirical antibiotics were considered adherent if they were consistent with current Australian Therapeutic Guidelines: Antibiotic, version 14. Non-adherent antibiotic regimens were categorised as adequate, insufficient or broader than required through consensus by a hospital panel comprised of an infectious disease physician and two senior pharmacists. A clinically relevant blood culture result was defined as an isolate that was deemed not to be a

Study	Wisdom 2015[296]
	probable contaminant.
Funding	None declared.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: [28-day mortality]: - Actual outcome: 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 (95% CI 0.73-3.92), p=0.22 3-6 hr (n=61): HR 1.12 (95% CI 0.47-2.92), p=0.72 >6 hr (n=60): HR 1.75 (95% CI 0.75-5.09), p=0.20 Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality]: - Actual outcome: 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 (95% CI 0.19-14.10), p=0.65 3-6 hr (n=35): HR 0.67 (95% CI 0.07-6.19), p=0.72 >6 hr (n=30): HR 0.57 (95% CI 0.06-5.70), p=0.63 Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 1: [28-day mortality]: - Actual outcome: 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 (95% CI 0.58-3.86), p=0.41 3-6 hr (n=26): HR 1.50 (95% CI 0.53-4.25), p=0.44 >6 hr (n=30): HR 2.25 (95% CI 0.91-5.59), p=0.08 Risk of bias: very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression.

Study	Wisdom 2015[296]
	Important: 4. Duration of hospital stay. 5. Duration of ICU stay 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

Table 237: YOKOTA 2014

Study	Yokota 2014[300]
Study type	Retrospective cohort
Number of studies (number of participants)	1 (n=1,279)
Countries and setting	Conducted in Brazil. ICU of a tertiary care, private hospital.
Line of therapy	Unclear
Duration of study	Follow up: unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: all patients were diagnosed with severe sepsis or septic shock based on the definitions of the International Sepsis Forum.
Stratum	Patients with positive blood culture (32.1%)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with severe sepsis and septic shock (68.5%).
Exclusion criteria	Not reported.
Recruitment/selection of patients	A retrospective cohort study was conducted from July 2005 to December 2012 at the ICU of a tertiary care, private hospital in Sao Paulo, Brazil.
Age, gender and ethnicity	Age - Mean (SD): 67 (±18). Gender (M:F): 738:542. Ethnicity: not reported
Indirectness of population	No indirectness
Interventions	Antibiotic treatment: broad-spectrum antibiotics in <1 hour Group 1: total study population Group 2: positive blood culture Concurrent medication/care: IV fluids for septic shock patients
Funding	The authors have no conflict of interest to report.

Study	Yokota 2014[300]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: 28-day mortality - Actual outcome: in-hospital mortality; Group 1: n=206 (55.5%), Group 2: n=60 (59.4%) Risk of bias: high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	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, duration of hospital stay, duration of critical care stay, number of organs supported (change is SOFA score), adverse events (inability to tolerate drugs).

Table 238: ZHANG 2015B

Study	Zhang 2015B[305]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=1058)
Countries and setting	Conducted in the USA. 1 academic hospital, ICU
Line of therapy	Mixed
Duration of study	January 2008 – December 2012
Method of assessment of guideline condition	Adequate
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	All hospitalised patients with severe sepsis or septic shock and a positive blood culture obtained while admitted to an ICU were eligible.
Exclusion criteria	Patients with polymicrobial infections.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age – Mean (SD): 61.7 (16.6). Gender (M:F): 58.3 male. Ethnicity: 63% White, 30% African-American
Indirectness of population	No indirectness
Interventions	Antimicrobial treatment classified as appropriate if the antibiotic regimen administered was active against the identified pathogen based on in vitro antimicrobial susceptibility testing results.

Study	Zhang 2015B[305]
Funding	Authors supported by industry grants.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 4: [Duration of hospital stay]: - Actual outcome: 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 post-infection hospital LOS Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 5: [Duration of ICU stay]: - Actual outcome: 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; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 1. 28-day mortality 2. Health-related quality of life (for example, as assessed by SF-12 or EQ-5D). 3. Admission to critical care as a proxy for disease progression. Important: 6. Number of organs supported (change is SOFA score). 7. Adverse events (inability to tolerate drugs).

H.2.3 IV fluid administration

Table 239: ALBIOS trial: CAIRONI 2014

Study	ALBIOS trial: Caironi 2014[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1818; 579 randomised within 6 hours)
Countries and setting	Conducted in Italy; Setting: 100 ICUs in Italy
Line of therapy	1st line

Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Stratification based on ≤6 hours versus >6 hours
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with severe sepsis or septic shock if: proven or suspected infection in at least one site, two or more SIRS criteria, presence of at least a severe and acute sepsis-related organ dysfunction as measured by the modified SOFA score
Exclusion criteria	<18 years, terminal state, known adverse reaction to albumin administration, severe sepsis or septic shock in patients after proven or suspected head injury (clinically active), congestive heart failure (NYHA class of 3 or 4), pathological conditions in which albumin administration is clinically indicated (hepatic cirrhosis with ascites, intestinal malabsorption syndrome, nephrotic syndrome, burns), more than 24 hours since inclusion criteria were met, religious objection to the administration of human blood products, inclusion in other experimental studies
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Albumin group: 70 (57-77); Crystalloid group: 69 (59-77). Gender (M:F): 1093/717. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=289) Intervention 1: Albumin. Immediately after randomisation: 300 ml 20% albumin. Subsequently, from day 1 until the end of the study, 20% albumin was administered on a daily basis to maintain serum albumin ≥30 g/l based on:(1) administration of 300 ml of 20% albumin solution (for a total of 60 g of albumin), if serum albumin concentration <25 g/l;(2) administration of 200 ml of 20% albumin solution (for a total of 40 g of albumin), if serum albumin concentration was ≥25 g/l and <30 g/l;(3) no infusion of albumin, if serum albumin concentration was ≥30 g/l. Duration 28 days. Concurrent medication/care: Crystalloid solution (n=290) Intervention 2: Crystalloids - Saline. Crystalloids were administered whenever necessary on clinical bases. Administration of 20% albumin was restricted, as protocol violation, to emergency use, based on standard criteria of each participating unit.. Duration 28 days. Concurrent medication/care: Not reported
Funding	Academic or government funding (Italian Medicines Agency)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus SALINE

Protocol outcome 1: Mortality at 28-day

- Actual outcome: Death from any cause at 90 days; Group 1: 115/283, Group 2: 116/286; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Length of stay - ICU at Define; Admission to critical care at Define; Number of organs supported at Define; Time to shock reversal at Define; Adverse events at Define; Length of stay - hospital at Define

Table 240: DOLECEK 2009

Study	Dolecek 2009[78]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in the Czech Republic; Single-centre study at an urban teaching hospital with 4 ICUs
Line of therapy	1st line
Duration of study	May 2005 – February 2008
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Severe sepsis
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients admitted to the ICU during the study period, who were ventilated and developed severe sepsis
Exclusion criteria	<18 years of age, severe coagulopathy, pregnancy, cardiac failure, acute renal failure, severe aortal regurgitation, aortal aneurysm, dysrhythmia, limitation of PiCCO
Recruitment/selection of patients	All patients, who were admitted to the ICU during the study period and who met the inclusion criteria, were screened
Age, gender and ethnicity	Age - Mean (range): ALB group: 47 (19-81); HES group: 43 (23-67). Gender (M:F): ALB group: 26:4; HES group: 22/4 Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: 20% albumin 100 ml every 12 hours. Duration: 72 hours max. Concurrent medication/care: Initial

	fluid administration in accordance with recommendations of the Surviving Sepsis Campaign (n=26) Intervention 2: 6% HES 130/0,4 250 ml every 6 hours. Duration: 72 hours max. Concurrent medication/care: Initial fluid administration in accordance with recommendations of the Surviving Sepsis Campaign
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus HYDROXYETHYL STARCH Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: 28-day mortality; Group 1: 4/30, Group 2: 6/26; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 241: FULLER 2010

Study	Fuller 2010[96]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=93)
Countries and setting	Conducted in the USA; Single-centre study
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients with septic shock triggering the EGDT protocol: systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg despite a crystalloid challenge of 20-30 ml/kg, or initial serum lactate concentration >4 mmol/litre
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Ag: PRBC group: average age: 63.5; Not-PRBC group: average age: 59.3. Gender (M:F): PRBC group: 22:12; Not-PRBC group: 33:26. Ethnicity: PRBC group: 44.1% Black, 8.8% Hispanic, 47.1% White, 0% other; Not-PRBC group: 37.3% Black, 15.3% Hispanic, 45.8% White, 1.7% other
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Packed red blood cells + EGDT. Average of 4.56 units per patient. Duration: Not reported Concurrent medication/care: Antibiotics (n=93) Intervention 2: EGDT only. Duration: Not reported. Concurrent medication/care: Antibiotics
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRBC + EGDT versus EGDT only Protocol outcome 1: Mortality at 28-day - Actual outcome for septic shock: hospital mortality; Group 1: 14/34, Group 2: 20/59; Risk of bias: low; Indirectness of outcome: No indirectness Protocol outcome 4: Duration of hospital stay - Actual outcome for septic shock: hospital length of stay; Group 1: 25.9 days, Group 2: 12.5 days; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Duration of critical care stay - Actual outcome for septic shock: ICU length of stay; Group 1: 11.4 days, Group 2: 3.8 days; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis

	Important: 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 242: HOLST 2014

Study	Holst 2014[127]
Study type	RCT (Patient randomised)
Number of studies (number of participants)	1 (n=998)
Countries and setting	Conducted in Denmark, Sweden, Norway and Finland; Multi-centre study at 32 participating ICUs
Line of therapy	1st line
Duration of study	03 December 2011 – 26 December 2013
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock
Subgroup analysis within study	Age (>70 years versus ≤70 years)
Inclusion criteria	Patients ≥18 years in the ICU, who fulfilled the criteria for septic shock and had a blood concentration of haemoglobin of 9 g/dl or less
Exclusion criteria	Documented wish against transfusion, acute myocardial ischemia or unstable angina pectoris, life-threatening bleeding, red cell transfusion during current ICU admission, withdrawal from active therapy or brain death, acute burn injury, lack of informed consent
Recruitment/selection of patients	All patients, who were admitted to the ICU during the study period and who met the inclusion criteria, were screened
Age, gender and ethnicity	Age - Median (IQR): Lower threshold group: 67 (57-73); Higher threshold group: 67 (58-75). Gender (M:F): Lower threshold group: 272:230; Higher threshold group: 259:237. Ethnicity: Not reported
Further population details	1. Age: >70 years (low threshold: n=173; high threshold: n=185) versus ≤70 years (low threshold: n=329; high threshold: n=311) 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(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. Concurrent medication/care: Not reported (n=496) Intervention 2: Leukoreduced red blood cells if blood concentration of 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. Concurrent medication/care: Not reported
Funding	Academic or government funding; one author received industry funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RED BLOOD CELLS FOR HIGH versus LOW THRESHOLD GROUP Protocol outcome 1: Mortality at 28-day - Actual outcome for septic shock: 90-day mortality; Group 1 (low threshold): 216/502, Group 2 (high threshold): 223/496; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RED BLOOD CELLS FOR HIGH versus LOW THRESHOLD GROUP (subgroup analysis) Protocol outcome 1: Mortality at 28-day (subgroup: >70 years) - Actual outcome for septic shock: 90-day mortality; Group 1 (low threshold): 93/173, Group 2 (high threshold): 98/185; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day (subgroup: ≤70 years) - Actual outcome for septic shock: 90-day mortality; Group 1 (low threshold): 123/329, Group 2 (high threshold): 125/311; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 243: MCINTYRE 2007

Study	McIntyre 2007A[195]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=496)
Countries and setting	Conducted in Canada; Multi-centre study at five participating hospitals
Line of therapy	1st line
Duration of study	2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Severe sepsis
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of infection, two or more systemic inflammatory response syndrome criteria, hypotension defined as the first documented systolic blood pressure of less than or equal to 90 mmHg or mean arterial blood pressure less than or equal to 65 mmHg or a decrease in systolic blood pressure of greater than or equal to 40 mmHg from baseline values
Exclusion criteria	Withdrawal of treatment within first six hours after severe sepsis was identified, development of severe sepsis after the first 24 hours following ICU admission or after seven days of hospitalisation, no index of admission for severe sepsis in the study period
Recruitment/selection of patients	Retrospective data analysis
Age, gender and ethnicity	Age - Mean (SD): 61.8 (16.5). Gender (M:F): 44% female. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	Type of fluid: (n=235) Intervention 1: Crystalloid. Duration: Not reported. Concurrent medication/care: Not reported (n=258) Intervention 2: Colloid + crystalloid. Duration: Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CRYSTALLOID versus COLLOID + CRYSTALLOID

Study	McIntyre 2007A[195]
Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: hospital mortality; Group 1: 101/235, Group 2: 121/258; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: ICU mortality; Group 1: 72/235, Group 2: 99/258; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Duration of hospital stay - Actual outcome for Severe sepsis: hospital length of stay – median (IQR); Group 1: 13 days (7-27), Group 2: 15 days (6-26); Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 0-2 L versus 2-4 L versus >4 L Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: hospital mortality; Group 1 (0-2 L): 97/210, Group 2 (2-4 L): 82/186; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: hospital mortality; Group 1 (0-2 L): 97/210, Group 3 (>4 L): 45/100; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: hospital mortality; Group 2 (2-4 L): 82/186, Group 3 (>4 L): 45/100; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: ICU mortality; Group 1 (0-2 L): 66/210, Group 2 (2-4 L): 66/186; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: ICU mortality; Group 1 (0-2 L): 66/210, Group 3 (>4 L): 41/100; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: ICU mortality; Group 2 (2-4 L): 66/186, Group 3 (>4 L): 45/100; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Duration of hospital stay	

Study	McIntyre 2007A[195]
- Actual outcome for Severe sepsis: hospital length of stay – median (IQR); Group 1 (0-2 L): 14 days (8-28), Group 2 (2-4 L): 13.5 days (6-26); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Duration of hospital stay - Actual outcome for Severe sepsis: hospital length of stay – median (IQR); Group 1 (0-2 L): 14 days (8-28), Group 3 (>4 L): 17 days (6-28); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Duration of hospital stay - Actual outcome for Severe sepsis: hospital length of stay – median (IQR); Group 2 (2-4 L): 13.5 days (6-26), Group 3 (>4 L): 75 days (6-28); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 244: MYBURGH 2012

Study	Myburgh 2012[206]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=6742 in total; 1937 sepsis patients)
Countries and setting	Conducted in Australia and New Zealand; Setting: Multi-centre study at the ICUs of 32 participating hospitals
Line of therapy	1st line
Duration of study	December 2009 – January 2012
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Sepsis
Subgroup analysis within study	Not applicable
Inclusion criteria	Judged by treating clinical to require fluid resuscitation, which was defined as the administration of a bolus of IV fluid over and above that required for maintenance or replacement fluids.

