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Sepsis

Sepsis: recognition, assessment and early management

NICE guideline 51

Appendices I to O

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None.

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Study	Mouncey 2015[827]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs)	**Population:** Patients with early signs of	**Total costs (mean per patient):**	**QALYs (mean per patient):** Intervention 1: 0.054	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominated (more expensive

Study design: Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level data for mortality and EQ-5D. Unit costs were applied to resource use. **Perspective:** UK NHS **Time horizon/Follow-up** 90 days QoL follow up **Treatment effect duration:** Resuscitation protocol was followed for 6 hours **Discounting:** Costs: NR; Outcomes: NR	septic shock **Patient characteristics:** N = 1251 Mean age: invtn 1 = 64.3 (15.5), intvn 2 = 66.4 (14.6) Male: invtn 1 = 58.6%, intvn 2 = 57% **Intervention 1:** Usual care The usual care group continued to receive monitoring, investigation and treatment as determined by the clinician. **Intervention 2:** Early Goal Directed Therapy (EGDT). Following a resuscitation protocol involving central venous catheter insertion with central venous oxygen saturation monitoring capability and intensive therapy of other interventions	Intervention 1: £11,424 Intervention 2: £12,414 Incremental (2−1): £989 (95% CI: -726 to 2,705; p=NR) **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** - Equipment and consumables – 2 monitors capable of oxygen saturation monitoring assumed to be needed per hospital. Costs of consumables including the catheter capable of monitoring, pressure transducers. - Blood products and dobutamine - Staff time to deliver the protocol; time for vascular catheter insertion and time for monitoring patients (assumed 10 minutes of nurse time per hr of the resus protocol). Staff time for training, assumed to be 20 minutes per ED staff member every 5 years (5 years assumed to be the life	Intervention 2: 0.054 Incremental (2−1): -0.001 (95% CI: -0.006 to 0.005); p=0.85)	and less benefit) Probability Intervention 2 cost-effective (£20K/30K threshold): 12%/12% (read from graph) **Analysis of uncertainty:** Some form of PSA undertaken [(a)] to generate cost effectiveness plane and cost effectiveness acceptability curve. 500 estimates obtained. Sensitivity analyses undertaken include: - Manufacturer list price used for monitoring machines instead of discounted price used in base case - Staff monitoring time varied from 10 minutes per hour in the base case to 5 and 15 minutes. - Location of protocol implementation; if protocol is implemented in the ED, staffneed to be trained but in critical care they do not. Sensitivity analysis assumed that the protocol was implemented either exclusively in the ED or critical care. - Re-admission data in the base case was gathered both from the health services questionnaire sent out and the Intensive Care National Audit & Research Centre Case Mix Programme Database. In a sensitivity analysis only the database was used to avoid any potential double counting. - Baseline covariates were adjusted for components of the Mortality in Emergency Department Sepsis (MEDS) score

		of the protocol) - Hospital stay/ICU stay - Re-admissions		- Costs and QALYs were assumed to be gamma distributed, compared to normally distributed in the base case. EGDT remained cost-ineffective in all sensitivity analyses.
Data sources				
Health outcomes: Mortality data taken from the RCT (proMISe trial) alongside the economic evaluation. **Quality-of-life weights:** EQ-5D scores were elicited at 90 days, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and 90 days. Zero QALYs were assumed for people who died before 90 days. **Cost sources:** Costs of monitor and central venous catheter with monitoring capability was derived from the manufacturer. These costs are over 50% discount on list prices. It was assumed each site would require 2 monitors which would have a lifespan on average of 5 years. Monitor costs per patient were calculated by dividing the total costs of the monitors (£4000) by the expected number of eligible patients over 5 years. Annual number of eligible patients calculated by taking average number of potentially eligible patients per site per year from the trial screening log data (23 patients per site per year). Some consumables sourced from hospital finance departments. Training costs per patient per hour derived from total training costs per site divided by eligible patients over 5 years. Blood products from NHS blood and transplant price list 2012. Drugs from BNF 2012. Staff costs and outpatient and community health service costs from PSSRU 2012. Hospital stay costs from NHS reference costs 2012.				
Comments				
Source of funding: NR **Limitations:** Adverse events not taken account of in cost effectiveness analysis (either their treatment costs or impact on QoL). Methodology behind probabilistic analysis unclear. Short time horizon.				
Overall applicability(d): Directly applicable **Overall quality:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years

(a) The paper states incremental costs and QALYs were estimated using 'a seemingly unrelated regression model', and they used 'the estimates of the means, variances and the covariance from the regression model to generate 500 estimates of incremental costs and QALYs from the joint distribution of these endpoints'. By generating a cost effectiveness plane and cost effectiveness acceptability curve this implies some kind of probabilistic analysis was done but the methodology quoted isn't clear.

I.14 Monitoring

None.

I.15 Patient education, information and support

None.

I.16 Training and education

Study	Suarez 2011[1076]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA/CUA (health outcome: Life Years Gained and QALYs) **Study design:** Within trial analysis **Approach to analysis:** Pre-education program cohort (2 months before program) was compared to a post education program cohort (4 months after program). Program consisted of a 2 month educational program of training physicians and nursing staff from the emergency department, medical, and surgical wards, and ICU in early recognition of severe sepsis and the treatments in the Surviving Sepsis Campaign (SSC) protocol. Unit costs applied to prospective study data. Multivariable regression models were used to adjust for baseline	**Population:** Patients with severe sepsis **Patient characteristics:** N = 2319 [(b)] Mean age = 62.2 (SD: 16.3) Male = 60.8% **Intervention 1:** Pre-intervention cohort, the 2 months prior to the educational program **Intervention 2:** Post intervention cohort, the 4 months following educational program.	**Total costs (mean per patient):** Intervention 1: £14,427 Intervention 2: £15,906 Incremental (2−1): £1,479 (95% CI: NR; p=NR) **Currency & cost year:** 2006 Spanish Euros presented here as 2006 UK pounds[(c)] **Cost components incorporated:** Unit costs for emergency visits, surgical and medical ward daily stays, and ICU daily stays. Cost associated with the pharmacological and non-pharmacological interventions of the SSC protocol. One of the goals of the SSC protocol is	**QALYs (mean per patient):** Intervention 1: 3.75 Intervention 2: 4.12 Incremental (2−1): 0.37 (95% CI: 0.02-0.73; p=NR) **Life Years Gained (mean per patient):** Intervention 1: 5.44 Intervention 2: 5.98 Incremental (2−1): 0.54 (95% CI: 0.02-1.05; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £5,476 per QALY gained (the 'adjusted' ICER) (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K threshold): 94% (read off graph) Probabilistic analysis was undertaken using non parametric bootstrapping with 2000 replications. **Analysis of uncertainty:** One way sensitivity analyses undertaken include: - Changing the rate for sepsis survivors from 0.51 to 0.39. Making this value even more restrictive. - Quality of life weight was changed from 0.69 to 0.75. - The ICER was also calculated for different utility values. Only for very low utility values (lower than 0.2) was the ICER more than £20,000 (read off graph). - Discounting of Life Years Gained and

differences of costs, QALYs, and Life Years Gained. **Perspective:** Spanish healthcare system perspective. **Time horizon/Follow-up:** Post intervention cohort was a 4 month period after intervention introduced. Costs were only considered up until hospital discharge. Lifetime horizon for life years. **Treatment effect duration:**[(a)] 4 months (post intervention cohort) **Discounting:** Costs: NA; Health outcomes: 3%		maintaining glucose control; the average cost per patient reported in a cost effectiveness analysis of insulin therapy was used. Patients who achieved the goal were applied the cost of the intensive therapy group, and patients who did not meet the goal were applied the cost of the conventional therapy group.		QALYs was changed from 3% to 0%. - Discounting of Life Years Gained and QALYs was changed from 3% to 5%. - The cost of the education and training program and cost of staff time spent attending the sessions was not included in base case. These costs were included in a sensitivity analysis. All sensitivity analyses generated results similar to that of the base case.
Data sources				
Health outcomes: Mortality and resource use data derived from a cohort before and after study (Ferrer 2008 [450]). Age and gender specific life expectancy for each survivor taken from the 2006 Spanish like expectancy tables. These were adjusted using the estimated reduction rate for sepsis survivors of 0.51 [945]. **Quality-of-life weights:** The quality of lie weight used was 0.69. This utility weight was obtained from a study of 6 month survivors of severe sepsis using the EQ-5D. [395] **Cost sources:** unit costs for emergency visits, surgical and medical ward daily stays, and ICU daily stays were from the Spanish National Health Institute. Pharmacological intervention costs from the SSC protocol were from the Spanish physician's desk reference. Non-pharmacological intervention costs were obtained from their suppliers. Insulin therapy cost was the average cost per patient from a cost effectiveness study on insulin therapy[1122] (€144 for intensive therapy and €72 for conventional therapy). All prices in the study were adjusted to 2006 values using the Spanish consumer price index. Long term costs after discharge were not included. The costs of the training program were not included in the base case, but were included in a sensitivity analysis (€54,270).				
Comments				
Source of funding: Supported by a grant from the Instituto de Salud Carlos III. **Limitations:** Only includes short term costs. Data on effectiveness from a cohort study, not RCT. Base case did not include cost if the intervention itself. Methodology not always clear; particularly around where adjusted ICER comes from. **Other:** The paper states that both the incremental costs and incremental QALYs/Life Years Gained were 'obtained by adjusting multivariable regression models to take into account possible baseline imbalances'. The ICER that is reported in the study is stated to be the 'adjusted ICER' (6,428 Euros or £5,476). It is unclear whether the 'adjusted' ICER reported is the deterministic or probabilistic ICER, however the paper states the ICER in the text (as well as a table) then immediately in the next sentence states that				

nearly all the bootstrap replications were below the threshold used of 30,000 euros. Thus implying this is likely to be the probabilistic ICER.
Overall applicability: Partially applicable[(d)] **Overall quality**[(e)] Potentially serious limitations

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) The post intervention cohort are those that would benefit from the 'treatment effect' of the education program. This cohort included patients during the 4 month period after the intervention. The time horizon for health outcome was lifetime so life expectancy was applied to the survivors. Therefore there is an assumption being made about the continuation of the study effect because life years will continue to vary between arms as different numbers of people will be alive in the pre and post intervention cohorts. The utility being applied to the groups is the same because the utility is the utility of sepsis survivors and is not impacted by the intervention except by the impact on mortality.

(b) Note that the study this economic evaluation is based on is included in the clinical review (Ferrer2008) and the number of patients included in the study is higher than that reported here because there was also a third observation period (one year after the pre intervention group, to test the longevity of the education program) included in the clinical paper that is separate to the pre and post intervention cohorts.

(c) Converted using 2006 purchasing power parities [883]

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix J: GRADE tables

J.1 Scoring systems

None.

J.2 Signs and symptoms

None.

J.3 Blood tests

None.

J.4 Lactate

None.

J.5 Serum creatinine

None.

J.6 Disseminated intravascular coagulation (DIC)

Table 1: Disseminated intravascular coagulation (DIC) and all-cause mortality

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DIC	Control	OR (95% CI)	Absolute		
28-day mortality - Gando 2008												
1	observational studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	65	264	1.22 (1.00 to 1.49)	-[4]	VERY LOW	CRITICAL
28-day mortality - Gando 2013												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	332	1.28 (1.14 to 1.44)	-[4]	VERY LOW	CRITICAL
28-day mortality - Ogura 2014												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	332	1.73 (1.09 to 2.75)	-[4]	VERY LOW	CRITICAL
In-hospital mortality - Gando 2007												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	11	34	4.22 (1.42 to 12.59)	-[4]	VERY LOW	CRITICAL
In-hospital mortality - Gando 2007A												

1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	28	40.50 (4.54 to 360.98)	-[4]	VERY LOW	CRITICAL
In-hospital mortality - Ogura 2014												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	332	1.55 (1.01 to 2.37)	-[4]	VERY LOW	CRITICAL

[1] Risk of bias mainly due to the lack of evidence that physicians treating patients were blinded to the DIC status. The assumed lack of blinding means that knowledge of DIC could affect treatment, which would possibly affect outcome.
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments)
[3] Downgraded by 1increment due to a very imprecise result expressed by a very wide confidence interval
[4] N/A as only adjusted or unadjusted OR was provided

J.7 Antimicrobial treatment

Table 2: <1 hour versus >1 hour (adult population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<1h versus >1h (multivariable analysis)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
8	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.87 (0.81 to 0.94)	-[2]	VERY LOW	CRITICAL
Mortality - ICU setting												

5	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Not estimable	-[2]	VERY LOW	CRITICAL
Mortality - ED setting												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Not estimable	-[2]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Absolute effect not estimable as the crude event rate for the control group was not provided
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 3: <2 hours versus >2 hours (adult population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<2h versus >2h (multivariable analysis)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
4	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.73 (0.51 to 1.04)	-[3]	VERY LOW	CRITICAL
Mortality - ICU setting												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.14 (0.02 to 0.88)	-[3]	VERY LOW	CRITICAL
Mortality - ED setting												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.78 (0.54 to 1.12)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 4: <3 hours versus >3 hours (adult population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<3h versus >3h (multivariable analysis)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
6	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.7 (0.57 to 0.86)	-[3]	VERY LOW	CRITICAL
Mortality - ICU setting												
1	observational	serious[1]	no serious	no serious	serious[2]	none	-	-	OR 0.8 (0.6 to	-[3]	VERY	CRITICAL

	studies		inconsistency	indirectness					1.07)		LOW	
Mortality - ED setting												
5	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.62 (0.47 to 0.82)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 5: <4 hours versus >4 hours (adult population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<4h versus >4h (multivariable analysis)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/25 (12%)	-	OR 0.86 (0.49 to 1.53)	-[3]	VERY LOW	CRITICAL
Mortality - ED setting												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.86 (0.49 to 1.53)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 6: <5 hours versus >5 hours (adult population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<5h versus >5h (multivariable analysis)	Control	OR (95% CI)	Absolute		
Mortality												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.65 (0.26 to 1.62)	-[3]	VERY LOW	CRITICAL
Mortality - ED setting												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.65 (0.26 to 1.62)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 7: <6 hours versus >6 hours (adult population)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<6h versus >6h (multivariable analysis)	Control	OR (95% CI)	Absolute		
Mortality												
3	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.72 (0.58 to 0.9)	-[3]	VERY LOW	CRITICAL
Mortality - ICU setting												
2	observational studies	serious[1]	serious[4]	no serious indirectness	serious[2]	none	-	-	OR 0.79 (0.57 to 1.08)	-[3]	VERY LOW	CRITICAL
Mortality - ED setting												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.67 (0.5 to 0.9)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided
[4] I2=60% (p=0.11)

Table 8: Hourly treatment delay (ICU, adult population)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hourly treatment delay (ICU)	Control	OR (95% CI)	Absolute		
In-hospital mortality												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 1.12 (1.1 to 1.14)	-[2]	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 9: Parenteral antibiotics prior to admission to hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral antibiotics prior to admission to hospital (GP)	Control	OR (95% CI)	Absolute		
Mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.58 (0.21 to 1.58)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 10: <1 hour versus >1 hour (PICU, paediatric population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral antibiotics prior to admission to hospital (GP)	Control	OR (95% CI)	Absolute		
Mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.6 (0.13 to 2.86)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 11: <2 hours versus >2 hours (PICU, paediatric population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral antibiotics prior to admission to hospital (GP)	Control	OR (95% CI)	Absolute		
Mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.41 (0.13 to 1.35)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 12: <3 hours versus >3 hours (PICU, paediatric population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parenteral antibiotics prior to admission to hospital (GP)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.25 (0.08 to 0.79)	-[3]	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

Table 13: <4 hours versus >4 hours (PICU, paediatric population)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parenteral antibiotics prior to admission to hospital (GP)**	**Control**	**OR (95% CI)**	**Absolute**		
Mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 0.28 (0.1	-[3]	VERY	CRITICAL

									to 0.81)		LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect not estimable as the crude event rate for the control group was not provided

J.8 IV fluid administration

Table 14: Clinical evidence profile: 6% HES versus 0.9% saline in adults with sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**6% HES versus 0.9% saline**	**Control**	**Relative (95% CI)**	**Absolute**		
90-day mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	248/976 (25.4%)	224/945 (23.7%)	RR 1.07 (0.92 to 1.25)	17 more per 1000 (from 19 fewer to 59 more)	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence profile: Crystalloid versus colloid plus crystalloid in adults with severe sepsis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Crystalloid versus colloid + crystalloid**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospital mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	101/235 (43%)	121/258 (46.9%)	RR 0.92 (0.75 to 1.12)	38 fewer per 1000 (from 117 fewer to 56 more)	VERY LOW	CRITICAL
ICU mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	72/235 (30.6%)	99/258 (38.4%)	RR 0.8 (0.62 to 1.02)	77 fewer per 1000 (from 146 fewer to 8 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: 20% albumin versus 6% HES in adults with severe sepsis

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**20% albumin versus 6% HES**	**Control**	**Relative (95% CI)**	**Absolute**		
28-day mortality												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/30 (13.3%)	6/26 (23.1%)	RR 0.58 (0.18 to 1.83)	97 fewer per 1000 (from 189 fewer to 192 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: 4% albumin versus 0.9% Sodium Chloride BP in adults with severe sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4% albumin versus 0.9% Sodium Chloride BP	Control	Relative (95% CI)	Absolute		
28-day mortality (univariate analysis)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	185/603 (30.7%)	217/615 (35.3%)	RR 0.87 (0.74 to 1.02)	46 fewer per 1000 (from 92 fewer to 7 more)	LOW	CRITICAL
28-day mortality (multivariate analysis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/452 (30.3%)	166/467 (35.5%)	OR 0.71 (0.52 to 0.97)	-[3]	HIGH	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Adjusted odds ratio

Table 18: Clinical evidence profile: Albumin versus crystalloids in adults with sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Albumin versus crystalloids	Control	Relative (95% CI)	Absolute		
All-cause mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	710/1937 (36.7%)	763/1941 (39.3%)	RR 0.93 (0.86 to 1.01)	28 fewer per 1000 (from 55 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
90-day mortality												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115/283 (40.6%)	116/286 (40.6%)	RR 1 (0.82 to 1.22)	0 fewer per 1000 (from 73 fewer to 89 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment because of inconsistencies regarding the study population
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 19: Clinical evidence profile: Albumin versus colloids in adults with sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Albumin versus	Control	Relative	Absolute		

studies		bias				considerations	colloids		(95% CI)			
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	54/143 (37.8%)	58/156 (37.2%)	RR 1.02 (0.76 to 1.36)	7 more per 1000 (from 89 fewer to 134 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment because of differences regarding the study population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: Packed red blood cells (PRBC) plus EGDT versus EGDT only in adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PRBC + EGDT versus EGDT	Control	Relative (95% CI)	Absolute		
Hospital mortality												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/34 (41.2%)	20/59 (33.9%)	RR 1.21 (0.71 to 2.08)	71 more per 1000 (from 98 fewer to 366 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence profile: Red blood cells (RBC) for low threshold (≤7g/dl) versus high threshold (≤9g/dl) in adults with septic shock

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RBC at low versus high threshold	Control	Relative (95% CI)	Absolute		
90-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	216/502 (43%)	223/496 (45%)	RR 0.97 (0.84 to 1.11)	13 fewer per 1000 (from 72 fewer to 49 more)	MODERATE	CRITICAL
90-day mortality - >70 years of age												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	93/173 (53.8%)	98/185 (53%)	RR 1.01 (0.84 to 1.23)	5 more per 1000 (from 85 fewer to 122 more)	MODERATE	CRITICAL
90-day mortality - 70 years or younger												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	123/329 (37.4%)	125/311 (40.2%)	RR 0.93 (0.77 to 1.13)	28 fewer per 1000 (from 92 fewer to 52 more)	MODERATE	CRITICAL

[1] Intervention does not fall within the 6-hour time frame

Table 22: Clinical evidence profile: 0-2 litres versus 2-4 litres of fluids in adults with severe sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	0-2L versus 2-4L	Control	Relative (95% CI)	Absolute		

Hospital mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/210 (46.2%)	82/186 (44.1%)	RR 1.05 (0.84 to 1.3)	22 more per 1000 (from 71 fewer to 132 more)	VERY LOW	CRITICAL
ICU mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/210 (31.4%)	66/186 (35.5%)	RR 0.89 (0.67 to 1.17)	39 fewer per 1000 (from 117 fewer to 60 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Clinical evidence profile: 0-2 litres versus >4 litres of fluids in adults with severe sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	0-2L versus >4L	Control	Relative (95% CI)	Absolute		
Hospital mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/210 (46.2%)	45/100 (45%)	RR 1.03 (0.79 to 1.33)	13 more per 1000 (from 94 fewer to 149 more)	VERY LOW	CRITICAL
ICU mortality												
1	observational	very	no serious	no serious	serious[2]	none	66/210	41/100	RR 0.77 (0.56	94 fewer per 1000 (from 180	VERY	CRITICAL

	studies	serious[1]	inconsistency	indirectness			(31.4%)	(41%)	to 1.04)	fewer to 16 more)	LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Clinical evidence profile: 2-4 litres versus >4 litres of fluids in adults with severe sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**2-4L versus >4L**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospital mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	82/186 (44.1%)	45/100 (45%)	RR 0.98 (0.75 to 1.28)	9 fewer per 1000 (from 112 fewer to 126 more)	VERY LOW	CRITICAL
ICU mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/186 (35.5%)	45/100 (45%)	RR 0.79 (0.59 to 1.05)	94 fewer per 1000 (from 185 fewer to 22 more)	VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Clinical evidence profile: High volume (20-40ml Ringer lactate/kg) versus low volume (20ml Ringer lactate/kg) in children with septic shock

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High volume versus low volume	Control	Relative (95% CI)	Absolute		
Cumulative 72-hour survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/74 (70.3%)	55/73 (75.3%)	RR 0.93 (0.77 to 1.14)	53 fewer per 1000 (from 173 fewer to 105 more)	MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

J.9 Escalation of care

None.