Exclusion criteria	<18 years of age, patients who had received more than 1000 ml of HES before screening, those with impending or current dialysis-dependent renal failure, those with evidence of intracranial haemorrhage on cranial computed tomography
Recruitment/selection of patients	All patients, who were admitted to the ICU during the study period and who met the inclusion criteria, were screened.
Age, gender and ethnicity	Total cohort (n=6742) Age - Mean (SD): HES group: 63.1 (17.0); Saline group: 62.9 (16.9). Gender (M:F): HES group: 2030/1326; Saline group: 20411343. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	Sepsis cohort only (n=1937) (n=979) Intervention 1: Hydroxyethyl starch. 6% HES 130/0.4 in 0.9%-saline 500-ml bags (Voluven, Fresenius Kabi). Maximum dose of 50 ml per kg of body weight per 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 per kg of body weight per 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
Funding	Academic or government funding; study treatment provided and dispensed by Fresenius Kabi
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYDROXYETHYL STARCH versus SALINE Protocol outcome 1: Mortality at 28-day - Actual outcome for Severe sepsis: 90-day mortality at 90 days; Group 1: 248/976, Group 2: 224/945; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 245: PATEL 2014

Study	Patel 2014[228]
Study type	Systematic Review
Number of studies (number of participants)	16 (n=4190)
Countries and setting	Conducted in Multiple countries; Single and multi-centre studies
Line of therapy	1st line
Duration of study	Not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Prospective randomised clinical trial reporting on adults in a critical or intensive care unit setting that have not been retracted; trial or subgroup of patients diagnosed before or at randomisation with sepsis of any severity, with or without baseline hypoalbuminaemia, receiving IV fluids as part of volume expansion and resuscitation, with or without improvement of hypoalbuminaemia; at least one exposure group that received IV human albumin solution of any concentration or type in any carrier solution after randomisation; at least one control group that received any IV fluid (crystalloid or colloid) of any strength or type in any carrier solution after randomisation; availability of all-cause mortality outcome data in the patients and comparison groups identified with the above criteria
Exclusion criteria	Not reported
Age, gender and ethnicity	Age - Median (range): 60.8 (45.0-76.0) for adults exposed to albumin solution. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: Systematic review: mixed 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=2068) Intervention 1: albumin. 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). Concurrent medication/care: Not reported

	(n=2122) Intervention 2: crystalloids (0.9% saline, Ringer's lactate). Duration: not reported. Concomitant medication/care: Not reported (n=156) Intervention 3: colloids (hydroxyethyl starch, gelatin). Duration: not reported. Concomitant medication/care: Not reported.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus CRYSTALLOID or COLLOID Protocol outcome 1: Mortality at 28-day - Actual outcome for sepsis: all-cause mortality; Group 1 (albumin): 710/1937, Group 2 (crystalloid): 763/1941; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 1: Mortality at 28-day - Actual outcome for sepsis: all-cause mortality; Group 1 (albumin): 54/143, Group 3 (colloid): 58/156 ; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 246: SAFE TRIAL: SAFE 2011

Study	**SAFE trial: Safe 2011[252]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1218) – part of the wider SAFE trial
Countries and setting	Conducted in Australia, New Zealand; Multi-centre study at ICUs in Australia and New Zealand
Line of therapy	1st line
Duration of study	Not reported

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with severe sepsis
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	For the SAFE study: All patients requiring IV fluids for intravascular volume depletion who do not have a clear indication or contraindication for albumin or saline
Exclusion criteria	For the SAFE study: cardiac surgery, following liver transplantation, patients with burns, indication that choice of fluid resuscitation cannot influence the primary outcome of death at 28 days, previous enrolment and completed follow-up in the SAFE study, previously received non-study fluids on the ICU
Age, gender and ethnicity	Age - Mean (SD): Albumin group: 60.5 (±17.2); saline group: 61.0 (±17.1). Gender (M:F): Albumin group: 359/244; saline group: 351/264. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=603) Intervention 1: 4% albumin (Albumex, CSL) in 500 ml bottles. Duration: Not reported. Concurrent medication/care: Not reported (n=615) Intervention 2: 0.9% Sodium Chloride BP (saline) in 500 ml bottles. Duration: Not reported. Concurrent medication/care: Not reported
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus SALINE Protocol outcome 1: Mortality at 28-day - Actual outcome: mortality at 28 days (univariate analysis); Group 1: 185/603, Group 2: 217/615; Risk of bias: high ; Indirectness of outcome: No indirectness - Actual outcome: mortality at 28 days (multivariate analysis); Group 1: 137/452, Group 2: 166/467; adjusted OR 0.71 (95% CI 0.52-0.97, p=0.03); Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis

	Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

Table 247: SANTHANAM 2008

Study	Santhanam 2008[254]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in India; Single-centre study
Line of therapy	1st line
Duration of study	Follow up (post intervention): until discharge or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged between 1 month and 12 years who were triaged as septic shock at the outpatient department
Exclusion criteria	younger than 30 days, shock due to hypovolaemia, haemorrhage, anaphylaxis, envenomation, diabetic ketoacidosis, inborn error of metabolism, drug toxicity, trauma, stridor, near fatal asthma, pre-hospital fluid resuscitation, grade 3 malnutrition, chronic systemic co-morbidities, genetic disorders, malignancies, immunocompromised conditions, human immunodeficiency virus, DNR orders, physician's decision not to treat, cardio-pulmonary arrest before arrival or within the first hour of resuscitation
Recruitment/selection of patients	All patients meeting the inclusion criteria during the study period.
Age, gender and ethnicity	Age - Range: 1 month - 12 years. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness

Interventions	(n=80) Intervention 1: Volume - High. 20-40 ml of Ringer Lactate/kilogram over 15 minutes plus dopamine if therapeutic goals were not achieved. Duration Not reported. Concurrent medication/care: Not reported (n=80) Intervention 2: Volume - Low. 20 ml of Ringer Lactate/kilogram over 20 minutes plus dopamine if therapeutic goals were not achieved. Duration Not reported. Concurrent medication/care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH versus LOW Protocol outcome 1: Mortality at 28-day - Actual outcome for Septic shock: Cumulative 72-hour survival; Group 1: 22/74, Group 2: 18/73; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported. 7. Time to reversal of shock Less important: 8. Adverse events

H.2.4 Escalation of care

Table 248: NINIS 2005

Study	Ninis 2005[217]
Study type	Case-control study
Number of studies (number of participants)	1 (n=498; 143 cases, 355 controls)
Countries and setting	Conducted in the UK; Setting: national hospital statistics
Duration of study	1 December 1997 – 28 February 1999
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Ninis 2005[217]
Subgroup analysis within study	Not applicable
Inclusion criteria	Children (0-16 years) who died from meningococcal disease during the study period; matched by age with three survivors (controls) from the same region of the country
Exclusion criteria	If meningococcal disease was considered to be unlikely
Recruitment/selection of patients	Cases identified through database and matched by age with three controls from the same region
Age, gender and ethnicity	Age: <1 year (n=121), 1-4 years (n=177), 5-14 years (n=91), 15-16 years (n=109). Gender (M:F): 268/230. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: children with meningococcal disease
Interventions	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)
Funding	Supported by a grant from the Meningitis Research Foundation

RESULTS AND RISK OF BIAS FOR: CASES versus CONTROLS

Protocol outcome 1: Mortality at 28 days
- Actual outcome: risk factors for death (univariable analysis):
Absence of paediatric care: 30/143 (21%) versus 33/355 (9%), OR 4.6 (95% CI 2.1-11, p<0.001)
Failure in supervision by consultant: 36/143 (25%) versus 50/355 (14%), OR 2.1 (95% CI 1.2-3.5, p=0.007)
Failure to recognize disease complications: 57/143 (40%) versus 79/355 (22%), OR 2.1 (95% CI 1.3-3.2, p=0.001)
Failure to recognize disease severity: 54/143 (38%) versus 76/355 (21%), OR 2.2 (95% CI 1.4-3.4, p=0.001)
Too little versus adequate fluid therapy: 32/131 (24%) versus 27/246 (11%), OR 2.5 (95% CI 1.4-4.7, p=0.004)
Too much fluid versus adequate fluid therapy: 7/131 (5%) versus 6/246 (2%), OR 2.8 (95% CI 0.8-10, p=0.12)
Inadequate inotropes: 54/122 (44%) versus 13/91 (14%), OR 5.8 (95% CI 2.3-14, p<0.001)
Risk of bias: Very high; Indirectness of outcome: Serious indirectness

Study	Ninis 2005[217]
Protocol outcome 1: Mortality at 28 days - Actual outcome: independent risk factors for death (multivariable analysis): Not under care of paediatrician: OR 66.0 (95% CI 3.6-1210, p=0.005) Failure of supervision by consultant: OR 19.5 (95% CI 1.8-213, p=0.015) Failure to recognise complications: OR 3.33 (95% CI 0.7-17, p=0.14) Failure to recognise severity: OR 0.51 (95% CI 0.1-2.5, p=0.40) Failure to administer inotropes: OR 23.7 (95% CI 2.6-213, p=0.005) Too little versus adequate fluid therapy: OR 1.49 (95% CI 0.2-12, p=0.59) Too much versus adequate fluid therapy: OR 19.4 (95% CI 0.2-1560, p=0.19) Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 249: SCHRAMM 2011

Study	Schramm 2011[256]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=984)
Countries and setting	Conducted in the USA; Setting: Single-centre study at a medical intensive care unit
Duration of study	January 2007 – September 2009
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with suspected infection, aged 18 or older, systolic blood pressure <90 mmHg despite fluid challenge with 20 ml/kg of crystalloid or lactate level >4 mmol/l
Exclusion criteria	Active bleeding, cardiogenic pulmonary oedema
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): baseline group: 66.3 (16.1); weekly feedback group: 68.7 (15.6); SRT activation group: 65.8 (15.9). Gender (M:F): baseline group 136/131; weekly feedback group 150/122; SRT activation group 249/174. Ethnicity

Study	Schramm 2011[256]
	(white race): baseline group 91%, weekly feedback group 89.3%, SRT activation group 89.4%
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(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) SRT (sepsis response team) activation group
Funding	Academic and government funding
RESULTS AND RISK OF BIAS FOR: BASELINE GROUP, WEEKLY FEEDBACK GROUP, SRT GROUP Protocol outcome 1: Mortality at 28 days - Actual outcome: 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), p=0.950 SRT group (n=423): OR 0.657 (95% CI 0.456-0.945), p=0.023 Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 250: SILVERMAN 2011

Study	Silverman 2011[273]

Study	Silverman 2011[273]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=273)
Countries and setting	Conducted in the USA; Setting: Single-centre study at a surgical intensive care unit
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Pre-bundle group (pre 2006): an infection plus 2 or more SIRS criteria, severe sepsis criteria included those patients identified as having sepsis and dysfunction of 1 or more organ systems, septic shock criteria included severe sepsis plus a serum lactate level that was more than 4 mmol/l and/or systolic blood pressure less than 90 mm Hg after a 20-ml/kg fluid bolus Bundle group (2006-2008): patients who met the criteria for severe sepsis or septic shock and received care in our SICU based on the sepsis bundle between 2006 and 2008 Bundle-plus group (September 2008 onwards): patients admitted to the SICU who met criteria for severe sepsis or septic shock and were cared for by the newly created SICU care team starting in September 2008
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): pre-bundle group: 72 (13); bundle group: 67 (16); bundle-plus group: 64 (15). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Pre-bundle group (n=186) Intervention 2: Bundle group: 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–

Study	Silverman 2011[273]
	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
Funding	Funding not stated
RESULTS AND RISK OF BIAS FOR: PRE-BUNDLE GROUP, BUNDLE GROUP, BUNDLE-PLUS GROUP Protocol outcome 1: Mortality at 28 days - Actual outcome: Mortality rate; 42% in the pre-bundle group, 28% in the bundle group, 20% in the bundle-plus group; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 5: Duration of intensive care stay - Actual outcome: 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; Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 6. Number of organs supported Less important: 7. Adverse events

Table 251: UMSCHEID 2015

Study	Umscheid 2015[285]
Study type	Pre-implementation/post-implementation study
Number of studies (number of participants)	1 (derivation cohort n=4575, alerts in pre-implementation period n=595, alerts in post-implementation period n=545)
Countries and setting	Conducted in the USA; Setting: Multi-centre study at three hospitals of the University of Pennsylvania

Study	Umscheid 2015[285]
Duration of study	Tool derivation: 1 October 2011 to 31 October 2011 Tool validation: 6 June 2012 to 5 July 2012 Pre-implementation analysis: 6 June 2012 to 4 September 2012 Post-implementation analysis: 6 June 2013 to 4 September 2013
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Established sepsis criteria
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients screened for sepsis criteria
Age, gender and ethnicity	Pre-implementation group (alerts n=595): Age – median (IQR): 62.0 (48.5-70.5). Gender: 297/298 F. Ethnicity: 58% White, 35% Black, 4% Other, 4% Unknown Post-implementation group (alerts n=545): Age – median (IQR): 59.7 (46.1-69.6). Gender: 271/274 F. Ethnicity: 57% White, 31% Black, 6% Other, 6% Unknown
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	Early warning response system (EWRS): all in-patients and non-critical care services screened continuously. If a patient met the EWRS criteria threshold, an alert was sent to the covering provider and rapid response coordinator.
Funding	Supported by a government grant

RESULTS AND RISK OF BIAS FOR: PRE-IMPLEMENTATION versus POST-IMPLEMENTATION GROUP (PEOPLE DISCHARGED WITH SEPSIS DIAGNOSIS)

Protocol outcome 1: Mortality at 28 days
- Actual outcome: Mortality: OR 0.98 (95% CI 0.63-1.53); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Mortality within 30 days of alert: OR 0.69 (95% CI 0.38-1.26); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Mortality or inpatient hospice transfer: OR 0.65 (95% CI 0.33-1.29); Risk of bias: High; Indirectness of outcome: No indirectness

Study	Umscheid 2015[285]
Protocol outcome 4: Duration of hospital stay - Actual outcome: Hospital LOS: Coefficient 1 (95% CI 0.87-1.16); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Duration of critical care stay - Actual outcome: ICU LOS: Coefficient 0.88 (95% CI 0.64-1.21); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse events -Actual outcome: RRT: OR 0.82 (95% CI 0.27-2.43); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 6. Number of organs supported

H.3 Inotropic agents and vasopressors

Table 252: BAI 2014

Study	Bai 2014[20]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=213)
Countries and setting	Conducted in China; Setting: Single-centre study at an ICU
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of septic shock treated between January 2011 and December 2012
Exclusion criteria	Death within 24 hours, persisting hypotension >1 hour before admission and no exact medical records, concomitant uncontrolled haemorrhage, concomitant cardiogenic shock, under 18 years old, death due to airway obstruction

Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): <2 hours group: 57.7 (12.2); 2 or more hours group: 59.4 (13.4). Gender (M:F): 116/97. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=213) Intervention 1: Inotrope – Noradrenalin/norepinephrine. Dosage not reported. Concurrent medication/care not reported
Funding	Funding not stated
RESULTS AND RISK OF BIAS FOR: NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28 days - Actual outcome: 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, p=0.003) per hour delay; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 253: BECK 2014

Study	**Beck 2014**[23]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=6514)
Countries and setting	Conducted in Canada, USA, and Saudi-Arabia; Setting: Multi-centre study at 28 participating ICUs in 3 countries
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Septic shock
Exclusion criteria	No other cause of shock, inadequate data acquisition
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 62.1 (16.1). Gender (M:F): 3711/2803. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=4376) Intervention 1: Inotrope – 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. Indirectness: serious indirectness (Phenylephrine is not included in the study protocol) (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
Funding	Authors received industry funding
RESULTS AND RISK OF BIAS FOR: INOTROPIC AGENTS Protocol outcome 1: Mortality at 28 days - Actual outcome: 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, p<0.001) for overall delay; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 254: ANNANE 2007