J.10 Inotropic agents and vasopressors

Table 26: Clinical evidence profile: Norepinephrine versus vasopressin for adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine versus vasopressin	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	150/382 (39.3%)	140/396 (35.4%)	RR 1.11 (0.93 to	39 more per 1000 (from 25 fewer to 117	MODERATE	CRITICAL

									1.33)	more)		
90-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	188/379 (49.6%)	172/392 (43.9%)	RR 1.13 (0.97 to 1.31)	57 more per 1000 (from 13 fewer to 136 more)	MODERATE	CRITICAL
ICU mortality												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	13/25 (52%)	11/28 (39.3%)	RR 1.26 (0.72 to 2.21)	102 more per 1000 (from 110 fewer to 475 more)	VERY LOW	CRITICAL
Requiring renal replacement therapy at 48 hours												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/15 (53.3%)	5/15 (33.3%)	RR 1.6 (0.68 to 3.77)	200 more per 1000 (from 107 fewer to 923 more)	VERY LOW	NOT IMPORTANT
New onset of tachyarrhythmias												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/15 (26.7%)	1/15 (6.7%)	RR 4 (0.5 to 31.74)	200 more per 1000 (from 33 fewer to 1000 more)	VERY LOW	NOT IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 27: Norepinephrine versus dopamine for adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine versus dopamine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/118 (43.2%)	67/134 (50%)	RR 0.86 (0.66 to 1.13)	70 fewer per 1000 (from 170 fewer to 65 more)	VERY LOW	CRITICAL
Mortality												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/40 (57.5%)	28/40 (70%)	RR 0.82 (0.59 to 1.15)	126 fewer per 1000 (from 287 fewer to 105 more)	VERY LOW	CRITICAL
Hospital mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/16 (43.8%)	10/16 (62.5%)	RR 0.7 (0.36 to 1.37)	188 fewer per 1000 (from 400 fewer to 231 more)	VERY LOW	CRITICAL
Incidence of arrhythmias												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/118 (11.9%)	51/134 (38.1%)	RR 0.31 (0.18 to 0.53)	263 fewer per 1000 (from 179 fewer to 312	LOW	NOT IMPORTANT

										fewer)		
Length of stay in the hospital (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	134	-	MD 0.7 lower (4.36 lower to 2.96 higher)	LOW	IMPORTANT
Length of stay on the ICU (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	134	-	MD 0.7 higher (1.15 lower to 2.55 higher)	LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Norepinephrine versus epinephrine for adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine versus epinephrine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24/82 (29.3%)	17/76 (22.4%)	RR 1.31 (0.76 to 2.24)	69 more per 1000 (from 54 fewer to 277 more)	MODERATE	CRITICAL

90-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30/82 (36.6%)	23/74 (31.1%)	RR 1.18 (0.76 to 1.83)	56 more per 1000 (from 75 fewer to 258 more)	MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Dopexamine versus dopamine for adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopexamine versus dopamine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/20 (25%)	4/21 (19%)	RR 1.31 (0.41 to 4.2)	59 more per 1000 (from 112 fewer to 610 more)	LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Norepinephrine plus dobutamine versus epinephrine for adults with septic shock

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine + dobutamine versus epinephrine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	58/169 (34.3%)	64/161 (39.8%)	RR 0.86 (0.65 to 1.14)	56 fewer per 1000 (from 139 fewer to 56 more)	MODERATE	CRITICAL
90-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/169 (50.3%)	84/161 (52.2%)	RR 0.96 (0.78 to 1.19)	21 fewer per 1000 (from 115 fewer to 99 more)	HIGH	CRITICAL
7-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/169 (20.1%)	40/161 (24.8%)	RR 0.81 (0.54 to 1.21)	47 fewer per 1000 (from 114 fewer to 52 more)	MODERATE	CRITICAL
14-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	44/169 (26%)	56/161 (34.8%)	RR 0.75 (0.54 to 1.04)	87 fewer per 1000 (from 160 fewer to 14 more)	MODERATE	CRITICAL
Mortality												

2	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	13/26 (50%)	13/26 (50%)	RR 1 (0.58 to 1.71)	0 fewer per 1000 (from 210 fewer to 355 more)	VERY LOW	CRITICAL
Mortality at discharge from ICU												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/169 (44.4%)	75/161 (46.6%)	RR 0.95 (0.75 to 1.21)	23 fewer per 1000 (from 116 fewer to 98 more)	HIGH	CRITICAL
Mortality at discharge from hospital												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/169 (48.5%)	84/161 (52.2%)	RR 0.93 (0.75 to 1.15)	37 fewer per 1000 (from 130 fewer to 78 more)	HIGH	CRITICAL
Number of serious adverse events during catecholamine infusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	41/169 (24.3%)	43/161 (26.7%)	RR 0.91 (0.63 to 1.31)	24 fewer per 1000 (from 99 fewer to 83 more)	LOW	NOT IMPORTANT
Number of serious adverse events after catecholamine infusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/169 (7.7%)	12/161 (7.5%)	RR 1.03 (0.49 to 2.19)	2 more per 1000 (from 38 fewer to 89 more)	LOW	NOT IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 31: Norepinephrine plus dopexamine versus norepinephrine plus epinephrine for adults with septic shock

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine + dopexamine versus epinephrine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/12 (16.7%)	3/10 (30%)	RR 0.56 (0.11 to 2.7)	132 fewer per 1000 (from 267 fewer to 510 more)	LOW	CRITICAL
90-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/12 (25%)	4/10 (40%)	RR 0.62 (0.18 to 2.16)	152 fewer per 1000 (from 328 fewer to 464 more)	LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Norepinephrine plus epinephrine versus norepinephrine plus dobutamine for adults with septic shock

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Norepinephrine + epinephrine versus norepinephrine + dobutamine	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15/30 (50%)	16/30 (53.3%)	RR 0.94 (0.57 to 1.53)	32 fewer per 1000 (from 229 fewer to 283 more)	LOW	CRITICAL
SOFA score at start (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	MD 0.8 higher (2.31 lower to 3.91 higher)	MODERATE	IMPORTANT
SOFA score at 24 hours (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	MD 0.7 higher (2.41 lower to 3.81 higher)	MODERATE	IMPORTANT
SOFA score at 48 hours (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	MD 0.6 higher (2.49 lower to 3.69 higher)	MODERATE	IMPORTANT

SOFA score at 72 hours (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	MD 0.6 higher (2.72 lower to 3.92 higher)	MODERATE	IMPORTANT
SOFA score at 96 hours (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	MD 0.8 higher (2.62 lower to 4.22 higher)	MODERATE	IMPORTANT
Acute coronary syndrome											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/30 (3.3%)	1/30 (3.3%)	RR 1 (0.07 to 15.26)	0 fewer per 1000 (from 31 fewer to 475 more)	LOW	NOT IMPORTANT
Arrhythmias											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/30 (13.3%)	6/30 (20%)	RR 0.67 (0.21 to 2.13)	66 fewer per 1000 (from 158 fewer to 226 more)	LOW	NOT IMPORTANT
Cerebral stroke											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0/30 (0%)	-	-	LOW	NOT IMPORTANT

Limb ischaemia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/30 (6.7%)	3/30 (10%)	RR 0.67 (0.12 to 3.71)	33 fewer per 1000 (from 88 fewer to 271 more)	LOW	NOT IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

J.11 Supplemental oxygen

None.

J.12 Use of bicarbonate

Table 33: Clinical evidence profile: bicarbonate versus no bicarbonate (28-day mortality)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bicarbonate versus no bicarbonate	Control	Relative (95% CI)	Absolute		
28-day mortality												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/36 (27.8%)	12/36 (33.3%)	RR 0.83 (0.41 to 1.68)	57 fewer per 1000 (from 197 fewer to 227 more)	VERY LOW	CRITICAL

1 Case-control study. Small sample size
2 Confidence interval crossed both standard MIDs

Table 34: Clinical evidence profile: bicarbonate versus no bicarbonate (Duration of critical care stay; Time to reversal of shock)

Quality assessment							Median [95% CI]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bicarbonate group	Control group	Relative (95% CI)	Absolute		
Duration of critical care stay												
1	observational studies	very serious[1]	not estimable[2]	no serious indirectness	not estimable[2]	none	44.5 [34-54] Hours	55 [39-60] Hours	-	-	VERY LOW	IMPORTANT

Time to reversal of shock											
1	observational studies	very serious[1]	not estimable[2]	no serious indirectness	not estimable[2]	none	11.5 [6.0-16.0] days	16.0 [13.5-19.0] days	-	-	VERY LOW	MPORTANT

1 Case-control study. Small sample size
2 Non-parametric results

J.13 Early goal-directed therapy (EGDT)

Table 9: Clinical evidence profile: EGDT versus Usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGDT versus Control	Control	Relative (95% CI)	Absolute		
Primary mortality outcome of each study												
5	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	495/2134 (23.2%)	582/2601 (22.4%)	RR 1.01 (0.9 to 1.12)	2 more per 1000 (from 22 fewer to 27 more)	LOW	CRITICAL
90-day mortality												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	460/1820 (25.3%)	598/2243 (26.7%)	RR 0.99 (0.89 to 1.11)	3 fewer per 1000 (from 29 fewer to 29 more)	MODERATE	CRITICAL
ICU admission												
3	randomised trials	serious[1]	serious inconsistency	no serious indirectness	no serious imprecision	none	1677/1856 (90.4%)	1902/2324 (81.8%)	RR 1.11 (1.09 to 1.14)	91 more per 1000 (from 75 more to 116 more)	LOW	CRITICAL
ICU length of stay for patient admitted to ICU (days) (Better indicated by lower values)												

4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1825	2051	-	MD 0.02 lower (0.47 lower to 0.43 higher)	MODERATE	IMPORTANT
ICU length of stay for patient admitted to ICU (days) - New Subgroup (Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1825	2051	-	MD 0.02 lower (0.47 lower to 0.43 higher)	MODERATE	IMPORTANT

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 or 2 increments because:
- The point estimate varies widely across studies, unexplained by subgroup analysis.
- The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis
- Heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis.

J.14 Monitoring

None.

J.15 Patient education, information and support

None.

J.16 Training and education

None.

Appendix K: Forest plots

K.1 Scoring systems

None.

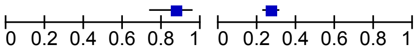
K.2 Signs and symptoms

K.2.1 Temperature

Figure 1: Sensitivity and specificity for temperature, adults

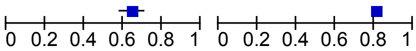
Temperature (adults): fever 38.5C and above to predict bacteriaemia in older patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pfitzenmeyer 1995	40	374	6	138	0.87 [0.74, 0.95]	0.27 [0.23, 0.31]



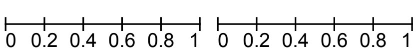
Temperature (adults): >38C to predict bacteriaemia in elderly patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lindvig 2014	158	361	87	1518	0.64 [0.58, 0.70]	0.81 [0.79, 0.83]



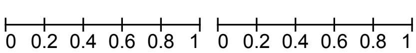
Temperature (adults): fever to predict bacteriaemia in elderly patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chassagne 1996	0	0	0	0	Not estimable	Not estimable



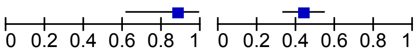
Temperature (adults): fever spike to predict bacteriaemia in elderly patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chassagne 1996	0	0	0	0	Not estimable	Not estimable



Temperature (adults): >39C to predict septic complications in adult patients undergoing cardiac surgery

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kreuzer 1992	14	53	2	41	0.88 [0.62, 0.98]	0.44 [0.33, 0.54]



Temperature (adults): abnormal temperature (hypothermia or fever) in shock patients admitted to tertiary care centre via ED

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Seigel 2012	193	0	96	0	0.67 [0.61, 0.72]	Not estimable

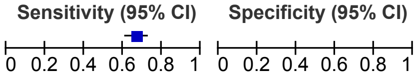
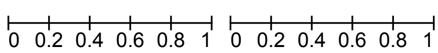


Figure 2: Sensitivity and specificity for temperature, children

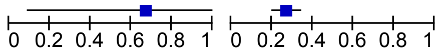
Temperature (children): predicting EOS / pneumonia in term new-borns >37 weeks

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hofer 2012A	0	0	0	0	Not estimable	Not estimable



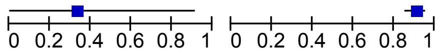
Temperature (children): >38C for predicting post-operative infectious complications

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Angel 1994	2	125	1	46	0.67 [0.09, 0.99]	0.27 [0.20, 0.34]



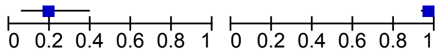
Temperature (children): >39C for predicting post-operative infectious complications

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Angel 1994	1	16	2	155	0.33 [0.01, 0.91]	0.91 [0.85, 0.95]



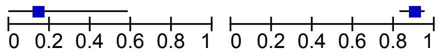
Temperature (children): <40C or >40C for predicting SBI in febrile infants 8-12 weeks

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonadio 1994	5	12	21	298	0.19 [0.07, 0.39]	0.96 [0.93, 0.98]



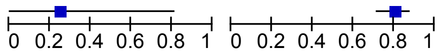
Temperature (children): age-specific temperature-pulse centiles >97th centile for prediciting SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	1	13	6	112	0.14 [0.00, 0.58]	0.90 [0.83, 0.94]



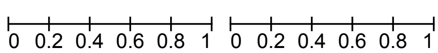
Temperature (children): age-specific temperature-pulse centiles >90th centile for prediciting SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	1	22	3	88	0.25 [0.01, 0.81]	0.80 [0.71, 0.87]



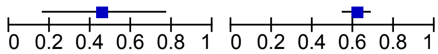
Temperature (children): age-specific temperature-pulse centiles >75th centile for prediciting SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



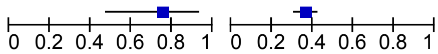
Temperature (children): age-specific temperature-pulse centiles >50th centile for prediciting SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	5	83	6	133	0.45 [0.17, 0.77]	0.62 [0.55, 0.68]



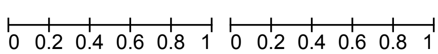
Temperature (children): age-specific temperature-pulse centiles >97th centile for prediciting SBI (meningococcal)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	12	191	4	109	0.75 [0.48, 0.93]	0.36 [0.31, 0.42]



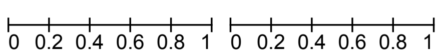
Temperature (children): age-specific temperature-pulse centiles 90th-97th centile for prediciting SBI (meningococcal)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



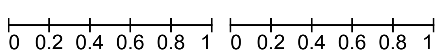
Temperature (children): age-specific temperature-pulse centiles 75th-90th centile for prediciting SBI (meningococcal)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



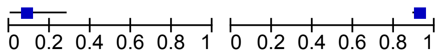
Temperature (children): age-specific temperature-pulse centiles 50th-75th centile for prediciting SBI (meningococcal)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



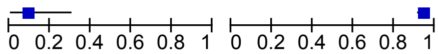
Temperature (children): <36C to predict bacteriaemia in neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hofer 2012	2	36	21	417	0.09 [0.01, 0.28]	0.92 [0.89, 0.94]



Temperature (children): >38.5C to predict bacteriaemia in neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hofer 2012	2	27	19	428	0.10 [0.01, 0.30]	0.94 [0.91, 0.96]



K.2.2 Heart rate

Figure 3: Sensitivity and specificity for heart rate, adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chassagne 1996	0	0	0	0	Not estimable	Not estimable

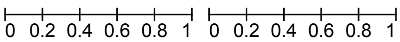
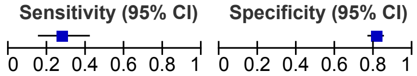


Figure 4: Sensitivity and specificity for heart rate, children

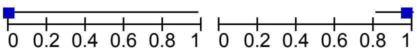
Heart rate (children): tachycardia >180/min or bradycardia <100/min to predict culture-proven EOS in term neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hofer 2012	14	81	37	344	0.27 [0.16, 0.42]	0.81 [0.77, 0.85]



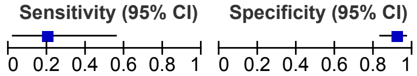
Heart rate (children): age-specific pulse centiles above 97th centile for SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	1	1	26	0.00 [0.00, 0.97]	0.96 [0.81, 1.00]



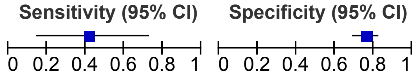
Heart rate (children): age-specific pulse centiles above 90th centile for SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	2	7	8	74	0.20 [0.03, 0.56]	0.91 [0.83, 0.96]



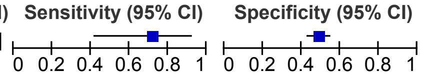
Heart rate (children): age-specific pulse centiles above 75th centile for SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	5	45	7	142	0.42 [0.15, 0.72]	0.76 [0.69, 0.82]



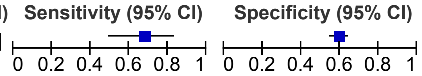
Heart rate (children): age-specific pulse centiles above 50th centile for SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	10	159	4	151	0.71 [0.42, 0.92]	0.49 [0.43, 0.54]



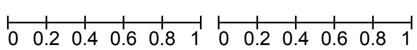
Heart rate (children): tachycardia for SBI in 3 months - 10 year olds

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	23	196	11	284	0.68 [0.49, 0.83]	0.59 [0.55, 0.64]



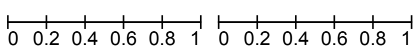
Heart rate (children): age-specific pulse centiles above 97th centile for predicting meningococcal sepsis in children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



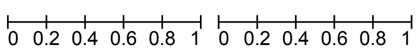
Heart rate (children): age-specific pulse centiles above 75th centile for predicting meningococcal sepsis in children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



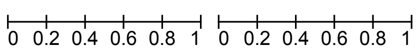
Heart rate (children): age-specific pulse centiles above 50th centile for predicting meningococcal sepsis in children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



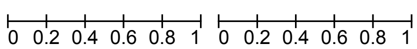
Heart rate (children): age-specific pulse centiles under 50th centile for predicting meningococcal sepsis in children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable



Heart rate (children): tachycardia for predicting meningococcal sepsis in children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brent 2011	0	0	0	0	Not estimable	Not estimable

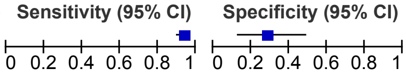


K.2.3 Blood pressure

Figure 5: Sensitivity and specificity for blood pressure, adults

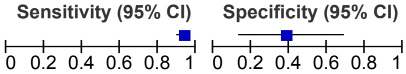
Blood pressure (adults): HTI of ABP drops <95 mmHg SAP to predict 28-day mortality in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dunser 2009A	230	20	16	8	0.93 [0.90, 0.96]	0.29 [0.13, 0.49]



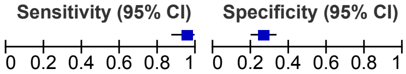
Blood pressure (adults): HTI of ABP drops <75 mmHg MAP to predict 28-day mortality in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dunser 2009A	244	8	17	5	0.93 [0.90, 0.96]	0.38 [0.14, 0.68]



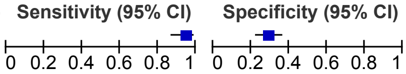
Blood pressure (adults): HTI of ABP drops <65 mmHg SAP to predict 28-day mortality in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dunser 2009A	73	145	4	52	0.95 [0.87, 0.99]	0.26 [0.20, 0.33]



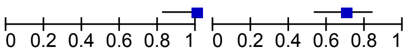
Blood pressure (adults): HTI of ABP drops <45 mmHg MAP to predict 28-day mortality in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dunser 2009A	80	134	5	55	0.94 [0.87, 0.98]	0.29 [0.23, 0.36]



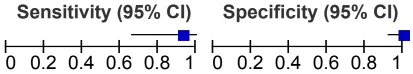
Blood pressure (adults): MAP 70 mmHg and under to predict onset of organ failure at 24h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	19	12	0	28	1.00 [0.82, 1.00]	0.70 [0.53, 0.83]



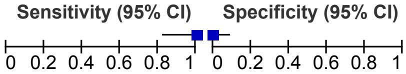
Blood pressure (adults): MAP 70 mmHg and under to predict onset of organ failure at 48h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	13	0	1	45	0.93 [0.66, 1.00]	1.00 [0.92, 1.00]



Blood pressure (adults): MAP 70 mmHg and under to predict onset of organ failure at 72h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	19	40	0	0	1.00 [0.82, 1.00]	0.00 [0.00, 0.09]



K.2.4 Respiratory rate

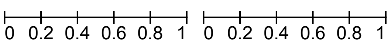
None.

K.2.5 Altered mental state

Figure 6: Sensitivity and specificity for altered mental state, adults

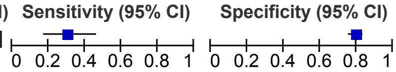
Altered mental state (adults): to predict bacteriaemia in elderly patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chassagne 1996	0	0	0	0	Not estimable	Not estimable



Altered mental state (adults): confusion to predict bacteriaemia in older patients

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pfitzenmeyer 1995	14	106	32	406	0.30 [0.18, 0.46]	0.79 [0.76, 0.83]

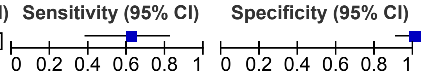


K.2.6 Level of consciousness

Figure 7: Sensitivity and specificity for level of consciousness, adults

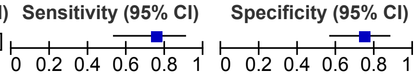
Level of consciousness (adults): CGS 11 and under to predict onset of organ failure at 24h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	13	0	8	38	0.62 [0.38, 0.82]	1.00 [0.91, 1.00]



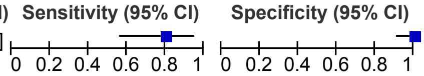
Level of consciousness (adults): CGS 11 and under to predict onset of organ failure at 48h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	18	9	6	26	0.75 [0.53, 0.90]	0.74 [0.57, 0.88]



Level of consciousness (adults): CGS 11 and under to predict onset of organ failure at 72h in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Slotman 1997	16	0	4	39	0.80 [0.56, 0.94]	1.00 [0.91, 1.00]



K.2.7 Oxygen saturation

None.

K.2.8 Urine output

None.

K.2.9 Diarrhoea

None.

K.3 Blood tests

Note: studies for coupled sensitivity/specificity are listed in alphabetical order. Setting, target condition, and actual cut-off value reported by each study are included in the study name.