Study	CATS trial: Annane 2007[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=330)
Countries and setting	Conducted in France; Setting: Multi-centre study at 19 participating ICU units
Line of therapy	1st line
Duration of study	Intervention time: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence (for less than 7 days) of: evidence of infection, at least two SIRS criteria, and at least two signs of tissue hypoperfusion or organ dysfunction (defined as: ratio of arterial oxygen tension over inspired fraction of oxygen of less than 280 mmHg, urinary output below 0.5 ml/kg of bodyweight/hour or below 30 ml/h for at least 1 hour, or arterial lactate concentration above 2 mmol/l, platelet count below 100x10^9 cells per litre)
Exclusion criteria	Pregnancy, under 18 years old, evidence of obstructive cardiomyopathy, acute myocardial ischaemia, pulmonary embolism, advanced stage cancer, malignant haemopathy, AIDS with a decision to withhold or withdraw aggressive therapy, persistent polymorphonuclear neutrophil count of less than 0.5x10^9 cells per litre, inclusion in another trial
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): 63 (50-73). Gender (M:F): 202/128. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(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
Funding	Academic or government funding (French Ministry of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADRENALIN/EPINEPHRINE versus ANY COMBINATION Protocol outcome 1: Mortality at 28-day - Actual outcome: Number of deaths at 28 days; Group 1: 64/161, Group 2: 58/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of deaths at 7 days; Group 1: 40/161, Group 2: 34/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of deaths at 90 days; Group 1: 84/161, Group 2: 85/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: At discharge from intensive care; Group 1: 75/161, Group 2: 75/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: At discharge from hospital; Group 1: 84/161, Group 2: 82/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of deaths at 14 days; Group 1: 56/161, Group 2: 44/169; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Length of stay - ICU - Actual outcome: Length of stay in intensive care; Other: Epinephrine group (median, IQR): 15 (7-31); norepinephrine group (median, IQR): 16 (6-32); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse events - Actual outcome: Number of adverse events during catecholamine infusion; Group 1: 43/161, Group 2: 41/169; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Number of adverse events after catecholamine infusion; Group 1: 12/161, Group 2: 13/169; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 6. Number of organs supported

Table 255: LAUZIER 2006

Study	**Lauzier 2006**[163]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in Multiple countries; Setting: Dual-centre study in Canada and France
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Criteria for septic shock, mean arterial pressure of 60 mmHg or less after a 1000-ml crystalloid bolus, vasopressors for less than 12 hours before randomisation, pulmonary artery occlusion pressure of 12 mmHg or higher, cardiac index of 3 l/min/m^2 or higher
Exclusion criteria	Younger than 16 years, receiving chronic dialysis, not expected to survive longer than 48 hours, pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Vasopressin group: 51.2 (17.2); norepinephrine group: 58.1 (17.5). Gender (M:F): 14/9. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Inotrope - Vasopressin. 0.04-0.20 U/min, 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, 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 mmHg. Antimicrobials, corticosteroids, analgesia, insulin used if needed
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VASOPRESSIN versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: ICU mortality; Group 1: 3/13, Group 2: 3/10; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 256: LEVY 1997

Study	Levy 1997[171]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in France; Setting: Single-centre study at a medical/surgical ICU
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Definable source of infection and/or positive blood cultures, after optimal fluid resuscitation and treatment with dopamine up to a dose of 20 µg/kg per min: mean arterial pressure of 60 mmHg or less, signs of altered perfusion as oliguria (<30 ml/h) or an increased lactate level (>2.5 mmol/l), and a cardiac index of more than 3.5 l/min/m^2
Exclusion criteria	See inclusion criteria
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Epinephrine group: 54 (10); norepinephrine-dobutamine group: 56 (9). Gender (M:F): 21/9. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(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/min during the first hour (n=15) Intervention 2: Inotrope - Any combination. Norepinephrine 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; dobutamine infused as a fixed dose of 5 µg/kg/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/min during the first hour

Funding	Other (Communitee of Clinical Research of Nancy University Hospital, grant of Lilly France)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADRENALIN/EPINEPHRINE versus ANY COMBINATION Protocol outcome 1: Mortality at 28-day - Actual outcome: All-cause mortality at unclear time point; Group 1: 9/15, Group 2: 8/15; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 257: MAHMOUD 2012

Study	Mahmoud 2012[184]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Egypt; Setting: Single-centre study at an ICU
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with septic shock presenting to the ICU between January 2008 and April 2010
Exclusion criteria	Cardiac disease, chronic renal or hepatic impairment, peripheral vascular diseases, coagulopathy, burns
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Norepinephrine-dobutamine group: 52.4 (4.5), norepinephrine-epinephrine group: 50.3 (6.5). Gender (M:F): 31/29. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(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=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)
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY COMBINATION versus ANY COMBINATION

Protocol outcome 1: Mortality at 28-day
- Actual outcome: 28-day mortality; Group 1: 15/30, Group 2: 16/30; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Length of stay - ICU
- Actual outcome: ICU length of stay; Other: Norepinephrine-dobutamine group (median, IQR): 7 (4-11); norepinephrine-epinephrine group (median, IQR): 6 (5-10); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Number of organs supported
- Actual outcome: SOFA score at Start; Group 1: mean 15.2 (SD 6.4); n=30, Group 2: mean 14.4 (SD 5.9); n=30; SOFA score 0-24 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: SOFA score at 24 hours; Group 1: mean 14.6 (SD 6.1); n=30, Group 2: mean 13.9 (SD 6.2); n=30; SOFA score 0-24 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: SOFA score at 48 hours; Group 1: mean 14.4 (SD 6.3); n=30, Group 2: mean 13.8 (SD 5.9); n=30; SOFA score 0-24 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: SOFA score at 72 hours; Group 1: mean 14.1 (SD 7); n=30, Group 2: mean 13.5 (SD 6.1); n=30; SOFA score 0-24 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: SOFA score at 96 hours; Group 1: mean 13.5 (SD 6.9); n=30, Group 2: mean 12.7 (SD 6.6); n=30; SOFA score 0-24 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse events
- Actual outcome: Acute coronary syndrome; Group 1: 1/30, Group 2: 1/30; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Arrhythmias; Group 1: 4/30, Group 2: 6/30; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Cerebral stroke; Group 1: 0/30, Group 2: 0/30; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome: Limb ischaemia; Group 1: 2/30, Group 2: 3/30; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay.

Table 258: MARIK 1994

Study	Marik 1994[189]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in USA; Setting: Single-centre study at an ICU at a teaching hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Definable source of infection and/or positive blood cultures, met standard criteria for sepsis, had a cardiac index greater than 3.2 $l/min/m^2$ and either a systemic vascular resistance index less than 1200 dyne $s/cm^5/m^2$ or a mean arterial pressure less than 60 mmHg after adequate fluid resuscitation, undergoing mechanical ventilation
Exclusion criteria	patients requiring dialysis, active upper gastrointestinal bleeding, unlikely to survive longer than 24 hours following initiation of the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Norepinephrine group: 46 (7); dopamine group: 46 (4). Gender (M:F): 11/9. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	Serious indirectness: Patients undergoing mechanical ventilation
Interventions	(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 for sedation, vecuronium infusion for neuromuscular blockade
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORADRENALIN/NOREPINEPHRINE versus DOPAMINE Protocol outcome 1: Mortality at 28-day - Actual outcome: All-cause mortality at unclear time point; Group 1: 5/10, Group 2: 6/10; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 259: MARTIN 1993

Study	Martin 1993[192]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in France; Setting: Single-centre study at an ICU of a university hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with hyperdynamic septic shock
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Dopamine group: 53 (19); norepinephrine group: 52 (12). Gender (M:F): 24/8. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear

Indirectness of population	No indirectness
Interventions	(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 µ/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
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORADRENALIN/NOREPINEPHRINE versus DOPAMINE Protocol outcome 1: Mortality at 28-day - Actual outcome: Hospital mortality at unclear time point; Group 1: 7/16, Group 2: 10/16; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 260: MARTIN 2015

Study	Martin 2015[191]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=324)
Countries and setting	Conducted in France; Setting: Single-centre at an ICUs of an academic hospital
Line of therapy	1st line
Duration of study	January 2009 – May 2013
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Not applicable
Subgroup analysis within study	Not applicable

Inclusion criteria	Aged 18 years or older, first episode of septic shock on ICU admission or during ICU stay
Exclusion criteria	Shock states not related to sepsis, patients requiring ECMO
Recruitment/selection of patients	All patients with septic shock.
Age, gender and ethnicity	Age – Mean (SD): 62 (15). Gender (M:F): 222/102. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=324) Intervention 1: Inotrope - Norepinephrine. Maximum dosage of norepinephrine was 0.79 µg/kg/minute (IQR 0.03-10 µg/kg/minute). Duration 60 hours (IQR 2-648 hours). Concurrent medication/care: dobutamine, isoproterenol, epinephrine, terlipressin, hydrocortison.
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: dose of norepinephrine greater than 1 µg/kg per minute as an independent predictor of mortality: OR 9.7 (95% CI 4.5-23), p<0.001. Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 261: MATHUR 2007

Study	**Mathur 2007**[194]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India; Setting: Single-centre study at an ICU of a university hospital
Line of therapy	1st line
Duration of study	Not clear

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	2 or more SIRS criteria
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Dopamine group: 54.60 (10.92); norepinephrine group: 52.76 (10.41). Gender (M:F): 32/18. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Inotrope - Dopamine. Dose range: 10-25 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
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOPAMINE versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: Non-survivors at unclear time point; Group 1: 19/25, Group 2: 14/25; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 262: MYBURGH 2008

Study	**Myburgh 2008[207]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=280)

Countries and setting	Conducted in Australia; Setting: Multi-centre study at 4 participating ICUs in Australia
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Deemed to require an infusion of epinephrine or norepinephrine for any cause at the time of enrolment
Exclusion criteria	Undergoing resuscitation for cardiac arrest or anaphylaxis, admission diagnosis of phaeochromocytoma or hypoadrenalism, taking monoamino oxidase inhibitors, death considered likely within 24 hours of randomisation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Epinephrine group: 59.4 (15.9), norepinephrine group: 60.4 (14.8). Gender (M:F): 170/110. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	Serious indirectness: A priori sepsis subgroup of larger study population
Interventions	(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
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADRENALIN/EPINEPHRINE versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: Mortality at 28 days; Group 1: 17/76, Group 2: 24/82; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Mortality at 90 days; Group 1: 23/74, Group 2: 30/82; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 263: PATEL 2010

Study	Patel 2010[229]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=252)
Countries and setting	Conducted in USA; Setting: Single-centre study; MICU
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years and older, admission to MICU, diagnosis of septic shock requiring vasopressor therapy after adequate fluid resuscitation
Exclusion criteria	Lack of infectious cause of shock, non-infectious aetiology of the SIRS response, allergy to study drugs, vasopressor therapy for >6 hours
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age: Not reported. Gender (M:F): Dopamine group: 64/70; norepinephrine group: 52/66. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=134) Intervention 1: Inotrope - Dopamine. 5-20 µg/kg/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. (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.
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOPAMINE versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: 28-day mortality; Group 1: 67/134, Group 2: 51/118; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Length of stay - hospital - Actual outcome: Length of stay in the hospital; Group 1: mean 14.2 Days (SD 16.3); n=134, Group 2: mean 13.5 Days (SD 13.3); n=118; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Length of stay - ICU - Actual outcome: Length of stay on the ICU; Group 1: mean 6.8 Days (SD 7.3); n=134, Group 2: mean 7.5 Days (SD 7.6); n=118; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse events - Actual outcome: Incidence of arrhythmias; Group 1: 51/134, Group 2: 14/118; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 6. Number of organs supported

Table 264: RUOKONEN 1993

Study	Ruokonen 1993[249]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=10)

Countries and setting	Conducted in Finland; Setting: Single-centre study at an ICU of a university hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hyperdynamic septic shock
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 45.1 (16.6). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=5) 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
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORADRENALIN/NOREPINEPHRINE versus DOPAMINE Protocol outcome 1: Mortality at 28-day - Actual outcome: Death at unclear time period; Group 1: 4/5, Group 2: 3/5; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 265: RUSSELL 2008

Study	Russell 2008[250]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=802)
Countries and setting	Conducted in Multiple countries; Setting: Multi-centre study at 27 participating centres in 3 countries (Australia, Canada, United States)
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 16 years who had septic shock that was resistant to fluids and low-dose norepinephrine
Exclusion criteria	Unstable coronary syndrome, use of open-label vasopressin during current hospital admission, malignancy, acute mesenteric ischemia, death anticipated within 12 hours, underlying chronic heart disease (NYHA class III or IV) and shock, physician and team were not committed to aggressive care, severe hyponatremia, traumatic brain injury, Raynaud’s phenomenon, systemic sclerosis or vasospastic diathesis, pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Norepinephrine group: 61.8 (16); vasopressin group: 59.3 (16.4). Gender (M:F): Norepinephrine group: 229/153; vasopressin group: 246/151. Ethnicity: 84% White
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(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 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 target mean arterial pressure.
Funding	Principal author funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORADRENALIN/NOREPINEPHRINE versus VASOPRESSIN

Protocol outcome 1: Mortality at 28-day
- Actual outcome: Death from any cause at 28 days; Group 1: 150/382, Group 2: 140/396; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: 90-day mortality; Group 1: 188/379, Group 2: 172/392; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Length of stay - hospital
- Actual outcome: Length of stay in the hospital; Other: Norepinephrine group (median, IQR): 26 (15-53); vasopressin group (median, IQR): 27 (13-52); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Length of stay - ICU
- Actual outcome: Length of stay on the ICU; Other: Norepinephrine group (median, IQR): 16 (8-32); vasopressin group (median, IQR): 15 (7-29); Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 6. Number of organs supported Less important: 7. Adverse events

Table 266: SCHMOELZ 2006

Study	**Schmoelz 2006**[255]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61 (41 in the arms extracted))
Countries and setting	Conducted in Germany; Setting: Single-centre study at an ICU at a university hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Septic shock, the need for norepinephrine in a dose of at least 0.05 µg/kg/min, over 18 years of age
Exclusion criteria	Pregnancy, pre-existing renal and cardiac dysfunction
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Dopexamine group: 56.70 (18.50); dopamine group: 49.24 (19.03). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Extra comments	Three-arm study (dopexamine, dopamine, placebo), only dopexamine and dopamine arms extracted
Indirectness of population	No indirectness
Interventions	(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
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOPEXAMINE versus DOPAMINE Protocol outcome 1: Mortality at 28-day - Actual outcome: 28-day mortality; Group 1: 5/20, Group 2: 4/21; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 267: SEGUIN 2002

Study	Seguin 2002[259]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in France; Setting: Dual-centre study at two participating ICUs at one hospital
Line of therapy	1st line

Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults older than 18 years, evidence of infection, at least 3 of the following criteria (temperature >38C or <36.5C, respiratory rate >20 breaths per minute or PaCO2 <32 mmHg or mechanical ventilation, heart rate >90 beats/min, white blood cell count >12,000/mm^3 or <4000/mm^3), at least 2 of the following criteria (plasma lactate >2 mmol/l or unexplained metabolic acidosis, hypoxaemia defined by PaCO2 <70 mmHg at room air or a PaO2/FiO2 ration <280 mmHg or need for mechanical ventilation, urine output <30 ml/h for at least 2 hours despite a fluid challenge of at least 500 ml, a platelet count <100,000/mm^3 or a decrease of 50% from previous value or unexplained coagulopathy), systolic blood pressure <90 mmHg despite capillary wedge pressure >12 mmHg
Exclusion criteria	Pregnancy, known allergy to indocyanine green, liver cirrhosis, acute myocardial infarction, enteral nutrition less than 4 hours before the beginning of the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Epinephrine group: 65 (12); dobutamine-norepinephrine group: 70 (13). Gender (M:F): 12/10. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Inotrope - Adrenalin/epinephrine. Starting dose of 0.1 µg/kg/min, increased by steps of 0.2 µg/kg/min 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/min, increased by steps of 0.2 µg/kg/min every 5 minutes to reach mean systemic arterial pressure between 70-80 mmHg Dobutamine: continuous infusion of 5 µg/kg/min. Duration not reported. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADRENALIN/EPINEPHRINE versus ANY COMBINATION

Protocol outcome 1: Mortality at 28-day
- Actual outcome: Death at unclear time period; Group 1: 4/11, Group 2: 5/11; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 268: SEGUIN 2006

Study	Seguin 2006[260]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in France; Setting: Single-centre study at a surgical ICU of a university hospital
Line of therapy	1st line
Duration of study	Intervention time: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Evidence of infection; at least three of the following criteria (temperature above 38C or less than 36.5C, respiratory rate more than 20 breaths per minute or arterial pressure in CO2 less than 32 mmHg or mechanical ventilation, heart rate more than 90 bpm, white blood cell count more than 12,000/mm^3 or less than 4,000/mm^3); at least two of the following criteria (plasma lactate more than 2 mmol/l or unexplained metabolic acidosis, hypoxemia defined by arterial pressure in oxygen less than 70 mmHg at room air or a ratio of PaO2 to FiO2 of less than 280 mmHg or a need for mechanical ventilation, urine output less than 30 ml/hour for at least 2 hours despite a fluid challenge of at least 500 ml, a platelet count of less than 100,000/mm^3 or a decrease of 50% from a previous value or unexplained coagulopathy); systolic blood pressure less than 90 mmHg despite an optimal volume loading defined by a pulmonary capillary wedge pressure more than 14 mmHg
Exclusion criteria	Pregnancy, history of oesophageal or gastric disease, history of oesophageal or gastric surgery
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Epinephrine group: 67 (13); dopexamine-norepinephrine group: 65 (10). Gender (M:F): 17/5. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Indirectness of population	No indirectness

Interventions	(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 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
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADRENALIN/EPINEPHRINE versus ANY COMBINATION Protocol outcome 1: Mortality at 28-day - Actual outcome: Mortality rate at 28 days; Group 1: 3/10, Group 2: 2/12; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Mortality rate at 90 days; Group 1: 4/10, Group 2: 3/12; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 269: DE BACKER 2010

Study	SOAP II trial: De Backer 2010[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1679)
Countries and setting	Conducted in Belgium, Austria and Spain; Setting: Multi-centre at the ICUs of 8 participating centres
Line of therapy	1st line
Duration of study	Intervention time: Maximum of 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock: 62% had septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients 18 years or older in whom a vasopressor agent was required for the treatment of shock were included

Exclusion criteria	Under 18 years of age, patients who had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock, serious arrhythmia (such as rapid atrial fibrillation or ventricular tachycardia), declared brain-dead
Recruitment/selection of patients	All patients meeting the inclusion criteria during the study period (19 December 2003 - 6 October 2007)
Age, gender and ethnicity	Age - Median (IQR): Dopamine group: 68 (55-76); Norepinephrine group: 67 (56-76). Gender (M:F): Dopamine group: 507/351; Norepinephrine group: 449/372. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(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 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.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOPAMINE versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome for shock (n=1656): Mortality at 28 days; 52.5% versus 48.5%, OR 1.17 (95% CI, 0.97-1.42, p=0.10). Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for septic shock (n=1044): 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. Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

Table 270: MORELLI 2009

Study	TERLIVAP trial: Morelli 2009[199]

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Italy; Setting: Single-centre study at an ICU
Line of therapy	1st line
Duration of study	Intervention + follow up: 48 hours + 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Septic shock with a mean arterial pressure below 65 mmHg despite appropriate volume resuscitation during ICU stay
Exclusion criteria	Under 18 years of age, catecholamine therapy prior to randomisation, pronounced cardiac dysfunction, chronic renal failure, severe liver dysfunction, significant valvular heart disease, present coronary artery disease, pregnancy, present or suspected acute mesenteric ischaemia or vasospastic diathesis
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (IQR): Vasopressin group: 66 (60; 74), norepinephrine: 64 (59; 72). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age: Not applicable/Not stated/Unclear 2. High risk of infection: Not applicable/Not stated/Unclear 3. Pregnancy: Not applicable/Not stated/Unclear
Extra comments	3-arm trial, only 2 arms extracted
Indirectness of population	No indirectness
Interventions	(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 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
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VASOPRESSIN versus NORADRENALIN/NOREPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: ICU mortality at unclear time period; Group 1: 8/15, Group 2: 10/15; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Length of stay - ICU - Actual outcome: ICU length of stay; Other: Vasopressin group (median, IQR): 17 (5; 27); norepinephrine group (median, IQR): 17 (7; 23); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Number of organs supported - Actual outcome: Requiring renal replacement therapy at 48 hours; Group 1: 5/15, Group 2: 8/15; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse events - Actual outcome: New-onset of tachyarrhythmias; Group 1: 1/15, Group 2: 4/15; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay.

Table 271: VENTURA 2015

Study	Ventura 2015[289]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Brazil; Setting: Single-centre at the PICU of an academic hospital
Line of therapy	1st line
Duration of study	February 2009 – July 2013
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Not applicable
Subgroup analysis within study	Not applicable

Inclusion criteria	Children 1 month to 15 years old with fluid-refractory septic shock
Exclusion criteria	Patients receiving vasoactive drugs prior to hospital admission, known cardiac disease, had already participated in the trial during the same hospital stay, refused to participate, DNR order
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Dopamine group: 39.6 months (46.3); Epinephrine group: 56.9 months (58.2). Gender (M:F): Dopamine group: 35/28; Epinephrine group: 35/22. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. High risk of infection: Not applicable / Not stated / Unclear 3. Pregnancy: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(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 20mml 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 20mml 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.
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOPAMINE versus ADRENALIN/EPINEPHRINE Protocol outcome 1: Mortality at 28-day - Actual outcome: Mortality at 28 days; Multiple logistic regression: dopamine versus epinephrine: OR 6.51 (95% CI 1.12-37.80), p=0.037. Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Critical: 2. Health-related quality of life. 3. Admission to critical care as a proxy for progression to severe sepsis Important: 4. Duration of hospital stay. 5. Duration of critical care stay. 6. Number of organs supported Less important: 7. Adverse events

H.4 Oxygen

None.

H.5 Use of bicarbonate

Table 272: ELSOLH 2010

Study	Elsolh 2010[83]
Study type	Case-control
Number of studies (number of participants)	1 (n=36 patients and 36 controls)
Countries and setting	Conducted in USA. Tertiary care hospital
Line of therapy	Unclear (all patients were managed according to standard protocols)
Duration of study	Follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients with septic shock
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical evidence of infection, evidence of systemic response to infection, the onset of shock within the previous 72h (as defined by a systolic blood pressure of <90 mm Hg despite adequate fluid replacement or a need for vasopressor for at least 1h), and hypo-perfusion or organ dysfunction attributable to sepsis.
Exclusion criteria	Pre-hospital cardiac arrest; indication for emergent surgery; liver cirrhosis or failure; end stage renal disease requiring dialysis; inappropriate initial antibiotic therapy.
Recruitment/selection of patients	Consecutive patients diagnosed with septic shock. A control group who met the same inclusion and exclusion criteria was matched 1:1 for age (±5 years), site of infection, and predicted mortality by APACHE II. The control group was comprised of patients who presented with septic shock during the same time period of the study.
Age, gender and ethnicity	Bicarbonate therapy: Age - Mean (SD): 68 (15). Gender (M:F): 23 male/13 female. Ethnicity: not stated Control: Age - Mean (SD): 65 (16). Gender (M:F): 20 male/16 female. Ethnicity: not stated
Indirectness of population	No indirectness

Study	Elsolh 2010[83]
Interventions	Group 1 (n=36) Intervention group: Bicarbonate therapy. Upon the physician's discretion, bicarbonate infusion (0.15 M, 0.1-0.2 mmol/kg ideal body weight/h) was initiated in patients with increased arterial lactate levels and pH<7.3. The infusion was discontinued when the pH was between 7.35 and 7.4 Concurrent medication/care: the hospital implemented a series of guidelines including a sepsis "bundle" protocol that combines early goal-detected therapy, intensive insulin therapy, hydrocortisone supplementation in stress doses, and an evaluation for drotrecogin alpha infusion, a daily sedation holiday, and a weaning protocol for intubated patients. All patients had arterial line placed on admission. Group 2 (n=36) Control group: patients in the control group were treated according to the sepsis bundle but without ever receiving bicarbonate infusion.
Funding	Not stated (Conflict of interest: none)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS Protocol outcome 1: 28-day mortality, or the nearest time point - Actual outcome: 28-day mortality; Group 1: n=10 (28% [14-45%]), Group 2: n=12 (33% [19-51%]; (p=0.79) Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 2: Duration of critical care stay - Actual outcome: length of ICU stay; Group 1: median 44.5 h [34-54], Group 2: median 55 h [39-60]; (p=0.01) Risk of bias: very high; Indirectness of outcome: No indirectness Protocol outcome 3: Time to reversal of shock - Actual outcome: median time until reversal of shock; Group 1: median 11.5 days [6.0-16.0], Group 2: median 16.0 days [13.5-19.0]; (p=0.09) Risk of bias: very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	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; Duration of hospital stay; Number of organs supported; Adverse events (long term disability; short-term heart failure)

H.6 Early goal-directed therapy

Table 273: ANGUS 2015

Study	ANGUS 2015[12]
Study type	Systematic Review
Number of studies (number of participants)	11 (n=5407)
Countries and setting	Conducted in Australia, Brazil, China, Finland, Hong Kong (China), Irish Republic, New Zealand, United Kingdom, USA; Setting: Three studies[139,247,298] were conducted in the USA. Of these one was a single-centre study (RIVERS 2001[247,247])and the other two were multicentre studies (JONES 2010[139,140] - 3 sites and YEALY 2014[298,298] - 31 sites). They were all set in the ED. One multicentre study (PEAKE 2014[232,232], the ARISE study) was set in 51 Ed sites across Australasia (Australia, New Zealand, Hong Kong, Finland and Republic of Ireland), and another (MOUNCEY 2015[201,201], the ARISE study) was set in 56 ED sites in the UK. In China there were four single and one multicentre (8 sites) studies set in unknown setting (no response to email communication), and in Brazil there was one multicentre (2 sites) study set in ED, ward and ICU.
Objectives	Primary objective: the pre-specified primary outcome was mortality in studies conducted in patients presenting to the ED with septic shock. If mortality at more than one time point was reported for a given trial, the mortality identified as the primary outcome for that study was used in the analysis for the systematic review. Additional analyses for mortality conducted were: mortality at 28 days, 90 days, and at hospital discharge for studies reporting these mortality outcomes. Secondary objective: to assess mortality at any time in patients with septic shock irrespective of presenting source.
Line of therapy	First line
Duration of study	Intervention + follow up: variable
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock: Sepsis, severe sepsis and septic shock
Subgroup analysis within study	Sys review – pre-specified in protocol: Presenting source (subgroup analysis was carried out to evaluate EGDT in all patients with septic shock irrespective of presenting source or timing - source subgroups were ED and other or unclear)
Sensitivity analysis	A priori explanations for heterogeneity: 1) methodological quality of the studies (using individual risk of bias domains); 2) harmonized studies (ARISE[232,232], ProCESS[298,298] and ProMISE[201,201]) versus non-harmonised studies; 3) control intervention (usual care versus another resuscitation protocol); 4) duration of intervention; 5) adult versus paediatric populations.

Study	ANGUS 2015[12]
Other analysis	Examination of small study effects conducted by construction and visual examination of funnel plots and Egger's statistic.
Inclusion criteria	RCTS; adult or paediatric patient populations with septic shock; Interventions: trials comparing EGDT with either usual care or another resuscitation strategy that did not incorporate EGDT. Definition of EGDT was based on Rivers et al as the protocolised administration of IV fluids, vasoactive agents and red cell transfusion to achieve the predetermined haemodynamic goals of CVP, MAP and SCVO2. Authors only analysed studies that reported mortality.
Exclusion criteria	Papers which reported physiological endpoints; papers were solely descriptive or non-randomised, and any studies published before 2000.
Recruitment/selection of patients	Population included was patients presenting to the ED with septic shock. Primary objective: 5 studies enrolled patients from presenting to the ED with septic shock. Secondary objective: remaining 6 studies: one enrolled patients presenting to either ED or recruited in-patients from the general ward or ICU, and in 5 (published in Chinese), patient could not be determined (no response to author contact).
Age, gender and ethnicity	Age - Other: Gender (M:F): Not reported. Ethnicity: Breakdown of ethnicities within each trial not reported
Further population details	1. Age: Systematic review: mixed (One out of eleven studies was a paediatric population). 2. High risk of infection: Systematic review: mixed 3. Pregnancy: Not applicable / Not stated / Unclear
Extra comments	Adult or paediatric patient populations with septic shock. The study by De Oiveria[72] is the only one in a paediatric population.
Indirectness of population	No indirectness: No indirectness
Interventions	(n=2459) Intervention 1: Bundle of care - EGDT. EGDT - a 6 hour resuscitation algorithm guided by the optimisation of haemodynamic goals targeting both CVP and MAP and a SCVO2 or 70% or greater. Duration 6 hour resuscitation period. Concurrent medication/care: IV fluids, vasopressors, dobutamine, blood transfusions etc. (n=2948) Intervention 2: Bundle of care - Standard therapy or protocol-based therapy. Usual care in five studies; alternative non-EGDT haemodynamic resuscitation strategy in five studies; usual care and protocolised standard therapy in one study. In one study (Jones et al), the alternative resuscitation was lactate clearance: Isotonic crystalloids, vasopressors, red cells and dobutamine to achieve CVP ≥ 8mmHg, MAP ≥ 65mmHg and lactate clearance >10%.
Funding	Funding not stated: the authors declared no conflict of interest
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EGDT versus STANDARD THERAPY OR PROTOCOL-BASED THERAPY	

Study	ANGUS 2015[12]
Protocol outcome 1: Mortality at 28-day - Actual outcome for Septic shock: Primary mortality outcome of each study at Study; Group 1: 495/2134, Group 2: 582/2601; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Septic shock: 90-day mortality at 90-day; Group 1: 460/1820, Group 2: 598/2243; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of stay - ICU at Define - Actual outcome for Septic shock: ICU length of stay for patients admitted to ICU at Study; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Admission to critical care at Define - Actual outcome for Septic shock: Admission to ICU at Study; Group 1: 1827/2006, Group 2: 2052/2474; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Number of organs supported at Define; Adverse events at Define; Time to reversal of shock at Define; Length of stay - hospital at Define
Limitations	Reporting of mortality across included studies was not uniform – 90-day mortality was primary study outcome in only 2 studies (and reported as the secondary outcome in one study); only 2 of the 11 studies were assessed as having low risk of bias (other than blinding of participants and personnel); the effect of individual patient confounders, as well as international and local variation in healthcare services (e.g. number of ED presentations and threshold for hospital and ICU admission); how EGDT was delivered across the sites and the nature of usual care

Table 274: NCT02030158 2015

Study	Australian and New Zealand Intensive Care Research Centre 2015[16]
Study type	Individual patient data meta-analysis (IPDMA); Time Perspective: prospective
Number of studies (number of participants)	3 (n= 4210) The combined recruitment into ProCESS, ARISE and ProMISE is 4210 patients with 3760 patients randomised either to receive EGDT or usual resuscitation.
Countries and setting	Conducted in Australia, Finland, Hong Kong (China), Irish Republic, New Zealand, United Kingdom, USA (USA - Protocolized Care for Early Septic Shock (ProCESS); Australasia - Australasian Resuscitation In Sepsis Evaluation (ARISE); and UK - Protocolised Management In Sepsis (ProMISe)). Though independent trials, but with a view to performing a subsequent individual patient data meta-analysis (IPDMA), efforts were made to harmonise the three, contemporaneous trials on key areas of their design, for example, trial protocol, entry criteria, data and data collection, primary and secondary outcomes, etc.
Objectives	This is the statistical analysis plan for an IPDMA of three EGDT clinical trials.