K.3.1 CRP, adults

Figure 8: Sensitivity and specificity for CRP (cut-off ≥5 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
de Kruif 2010. ED. BI (9 mg/l)	72	29	1	5	0.99 [0.93, 1.00]	0.15 [0.05, 0.31]
Hambach 2002. Hospital. Infection (5 mg/l)	54	84	0	4	1.00 [0.93, 1.00]	0.05 [0.01, 0.11]
Kim 2014A. Setting unclear. Mortality (8.88 mg/l)	15	37	3	74	0.83 [0.59, 0.96]	0.67 [0.57, 0.75]
Kim 2014A. Setting unclear. Sepsis/SS (6.84 mg/l)	35	34	5	59	0.88 [0.73, 0.96]	0.63 [0.53, 0.73]

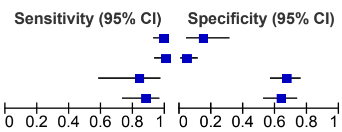


Figure 9: Sensitivity and specificity for CRP (cut-off ≥10 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Adams 2005. ED. Bacteraemia (10 mg/l)	70	934	4	205	0.95 [0.87, 0.99]	0.18 [0.16, 0.20]

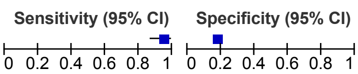


Figure 10: Sensitivity and specificity for CRP (cut-off ≥20 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gaini 2006A. Hospital. Sepsis/SS (38 mg/l)	110	15	28	21	0.80 [0.72, 0.86]	0.58 [0.41, 0.74]
Muller 2010. Hospital. Bacteraemia (20 mg/l)	70	775	3	77	0.96 [0.88, 0.99]	0.09 [0.07, 0.11]
Nakamura 2009. Hospital. Bacteraemia (35 mg/l)	49	30	16	21	0.75 [0.63, 0.85]	0.41 [0.28, 0.56]
Stucker 2005. Hospital. Infection (30 mg/l)	46	107	4	60	0.92 [0.81, 0.98]	0.36 [0.29, 0.44]
Yonemori 2001. Neutropenia. Infection (30.8 mg/l)	0	0	0	0	Not estimable	Not estimable

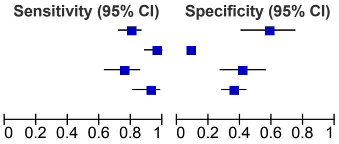


Figure 11: Sensitivity and specificity for CRP (cut-off ≥50 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gaini 2006A. Hospital. Sepsis/SS (50 mg/l)	99	13	39	22	0.72 [0.63, 0.79]	0.63 [0.45, 0.79]
Hambach 2002. Hospital. Infection (50 mg/l)	51	52	3	36	0.94 [0.85, 0.99]	0.41 [0.31, 0.52]
Jekarl 2013. ED. Sepsis/SS/shock (55 mg/l)	13	66	3	95	0.81 [0.54, 0.96]	0.59 [0.51, 0.67]
Kim 2015B. ED. Mortality (67.5 mg/l)	159	333	28	149	0.85 [0.79, 0.90]	0.31 [0.27, 0.35]
Kofoed 2007. Hospital. BI (60 mg/l)	101	14	16	20	0.86 [0.79, 0.92]	0.59 [0.41, 0.75]
Meynaar 2011. ICU. Sepsis (50 mg/l)	277	343	42	103	0.87 [0.83, 0.90]	0.23 [0.19, 0.27]
Muller 2010. Hospital. Bacteraemia (50 mg/l)	65	699	8	153	0.89 [0.80, 0.95]	0.18 [0.15, 0.21]
Pettila 2002A. ICU. Mortality (66 mg/l)	11	9	31	57	0.26 [0.14, 0.42]	0.86 [0.76, 0.94]
Povoa 2005A. ICU. Infection (87 mg/l)	71	26	5	158	0.93 [0.85, 0.98]	0.86 [0.80, 0.91]
Shaaban 2010. ICU. Infection (70 mg/l)	28	6	2	32	0.93 [0.78, 0.99]	0.84 [0.69, 0.94]
Sierra 2004. ICU. Sepsis (80 mg/l)	105	11	6	77	0.95 [0.89, 0.98]	0.88 [0.79, 0.94]
Yonemori 2001. Neutropenia. Bact. (68.6 mg/l)	0	0	0	0	Not estimable	Not estimable

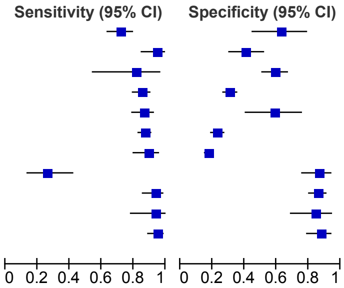


Figure 12: Sensitivity and specificity for CRP (cut-off ≥100 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aalto 2004. ED. BSI (125 mg/l)	11	15	2	64	0.85 [0.55, 0.98]	0.81 [0.71, 0.89]
Castelli 2004. ICU. Sepsis/SS (128 mg/l)	22	21	11	96	0.67 [0.48, 0.82]	0.82 [0.74, 0.89]
Castelli 2006. ICU. Sepsis/SS/shock (128 mg/l)	68	19	43	125	0.61 [0.52, 0.70]	0.87 [0.80, 0.92]
Cheval 2000. ICU. Sepsis (100 mg/l)	30	17	2	11	0.94 [0.79, 0.99]	0.39 [0.22, 0.59]
Gaini 2006A. Hospital. Sepsis/SS (100 mg/l)	87	2	50	33	0.64 [0.55, 0.72]	0.94 [0.81, 0.99]
Hambach 2002. Hospital. Infection (100 mg/l)	45	34	9	54	0.83 [0.71, 0.92]	0.61 [0.50, 0.72]
Kim 2011. ED. Bacteraemia (100 mg/l)	22	81	16	167	0.58 [0.41, 0.74]	0.67 [0.61, 0.73]
Moreira 2010. Hospital. Sepsis (110 mg/l)	44	13	6	47	0.88 [0.76, 0.95]	0.78 [0.66, 0.88]
Muller 2010. Hospital. Bacteraemia (100 mg/l)	59	571	14	281	0.81 [0.70, 0.89]	0.33 [0.30, 0.36]

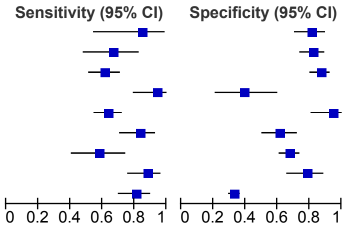


Figure 13: Sensitivity and specificity for CRP (cut-off ≥150 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bell 2003. Hospital. Bacteraemia (185 mg/l)	10	5	2	16	0.83 [0.52, 0.98]	0.76 [0.53, 0.92]
Hambach 2002. Hospital. Infection (150 mg/l)	37	23	17	65	0.69 [0.54, 0.80]	0.74 [0.63, 0.83]
Hillas 2010. ICU. Severe sepsis (152 mg/l)	19	8	3	15	0.86 [0.65, 0.97]	0.65 [0.43, 0.84]
Hillas 2010. ICU. Severe sepsis (157.5 mg/l)	17	7	1	20	0.94 [0.73, 1.00]	0.74 [0.54, 0.89]
Hoeboer 2012. ICU. Bloodstream inf. (196 mg/l)	11	36	1	54	0.92 [0.62, 1.00]	0.60 [0.49, 0.70]
Oberhoffer 1999A. ICU. Mortality (198 mg/l)	38	37	20	148	0.66 [0.52, 0.78]	0.80 [0.74, 0.86]

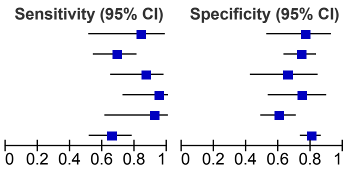


Figure 14: Sensitivity and specificity for CRP (cut-off ≥200 mg/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hoeboer 2012. ICU. Septic shock (208 mg/l)	24	15	10	52	0.71 [0.53, 0.85]	0.78 [0.66, 0.87]
Muller 2010. Hospital. Bacteraemia (200 mg/l)	45	307	28	545	0.62 [0.50, 0.73]	0.64 [0.61, 0.67]

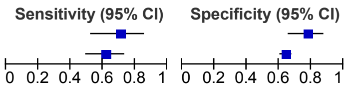


Figure 15: AUC for CRP to diagnose sepsis, severe sepsis and septic shock (divided by setting), adults

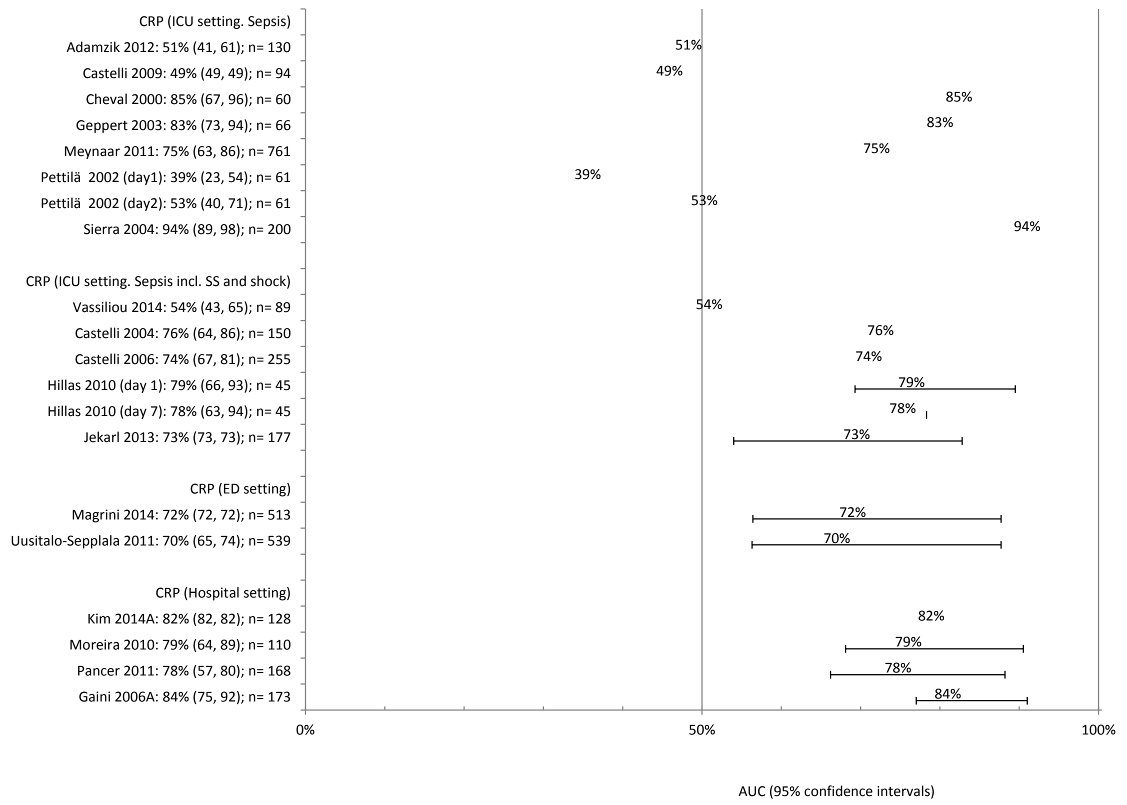


Figure 16: AUC for CRP to diagnose infection (divided by setting), adults

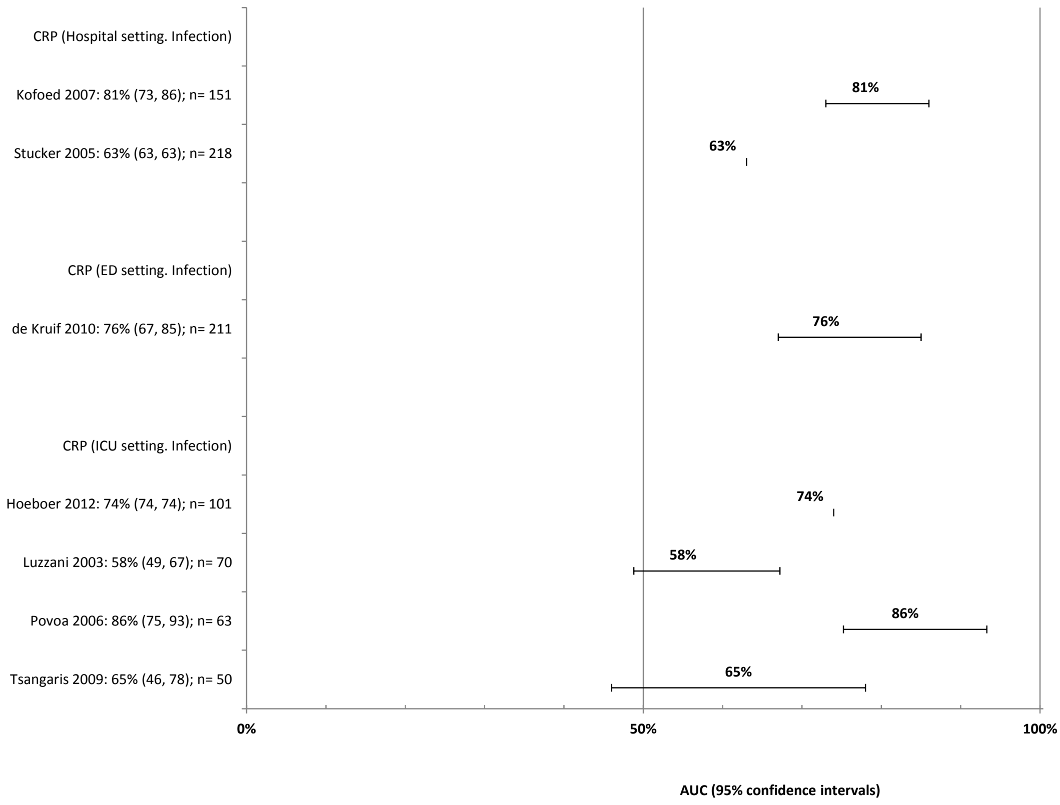


Figure 17: AUC for CRP to diagnose bacteraemia (divided by setting), adults

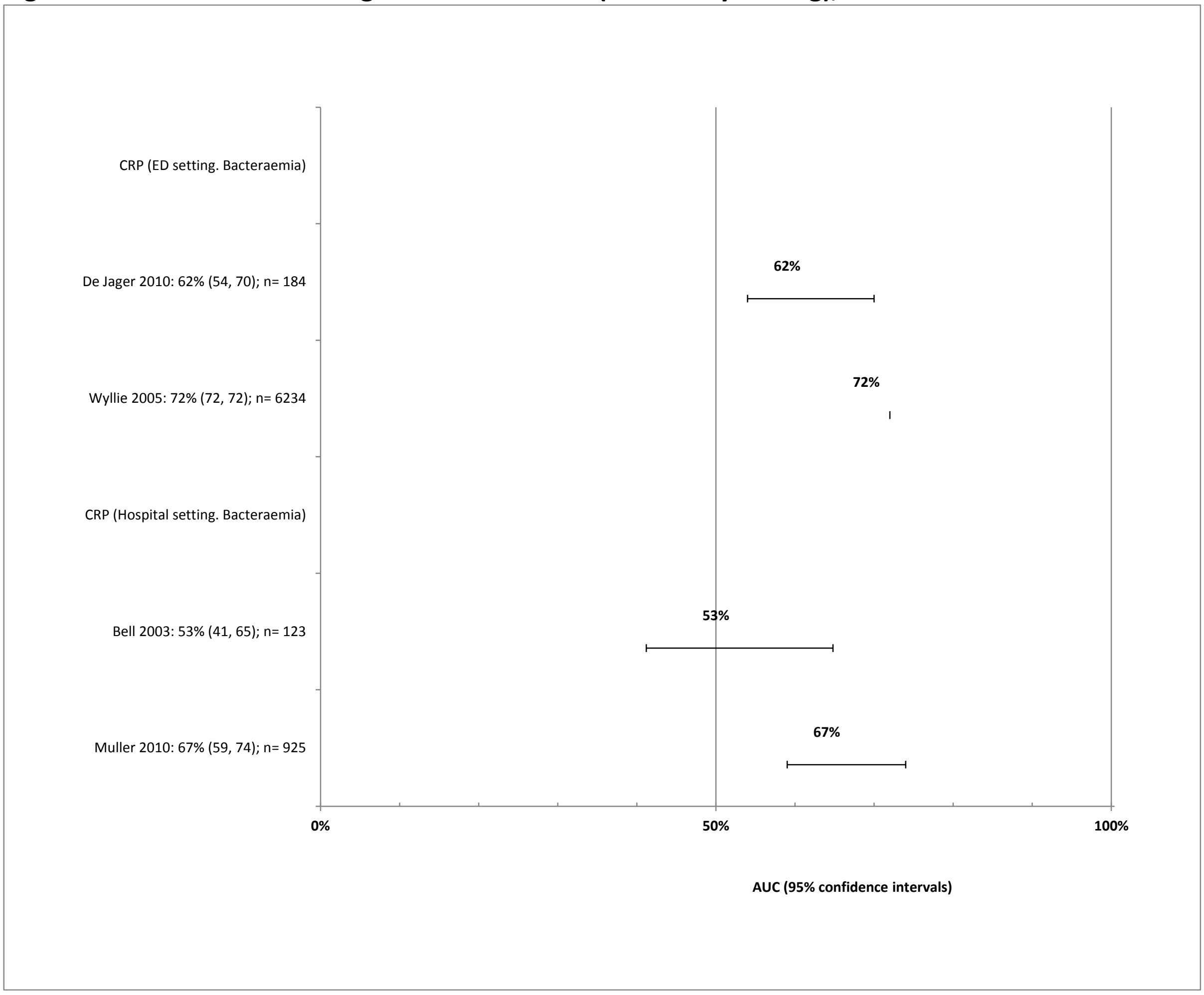


Figure 18: AUC for CRP to diagnose mortality (divided by setting), adults

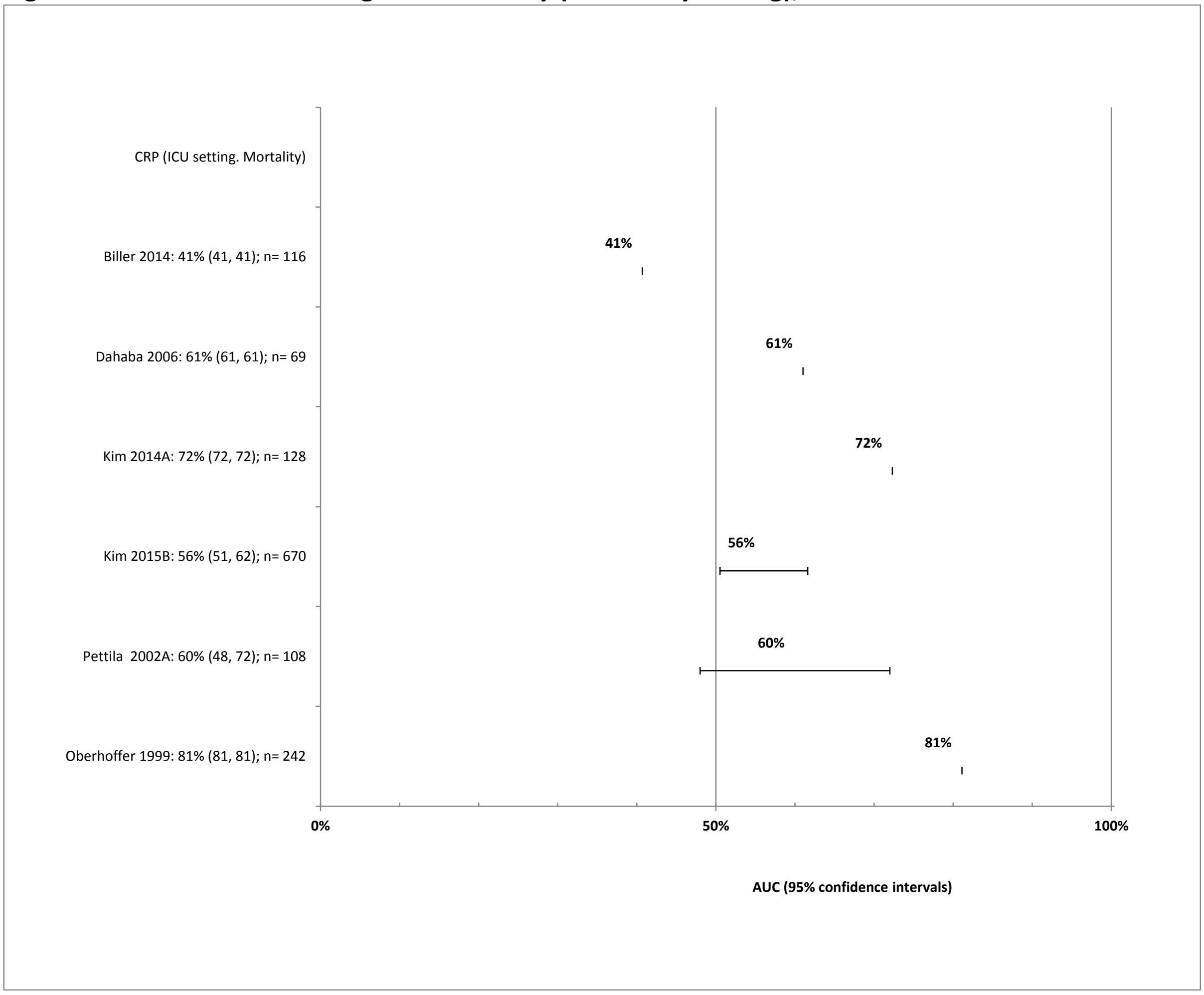


Figure 19: AUC for CRP to diagnose infection or bacteraemia in the immunocompromised subgroup (divided by setting), adults

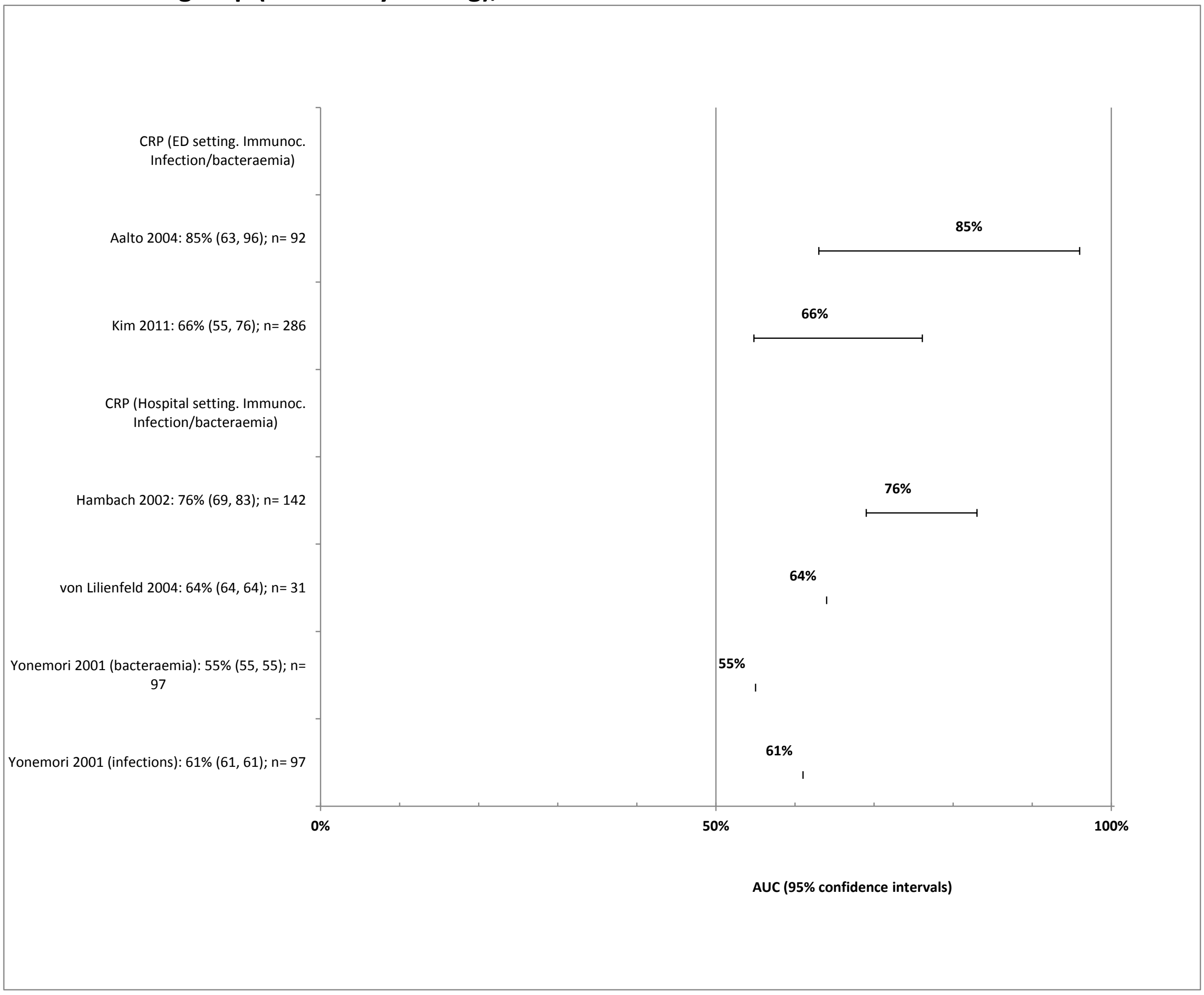


Figure 20: Odds ratio for CRP ratio (follow-up/initial level), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Ha 2011. Hospital. Bacteraemia	2.9507	1.3637		19.12 [1.32, 276.86]