Study	Australian and New Zealand Intensive Care Research Centre 2015[16]
Line of therapy	First line
Duration of study	Intervention + follow up: variable
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Septic shock: Sepsis, severe sepsis and septic shock
Subgroup analysis within study	Pre-determined, clinically important, pre-randomisation subgroups of interest will relate to site, patient and care delivery factors: Site factors: Country, Type of hospital, Annual admissions, Annual ED presentations, Number ICU beds, Ratio of ICU to hospital beds, Annual ICU admissions, Specialist staffing in ICU, EGDT delivery model Patient factors:, Age, Sex, Race/ethnicity, Obesity, APACHE II score, MEDS score, SOFA score, Source of infection, Infectious aetiology, Presentation - refractory hypotension, Presentation – hypoperfusion, Receipt of vasopressors, Receipt of invasive ventilation Care delivery factors: Interval between ED presentation and first administration of antimicrobials, Interval between ED presentation and starting intervention, Time of admission (day/night and weekend/weekday), Volume of fluid
Other analysis	Data management: Data management Prior to pooling the data from the three trials, the clinical report forms for each trial will be compared and similarities/dissimilarities discussed across the trial teams to inform the final structure and specification of the IPDMA dataset. Similar variables will be double-checked for consistency across the trials (analysis of distribution, range and summary statistics) prior to being finally imported into the IPDMA database. (Unlike ARISE and ProMISE - which are two-arm trials comparing EGDT with usual resuscitation, ProCESS is a three-arm trial with the additional arm evaluating protocolised usual resuscitation (termed protocolised standard care). Data from ProCESS for patients recruited and randomised to protocolised standard care (n=450) will be excluded from the analysis of the primary objective but retained for possible inclusion in the analyses of relevant secondary objectives.) Analysis plan: The IPDMA will be performed using one stage, multi-level (patients nested in sites nested in trials), mixed modelling. Heterogeneity between trials will be determined by fitting a fixed interaction term between treatment and trial, while overall treatment effect will be reported with trial treated as a fixed effect and site treated as a random effect. A secondary analysis will adjust for important baseline covariates, including: age; sex; APACHE II score; SBP<90 mm Hg; and use of invasive mechanical ventilation. Primary outcome 90 day all-cause mortality - logistic, mixed modelling, with terms for trial and site, reported as odds ratios with 95% confidence intervals (CI) Secondary/intermediate outcomes Hospital (censored at 60 days) and 28-day mortality - binomial, mixed modelling reported as odds ratios with 95% CI Survival analysis - Appropriate survival

Study	Australian and New Zealand Intensive Care Research Centre 2015[16]
	analysis techniques, e.g. Cox proportional hazards regression reported as Hazards Ratio with 95% CI if proportionality assumption holds Duration of stay in ED, ICU and hospital - assessed for normality, appropriate transformation reported as ratios of geometric means with 95% CI, accounting for impact of survivorship Receipt of and duration of mechanical ventilation, vasopressor support and renal replacement therapy - binomial, mixed modelling reported as odds ratios with 95% CI Where relevant, any assumptions underlying analyses will be detailed and reported. All results will be reported in tabular form and displayed using forest plots with 95% CI. All analyses will be performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value of 0.05 will be considered to be statistically significant.
Inclusion criteria	Enrolled into one of the three studies (ARISE, ProMISe or ProCESS) to either Early Goal Directed Therapy or usual resuscitation
Exclusion criteria	N/A
Recruitment/selection of patients	Enrolled into one of the three studies (ARISE, ProMISe or ProCESS) to either Early Goal Directed Therapy or usual resuscitation
Age, gender and ethnicity	Age - Other: Gender (M:F): Not reported. Ethnicity: Breakdown of ethnicities within each trial not reported
Further population details	Severe sepsis and septic shock
Extra comments	N/A
Indirectness of population	No indirectness: No indirectness
Interventions	Early Goal-Directed Therapy (EGDT) Usual resuscitation
Funding	Australian and New Zealand Intensive Care Research Centre
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EGDT versus STANDARD THERAPY OR PROTOCOL-BASED THERAPY Study not yet reported. Estimated completion date: July 2015 (final data collection date for primary outcome measure)	
Protocol outcomes not reported by the study	Quality of life at Define; Number of organs supported at Define; Adverse events at Define; Time to reversal of shock at Define; Length of stay - hospital at Define

H.7 Monitoring

H.7.1 Lactate clearance

Table 275: ARNOLD 2009

Study	**Arnold 2009[15]**
Study type	Prospective cohort
Number of studies (number of participants)	1 (n=166) ED patients with severe sepsis
Country and setting	USA. Three urban hospitals
Funding	Grant from the National Institutes of Health/ National Institutes of General Medical Sciences (K23GM83211); grant from the National Institutes of Health/ National Institutes of General Medical Sciences (K23GM76652)
Duration of study	3 years follow up
Age, gender, ethnicity	Mean age: 66±15. Gender – female, n (%): 83 (50). Ethnicity: not stated.
Patient characteristics	Initial serum lactate >4mmol/litre, n (%) 90 (54)
Index test/s	lactate
Reference standard	N/A
Target condition	Hospital diagnosis of sepsis
Results: primary outcome= in-hospital mortality **Lactate clearance vs. lactate non-clearance (>10% over the first 6 hours)** **Lactate clearance (n=151)** **Lactate non-clearance (n=15)**	Initial serum lactate, mean (SD) 4.5 (2.7) Serial serum lactate, mean (SD) 2.3 (1.8) Mortality, n(%) 29 (19) Initial serum lactate, mean (SD) 3.9 (1.7)

Study	Arnold 2009[15]
	Serial serum lactate, mean (SD) 5.1 (2.9) Mortality, n(%) 9 (60)
Survivors vs. non-survivors	
Survivors (n=128)	Initial serum lactate, mean (SD) 4.3 (2.6)
Non-survivors (n=38)	Initial serum lactate, mean (SD) 4.7 (2.8)
Survivors (n=128)	Serial serum lactate, mean (SD) 2.2 (1.6)
Non-survivors (n=38)	Serial serum lactate, mean (SD) 3.6 (2.8)
Lactate clearance ≥10%, n (%)	
Survivors (n=128)	122 (95)
Non-survivors (n=38)	29 (76)
	From this, sensitivity and specificity calculated: TP: 122, FN: 6, FP: 29, TN: 9
Multivariable logistic regression analysis	
Lactate non-clearance- mortality	
Coefficient	1.59
OR	4.9
95%CI	1.5-15.9
General limitations (according to QUADAS 2)	Observational design, small sample size. Indirectness: none. Risk of bias: very high.

Table 276: DETTMER 2015

Study	Dettmer 2015[76]
Study type and analysis	Retrospective cohort
Number of studies (number of participants)	1 (132). This was a sub-group that had lactate monitoring, out of 243 in the whole study, which also looked at the effect of monitoring vs not monitoring
Country and setting	USA; urban academic ED
Funding	Not reported
Duration of study	16 months
Age, gender, ethnicity	Age 61.6(15.8) 56 % male 42% 'Caucasian'; 58% 'other'
Patient characteristics	Main co-morbidities: CHF, DM, ESRD, COPD, liver disease, malignancy; main source of infection was pulmonary (14%), urinary (21%), intra-abdominal(8.3%), skin/soft tissue (3.8%) and blood (9.8%); 31% mechanical ventilation; 13% corticosteroids.. Inclusion: presence of severe sepsis or septic shock and an initial ED lactate level of 4 mmol/litre Exclusion: ED length of stay <2 hours, DNR/DNI status and patient transfer to a unit outside hospital network
Prognostic variable	Lactate clearance
Target condition	28 day mortality
Results:	***Effect of magnitude of lactate reduction on mortality (sub-group analysis restricted to those with serial lactate measurements)*** **Unadjusted** There was a significant (p<0.001) association between greater relative lactate reduction towards normal and reduced 28 day mortality. For those with a lactate reduction >40% 4/64 died; for those with a lactate reduction ≤40% 26/68 died, a RR of 0.24. **Diagnostic accuracy**

Study	Dettmer 2015[76]
	From the risk data above, the raw diagnostic data for lactate clearance at a threshold of 40% were calculated to be: TP60, FN: 42, FP: 4, TN: 26.
General limitations	

Table 277: MARTY 2013

Study	Marty 2013[193]
Study type and analysis	Prospective cohort
Number of studies (number of participants)	1 (94)
Country and setting	France; university hospital ICU
Funding	No financial conflicts of interest
Duration of study	1 year
Age, gender, ethnicity	Age 58 (16) years 56% male Ethnicity not reported
Patient characteristics	Sepsis origin from pulmonary (29%), digestive (28%), urinary (4%) and other (39%); SAPS 2 60(17); MAP at admission: 66.5(10.3) mmHg; Scv02 73.3(9.4) Inclusion: severe sepsis or septic shock, from the ED. Exclusion: Age <19 years, pregnancy, ICU acquired severe sepsis
Prognostic variable	Initial lactate Lactate clearance
Target condition	28 day mortality
Results:	**Unadjusted** Survivors (n=52) had an initial lactate of 5 (3.1) and non-survivors (n=42) had an initial lactate of 6.9 (4.3) [p=0.049]. Survivors (n=52) had lactate clearance from baseline to 6 hours of 13% (381) and non-survivors (n=42) had lactate clearance

Study	Marty 2013[193]
	of -13 (67) [p=0.021]. **Diagnostic accuracy** Initial lactate at a threshold of 5.4 mmol/litre: sens: 0.77 (0.63-0.87); spec: 0.55(.39-0.70) Lactate clearance at a threshold of 7.7%: sens: 0.63(0.49-0.76); spec: 0.56(0.40-0.72)
General limitations	

Table 278: NGUYEN 2004

Study	Nguyen 2004[214]
Study type	Prospective observational case series.
Number of studies (number of participants)	1 (n=111: n=53 severe sepsis; n=58 septic shock)
Country and setting	USA. Urban emergency department and ICU (Henry Ford Hospital)
Funding	Not stated
Duration of study	1 year
Age, gender, ethnicity	Age: 64.9±16.7 years. Gender: 53.2% M/46.8% F. Ethnicity: not stated.
Patient characteristics	Inclusion: patients admitted for >48 h to the interdisciplinary ICU of the university hospital Exclusion: primary fatal condition such as severe head injury resulting in cerebral death that was not combined with an infectious complication. Lactate (mmol/litre): 6.9±4.6 Lactate clearance, %: 27.1±44.4
Index test/s	Lactate
Reference standard	N/A
Target condition	Mortality
Results: Mortality Lactate, mmol/litre	 n=64 survivors n=47 non-survivors survivors (n=64): 6.1±4.4

Study	Nguyen 2004[214]
Lactate clearance, %	nonsurvivors (n=47): 8.0±4.7 survivors (n=64): 38.1±34.6 nonsurvivors (n=47): 12.0±51.6 Lactate clearance at <10% threshold: 0.45 sensitivity and 0.84 specificity
General limitations (according to QUADAS 2)	Observational design, case series. Indirectness: none. Risk of bias: very high.

Table 279: PUSKARICH 2013

Study	Puskarich 2013[245]
Study type and analysis	Prospective cohort (based on patients from one arm in an RCT)
Number of studies (number of participants)	1 (187)
Country and setting	USA; large urban tertiary care hospitals
Funding	Academic grant; no financial conflicts of interest
Duration of study	2 years
Age, gender, ethnicity	Age survivors 60, non survivors 67; survivors 53.8% male, non survivors 56.8% male; survivors 52.4% white, 37.8% black American, 9% Hispanic and 0.7% other. Non-survivors 61.4% white, 36.4% black American, 0% Hispanic and 2.2% other.
Patient characteristics	Inclusion: age >17; suspected infection, 2 or more systemic inflammation criteria; systolic bp <90 mmHg OR lactate >4 mmol/litre; 2 serial lactate measurements; initial lactate >2 mmol/litre Exclusion:
Index test	Initial lactate Lactate clearance
Target condition	In–hospital Survival (note this is the opposite of mortality)

Study	Puskarich 2013[245]
Results:	**Unadjusted** Non-survivors lactate 5.9(IQR:3.4-8.3)[n=44] mmol/litre; survivors lactate 4.3 (IQR: 3-6.1)[n=143] mmol/litre Lactate clearance of 50% or more (compared to <50%) lead to an OR of 4.3(1.8-10.2) of survival. Thus is equivalent to an OR of 0.23(0.09-0.56) for mortality Initial lactate of >4 (compared to 2-4) led to an OR of 1.5(0.8-3.3) for mortality **Diagnostic accuracy analysis** Initial lactate AUC (95% CI): 0.64 for predicting 28 day mortality lactate clearance AUC (95% CI): 0.67 for predicting 28 day mortality The paper did not originally provide details on the actual diagnostic accuracy at specific thresholds. However the authors kindly provided the following information after we contacted them: Patient with initial lactate >2 mmol/litre (n = 187) Accuracy in detecting SURVIVAL: Initial lactate < 4 mmol/litre 46.8 63.6 ≥ 10% Relative lactate clearance 86.7 20.5 ≥50% Relative lactate clearance 44.8 84.1 Note that to detect mortality it can easily be shown that you reverse the direction of the threshold (ie > to <) and also switch the sensitivity and specificity

Table 280: WALKER 2013

Study	Walker 2013[293]
Study type and analysis	Retrospective observational study
Number of studies (number of participants)	1 (78)
Country and setting	UK; tertiary hospital with ICU admitting >1000 level 3 patients/year

Study	Walker 2013[293]
Funding	None; no conflicts of interest
Duration of study	Three year retrospective study
Age, gender, ethnicity	Median (IQR) age 56(40-66); 43% female; ethnicity not defined
Patient characteristics	Consecutive adults (age $\geq$16) with sepsis admitted directly from the ED to the ICU of a tertiary UK hospital. Mean (95% CI) APACHE II score: 24.6 (22.5-26.7); initial lactate median (IQR): 4.9(2.1-7.8), LC median (IQR): 26.9% (-0.1% to 50.6%). Inclusion: primary diagnosis of infection or sepsis Exclusion: no record of arterial lactate measurement in ED; confirmed diagnosis was not sepsis or infection; unobtainable written notes
Prognostic variable	Lactate Lactate clearance
Confounders / stratification strategy	In addition to the above, age and APACHE II score (applied to logistic regression and Cox models only)
Target condition	30 day mortality
Results:	**Unadjusted** Survivors: median initial lactate 3.4 mmol/litre (IQR: 1.8-6.4)[n=53]; Non-survivors: 6.0 mmol/litre (IQR: 4.2-13.3)[n=25] Survivors: lactate clearance 37.2% (IQR: 1.4%-55%)[n=53]; Non-survivors: 10.5% (IQR: -0.7% to 29.5%)[n=25] **Diagnostic accuracy analysis [for those with abnormal admission lactate (>2 mmol/l), n=64]** AUC for initial lactate level as predictor of 30 day mortality: 0.57(95% CI: 0.43-0.71)

Study	Walker 2013[293]
	(AUC for initial lactate level as predictor of 30 day mortality in all (n=78) patients: 0.68(95% CI: 0.57-0.80) AUC for lactate *non*-clearance as predictor of 30 day mortality: 0.79(95% CI: 0.68-0.90) Based on the ROC curve for lactate *non*-clearance, the optimal clearance threshold was chosen as 36%. Using this threshold, lactate clearance at 6 hours of 36% or less predicted 28 day mortality with sensitivity of 88%, specificity of 64.1%, PPV of 61.1% and NPV of 89.3% The following additional supplementary data were received from the authors after we contacted them requesting further information: *Please find attached the ROC curve coordinates for our lactate clearance study. Note that these are for patients in our study that had abnormal lactate (>2) at presentation.* *1. Lactate non-clearance. NB to derive lactate clearance, the values in the first column need to be subtracted from 100.*

Coordinates of the Curve

Test Result Variable(s): lactate non-clearance

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
10.3978	1.000	1.000
13.0204	1.000	.974
18.1641	1.000	.949
22.1552	1.000	.923
27.4063	1.000	.897
32.8604	1.000	.872
34.0247	1.000	.846
34.7157	.960	.846
35.2576	.960	.821

Study	Walker 2013[293]			
	35.6846	.960	.795	
	37.8846	.960	.769	
	41.9444	.960	.744	
	44.3071	.960	.718	
	44.8626	.960	.692	
	45.1515	.960	.667	
	45.5682	.920	.667	
	46.1063	.920	.641	
	46.4773	.920	.615	
	47.9846	.920	.590	
	49.4192	.920	.564	
	49.4841	.920	.538	
	50.2031	.920	.513	
	51.4896	.920	.487	
	54.3060	.920	.462	
	58.1918	.920	.436	
	60.7936	.880	.436	
	62.1094	.880	.410	
	62.6705	.880	.385	
	63.4205	.880	.359	
	64.4818	.840	.359	
	67.0101	.800	.359	
	69.5283	.760	.359	
	70.2190	.760	.333	
	70.4445	.760	.308	
	70.9398	.720	.308	
	72.0557	.680	.308	
	72.7821	.680	.282	

Study	Walker 2013[293]		
	73.7380	.680	.256
	75.2005	.680	.231
	77.8089	.680	.205
	81.1321	.680	.179
	83.0619	.640	.179
	84.1082	.600	.179
	84.7195	.600	.154
	86.4468	.560	.154
	88.5000	.560	.128
	89.2368	.520	.128
	90.5508	.480	.128
	91.7755	.440	.128
	92.6282	.400	.128
	94.2857	.400	.103
	95.4451	.360	.103
	96.6667	.320	.103
	99.1739	.280	.103
	105.4848	.240	.103
	110.3515	.240	.077
	112.5684	.240	.051
	118.9813	.200	.051
	123.5462	.200	.026
	124.1882	.160	.026
	131.0049	.120	.026
	163.7500	.080	.026
	195.6757	.040	.026
	213.7299	.040	.000
	227.1084	.000	.000

Study	Walker 2013[293]
	2. Initial Lactate

Coordinates of the Curve

Test Result Variable(s): lac0

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
1.0000	1.000	1.000
2.0150	.960	.923
2.0650	.920	.923
2.1500	.920	.897
2.2500	.920	.872
2.4000	.880	.872
2.5500	.840	.872
2.6700	.840	.846
2.7700	.840	.821
2.9500	.800	.821
3.1500	.760	.769
3.2500	.760	.744
3.3500	.760	.692
3.5500	.760	.667
3.9000	.760	.641
4.1500	.760	.615
4.2500	.720	.615
4.5000	.680	.615
4.7500	.640	.615
4.9000	.640	.590

Study	Walker 2013[293]		
	5.0500	.640	.564
	5.2000	.600	.564
	5.3500	.520	.538
	5.6000	.520	.462
	5.8500	.520	.436
	5.9500	.520	.385
	6.1000	.480	.385
	6.3000	.480	.359
	6.5000	.480	.333
	6.9500	.440	.308
	7.3500	.440	.282
	7.5000	.440	.256
	7.7000	.400	.256
	7.8500	.360	.256
	7.9500	.320	.256
	8.2000	.320	.231
	8.6000	.320	.205
	8.8500	.320	.179
	9.0000	.320	.154
	9.2000	.320	.128
	9.4000	.320	.103
	11.2500	.280	.103
	13.1500	.280	.077
	13.5000	.240	.077
	13.7500	.200	.077
	13.9000	.160	.077
	14.5000	.120	.077
	17.0000	.040	.000

Study	Walker 2013[293]
	20.0000 .000 .000 From these data we used the following thresholds and sensitivity/specificity values for the review. These were chosen on the basis that they approximated to the thresholds measured by other studies and represented reasonably high resolution increments without 'dominating' the review data. Lactate clearance: Threshold sens spec <9.4% 0.48 0.87 <18.9% 0.68 0.82 <29.8% 0.76 0.67 <39.2% 0.88 0.56 <49.8% 0.92 0.49 <58.1% 0.96 0.23 Initial lactate: 1 mmol/L 1.0 0 2.01 mmol/L 0.96 0.08 2.4 mmol/L 0.88 0.13 2.95 mmol/L 0.8 0.18 3.55 mmol/L 0.76 0.33 4.15 mmol/L 0.76 0.38 4.5 mmol/L 0.68 0.39 5.05 mmol/L 0.64 0.44 5.6 mmol/L 0.52 0.54

H.7.2 Use of scoring systems

Table 281: KELLETT 2013

Study	Kellett 2013[146]
Study type	Retrospective cohort (MediTech database)
Number of studies (number of participants)	n=18,827 surgical patients
Countries and Settings	Canada, hospital
Funding	No funding
Duration of study	Jan 2005–June 2011
Age, gender, ethnicity	Age: mean age 55.8 (SD 18.7) years (of the 15,230 patients who had a second score recorded) Male/Female: not stated Ethnicity: not stated.
Patient characteristics	85.4% general surgery; 8.2% orthopaedic; 6.0% neuro-surgical; 0.4% major trauma. None of the 1018 patients admitted to ICU were included
Prognostic factors/tests	Abbreviated ViEWS (does not include mental status) The original ViEWS attributes up to 3 points to seven variables (i.e. temperature, systolic blood pressure, oxygen saturation, the use of supplemental oxygen, mental status, and pulse and breathing rate) and, hence, has a maximum value of 21 points. Since the abbreviated ViEWS does not include mental status its maximum value is 18 points (i.e. it attributes up to 3 points to six variables). First ViEWS recorded on admission Second ViEWS recorded 2.0 (SD 2.4) h after admission (median 1.0, range 0-24) h (81.0% of patients) Third ViEWS recorded 25.6 (SD 3.4) h after admission (median 25.0, range 0-48) h (69.6% of patients)
Patient outcomes	In hospital mortality
Results	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).
General limitations according to QUADAS II	Retrospective design, single centre, low number of in-hospital death.

Study	Kellett 2013[146]
	Indirectness: Surgical patients, not specific to sepsis. Risk of bias: very high.

Table 282: KELLETT 2013A

Study	Kellett 2013A[144]
Study type	Retrospective cohort (MediTech database)
Number of studies (number of participants)	n=18,853 acutely ill medical patients
Countries and Settings	Canada, hospital
Funding	No funding
Duration of study	Jan 2005–June 2011
Age, gender, ethnicity	Age: mean age 66.1 (SD 18.5) years Male/Female: not stated Ethnicity: not stated.
Patient characteristics	Age >15 years; medical patients
Prognostic factors/tests	Abbreviated ViEWS (does not include mental status) The original ViEWS attributes up to 3 points to seven variables (i.e. temperature, systolic blood pressure, oxygen saturation, the use of supplemental oxygen, mental status, and pulse and breathing rate) and, hence, has a maximum value of 21 points. Since the abbreviated ViEWS does not include mental status its maximum value is 18 points (i.e. it attributes up to 3 points to six variables). First ViEWS recorded on admission Second ViEWS recorded 10.4 (SD 20.1) h after admission (median 5.0, range 0-549) h Third ViEWS recorded 34.9 (SD 21.7) h after admission (median 30.0, range 3-578) h
Patient outcomes	In hospital mortality
Results	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

Study	Kellett 2013A[144]
	only one point for any value of the initial abbreviated ViEWS
General limitations according to QUADAS II	Retrospective design, single centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.

Table 283: KELLETT 2015

Study	Kellett 2015[143]
Study type	Retrospective cohort (electronic medical record)
Number of studies (number of participants)	n=44,531 acutely ill medical patients
Countries and Settings	Canada, hospital
Funding	No conflict of interest to declare
Duration of study	Jan 2005–June 2011
Age, gender, ethnicity	Age: average age 67.5 (SD 17.9) years Male/Female: not stated Ethnicity: not stated.
Patient characteristics	Age >15 years; acutely ill
Prognostic factors/tests	ViEWS (Each vital sign was awarded from 0 to 3 ViEWS weighted points that were then averaged for every 24 hour period for five days after admission and five days before death. These averaged points were then combined, according to the average hospital length of stay, to obtain an approximation for the trajectory of each vital sign in the average patient while in hospital)
Patient outcomes	30-day mortality
Results	See table below. 30-day mortality: 4.6% (2067 patients) 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

Study	Kellett 2015[143]
General limitations according to QUADAS II	Retrospective design, single centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.

Results from Kellett 2015[143,145]. VitalPAC Early Warning Score (ViEWS) Weighted Points for vital signs on admission and at death or discharge.

Survived 30 days	Average ViEWS weighted points		Change	
Ranked by change	**On admission**	**At discharge**	**-in hospital**	**-per day**
Breathing rate	0.24 SD 0.71	0.10 SD 0.49	-0.14	-0.015
Breathing rate + Heart rate	0.24 SD 0.42	0.13 SD 0.33	-0.11	-0.012
Heart rate	0.24 SD 0.50	0.15 SD 0.39	-0.09	-0.009
Breathing rate + Oxygen saturation	0.28 SD 0.52	0.21 SD 0.43	-0.07	-0.007
Breathing rate + Systolic blood pressure	0.19 SD 0.42	0.13 SD 0.33	-0.06	-0.006
Breathing rate + Temperature	0.22 SD 0.42	0.18 SD 0.34	-0.04	-0.004
Oxygen saturation	0.31 SD 0.65	0.31 SD 0.64	0	0
Systolic blood pressure	0.14 SD 0.43	0.14 SD 0.41	0	0
Temperature	0.19 SD 0.43	0.26 SD 0.47	0.07	0.007
Died in hospital within 30 days	**Average ViEWS weighted points**		**Change**	
Ranked by change	**On admission**	**At death**	**-in hospital**	**-per day**
Breathing rate	0.92 SD 1.22	1.46 SD 1.34	0.54	0.067
Breathing rate + Oxygen saturation	0.80 SD 0.85	1.30 SD 0.97	0.5	0.062
Oxygen saturation	0.67 SD 1.02	1.15 SD 1.26	0.48	0.059
Breathing rate + Heart rate	0.75 SD 0.79	1.16 SD 0.88	0.41	0.051
Breathing rate + Systolic blood pressure	0.67 SD 0.77	1.06 SD 0.86	0.39	0.048
Breathing rate + Temperature	0.66 SD 0.74	1.00 SD 0.77	0.34	0.042

Survived 30 days	Average ViEWS weighted points		Change	
Heart rate	0.58 SD 0.74	0.84 SD 0.88	0.26	0.032
Systolic blood pressure	0.40 SD 0.86	0.64 SD 1.10	0.24	0.03
Temperature	0.40 SD 0.75	0.52 SD 0.82	0.12	0.015

Table 284: MURRAY 2014

Study	Murray 2014[204]
Study type	Retrospective cohort (electronic medical record, MediTech)
Number of studies (number of participants)	n=44,531 acutely ill medical patients
Countries and Settings	Canada, hospital
Funding	No funding
Duration of study	Jan 2005–June 2011
Age, gender, ethnicity	Age: not stated Male/Female: not stated Ethnicity: not stated.
Patient characteristics	Age >15 years; acutely ill
Prognostic factors/tests	ViEWS (Each vital sign was awarded from 0 to 3 ViEWS weighted points that were then averaged for every 24 hour period for five days after admission and five days before death. These averaged points were then combined, according to the average hospital length of stay, to obtain an approximation for the trajectory of each vital sign in the average patient while in hospital)
Patient outcomes	30-day in-hospital mortality
Results (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 average daily AbEWS of patients with an admission AbEWS of 0-2 trended upwards, with the average score of those who died within 30 days rising more steeply. In contrast the average daily AbEWS of all patients

Study	Murray 2014[204]
	admitted with an AbEWS on admission ≥7 trended downwards, with the average 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.
General limitations according to QUADAS II	Retrospective design, single centre. Indirectness: Acutely ill patients, not specific to sepsis. Risk of bias: high.