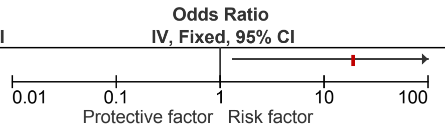


Figure 21: Odds ratio for CRP >8 mg/l versus CRP ≤8 mg/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
Leth 2013. Hospital. Bloodstream infection	1.8017	1.0205	6.06 [0.82, 44.78]

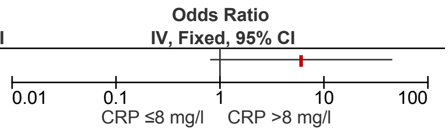


Figure 22: Odds ratio for CRP for diagnosing sepsis, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Uusitalo-Sepplala 2011. ED. Sepsis/SS	0.2852	0.0975		1.33 [1.10, 1.61]

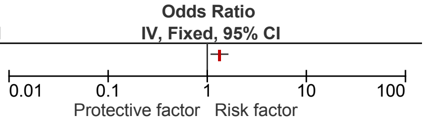
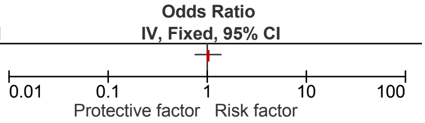


Figure 23: Odds ratio for CRP for diagnosing severe sepsis, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Uusitalo-Sepplala 2011. ED. Sepsis/SS	0.0198	0.1505		1.02 [0.76, 1.37]



K.3.2 CRP, children

Figure 24: Sensitivity and specificity for CRP (cut-off ≥20mg/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI (20mg/l)	83	123	11	191	0.88 [0.80, 0.94]	0.61 [0.55, 0.66]
Andreola 2007. ED. SBI (32mg/l)	79	77	15	237	0.84 [0.75, 0.91]	0.75 [0.70, 0.80]
Andreola 2007. ED. SBI (40mg/l)	67	59	27	255	0.71 [0.61, 0.80]	0.81 [0.76, 0.85]
Enguix 2001. N/PICU. Bacterial sepsis (22.1mg/l)	28	7	4	31	0.88 [0.71, 0.96]	0.82 [0.66, 0.92]
Fernandez-L 2003. ED/hospital. IBI (27.5mg/l)	117	51	33	152	0.78 [0.71, 0.84]	0.75 [0.68, 0.81]
Fouzas 2010. ED. SBI (20mg/l)	53	41	50	264	0.51 [0.41, 0.61]	0.87 [0.82, 0.90]
Freyne 2013. ED. Bacterial sepsis (20mg/l)	6	6	1	33	0.86 [0.42, 1.00]	0.85 [0.69, 0.94]
Galetto-Lacour 2003. ED. SBI (40mg/l)	23	15	6	55	0.79 [0.60, 0.92]	0.79 [0.67, 0.87]
Hatherill 1999. PICU. Septic shock (20mg/l)	70	37	7	61	0.91 [0.82, 0.96]	0.62 [0.52, 0.72]
Hatherill 1999. PICU. Septic shock (30mg/l)	62	29	15	69	0.81 [0.70, 0.89]	0.70 [0.60, 0.79]
Hatherill 1999. PICU. Septic shock (40mg/l)	61	23	16	75	0.79 [0.68, 0.88]	0.77 [0.67, 0.85]
Isaacman 2002. ED. Bacterial infection (44mg/l)	18	43	11	184	0.62 [0.42, 0.79]	0.81 [0.75, 0.86]
Lacour 2001. ED. SBI (40mg/l)	25	47	3	140	0.89 [0.72, 0.98]	0.75 [0.68, 0.81]
Pratt 2007. ED. SBI (30mg/l) [+12hrs]	11	23	0	40	1.00 [0.72, 1.00]	0.63 [0.50, 0.75]
Pratt 2007. ED. SBI (30mg/l) [≤12hrs]	4	10	2	29	0.67 [0.22, 0.96]	0.74 [0.58, 0.87]
Simon 2008. PICU. Bacterial SIRS (20mg/l)	24	30	1	9	0.96 [0.80, 1.00]	0.23 [0.11, 0.39]
Simon 2008. PICU. Bacterial SIRS (40mg/l)	24	23	1	16	0.96 [0.80, 1.00]	0.41 [0.26, 0.58]

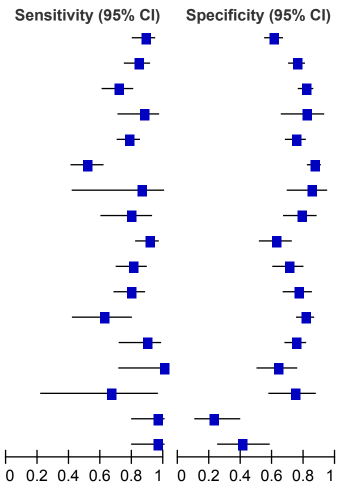


Figure 25: Sensitivity and specificity for CRP (cut-off ≥50mg/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI (80mg/l)	43	17	51	297	0.46 [0.35, 0.56]	0.95 [0.91, 0.97]
Hatherill 1999. PICU. Septic shock (50mg/l)	59	20	18	78	0.77 [0.66, 0.86]	0.80 [0.70, 0.87]
Pratt 2007. ED. SBI (50mg/l) [+12hrs]	9	20	2	43	0.82 [0.48, 0.98]	0.68 [0.55, 0.79]
Pratt 2007. ED. SBI (50mg/l) [≤12hrs]	3	3	3	36	0.50 [0.12, 0.88]	0.92 [0.79, 0.98]
Pratt 2007. ED. SBI (70mg/l) [+12hrs]	8	13	3	50	0.73 [0.39, 0.94]	0.79 [0.67, 0.89]
Pratt 2007. ED. SBI (70mg/l) [≤12hrs]	2	1	4	38	0.33 [0.04, 0.78]	0.97 [0.87, 1.00]
Pulliam 2001. ED. SBI (70mg/l)	11	6	3	57	0.79 [0.49, 0.95]	0.90 [0.80, 0.96]
Rey 2007. PICU. Sepsis (56.5mg/l)	90	80	35	154	0.72 [0.63, 0.80]	0.66 [0.59, 0.72]
Rey 2007. PICU. Sepsis (65.5mg/l)	80	63	45	171	0.64 [0.55, 0.72]	0.73 [0.67, 0.79]
Segal 2014. ED. Bacterial infection (55mg/l)	72	43	31	227	0.70 [0.60, 0.79]	0.84 [0.79, 0.88]
Shaoul 2008. NICU. Positive blood culture (85mg/l)	35	122	15	254	0.70 [0.55, 0.82]	0.68 [0.63, 0.72]
Simon 2008. PICU. Bacterial SIRS (60mg/l)	15	18	10	21	0.60 [0.39, 0.79]	0.54 [0.37, 0.70]
Thayyil 2005. Hospital. SBI (50mg/l)	6	20	2	44	0.75 [0.35, 0.97]	0.69 [0.56, 0.80]

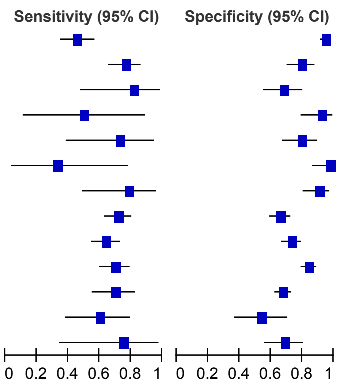


Figure 26: Sensitivity and specificity for CRP (cut-off ≥100mg/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baez 2011. ICU. Post-op sepsis (100mg/l) [24hrs]	34	16	7	46	0.83 [0.68, 0.93]	0.74 [0.62, 0.84]
Baez 2011. ICU. Post-op sepsis (100mg/l) [48hrs]	37	19	4	43	0.90 [0.77, 0.97]	0.69 [0.56, 0.80]
Baez 2011. ICU. Post-op sepsis (110mg/l) [24hrs]	38	24	3	38	0.93 [0.80, 0.98]	0.61 [0.48, 0.73]
Baez 2011. ICU. Post-op sepsis (110mg/l) [48hrs]	36	7	5	55	0.88 [0.74, 0.96]	0.89 [0.78, 0.95]

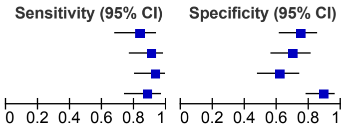


Figure 27: Sensitivity and specificity for CRP (cut-off ≥150mg/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baez 2011. ICU. Post-op sepsis (150mg/l) [48hrs]	36	17	5	45	0.88 [0.74, 0.96]	0.73 [0.60, 0.83]

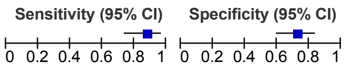


Figure 28: Sensitivity and specificity for CRP (cut-off ≥200mg/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baez 2011. ICU. Post-op sepsis (200mg/l) [48hrs]	36	15	5	47	0.88 [0.74, 0.96]	0.76 [0.63, 0.86]

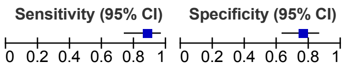


Figure 29: Sensitivity and specificity for change in CRP per day, children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nahum 2012. Setting unclear. EBI (0mg/l)	27	51	4	39	0.87 [0.70, 0.96]	0.43 [0.33, 0.54]
Nahum 2012. Setting unclear. EBI (10mg/l)	25	24	6	66	0.81 [0.63, 0.93]	0.73 [0.63, 0.82]
Nahum 2012. Setting unclear. EBI (20mg/l)	19	17	12	73	0.61 [0.42, 0.78]	0.81 [0.71, 0.89]
Nahum 2012. Setting unclear. EBI (30mg/l)	16	9	16	81	0.50 [0.32, 0.68]	0.90 [0.82, 0.95]
Nahum 2012. Setting unclear. EBI (40mg/l)	12	4	19	86	0.39 [0.22, 0.58]	0.96 [0.89, 0.99]
Nahum 2012. Setting unclear. EBI (50mg/l)	8	2	23	88	0.26 [0.12, 0.45]	0.98 [0.92, 1.00]

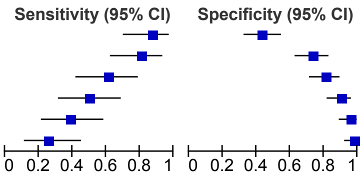
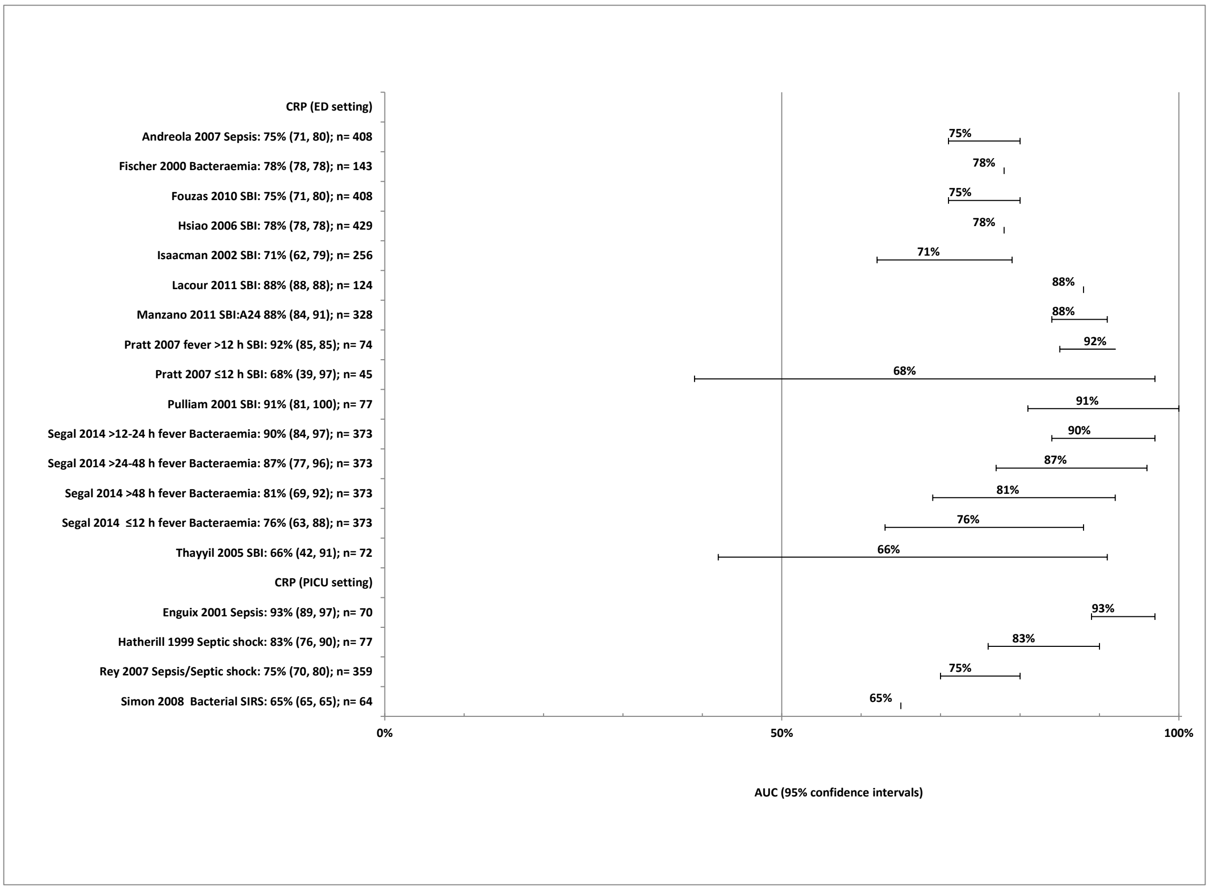


Figure 30: AUC for CRP to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



K.3.3 CRP, neonates

Figure 31: Sensitivity and specificity for CRP (cut-off <5 mg/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nosrati 2014. Tertiary care. SBI (2mg/l)	43	247	5	106	0.90 [0.77, 0.97]	0.30 [0.25, 0.35]
Nosrati 2014. Tertiary care. SBI (4mg/l)	42	219	6	134	0.88 [0.75, 0.95]	0.38 [0.33, 0.43]

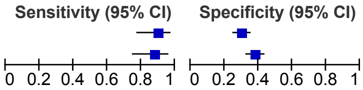


Figure 32: Sensitivity and specificity for CRP (cut-off ≥5mg/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Enguix 2001. PICU. Bacterial sepsis (6.1mg/l)	19	4	1	22	0.95 [0.75, 1.00]	0.85 [0.65, 0.96]
Nosrati 2014. Tertiary care. SBI (6mg/l)	41	187	7	166	0.85 [0.72, 0.94]	0.47 [0.42, 0.52]

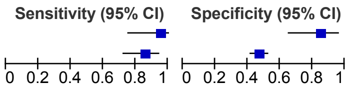


Figure 33: Sensitivity and specificity for CRP (cut-off ≥10mg/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jacquot 2009. NICU. Late onset sepsis (10mg/l)	17	6	13	37	0.57 [0.37, 0.75]	0.86 [0.72, 0.95]
Nosrati 2014. Tertiary care. SBI (10mg/l)	40	138	8	215	0.83 [0.70, 0.93]	0.61 [0.56, 0.66]
Sherwin 2008. NICU. Late onset sepsis (18mg/l)	21	7	31	105	0.40 [0.27, 0.55]	0.94 [0.88, 0.97]

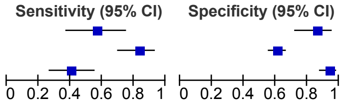


Figure 34: Sensitivity and specificity for CRP (cut-off ≥20mg/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI (20mg/l)	57	141	45	649	0.56 [0.46, 0.66]	0.82 [0.79, 0.85]
Bilavsky 2009. Hospital. SBI (40mg/l)	45	62	57	728	0.44 [0.34, 0.54]	0.92 [0.90, 0.94]
Bressan 2010. ED. SBI (20mg/l) [less than 12hrs]	12	5	13	69	0.48 [0.28, 0.69]	0.93 [0.85, 0.98]
Bressan 2010. ED. SBI (20mg/l) [more than 12hrs]	5	2	0	51	1.00 [0.48, 1.00]	0.96 [0.87, 1.00]
Gomez 2010. ED. SBI (20mg/l)	146	207	52	613	0.74 [0.67, 0.80]	0.75 [0.72, 0.78]
Nosrati 2014. Tertiary care. SBI (20mg/l)	38	56	10	297	0.79 [0.65, 0.90]	0.84 [0.80, 0.88]
Nosrati 2014. Tertiary care. SBI (30mg/l)	32	28	16	325	0.67 [0.52, 0.80]	0.92 [0.89, 0.95]
Nosrati 2014. Tertiary care. SBI (40mg/l)	27	21	21	332	0.56 [0.41, 0.71]	0.94 [0.91, 0.96]
Olaciregui 2009. ED. SBI (20mg/l)	52	42	30	223	0.63 [0.52, 0.74]	0.84 [0.79, 0.88]
Olaciregui 2009. ED. SBI (30mg/l)	48	29	34	236	0.59 [0.47, 0.69]	0.89 [0.85, 0.93]
Olaciregui 2009. ED. Sepsis/bacteraemia (30mg/l)	8	86	7	246	0.53 [0.27, 0.79]	0.74 [0.69, 0.79]
Pavcnick 2004. NICU. Sepsis (23mg/l)	23	3	10	24	0.70 [0.51, 0.84]	0.89 [0.71, 0.98]

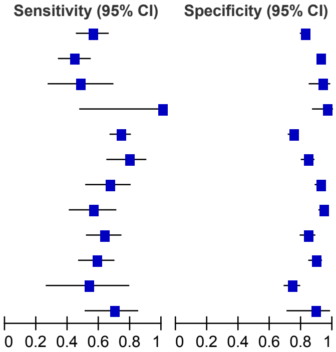


Figure 35: Sensitivity and specificity for CRP (cut-off ≥50mg/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI (80mg/l)	24	14	78	776	0.24 [0.16, 0.33]	0.98 [0.97, 0.99]
Gomez 2010. ED. SBI (70mg/l)	186	249	12	571	0.94 [0.90, 0.97]	0.70 [0.66, 0.73]

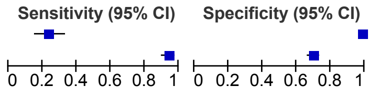
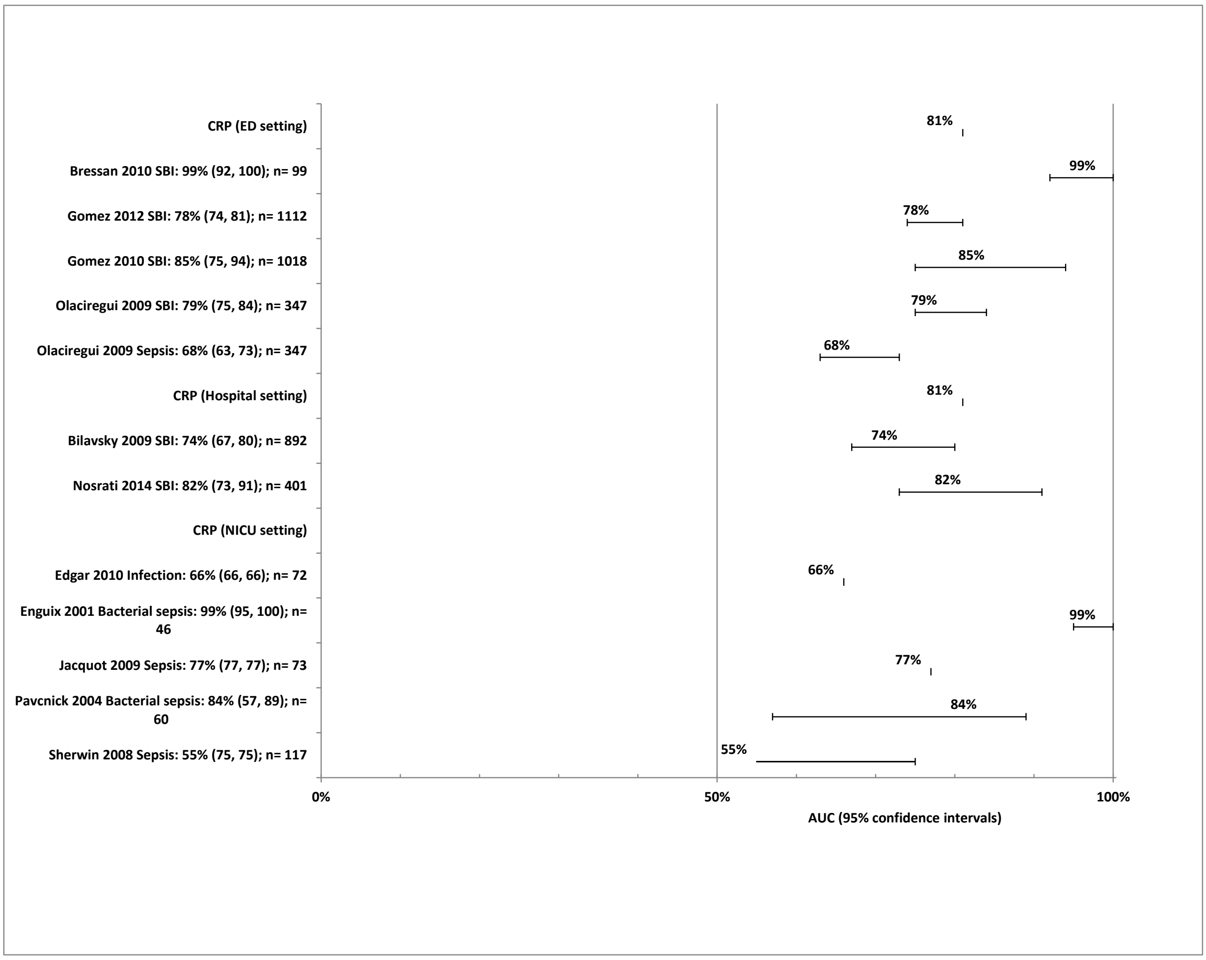