H.8 Patient education, information and support

Table 285: CLARK 2013

Study	Clark 2013[64]
Aim	To gain understanding of parents' and children's needs and experiences when accessing follow-up services
Population	Parent/legal guardian of children (aged <18 years at the time of illness) who had survived meningitis or septicaemia between January 2000 and May 2010, living in the UK or Ireland. Stage one: Survey Members of Meningitis Research Foundation (MRF), individuals with experience of meningitis and septicaemia, were sent a targeted email invitation or letter and a participant information sheet. A general invitation was also placed in MRF's e-newsletter and social media websites. The questionnaire was completed online or paper format. Three hundred and thirty four questionnaires were completed. Participants were excluded if they were not resident in the UK or Ireland, not the parent or legal guardian (N= 89), had experienced disease prior to 2000 or had experience of adult illness (18 years old or more at the time of disease). The final survey sample consisted of 194 parents. The mean age of children at time of illness was 3 years 10 months, and median time since illness was 5 years. Stage two: Follow-up interviews A sample of participants who had consented to be interviewed were contacted. Only participants reporting permanent after-effects, and who had accessed aftercare and support were interviewed. Eighteen patients were interviewed either face-to-face in their homes (n=9) or by telephone (n=9)
Setting	UK, Ireland
Study design and methodology	Stage one: Survey The survey was designed to elucidate disease history, which services were required by children after meningitis and septicaemia, whether follow-up was offered according to the National Institute for Health and Clinical Excellence (NICE) guidelines[212], how easy it was to access services, and

Study	Clark 2013[64]
	parental opinion of the care provided in terms of usefulness and satisfaction. Language and multiple choice questions were informed by a previous member survey, consultation with specialists and a piloting process involving 10 MRF members. Stage two: Follow-up interviews The interview was semi-structured, beginning with an open question inviting parents to provide a narrative background of their child's illness leading up to them requiring aftercare. Further questions explored parents' opinions of the care their children received. All but one of the interviews were digitally recorded and fully transcribed. The transcripts and researchers notes were anonymised.
Analysis methods	Stage one: Survey • Descriptive statistics used in analysis of data • Multivariable logistic regression used to examine associations between permanent sequelae and causative organism (specifically pneumococcal disease Stage two: Follow-up interviews • Qualitative analysis employed the constant comparison method from grounded theory • Transcripts were read individually and units of text were coded using terms relevant to participants' experiences and the research question. T • Coded transcripts were scrutinised for differences and similarities within emerging themes
Survey results	Mean age of children at time of illness: 3 years 10 months Median time since illness: 5 years Country: England; 75%, remaining UK; 22%, Ireland; 3% Disease form: • Meningitis: n=76 (39.2%) • Septicaemia: n=16 (8.3%) • Both meningitis and septicaemia: 102 (52.6%) • Total patients: n=194 Severity of after-effects: • No after-effects: n= 45 (23.2%) • Moderate short term: n=14 (7.2%) • Severe short term: n= 31 (16.0%) • Moderate permanent: n= 43 (22.2%) • Severe permanent: n= 39 (20.1%) • Moderate and severe permanent: n= 1 (0.5%)

Study	Clark 2013[64]	
	• Too soon to tell if permanent: n= 6 (3.1%) • Too soon to tell if any: n= 15 (7.7%) Most parents reported that their child had either moderate or severe permanent after-effects (most common being psychosocial problems) Half of respondents reported that their child's needs were met, and half stated their child's needs were not fully met.	
Themes with findings	Accessing appropriate support and follow-up care	Navigating the system • 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 • Parents felt they had to 'learn the language' and when coming home from hospital parents did not know 'what to do next' • For parents who did not find it difficult to navigate the systems in place, organisational barriers had been overcome • Often there was a key point of contact who was 'proactive' and instigated further appointments
		• 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 often mentioned in examples where young age did not present a barrier to diagnosis or access
		Poorly appreciated link between meningitis and sequelae • Accessing support at school was difficult when the child has had less visible, psychosocial and cognitive after-effects of meningitis and there was little appreciation of the link between meningitis and long term psychosocial after-effects • 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
		Appropriateness of support and aftercare • Appropriateness of services depended on how much time and attention parents felt was paid to their child's individual needs. Some parents felt that this was adequate while others did not
	Communication	Debrief before discharge • Some parents felt they were not 'warned' or told that there could be potential cognitive and behavioural aftereffects, others were told to 'wait and see' • Parents felt a lot of the frustration and distress may have been reduced if there had been better, more standardised ways of communication
		Involving parents

Study	Clark 2013[64]	
		• Parents wanted to be involved and informed about their child's care and support, and often worried about their child being able to reach their potential • The expectations of the child differed between parents, school teachers or health professionals and there seemed to be little management of this aspect of aftercare • In cases where the parents felt listened to and involved, the care package appeared more tailored to the needs of parent and child
		Communication between professionals • Poor communication between different specialists resulted in support that was unresponsive to the child's needs • When professionals did communicate, parents felt that there were shared plans and goals which facilitated meeting their child's needs • Multidisciplinary team meetings involving parents, school staff and health visitors enhanced communication and cooperation in meeting the needs of the child
Limitations	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).	
Applicability of evidence	Applicable to the review target population and setting	

Table 286: DE 2014

Study	De 2014B[74]
Aim	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
Population	n=36 parents of 27 infants aged <3 months with fever and admitted to tertiary children's hospital Age range: 23-44 years. Gender: 22 female / 14 male. Ethnicity: not stated Infant's age: ≤4 weeks; n=9 >4-8 weeks; n=14 >8-12 weeks; n=4 Infants illness duration: ≤2 days; n=15

Study	De 2014B[74]	
	>2-3 days; n=8 >3 days; n=4 Infants duration of admission: ≥2-3 days; n=14 >3-5 days; n=11 >5 days; n=2 Final diagnosis of infant Viral illness; n=18 Urinary tract infection; n=8 Bacteraemia; n=1	
Setting	Australia, children's tertiary care hospital in Sydney, between 1 November 2011 to December 2012	
Study design and methodology	Sampling methods: convenience sampling, no attempt to control for sampling bias. Semi-structured face-to-face interviews just prior to hospital discharge. Interview prompts were developed from literature review, clinical experience, feedback from paediatricians and researchers, and piloted on 5 parents. If both parents participated, they were interviewed together Interviews were audio recorded and transcribed verbatim. Participant recruitment was continued until no new knowledge was being obtained in the concurrent analysis (saturation).	
Analysis methods	Transcripts were entered into Hyper RESEARCH, a software package used to score, code and search. Data collection and data analysis were conducted concurrently following grounded theory principles (coded and thematically analysed). One author identified concepts inductively from the data, and similar concepts were grouped into themes. A second author reviewed the transcripts to ensure all data had been captured (interviewer triangulation). Conceptual links among themes were identified and mapped into thematic schema.	
Themes with findings	Parental attitudes at the time of presentation to hospital: Expecting	Overwhelming responsibility: • Many participants felt overwhelmed by the responsibility of caring for their infant • Many participants feared the possibility of a serious underlying infection such as meningitis • Some believed fever by itself could cause adverse effects such as seizures • Some participants believed they had done something wrong in terms of fever management

Study	De 2014B[74]	
	reassurance and support	Heightened vulnerability: • Participants believed young infants were more vulnerable than older children, had a weaker immune system and could deteriorate rapidly • There was apprehension about missing cues of serious illness. • First time parents were particularly anxious
	Parental attitudes and experiences during the course of hospitalisation: Facilitators for parent empowerment	Medical attentiveness: • Participants felt reassured by prompt and thorough assessment, in particular mothers • Many found the tests distressing to watch but expressed relief the worst possibilities were being ruled out • Some perceived the doctors and nurses were very professional and skilled and felt comforted their fears were being ruled out
		Medical partnership: • Participants who felt the medical team engaged and supported them experienced a heightened sense of involvement and control • There was enhanced trust in the medical team when there was a clear explanation of the management plan, timely updates and opportunities to discuss treatment options • In a couple instances, medication dose errors or multiple attempts at cannulation caused some anger and frustration, but honest explanation was appreciated and helped re-establish trust
		Sense of validation: • Participants feared they would be dismissed as 'over protective' or 'paranoid' but felt relieved if their concerns were recognised as appropriate
		Gaining closure: • Participants felt reassured when the fever resolved and their infant resumed normal sleep, feeding and settling patterns • Receiving a definite diagnosis was of paramount importance for most participants
	Barriers to empowerment	Unmet medical seriousness: • Participants experienced disbelief and shock when their infant had to be hospitalised and undergo medical tests, and many were alarmed by the perceived urgency and degree of medical scrutiny, causing participants to immediately 'assume the worst'
		Relinquished control: • Participants often felt excluded from or unable to contribute meaningfully to the medical management and decision making

Study	De 2014B[74]	
		• Participants felt powerless when witnessing their infant’s distress and pain, and found the lumbar puncture particularly distressing. • Some participants found waiting for the test results was agonising
		Unmet expectation of support: • Some participants felt the explanation of test procedure or treatment was inadequate and doubted the necessity of invasive tests considering the intervention was simply complying with hospital protocols • Others considered the explanation for conducting the tests was given in a manner that made them ‘fear the worst’ • Participants expressed anger and disappointment when they a perceived a lack of empathy from health professionals • Participants who were informed their infant had a viral illness were frustrated believing this was an inadequate, ambiguous and inconclusive explanation of the fever
		Limited capacity for advocacy: • 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	Ethical consent not reported Survey carried out on inpatients- can influence how patients responded (may attempt to please the interviewer) One researcher was involved in data collection and analysis and only preliminary themes were discussed with a second Unclear how theme saturation was assessed (not reported)	
Applicability of evidence	Applicable to the review target population and setting	

Table 287: GALLOP 2015

Study	Gallop 2015[101]
Aim	To explore and describe the subjective experiences and long-term impact of severe sepsis on survivors of severe sepsis and their informal caregivers
Population	Patients (n=22) ≥18 years who had 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 Recruitment: Clinical ICU staff at each site reviewed patient records post-discharge to identify patients at least 18 years old who had experienced a

Study	Gallop 2015[101]	
	severe sepsis episode (defined as presence of infection, systemic inflammatory response syndrome, and at least one organ failure) in the previous 12 months and had been cared for in the ICU. Caregivers were recruited through eligible patients Exclusions: Lack of local language fluency, traumatic brain injury, pre-existing cognitive disorder, moribund status, and currently participating in a clinical trial for severe sepsis.	
Setting	Following discharge from St Thomas' hospital, (UK) and the University of Alabama at Birmingham Hospital (level 1 trauma centre hospital) (United States)	
Study design and methodology	Semi-structured interviews, experienced qualitative researchers following semi-structured patient or caregiver interview guides. Interviews lasted up to 1 hour and were audio recorded and transcribed verbatim for analysis. The majority of interviews were conducted face-to-face (17 out of 22 patient interviews and 11 out of 17 caregiver interviews conducted face-to-face)	
Analysis methods	• Qualitative analysis on the interview transcripts using thematic analysis (inductive and deductive coding to identify, analyse, and report patterns (themes) across a dataset) • Four researchers were involved in the analysis, and the lead analyst worked through each transcript (using qualitative analysis software • Atlas.ti v5.5) to code aspects that may form the bases of repeated patterns (themes)) • Coding and potential themes discussed in analytic meetings • Adequacy of data saturation was assessed by: ○ Use of a saturation table (demonstrated no new codes were identified in the last four interviews, and codes that were added toward the end of the coding process were subthemes providing additional detail and definition of existing theme content) ○ Collective judgment by the analysis team during coding review that there was sufficient depth in the analysis support conclusion that at least a certain level of thematic saturation was achieved within the interview sample	
Themes with findings	Awareness and knowledge of severe sepsis	The level of awareness of severe sepsis as a diagnosis the patient had received varied greatly among patients and caregivers as did 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
		Some participants were vaguely aware that the term "sepsis" had been used at some point but did not actively seek further information
		There was a general lack of understanding of severe sepsis
		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
	Experience of hospitalisation	Recollections of waking up in intensive care varied 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'
		Some patients stated that they had missed days of their life as they did not remember anything of that time

Study	Gallop 2015[101]	
		Several patients reported experiencing strange dreams, hallucinations, and/or paranoia when they regained consciousness
		Caregivers expressed their concern of possible lasting brain damage or personality changes.
		Despite patients having little or no memory of their time in intensive care, caregivers recalled this as a frightening and worrying time, seeing the patient dependent on life support in intensive care was often particularly distressing
		Caregivers were very active despite the patients being sedated, they reported visiting the patient every day or ensuring that someone visited the patient every day
		Caregivers reported talking to the patient in the hope that they could hear them and spending a lot of time in the waiting room in between visiting hours
		Three caregivers reported being in the waiting room when other families informed that the patient had died, which made them imagine themselves in that situation
		Several patients also had considerable mobility difficulties and some were unable to roll over or sit up in bed without assistance
	On-going impact of severe sepsis	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
		The impairments meant they had difficulties with self-care during recovery arose due to impairments particularly after discharge from hospital
		Six patients who had been independent prior to having severe sepsis had become completely dependent on others , while for others the impact on independence was short term
		Patients described feelings of helplessness, embarrassment, and anger 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 severe sepsis, and a heightened awareness and avoidance of infections to prevent recurrence
		For some patients the experience of severe sepsis had changed their outlook on life, their lifestyle and personality in both negative and positive ways
	Impact on caregivers	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

Study	Gallop 2015[101]	
		cases caregivers were unable to leave the patient on their own, restricting their usual activities, work, freedom, and independence
		The reduced freedom and burden of caregiving along with distress related to the patient's condition had a lasting emotional impact on caregivers
		Caregivers reported feelings of frustration, guilt, anxiety, and stress related to their role as a caregiver
	Support after severe sepsis	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 more of a challenge for UK patients (n=4) and caregivers who had received inpatient care a long way from their home)
Limitations		
Applicability of evidence	Applicable to the review target population and setting	

H.9 Education and training

Table 288: CAMPBELL 2008

Study	Campbell 2008[42]
Aim	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).
Study design, population, and setting	Cohort study (1 group pre-test/post-test quasi-experimental) 6 nurses (2 from each shift); 60 chart audits pre-test and 60 post-test. 16-bed ICU, USA
Methods	Nurse champions attended 3 informational sessions, and had the opportunity to review all components of the Keystone: ICU Sepsis Project, and received instruction about the role and responsibilities of nurse champions. They took a competency examination after the educational sessions and had to achieve at least 90% pass rate. ICU Educational sessions:

	ICU staff meeting (nurse manager) • Introduction to Keystone ICU Sepsis Project • “Josie King” video • Role of the quality management (QM) special projects coordinator with the sepsis project • Safety attitude questionnaire ICU staff meeting (ICU education coordinator) • Keystone ICU sepsis protocol overview • Definitions of systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis • Surviving sepsis campaign ICU staff meeting (pharmaceutical representative) • Prevalence of sepsis/severe sepsis in hospital/mortality rates • Treatment options • Xigris (Patient criteria, administration) ICU staff meeting (ICU education coordinator) • Marquette General Health Systems (MGHS) sepsis order sets (adults_/ICU daily care sheet • American Association of Critical Care Nurses (AACN) standards of care • Nurse champion role and responsibilities • Sepsis quiz
Findings	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.
Limitations	High attrition rates of nursing staff.
Quality assessment/ Comments	Population, methods and analysis are well reported.

Table 289: CAPUZZO 2012

Study	Capuzzo 2012[43]
Aim	To assess the trend of the mortality rate of adults admitted to hospital for at least 1 night in relationship with a hospital staff education program on sepsis/septic shock.
Study design, population, and setting	Retrospective cohort study (discharge database) 4850 hospital beds; 164 ICU beds for adults. Number of hospital staff (physicians and nurses) = 9705 6 hospitals, Italy
Methods	Educational package for multidisciplinary sepsis teams (doctors, nurses, intensive care, ED, microbiologists and pharmacists) by the Regional Health Agency, in July 2007. They were taught about principles of adult learning, problem-based learning, and Surviving Sepsis guidelines (epidemiology, morbidity and mortality of SS/SS, scientific literature, electronic presentations for lectures, format of clinical cases for practice training, and booklets reporting clinic and laboratory signs of SS/SS. They were provided with educational material (scientific literature, electronic presentations for lectures, scenarios of clinical cases for practice training and booklets) and started delivering courses and seminars each to their own staff, in October 2007. The educational courses included delivery of short lectures and discussions, as well as problem-based learning on SS/SS scenarios. A typical course session held in the study hospital lasted 4 hours, included the presentation of the objective of the course, definition, general and local epidemiology, early recognition, early goal-detected therapy, microbiological diagnosis, and early antibiotic treatment of SS/SS.
Findings	In comparison with the period before education (Dec 2003 to Oct 2007), the RR of death for the inpatients in the period Nov 2007 to Dec 2008 was 0.93 (0.87-0.99) and the RR for the inpatients 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.
Limitations	The educational project on SS/SS involved only 30%of the hospital clinical staff. Limited information to characterise the population. No data about the compliance with treatment guidelines, or quality indicators assessing the change in process of care as training results. The long period considered in the time series analysis could have compromised the ability to associate the reduction in mortality with education.
Quality assessment/ Comments	Population poorly reported; methods and analysis are well reported.