Figure 36: AUC for CRP to diagnose sepsis, severe sepsis and septic shock (divided by setting), neonates



K.3.4 WBC, adults

Figure 37: Sensitivity and specificity for WBC (<1x10^9/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Svaldi 2001. Hospital. Sepsis/SS/septic shock	23	15	13	22	0.64 [0.46, 0.79]	0.59 [0.42, 0.75]

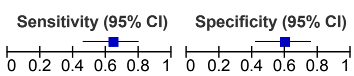


Figure 38: Sensitivity and specificity for WBC (>1x10^9/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Svaldi 2001. Hospital. Sepsis/SS/septic shock	34	15	2	22	0.94 [0.81, 0.99]	0.59 [0.42, 0.75]

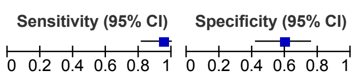


Figure 39: Sensitivity and specificity for WBC (<4x10^9/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cavallazzi 2010. ICU. Infection	4	4	38	99	0.10 [0.03, 0.23]	0.96 [0.90, 0.99]

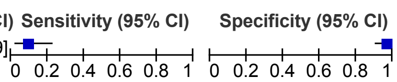


Figure 40: Sensitivity and specificity for WBC (>11x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2013. ED. Sepsis/SS/septic shock	10	69	6	92	0.63 [0.35, 0.85]	0.57 [0.49, 0.65]

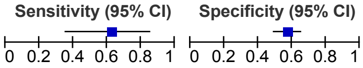


Figure 41: Sensitivity and specificity for WBC (>12x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cavallazzi 2010. ICU. Infection	22	42	20	61	0.52 [0.36, 0.68]	0.59 [0.49, 0.69]
Tsangaris 2009. ICU. Infection	18	13	9	10	0.67 [0.46, 0.83]	0.43 [0.23, 0.66]

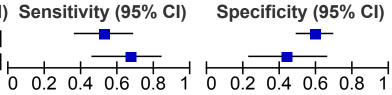


Figure 42: Sensitivity and specificity for WBC (>15x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Oberhoffer 1999A. ICU. Mortality	16	40	32	158	0.33 [0.20, 0.48]	0.80 [0.74, 0.85]

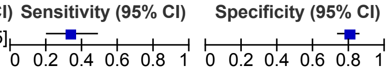


Figure 43: Sensitivity and specificity for WBC (>20.3x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hoeboer 2012. ICU. BI	7	14	5	74	0.58 [0.28, 0.85]	0.84 [0.75, 0.91]

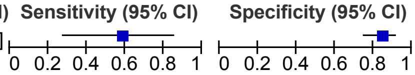


Figure 44: Sensitivity and specificity for WBC (<4.3x10⁹/l and >11x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caterino 2004. ED. Bacteraemia	24	23	10	44	0.71 [0.53, 0.85]	0.66 [0.53, 0.77]

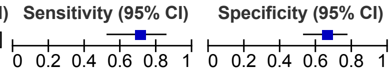


Figure 45: Sensitivity and specificity for WBC (≤4x10⁹/l and ≥12x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stucker 2005. Hospital. Infection	15	18	35	150	0.30 [0.18, 0.45]	0.89 [0.84, 0.94]

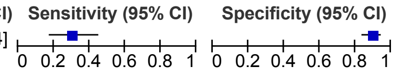


Figure 46: Sensitivity and specificity for WBC (≤5x10⁹/l and ≥20x10⁹/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Muller 2010. Hospital. Bacteraemia	16	136	57	716	0.22 [0.13, 0.33]	0.84 [0.81, 0.86]

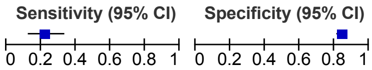


Figure 47: AUC for WBC to diagnose (1) sepsis, severe sepsis, septic shock; bacteraemia or infection; (3) mortality (divided by setting), adults

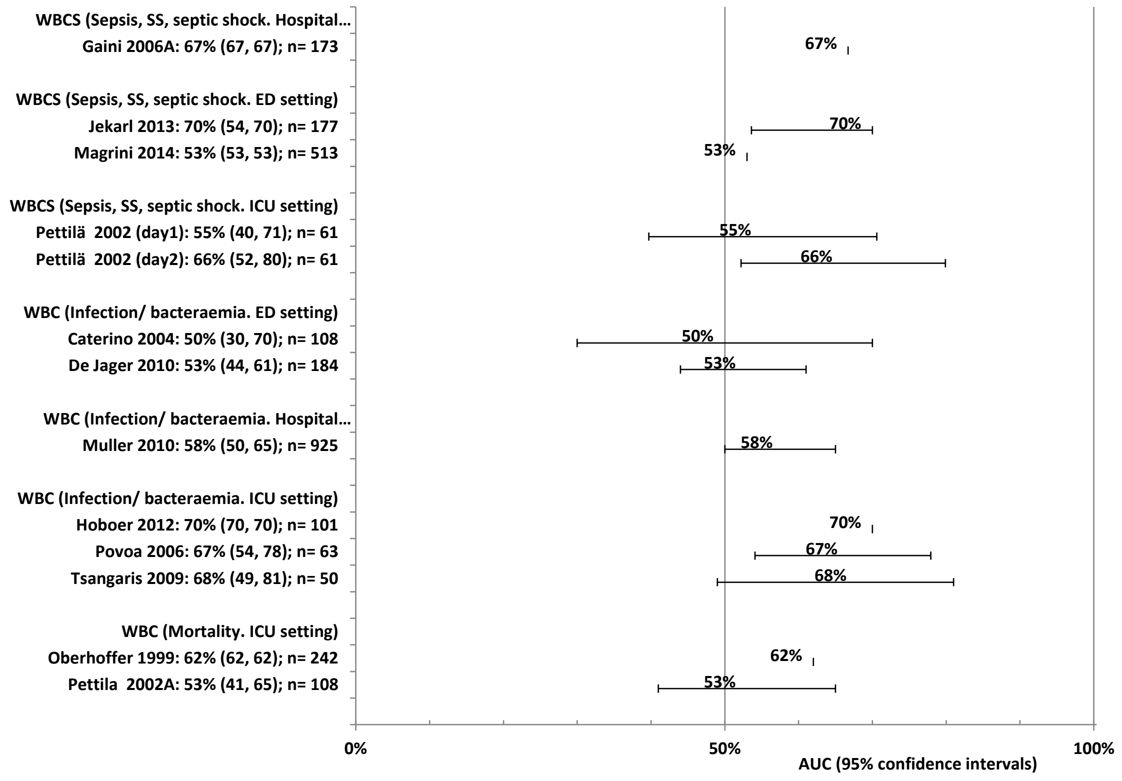


Figure 48: Odds ratio for WBC (>12x10⁹/l), adults

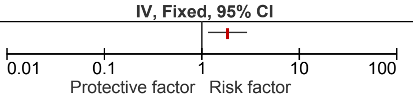
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Freund 2012. ED. Sepsis/SS/septic shock	0.6043	0.2282		1.83 [1.17, 2.86]	

Figure 49: Odds ratio for WCC (<4x10⁹/l or >20x10⁹/l), adults

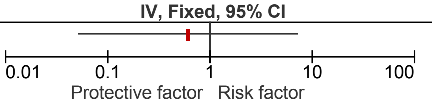
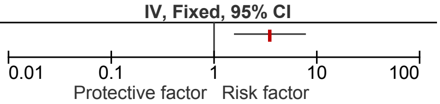
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Patterson 2012. ED. Bacteraemia	-0.4943	1.2573		0.61 [0.05, 7.17]	

Figure 50: Odds ratio for WBC (≤4x10^9/l or ≥12x10^9/l), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Stucker 2005. Hospital. Infection	1.2528	0.4023		3.50 [1.59, 7.70]	



K.3.5 WBC, children

Figure 51: Sensitivity and specificity for WBC (<5x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Rudinsky 2009. ED. SBI.	6	68	123	788	0.05 [0.02, 0.10]	0.92 [0.90, 0.94]		

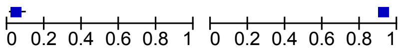


Figure 52: Sensitivity and specificity for WBC (>10x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Pratt 2007. ED. SBI. [less than12 hrs]	3	27	3	12	0.50 [0.12, 0.88]	0.31 [0.17, 0.48]		
Pratt 2007. ED. SBI. [more than12 hrs]	11	33	0	30	1.00 [0.72, 1.00]	0.48 [0.35, 0.61]		
Rudinsky 2009. ED. SBI.	93	454	36	402	0.72 [0.64, 0.80]	0.47 [0.44, 0.50]		

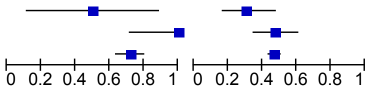


Figure 53: Sensitivity and specificity for WBC (>10.47x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI	80	165	14	149	0.85 [0.76, 0.92]	0.47 [0.42, 0.53]		

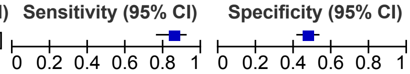


Figure 54: Sensitivity and specificity for WBC (>15x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI	49	77	45	237	0.52 [0.42, 0.63]	0.75 [0.70, 0.80]		
De 2014. ED. Bactaraemia/SBI.	336	763	378	2416	0.47 [0.43, 0.51]	0.76 [0.74, 0.77]		
Fouzas 2010. ED. SBI.	54	65	49	240	0.52 [0.42, 0.62]	0.79 [0.74, 0.83]		
Mahajan 2014. Setting unclear. SBI.	17	46	13	150	0.57 [0.37, 0.75]	0.77 [0.70, 0.82]		
Nademi 2001. ED. Serious infection.	4	5	37	95	0.10 [0.03, 0.23]	0.95 [0.89, 0.98]		
Pratt 2007. ED. SBI. [less than12 hrs]	1	13	5	26	0.17 [0.00, 0.64]	0.67 [0.50, 0.81]		
Pratt 2007. ED. SBI. [more than12 hrs]	9	20	2	43	0.82 [0.48, 0.98]	0.68 [0.55, 0.79]		
Pulliam 2001. ED. SBI.	9	21	5	42	0.64 [0.35, 0.87]	0.67 [0.54, 0.78]		
Rudinsky 2009. ED. SBI.	54	223	75	633	0.42 [0.33, 0.51]	0.74 [0.71, 0.77]		
Thayyil 2005. ED. SBI.	4	30	4	34	0.50 [0.16, 0.84]	0.53 [0.40, 0.66]		

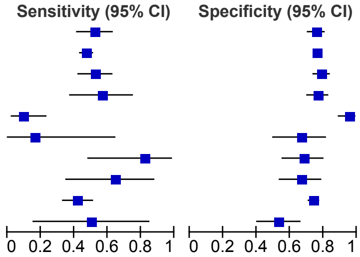


Figure 55: Sensitivity and specificity for WBC (>17.1x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Isaacman 2002. ED.	20	45	9	182	0.69 [0.49, 0.85]	0.80 [0.74, 0.85]		

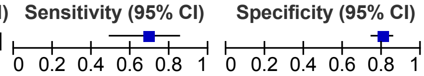


Figure 56: Sensitivity and specificity for WBC (>17.5x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Pratt 2007. ED. SBI. [less than12 hrs]	1	10	5	29	0.17 [0.00, 0.64]	0.74 [0.58, 0.87]		
Pratt 2007. ED. SBI. [more than12 hrs]	8	13	3	50	0.73 [0.39, 0.94]	0.79 [0.67, 0.89]		

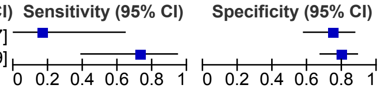


Figure 57: Sensitivity and specificity for WBC (>19x10⁹/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mahajan 2014. Setting unclear. SBI.	14	19	16	177	0.47 [0.28, 0.66]	0.90 [0.85, 0.94]

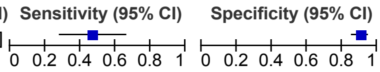


Figure 58: Sensitivity and specificity for WBC (>20x10⁹/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
De 2014. ED. Bactaraemia/SBI.	186	318	528	2861	0.26 [0.23, 0.29]	0.90 [0.89, 0.91]
Nademi 2001. ED. Serious infection.	12	7	29	93	0.29 [0.16, 0.46]	0.93 [0.86, 0.97]
Rudinsky 2009. ED. SBI.	21	60	108	796	0.16 [0.10, 0.24]	0.93 [0.91, 0.95]

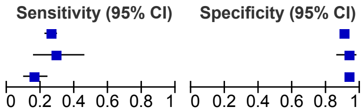


Figure 59: Sensitivity and specificity for WBC (>25x10⁹/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Rudinsky 2009. ED. SBI.	3	17	126	839	0.02 [0.00, 0.07]	0.98 [0.97, 0.99]

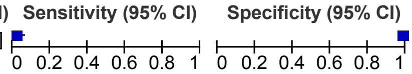


Figure 60: Sensitivity and specificity for WBC (<5 or >15 x10⁹/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Freyne 2013. ED. Bacterial sepsis.	6	17	1	22	0.86 [0.42, 1.00]	0.56 [0.40, 0.72]
Rudinsky 2009. ED. SBI.	61	291	68	565	0.47 [0.38, 0.56]	0.66 [0.63, 0.69]

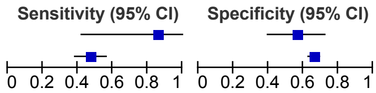
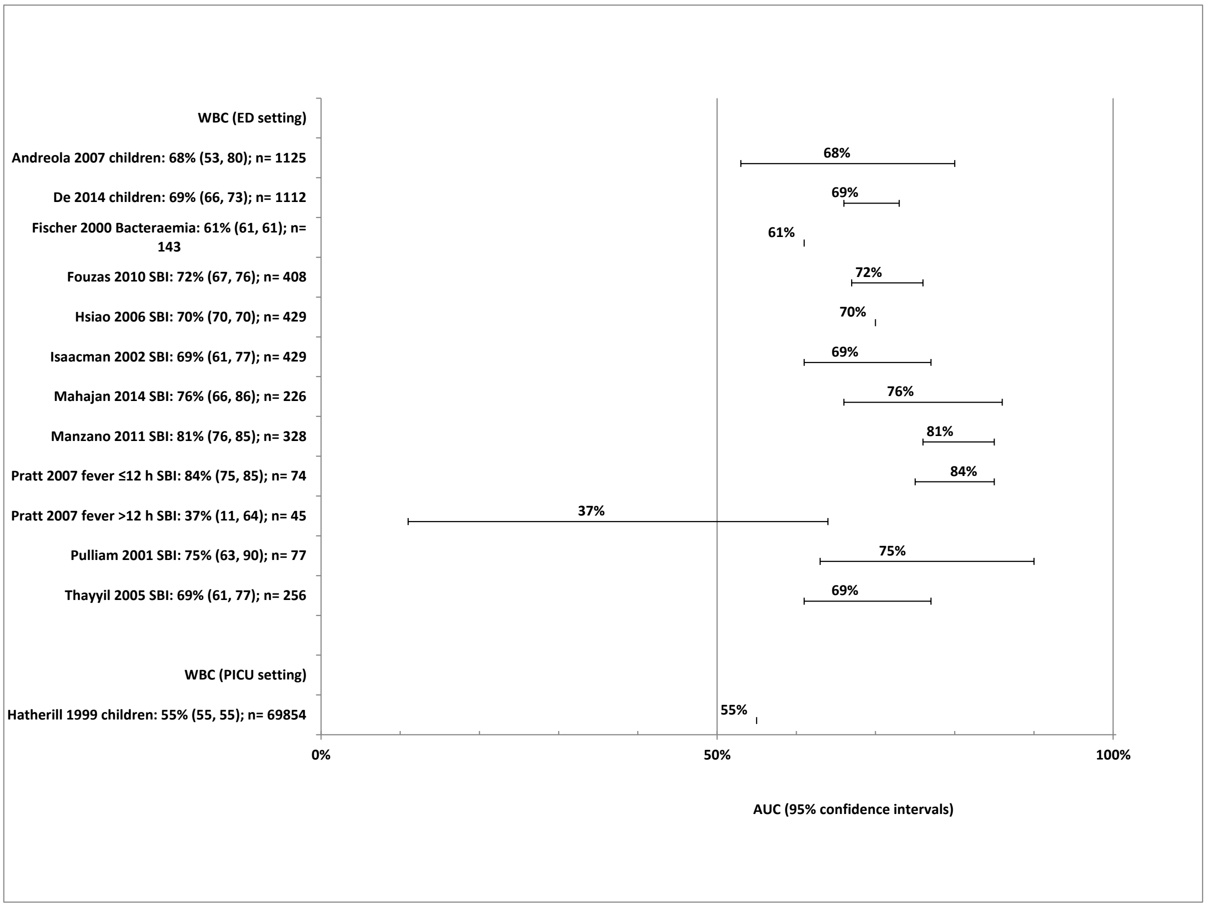


Figure 61: AUC for WBC to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



K.3.6 WBC, neonates

Figure 62: Sensitivity and specificity for WBC (<1x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	10	6	9646	60192	0.00 [0.00, 0.00]	1.00 [1.00, 1.00]

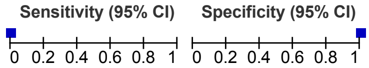


Figure 63: Sensitivity and specificity for WBC (<5x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	676	2348	8980	57850	0.07 [0.06, 0.08]	0.96 [0.96, 0.96]

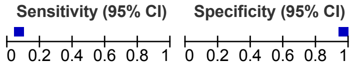


Figure 64: Sensitivity and specificity for WBC (>5x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003. ED. Bacteraemia.	24	3591	6	189	0.80 [0.61, 0.92]	0.05 [0.04, 0.06]

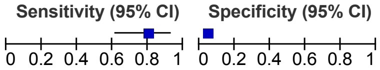


Figure 65: Sensitivity and specificity for WBC (>10x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003. ED. Bacteraemia.	14	2196	9	1591	0.61 [0.39, 0.80]	0.42 [0.40, 0.44]

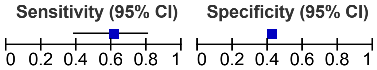


Figure 66: Sensitivity and specificity for WBC (>15x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI.	49	126	53	664	0.48 [0.38, 0.58]	0.84 [0.81, 0.87]
Bonsu 2003. ED. Bacteraemia.	8	834	9	2959	0.47 [0.23, 0.72]	0.78 [0.77, 0.79]

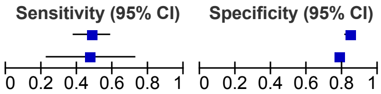


Figure 67: Sensitivity and specificity for WBC (>20x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI.	22	38	80	752	0.22 [0.14, 0.31]	0.95 [0.93, 0.97]
Bonsu 2003. ED. Bacteraemia.	2	266	7	3535	0.22 [0.03, 0.60]	0.93 [0.92, 0.94]
Hornik 2012. NICU. Bacterial sepsis.	2182	12160	7474	48038	0.23 [0.22, 0.23]	0.80 [0.79, 0.80]

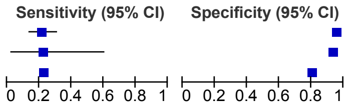


Figure 68: Sensitivity and specificity for WBC (>25x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003. ED. Bacteraemia.	1	76	4	3729	0.20 [0.01, 0.72]	0.98 [0.98, 0.98]

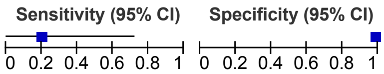


Figure 69: Sensitivity and specificity for WBC (>30x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003. ED. Bacteraemia.	0	38	2	3770	0.00 [0.00, 0.84]	0.99 [0.99, 0.99]

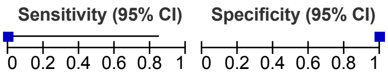


Figure 70: Sensitivity or specificity for WBC (>50x10⁹/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	97	542	9559	59656	0.01 [0.01, 0.01]	0.99 [0.99, 0.99]

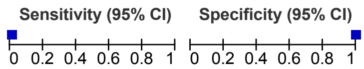


Figure 71: Sensitivity and specificity for WBC (<4 or ≥20x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sherwin 2008. NICU. Neonate late onset sepsis.	11	28	41	84	0.21 [0.11, 0.35]	0.75 [0.66, 0.83]

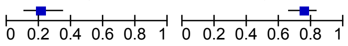


Figure 72: Sensitivity and specificity for WBC (>15 or <5 x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI.	51	173	51	617	0.50 [0.40, 0.60]	0.78 [0.75, 0.81]
Bonsu 2003. ED. Bacteraemia.	17	1060	9	2725	0.65 [0.44, 0.83]	0.72 [0.71, 0.73]
Bressan 2010. ED. SBI. [fever less than 12 hrs]	7	9	18	65	0.28 [0.12, 0.49]	0.88 [0.78, 0.94]
Bressan 2010. ED. SBI. [fever more than 12 hrs]	4	5	1	48	0.80 [0.28, 0.99]	0.91 [0.79, 0.97]

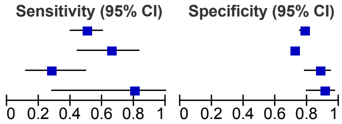


Figure 73: Sensitivity and specificity for WBC (>20 or <4.1 x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2009. Hospital. SBI.	22	62	80	728	0.22 [0.14, 0.31]	0.92 [0.90, 0.94]

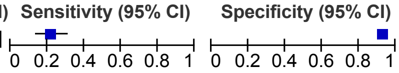


Figure 74: Sensitivity and specificity for WBC (>20 or <5 x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003. ED. Bacteraemia.	8	455	9	3338	0.47 [0.23, 0.72]	0.88 [0.87, 0.89]

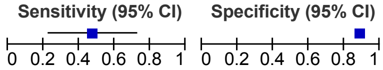
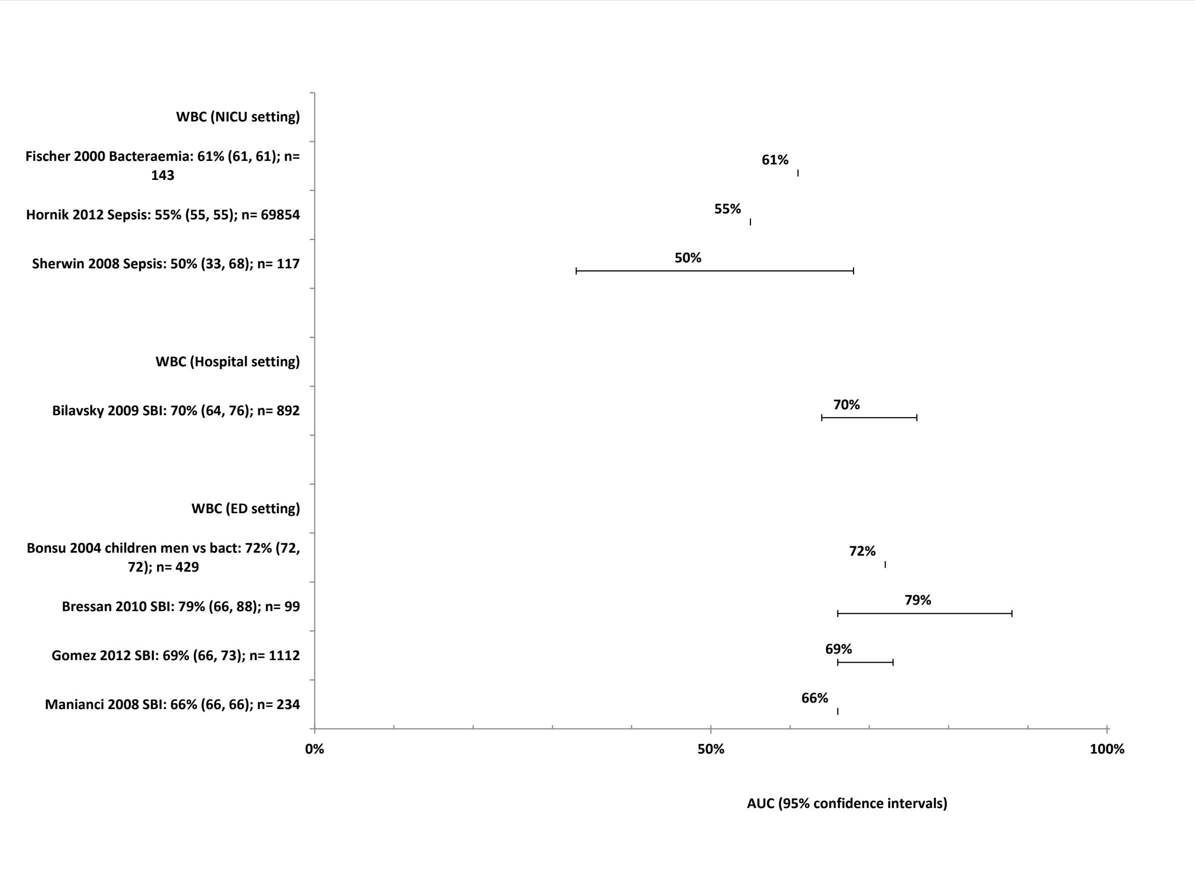


Figure 75: AUC for WBC to diagnose sepsis, severe sepsis and septic shock (divided by setting), neonates



K.3.7 Leukocytes, adults

Figure 76: Multivariable odds ratio for leukocyte count, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
de Kruif 2010. ED. Bacterial infection	0.1178	0.0616		1.13 [1.00, 1.27]

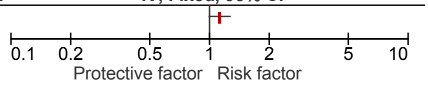


Figure 77: AUC for leukocyte sedimentation rate, adults

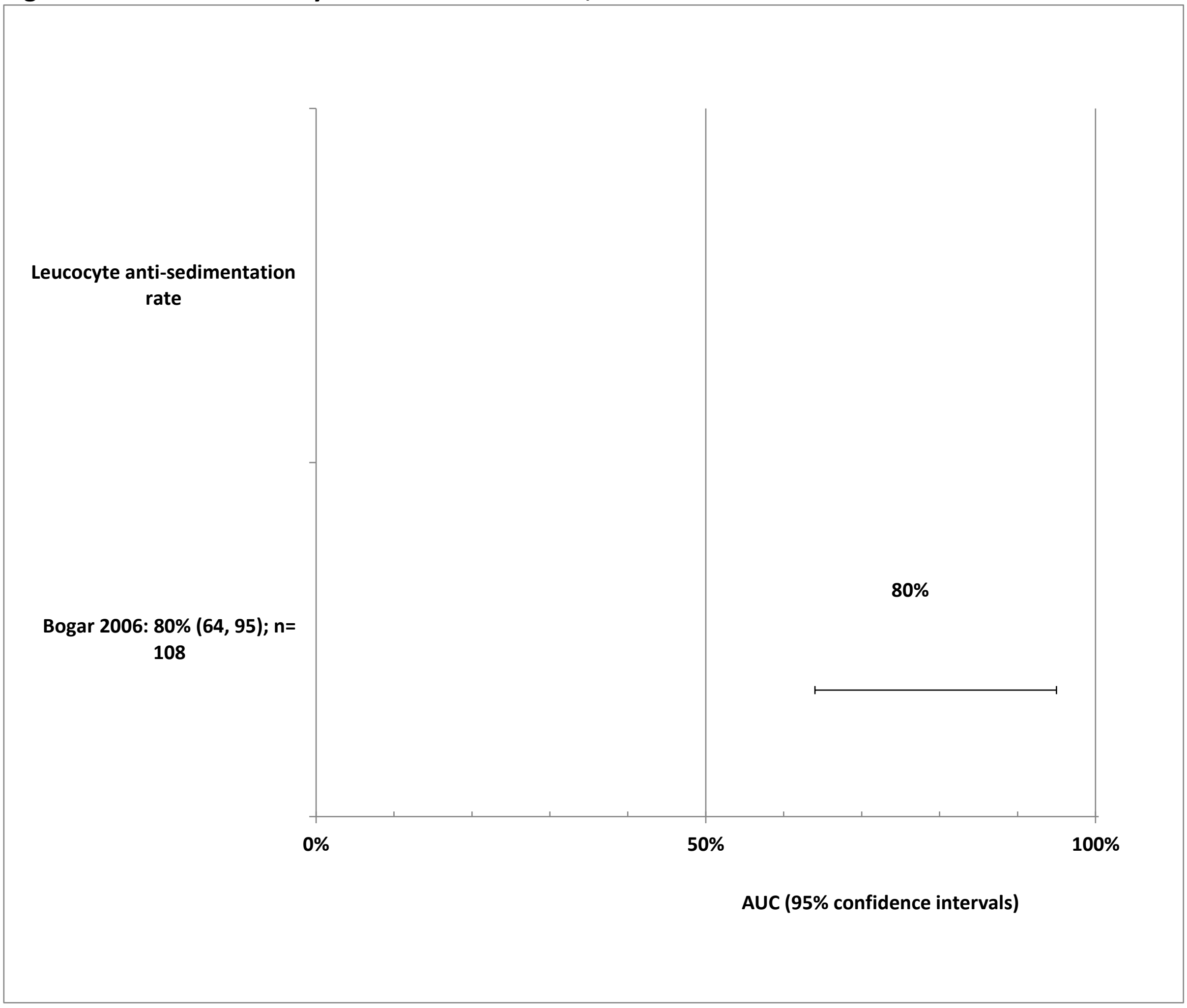
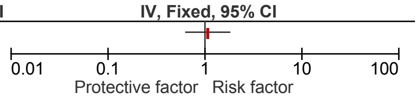


Figure 78: Odds ratio for leukocyte count ≥4x10⁹/l or ≤12x10⁹/l compared to <4x10⁹/l or >12x10⁹/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Leth 2013. Hospital. Bloodstream infection	0.0677	0.2654		1.07 [0.64, 1.80]



K.3.8 Leukocytes, children

Figure 79: Sensitivity and specificity for leukocytes (>7.1x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Fernandez-lopez 2003. ED/hospital. IBI.	81	48	69	154	0.54 [0.46, 0.62]	0.76 [0.70, 0.82]		

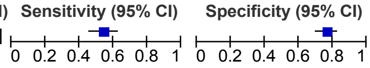


Figure 80: Sensitivity and specificity for leukocytes (>15x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Galetto-Lacour 2003. ED. SBI.	15	18	14	52	0.52 [0.33, 0.71]	0.74 [0.62, 0.84]		
Lacour 2001. ED. SBI.	19	22	9	74	0.68 [0.48, 0.84]	0.77 [0.67, 0.85]		

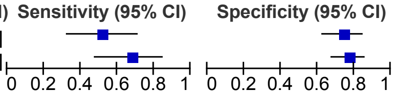
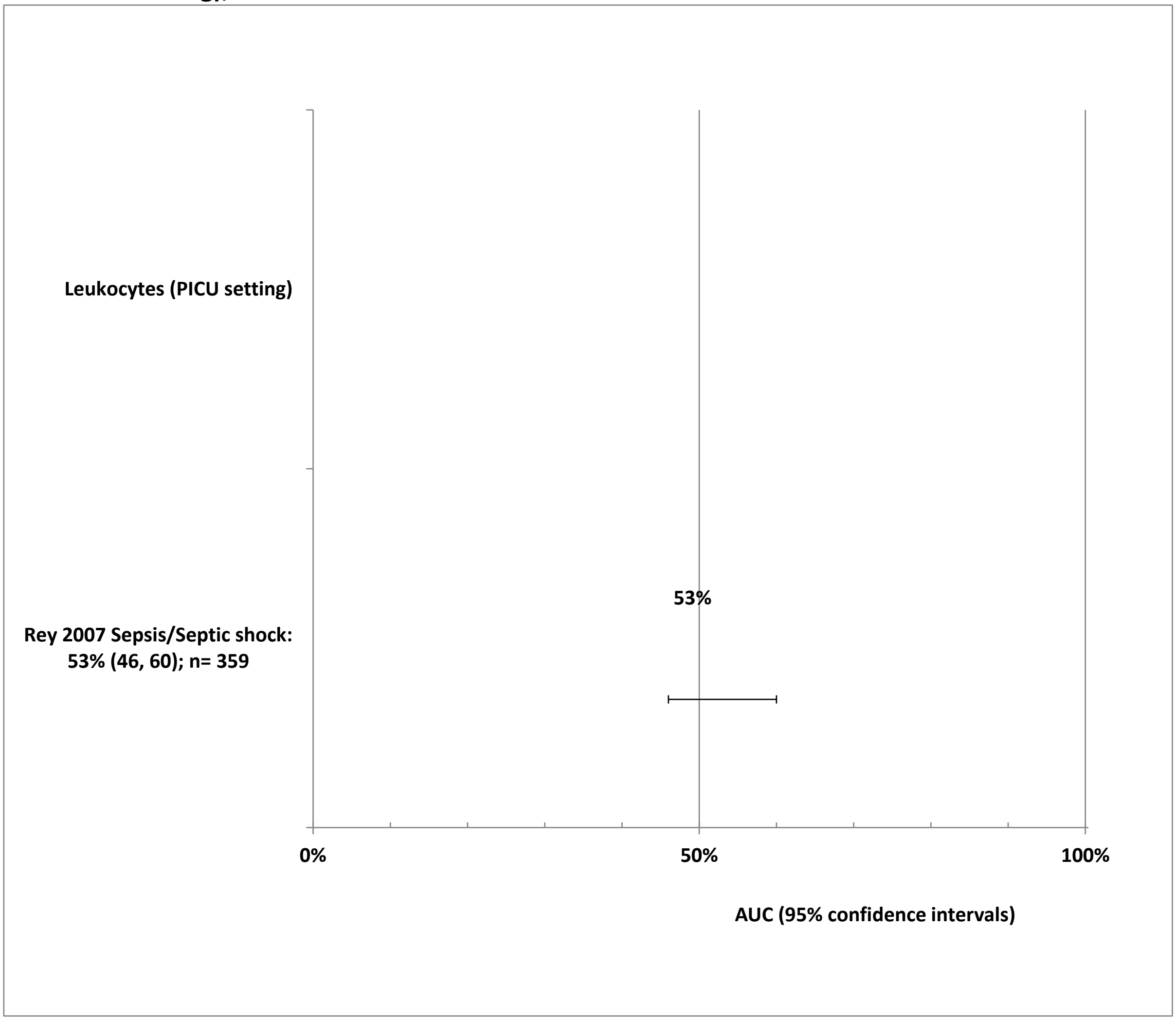


Figure 81: AUC for leukocytes to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



K.3.9 Leukocytes, neonates

Figure 82: Sensitivity and specificity for leukocytes (>10x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Olaciregui 2009. ED. SBI.	60	111	22	154	0.73 [0.62, 0.82]	0.58 [0.52, 0.64]

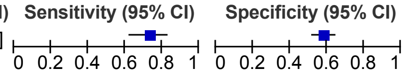


Figure 83: Sensitivity and specificity for leukocytes (>15x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Olaciregui 2009. ED. SBI.	31	42	51	223	0.38 [0.27, 0.49]	0.84 [0.79, 0.88]

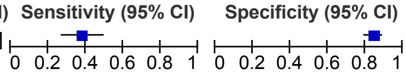
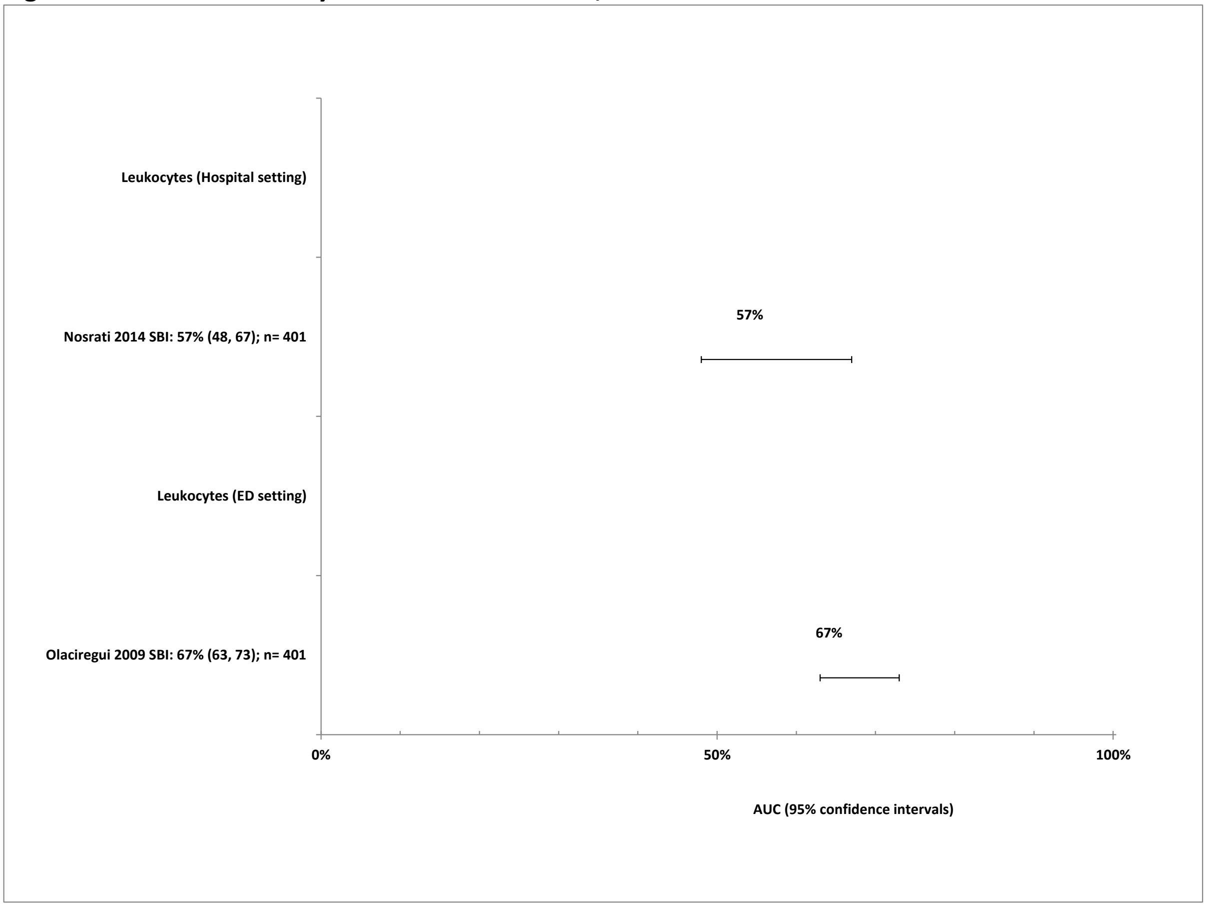


Figure 84: AUC for leukocyte sedimentation rate, neonates



K.3.10 Neutrophils, adults

Figure 85: Sensitivity and specificity for neutrophil count (cut-off 7.5x10^9/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kofoed 2007. Hospital. BI	87	12	30	22	0.74 [0.65, 0.82]	0.65 [0.46, 0.80]

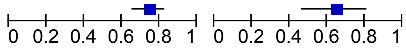


Figure 86: AUC for neutrophil count (divided by setting), adults

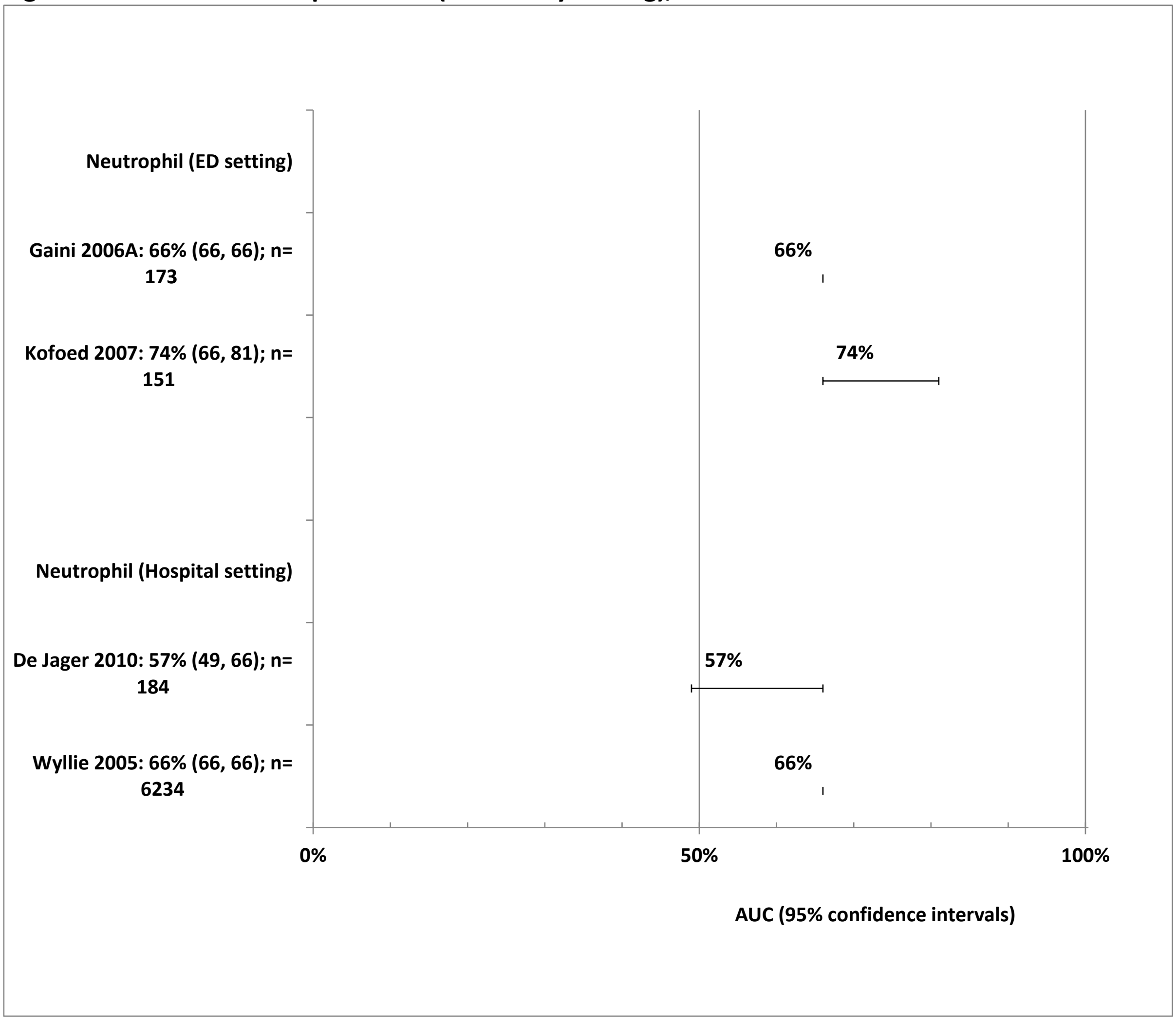


Figure 87: Odds ratio for neutrophil count (>80%), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Chase 2012. ED. Bacteraemia	0.5653	0.1168		1.76 [1.40, 2.21]

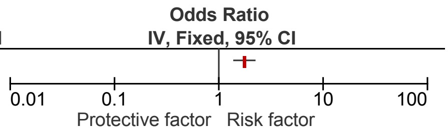
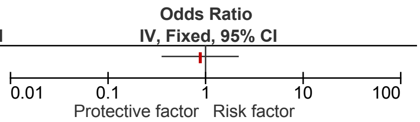


Figure 88: Odds ratio for neutrophil count ≥2x10^9/l or ≤7x10^9/l compared to <2x10^9/l or >7x10^9/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Leth 2013. Hospital. Bloodstream infection	-0.1278	0.456		0.88 [0.36, 2.15]



K.3.11 Neutrophils, children

Figure 89: Sensitivity and specificity for neutrophil count (cut-off 6.45x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI	77	118	17	196	0.82 [0.73, 0.89]	0.62 [0.57, 0.68]

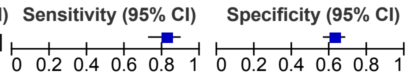


Figure 90: Sensitivity and specificity for neutrophil count (cut-off 10x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andreola 2007. ED. SBI	28	68	66	246	0.30 [0.21, 0.40]	0.78 [0.73, 0.83]
De 2014. ED. Bactaraemia/SBI.	293	699	421	2480	0.41 [0.37, 0.45]	0.78 [0.77, 0.79]
Mahajan 2014. Setting unclear. SBI.	14	23	16	173	0.47 [0.28, 0.66]	0.88 [0.83, 0.92]
Pratt 2007. ED. SBI. [less than12 hrs]	1	9	5	30	0.17 [0.00, 0.64]	0.77 [0.61, 0.89]
Pratt 2007. ED. SBI. [more than12 hrs]	7	12	4	51	0.64 [0.31, 0.89]	0.81 [0.69, 0.90]