Table 290: COOPER 2010

Study	Cooper 2010[66]
Aim	Processes used in a simulated environment to recognise and act on clinical cues of deterioration.
Study design,	51 final year undergraduate nursing students

population, and setting	July 2008
Methods	Two, 7 minute patient scenarios (hypovolaemic and septic shock) on a computerised mannequin. Questionnaires were given prior to participant's knowledge of deteriorating patients. Scenarios were developed from the patients presenting condition. Participants were stopped at random points and disengaged in scenario to then answer 17 yes/no questions on patient deterioration. Scenario went for 30 minutes. Participants were told the initial presentation of patient. Video-based reflective review and interviews
Findings	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]).
Limitations	Nursing student population, undergraduate level.

Table 291: ENDACOTT 2010

Study	Endacott 2010[84]
Aim	Processes used in a simulated environment to recognise and act on clinical cues of deterioration.
Study design, population, and setting	Qualitative 51 final year undergraduate nursing students July 2008
Methods	Two, 7 minute patient scenarios (hypovolaemic and septic shock) on a computerised mannequin. Questionnaires were given prior to participant's knowledge of deteriorating patients. Scenarios were developed from the patients presenting condition. Participants were stopped at random points and disengaged in scenario to then answer 17 yes/no questions on patient deterioration. Scenario went for 30 minutes. Participants were told the initial presentation of patient. Video based reflective review and interviews
Findings	Thematic analysis on: • Initial response (patient vitals, symptoms, pain) • Differential recognition of cues (response to cues in scenario, not following responses could lead to ignore other cues) • Accumulation of patient signs (rather than a single sign) • Diversionary activities (unable to tell how useful tests ordered would be)
Limitations	Nursing student population, undergraduate level.

Table 292: FERRER 2008

Study	Ferrer 2008[90]
Aim	To investigate the effects that a national education program, based on SSC, had on care and hospital mortality for severe sepsis.
Study design, population, and setting	Prospective cohort n=2593 patients in ICU (854 pre-intervention [Nov-Dec 2005], 1465 post [March-June 2006], 274 follow-up [Nov-Dec 2006]) 59 ICUs in Spain.
Methods	All centres were provided with the following: • PowerPoint presentation on sepsis, including algorithm. • SSC guideline posters (to be displayed in prominent areas for example, in ICU or ED). • SSC pocket cards. • Sepsis early recognition posters.
Findings	Sepsis resuscitation bundle (P values): • Measure lactate: <0.001 • Blood cultures before antibiotics: <0.001 • Broad-spectrum antibiotics: 0.24 • Fluids and vasopressors: <0.008 • Central venous pressure ≥8 mm Hg: 0.007 • Central venous oxygen saturation ≥70% • All resuscitation measures: <0.001 Sepsis management bundle: • Consideration of low-dose steroids for septic shock according to ICU policy: <0.001 • Consideration of drotecogin alfa (activated) according to ICU policy: <0.001 • Glucose control: 0.02 • Plateau-pressure control: 0.15 • All management measures: 0.001 Administration of medication (low dose steroids): <0.001 Administration of medication (drotrecogin alfa (activated): 0.20 Time from presentation (minutes): • Serum lactate measured: 0.18 • Blood culture obtained: 0.03

	• Antibiotics administered: 0.003 • Central venous pressure ≥8 mm Hg achieved: 0.79 • Central venous oxygen saturation
Limitations	Study was well-reported, large sample size.

Table 293: JEFFERIES 2011

Study	**Jefferies 2011**[135]
Aim	Usage and preference for education tools by clinicians.
Study design, population, and setting	Survey n=92 clinicians Mount Sinai hospital, tertiary perinatal centre
Methods	Interactive seminars: recommendations explained, also received written information and laminated pocket card summary of recommendations. Web-based management algorithm: used to determine appropriate investigation/management Web-based tutorial: self-directed including information on neonatal sepsis, explanation of recommendations and self-assessment.
Findings	No difference (p>0.05) in knowledge assessment immediately after seminar and 3 months later. Comfortable using recommendations 88% Compliance with recommendations = 83% Use of pocket card: 76%, Nurses = 100%, Residents and fellows = 86%, 79% continued to use it after implementation period. Use of seminars: 76% Use of web tutorial: n=1 Use of algorithm: n=4
Limitations	Only for newborns at risk of sepsis, feedback form optional

Table 294: LI 2012

Study	**Li 2012**[172]
Aim	To compare the effect of two education programmes on sepsis.
Study design, population, and setting	Systematic review n=98 medical postgraduates, years 1-4. Medical simulation centres in emergency department in 4 hospitals in Asia (Taiwan, Singapore and India).

	June 2009, December 2009, April 2010.
Methods	All received a 5 hour course: First group: didactic lectures (on sepsis, central line insertion, resuscitation bundle, endotracheal intubation, EDGT) followed by a skills workshop and simulated case scenario (30 minutes: 61 year-old man with fever and cough as the primary complaint for the past few days, vital signs given; team consisted of team leader, nurse and one or two proceduralists, family members, consultant and radiology technician). Second group: skills workshop and simulated case scenario, followed by didactic lectures.
Findings	The study reported significant differences in both groups (pre-test versus post-test) for all postgraduate years (1-4). There was no difference between two groups.
Limitations	Sample size in each group 49. Medical student population.

Table 295: LIAW 2011

Study	Liaw 2011[173]
Aim	Identifying educational needs and strategies for nurses who provide care to deteriorating patients.
Study design, population, and setting	Literature review (2000-2010), 26 papers included Papers included that identified the educational needs of ward nurses or education programs for deteriorating patients.
Methods	Search in CINAHL, PubMed, ScienceDirect, Scopus and Web of Science. Papers had to identify the educational needs of nurses for identifying and managing deteriorating patients, include only nurses who worked in general ward settings in sample, be peer reviewed and in English.
Findings	Three themes were identified for ward nurses' educational needs: • Recognizer: Prior experience and knowledge of recognising deteriorating patients is important for nurses to detect future deteriorating patients, availability of resources, monitoring of vital signs, and education of nurses on appropriate patient assessment. • Reporter: Early warning scoring systems, need for nurses to use medical language, communication between medical and nursing staff. • Responder: Education on knowledge and skills required for interventions, experience to be able to execute appropriate clinical judgement. The four educational programs identified were analysed by three themes: • Course content: 5 programmes identified, 3 for medical and nursing staff (Acute Life Threatening Events Recognition & Treatment [ALERT], Multi-professional Full-scale Simulation [MFS], COMPASS, Acute Illness Management [AIM]). ALERT & AIM focus on algorithm. AIM & MFS utilise mnemonic ABCDE (airway, breathing, circulation, disability, exposure). MRS & COMPASS use mnemonic SBAR (Situation, background, assessment, recommendations). All programmes educated participants on early preventive treatments and knowledge of common emergencies, such as sepsis, and managing adverse physiological signs. AIM & COMPASS included review of relevant anatomy, pathophysiology.

	• Teaching strategies: Combinations of self-directed learning, didactic face-to-face, experiential learning. • Evaluation of learning outcomes: Study on ALERT found significantly higher score on knowledge of acute care pre-attending ALERT than post. ALERT improved attitudes of staff, confidence in recognising critically ill patients, improving mortality, improved recollection of procedures and going to senior staff for help. 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.
Limitations	Did not review studies for methodological bias

Table 296: MACREDMOND 2010

Study	MacRedmond 2010[180]
Aim	Interventions of management protocol for recognition and initial treatment of severe sepsis.
Study design, population, and setting	Pilot cohort 86 ED nurses St Paul's Hospital, tertiary care teaching hospital, Canada.
Methods	Management algorithm, order set, EGDT and education campaign for ED nurses and physicians. 4 hour education session: lecture by ED/ICU physician (explain sepsis, early recognition and sepsis algorithm), then practical instruction and demonstration, ED nurses buddied with ICU nurses. Algorithm also posted in ICU. Order set of initial investigations, management and treatment. Championing of protocol by ED physicians.
Findings	Nurses improved in identification of septic patients p=0.002. Sensitivity identification of sepsis improved from 75% to 92.3%. Specificity was not significant. Hospital mortality lower ARR = 24% (3-47%) Time to antibiotics at follow-up: 0.3 (0-1.6) p=0.01 at follow-up audit Time to initiation of EGDT: 3.2 (2.0 – 5.8) p=0.004 Time to achievement of resuscitation goals: 6.7 (3.3-12.6) p=0.0006
Limitations	n=86, assessed implementation of protocol and not training.

Table 297: MAH 2009

Study	Mah 2009[182]
Aim	Reinforce education of sepsis bundle through use of mannequin simulation in pre-existing teams

Study design, population, and setting	Cohort 74 clinicians Connecticut Simulation Center at Harford Hospital
Methods	Ten-item multiple choice pre-test. In pre-existing workplace teams undertook a 30-35 minute mannequin based simulation. 3 parts: • 15-20 minutes, patient admitted hypoxic, ARDS, intubated and manually ventilated. LBP, rapid heart rate, inadequate intravascular volume, fever severe infection, needing to be resuscitated. • 8-10 minutes, 1 hour post admission, patient's vitals stabilising, LBP, inadequate circulation. • 8-10 minutes, 6 hours post admission, patient's vitals stabilising, require high does vasopressors for BP, inadequate circulation. All materials usually available were available in the simulation and a nursing facilitator was available for any equipment issues. 2 remote observers (critical care physician and nurse) scored participants on a checklist. Mannequin required 12 items on checklist for optimal treatment of sepsis. After the simulation the team was debriefed by senior critical care physician, discussion was encouraged and a number of questions asked to the participants. The video of the simulation was played back and paused and questions asked to participants. Post-test after simulation and debriefing.
Findings	Pre-test score: 64.6%±16.6% (30-100%) Task completion: 60.4% (41.7-75%) Overall sepsis knowledge/task completion: p=0.007 Specific knowledge/task completion: not significant P=<0.001
Limitations	Small sample small

Table 298: MULLER 2012

Study	Muller 2012[203]
Aim	To evaluate the effect of two different training interventions on final year medical students.
Study design, population, and setting	RCT 61 medical final year medical students. 59 completed. Medical simulation Centre of Carl Gustav Carus University All training was 1.5 days
Methods	Randomised to 3 groups (All received a lecture on guidelines for severe sepsis and septic shock):

	• CRM group (CRM): theoretical lecture on situation awareness, case study video of cardiac arrest situation (not related to sepsis), abstract psychological exercises, commentary driving, mental simulation exercises and a virtual sepsis case which groups both presented and went through step-by-step. • Simulator group (SIM): in subgroups of 6-7. Ten scenarios of sepsis cases of 20 minutes, followed by a 25-minute debrief. In each scenario 3 participants were in the role of a physician in charge, junior doctor and attending physician, while the other participants observed. • Control group (CG): no training Before and after all participants where the physician in charge in a 10 minute scripted sepsis scenario. Two instructors played the role of a nurse and junior doctor that carried out any orders if asked. All participants completed 2 questionnaires (13 on perception, 4 on recognition and 4 on anticipation). First questionnaire carried out at random time point between 4-6 minutes. Second at random time point between 8-10 minutes. Additionally, the participants were assessed on their performance in each simulation.
Findings	**Pre and post test** SIM perception, p=0.01 SIM recognition, p=0.13 SIM anticipation, p=0.07 SIM total, p=0.04 CRM perception, p=0.23 CRM recognition, p=0.06 CRM anticipation, p=0.51 CRM total, p=0.14 CG perception, p=0.16 CG recognition, p=0.015 CG anticipation, p=0.59 CG total, p=0.06
Limitations	Small sample size.

Table 299: NGUYEN 2012

Study	Nguyen 2012[215]
Aim	Utility and effectiveness of sepsis education program.
Study design, population, and	Prospective observational cohort All patients at the emergency department between 2003 and 2006 with severe sepsis or septic shock (96 included in analysis)

setting	Emergency department at 350-bed community-based teaching centre.
Methods	Comprehensive sepsis education program including: formal lectures, educational/guideline reminders made available in ICU and inpatient charts, key physicians and nurses advocated and communicated information, reinforced SSC guideline in daily rounds.
Findings	Control group versus 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
Limitations	Small sample size, retrospective retrieval of control group data, control group younger

Table 300: NGUYEN 2009

Study	Nguyen 2009[213]
Aim	To increase knowledge of treatment for severe sepsis and septic shock through simulation based teaching at medical school.
Study design, population, and setting	Prospective cohort Medical students at all levels of training University based medical simulation centre
Methods	Participants tested three times:

	• Pre-test – prior to participating in simulation course • Post-test – immediately after participating in simulation course • 2-weeks post-test – 2 weeks after participating in simulation course Education/simulation included: • Didactic lectures: Sepsis lectures included definitions, pathophysiology and early management of severe sepsis and sepsis shock. Early goal directed therapy (EGDT), including case scenario, was explained. • Septic shock patient simulation: 20 minutes to complete. Team had roles of leader, nurse, proceduralist for central line placement and proceduralist for intubation. One course instructor, such as a family member or paramedic, as necessary, was not involved in treating the patient or giving instructions, while a second course instructor completed a 21-item task checklist. A computer-controlled mannequin providing responses (for example, change in heart rate or blood pressure) to treatments for sepsis. The scenario involved a 61-year old man with a history of hypertension, diabetes and coronary artery disease. The only symptoms expressed by the patient were a cough of 2 days with shortness of breath, malaise and fever. Signs: 38.3 degree Celsius, 102 heart rate per minute, 80/50 blood pressure, SaO_2 92%, 22 per minute respiratory rate. Test included knowledge on EGDT, central line placement, incubation technique and sepsis patient scenarios. Example 5-hour course session: 14:00-14:10 hours Course Introduction of Goals and Objectives 14:10-14:30 hours Pre-test 14:30-15:00 hours Central line placement and intubation technique lecture 15:00-16:00 hours Severe sepsis, septic shock and EGDT lecture 16:00-16:10 hours Break 16:10-17:10 hours Central line placement and intubation simulation 17:10-17:15 hours Break 17:15-18:35 hours Septic shock patient simulation 18:35-18:40 hours Break 18:40-19:00 hours Post-test Post-test repeated after 2 weeks
Findings	20.6% believed pre-test was too hard. All believed post-test was either appropriate or too easy. Significantly higher test scores post-test compared with pre-test in all participants.

Limitations	n=63, medical students only, funding from Edwards Lifesciences.

Table 301: OWEN 2014

Study	Owen 2014[226]
Aim	To explore the design, implementation, and evaluation of continuing inter-professional development.
Study design, population, and setting	Prospective cohort 45 health professionals University of Virginia
Methods	First activity: Reflective and experiential learning (reflecting on working in teams). Five to six team members applying social identity theory, discussing and reflecting on interprofessional group processes, and learning and team working in implementing sepsis guidelines. Second activity: Role coding from SSC, videotape on roles of health professionals in SSC.
Findings	Reported no significant differences in pre and post test scores in first activity, second activity had only 11 participants, so no statistical analysis was performed.
Limitations	Small sample size. Statistical analysis could not be performed as only 11 people in second and third activity. Allocation to groups.

Table 302: YOUSEFI 2012

Study	Yousefi 2012[303]
Aim	Effect on attitude, knowledge and practice of education program.
Study design, population, and setting	Quasi-experimental study. 64 ICU nurses (minimum 1 year experience). Shariati Hospital, Isfahan, Iran)
Methods	One day, 8 hour, workshop on sepsis, a questionnaire, and education pamphlets on sepsis. Presentation on sepsis as a PowerPoint presented by health professionals and a patient scenario.
Findings	Knowledge, attitude and practice reported as significantly higher in intervention group compared with control (p=<0.05).
Limitations	Unclear analysis and exact measure were not stated.

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