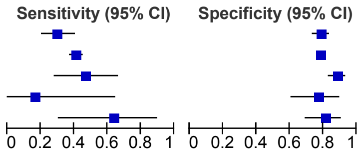


Figure 91: Sensitivity and specificity for neutrophil count (cut-off 10.2x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pulliam 2001. ED. SBI.	10	15	4	48	0.71 [0.42, 0.92]	0.76 [0.64, 0.86]

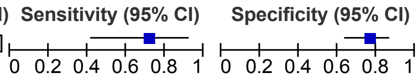


Figure 92: Sensitivity and specificity for neutrophil count (cut-off 10.6x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Isaacman 2002. ED.	20	48	9	179	0.69 [0.49, 0.85]	0.79 [0.73, 0.84]

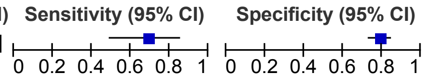


Figure 93: Sensitivity and specificity for neutrophil count (cut-off 11x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pratt 2007. ED. SBI. [less than12 hrs]	1	7	5	32	0.17 [0.00, 0.64]	0.82 [0.66, 0.92]
Pratt 2007. ED. SBI. [more than12 hrs]	6	12	5	51	0.55 [0.23, 0.83]	0.81 [0.69, 0.90]

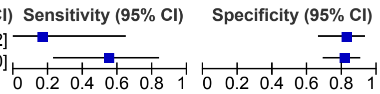


Figure 94: Sensitivity and specificity for neutrophil count (cut-off 12x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pratt 2007. ED. SBI. [less than12 hrs]	1	6	5	33	0.17 [0.00, 0.64]	0.85 [0.69, 0.94]
Pratt 2007. ED. SBI. [more than12 hrs]	6	10	5	53	0.55 [0.23, 0.83]	0.84 [0.73, 0.92]

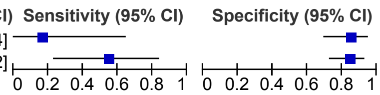


Figure 95: Sensitivity and specificity for neutrophil count (cut-off 13x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
De 2014. ED. Bactaraemia/SBI.	150	223	564	2956	0.21 [0.18, 0.24]	0.93 [0.92, 0.94]

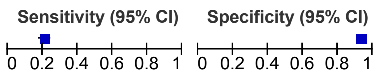


Figure 96: Sensitivity and specificity for neutrophil count (cut-off 15x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
De 2014. ED. Bactaraemia/SBI.	150	223	564	2956	0.21 [0.18, 0.24]	0.93 [0.92, 0.94]

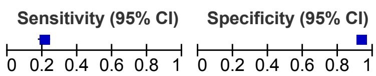
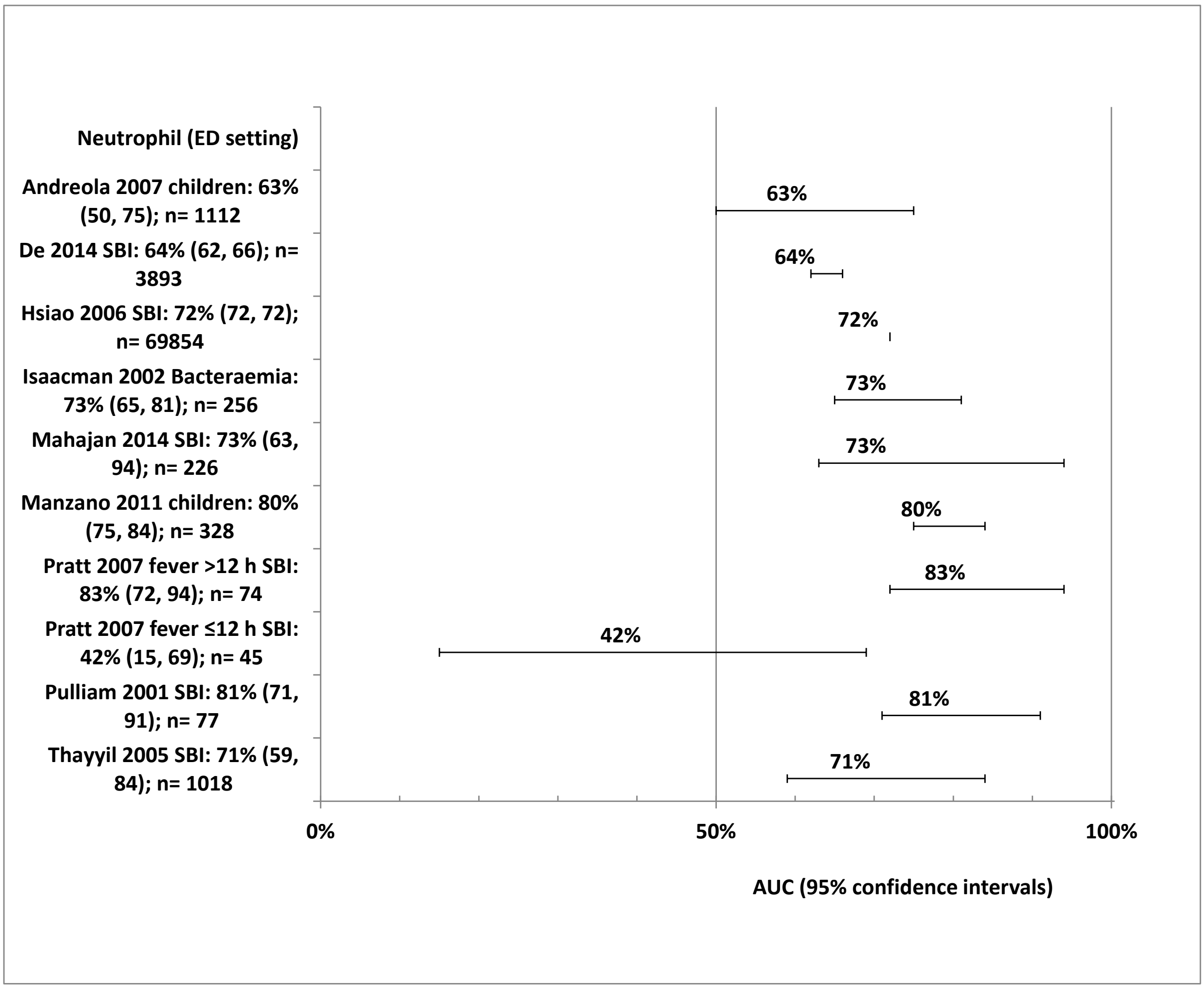


Figure 97: AUC for neutrophils to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



K.3.12 Neutrophils, neonates

Figure 98: Sensitivity and specificity for neutrophil count (cut-off 1x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	232	1204	9424	58994	0.02 [0.02, 0.03]	0.98 [0.98, 0.98]

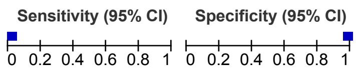


Figure 99: Sensitivity and specificity for neutrophil count (cut-off 1.5x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	483	2709	9173	57489	0.05 [0.05, 0.05]	0.95 [0.95, 0.96]

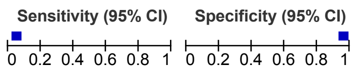


Figure 100: Sensitivity and specificity for neutrophil count (cut-off 10x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bressan 2010. ED. SBI. [fever less than 12 hrs]	5	2	20	72	0.20 [0.07, 0.41]	0.97 [0.91, 1.00]
Bressan 2010. ED. SBI. [fever more than 12 hrs]	4	0	1	53	0.80 [0.28, 0.99]	1.00 [0.93, 1.00]
Sherwin 2008. NICU. Neonate late onset sepsis.	17	8	35	104	0.33 [0.20, 0.47]	0.93 [0.86, 0.97]

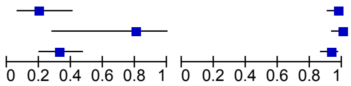
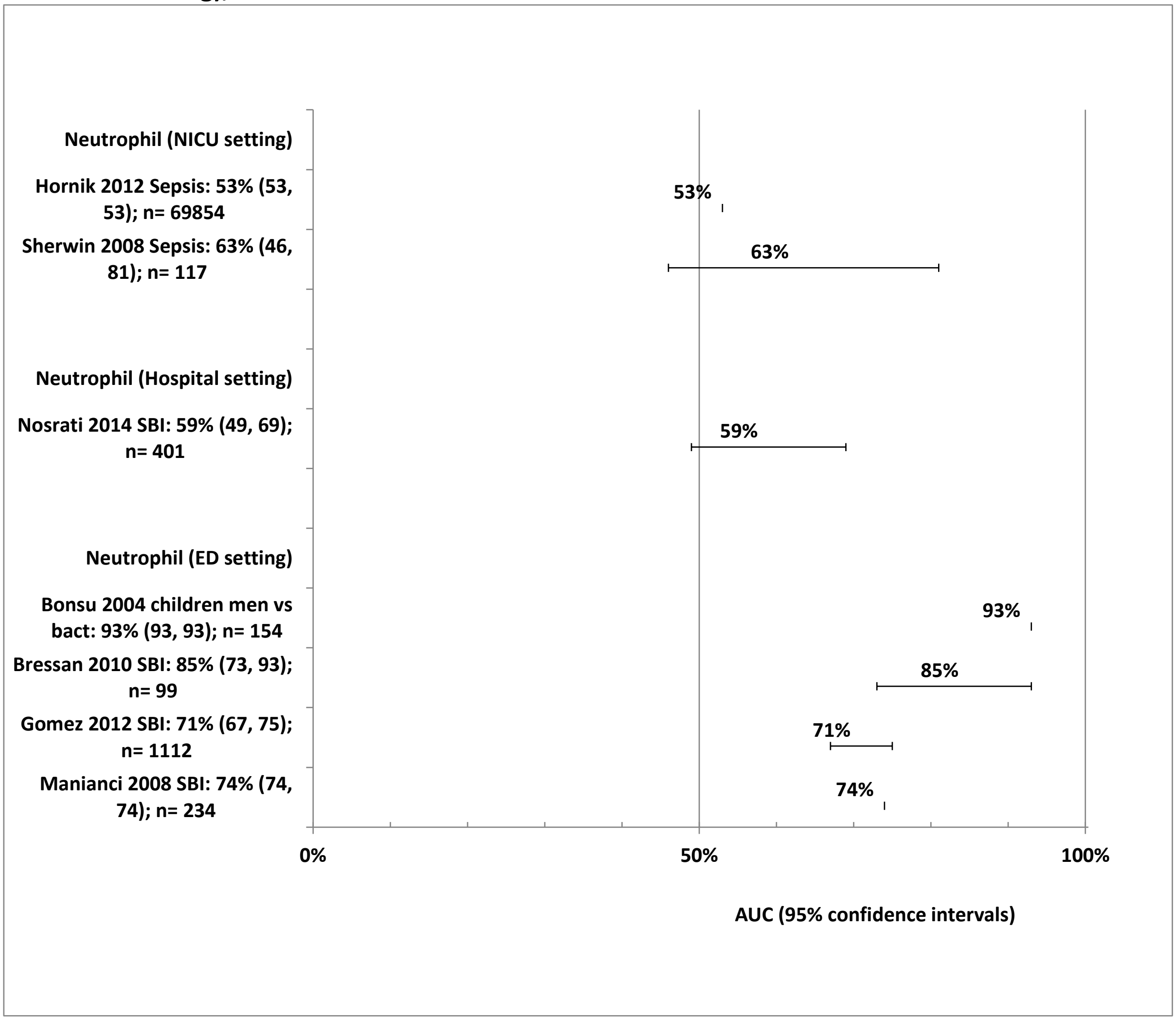
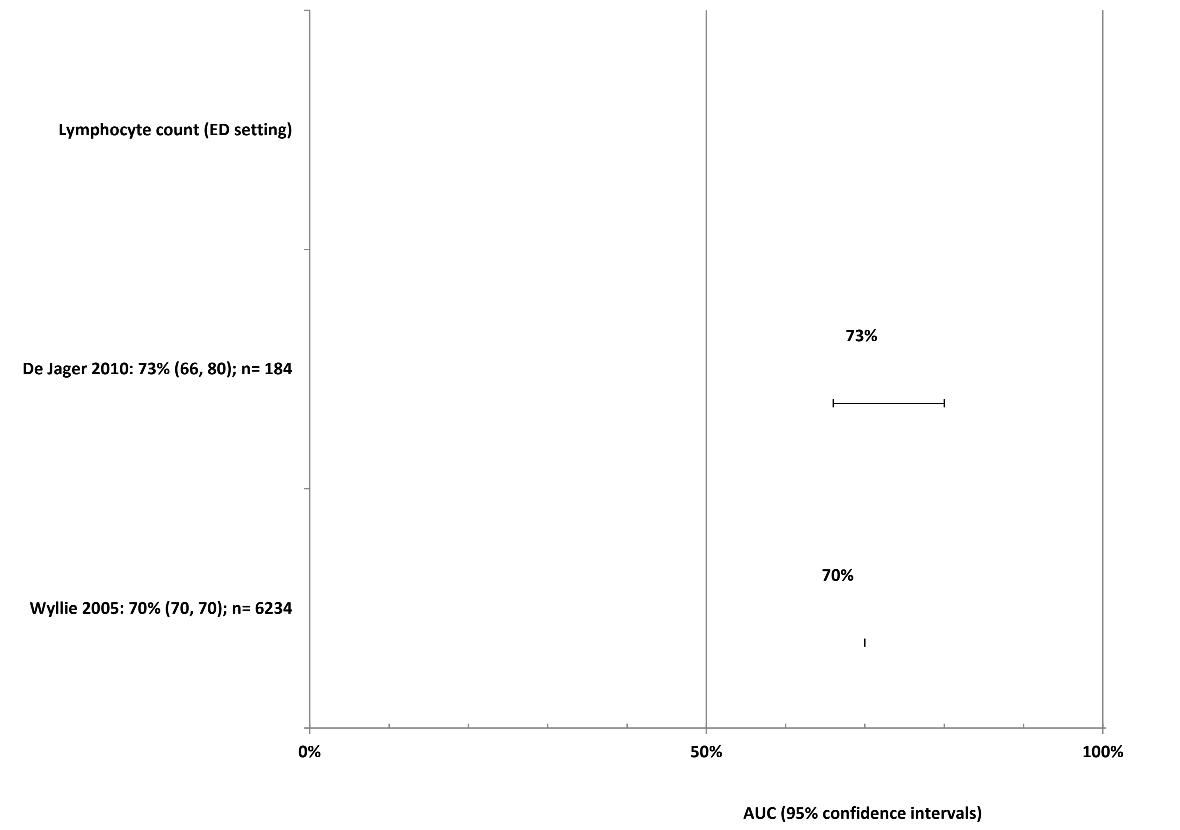


Figure 101: AUC for neutrophils to diagnose sepsis, severe sepsis and septic shock (divided by setting), neonates



K.3.13 Lymphocytes, adults

Figure 102: AUC for lymphocyte count, adults



K.3.14 Lymphocytes, children

None.

K.3.15 Lymphocytes, neonates

None.

K.3.16 Lactate, adults

Figure 103: Sensitivity and specificity for lactate (>1.5 mmol/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hoeboer 2012. ICU. BI	10	35	2	54	0.83 [0.52, 0.98]	0.61 [0.50, 0.71]		

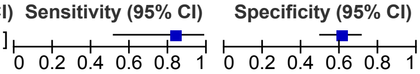


Figure 104: Sensitivity and specificity for lactate (>1.7 mmol/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hoeboer 2012. ICU. Mortality	40	9	27	26	0.60 [0.47, 0.72]	0.74 [0.57, 0.88]

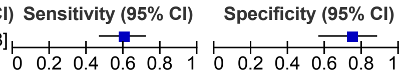


Figure 105: AUC for lactate to diagnose (1) sepsis, severe sepsis, septic shock; (2) bacteraemia or infection; (3) mortality, adults

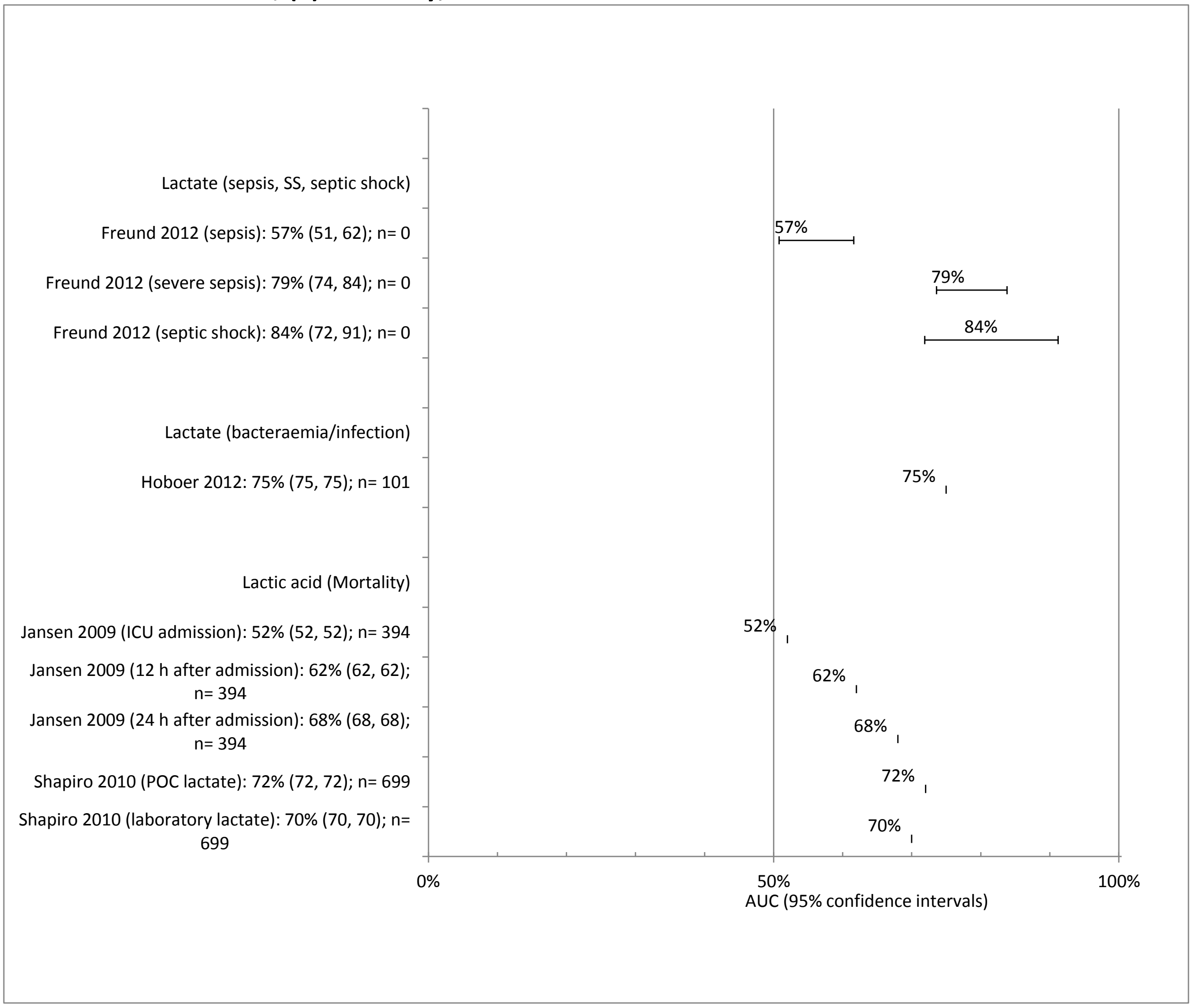


Figure 106: Odds ratio for lactate (>2 mmol/l) for the diagnosis of severe sepsis, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Freund 2012. ED. Sepsis/SS/septic shock	2.3869	0.262		10.88 [6.51, 18.18]

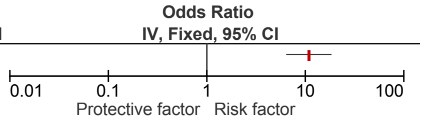
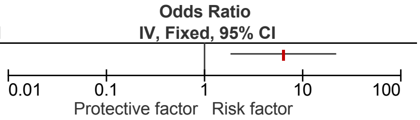


Figure 107: Odds ratio for lactate (>2 mmol/l) for the diagnosis of septic shock, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Freund 2012. ED. Sepsis/SS/septic shock	1.85	0.6245		6.36 [1.87, 21.63]



K.3.17 Lactate, children

None.

K.3.18 Lactate, neonates

None.

K.3.19 Bands, adults

Figure 108: Sensitivity and specificity for bands (>8.5%), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mare 2015. ICU. Sepsis	51	27	9	68	0.85 [0.73, 0.93]	0.72 [0.61, 0.80]

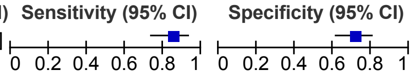


Figure 109: Sensitivity and specificity for bands (>10%), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cavallazzi 2010. ICU. Infection	18	8	24	95	0.43 [0.28, 0.59]	0.92 [0.85, 0.97]

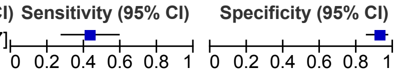
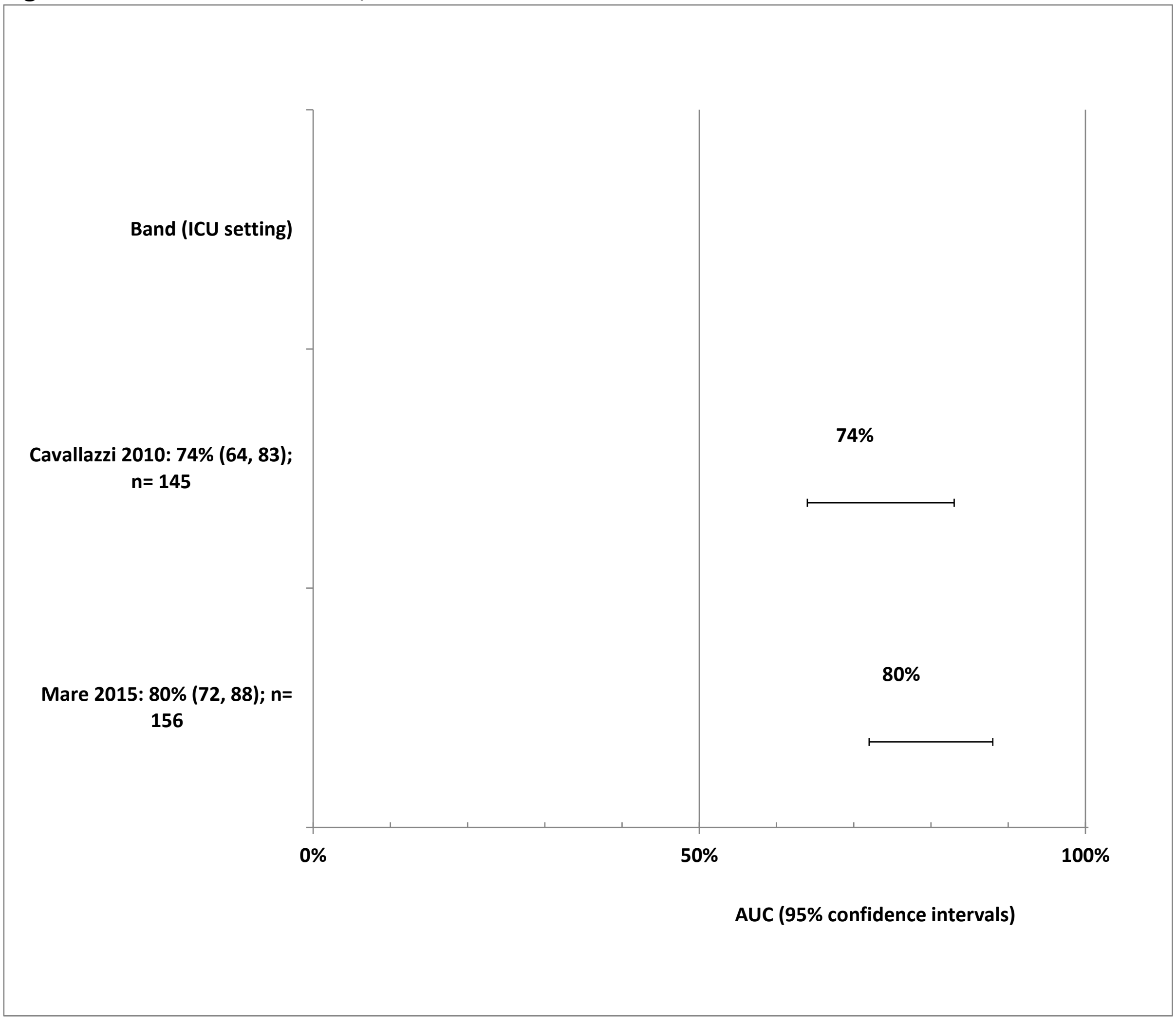


Figure 110: AUC for bands, adults



K.3.20 Bands, children

Figure 111: Sensitivity and specificity for bands (>1.5x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Galetto-Lacour 2003. ED. SBI.	3	5	26	65	0.10 [0.02, 0.27]	0.93 [0.84, 0.98]
Lacour 2001. ED. SBI.	8	9	20	87	0.29 [0.13, 0.49]	0.91 [0.83, 0.96]
Mahajan 2014. Setting unclear. SBI.	6	13	24	183	0.20 [0.08, 0.39]	0.93 [0.89, 0.96]

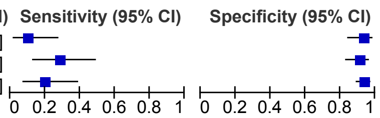


Figure 112: Sensitivity and specificity for bands (>1.8x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mahajan 2014. Setting unclear. SBI.	6	7	24	189	0.20 [0.08, 0.39]	0.96 [0.93, 0.99]

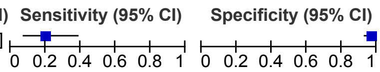
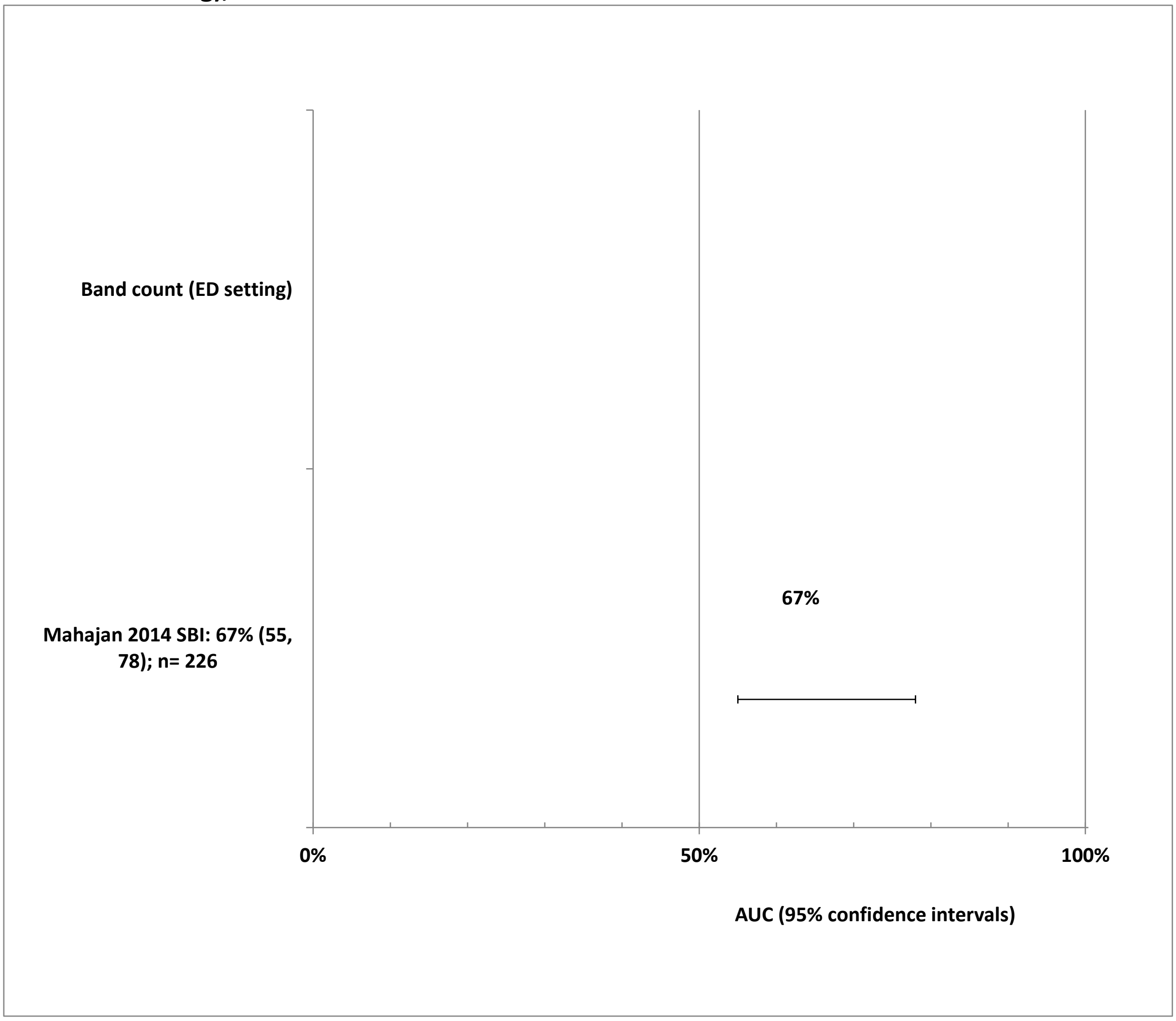


Figure 113: AUC for bands to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



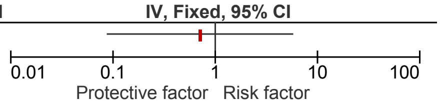
K.3.21 Bands, neonates

None.

K.3.22 Haemoglobin, adults

Figure 114: Odds ratio for haemoglobin (≤100 g/l), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Patterson 2012. ED. Bacteraemia	-0.3425	1.0628		0.71 [0.09, 5.70]	



K.3.23 Haemoglobin, children

None.

K.3.24 Haemoglobin, neonates

None.

K.3.25 Urea, adults

Figure 115: Sensitivity and specificity for urea (>11 mmol/l), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Muller 2010. Hospital. Bacteraemia	23	187	50	665	0.32 [0.21, 0.43]	0.78 [0.75, 0.81]

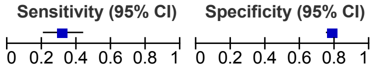
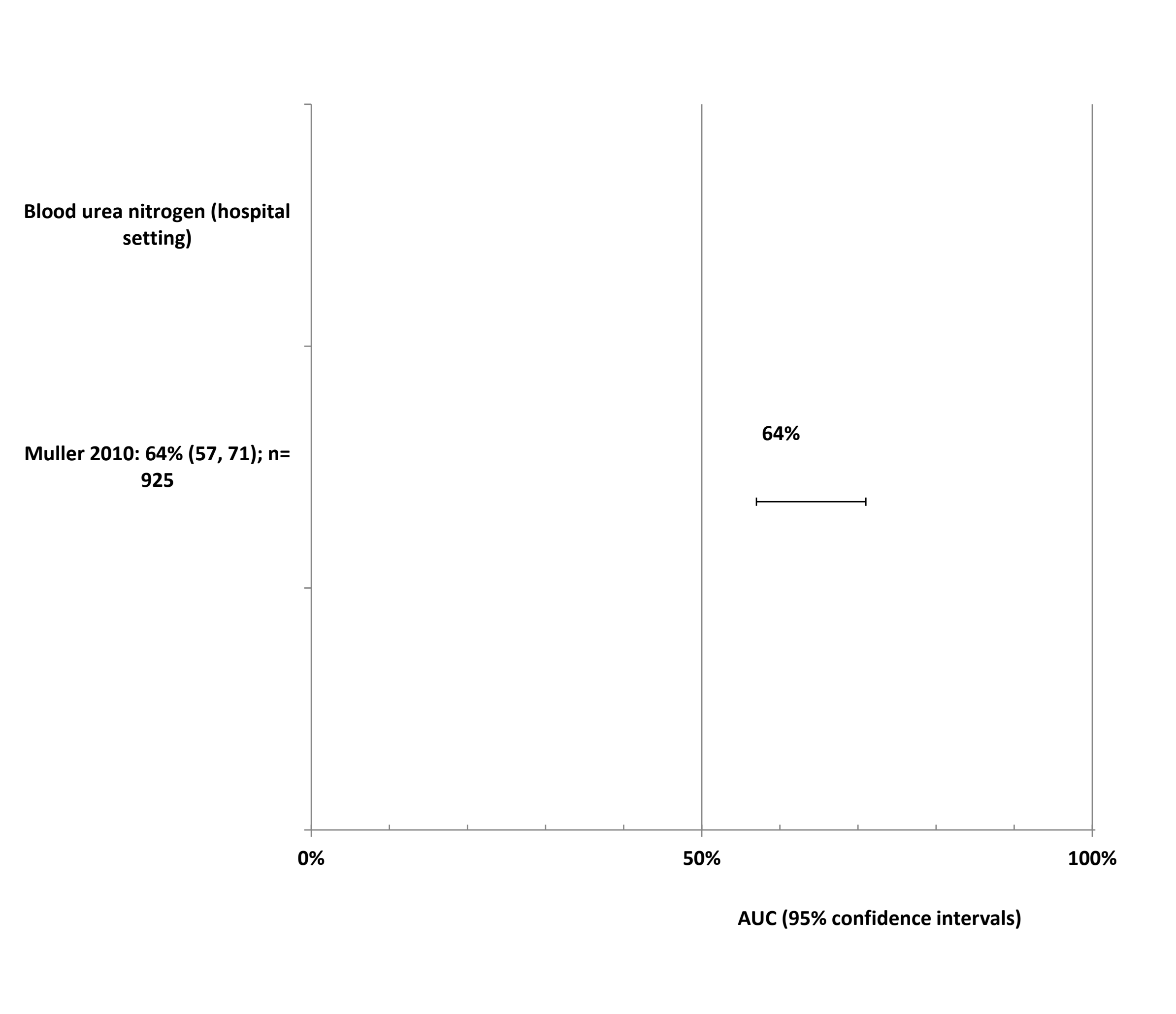


Figure 116: AUC for urea, adults



K.3.26 Urea, children

None.

K.3.27 Urea, neonates

None.

K.3.28 Creatinine, adults

None.

K.3.29 Creatinine, children

None.

K.3.30 Creatinine, neonates

None.

K.3.31 Platelets, adults

Figure 117: AUC for platelet count (divided by setting), adults

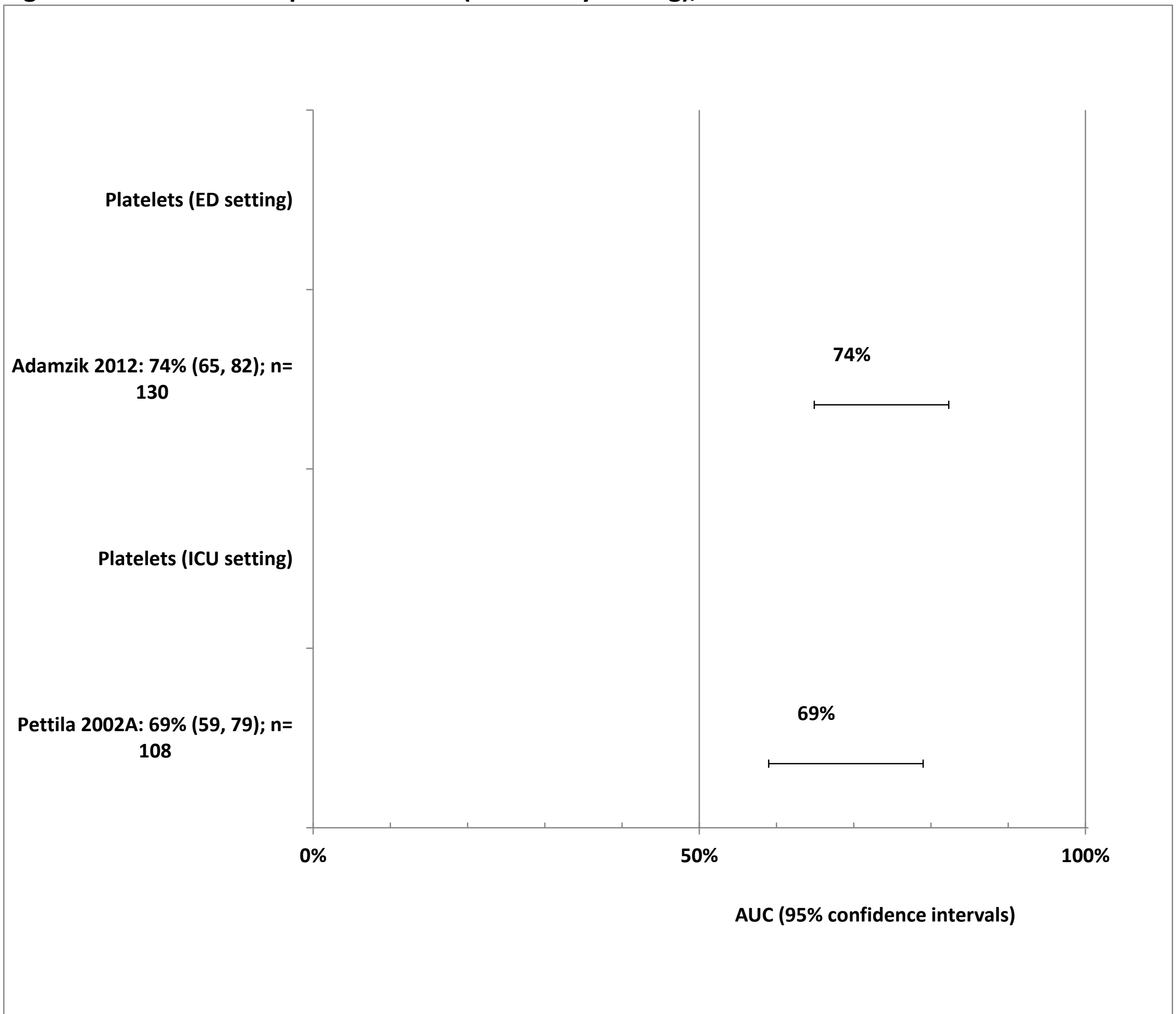
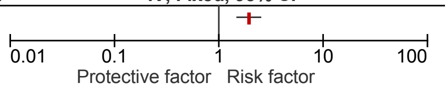


Figure 118: Odds ratio for platelets (<150x10^9/l), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Chase 2012. ED. Bacteraemia	0.6627	0.1312		1.94 [1.50, 2.51]



K.3.32 Platelets, children

Figure 119: Sensitivity and specificity for platelets (>68x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2015A. ED. Sepsis.	19	10	13	33	0.59 [0.41, 0.76]	0.77 [0.61, 0.88]

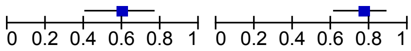


Figure 120: Sensitivity and specificity for platelets (>400x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fouzas 2010. ED. SBI.	88	165	15	140	0.85 [0.77, 0.92]	0.46 [0.40, 0.52]

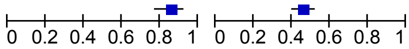


Figure 121: Sensitivity and specificity for platelets (>450x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fouzas 2010. ED. SBI.	85	90	18	215	0.83 [0.74, 0.89]	0.70 [0.65, 0.76]

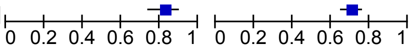


Figure 122: Sensitivity and specificity for platelets (>500x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fouzas 2010. ED. SBI.	54	68	49	237	0.52 [0.42, 0.62]	0.78 [0.73, 0.82]

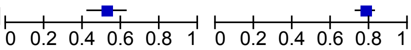


Figure 123: Sensitivity and specificity for platelets (>600x10^9/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fouzas 2010. ED. SBI.	23	30	80	275	0.22 [0.15, 0.32]	0.90 [0.86, 0.93]

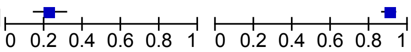


Figure 124: Sensitivity and specificity for platelets (20% increase), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baez 2011. ICU. Post op sepsis. [24 hrs]	38	38	3	24	0.93 [0.80, 0.98]	0.39 [0.27, 0.52]
Baez 2011. ICU. Post op sepsis. [48 hrs]	39	50	2	12	0.95 [0.83, 0.99]	0.19 [0.10, 0.31]

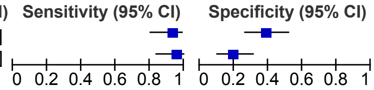
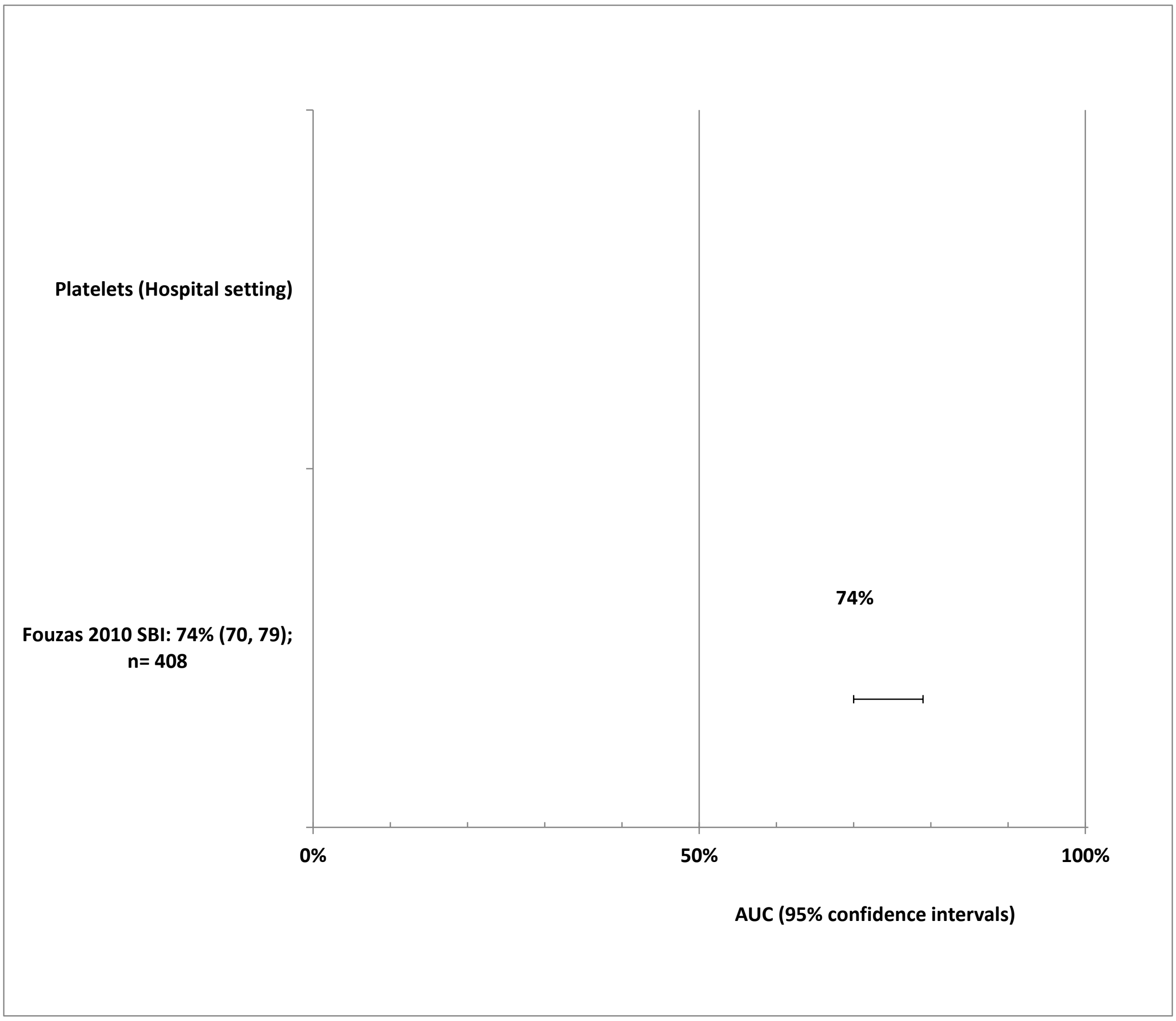


Figure 125: AUC for platelets to diagnose sepsis, severe sepsis and septic shock (divided by setting), children



K.3.33 Platelets, neonates

Figure 126: Sensitivity and specificity for platelets (>50x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	744	1324	8912	58874	0.08 [0.07, 0.08]	0.98 [0.98, 0.98]

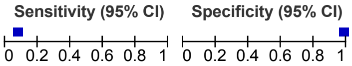


Figure 127: Sensitivity and specificity for platelets (>100x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sherwin 2008. NICU. Neonate late onset sepsis.	9	8	43	104	0.17 [0.08, 0.30]	0.93 [0.86, 0.97]

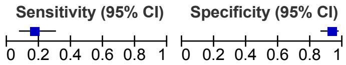


Figure 128: Sensitivity and specificity for platelets (<100x10^9/l), neonates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hornik 2012. NICU. Bacterial sepsis.	2211	6622	7445	53576	0.23 [0.22, 0.24]	0.89 [0.89, 0.89]

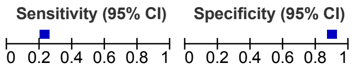
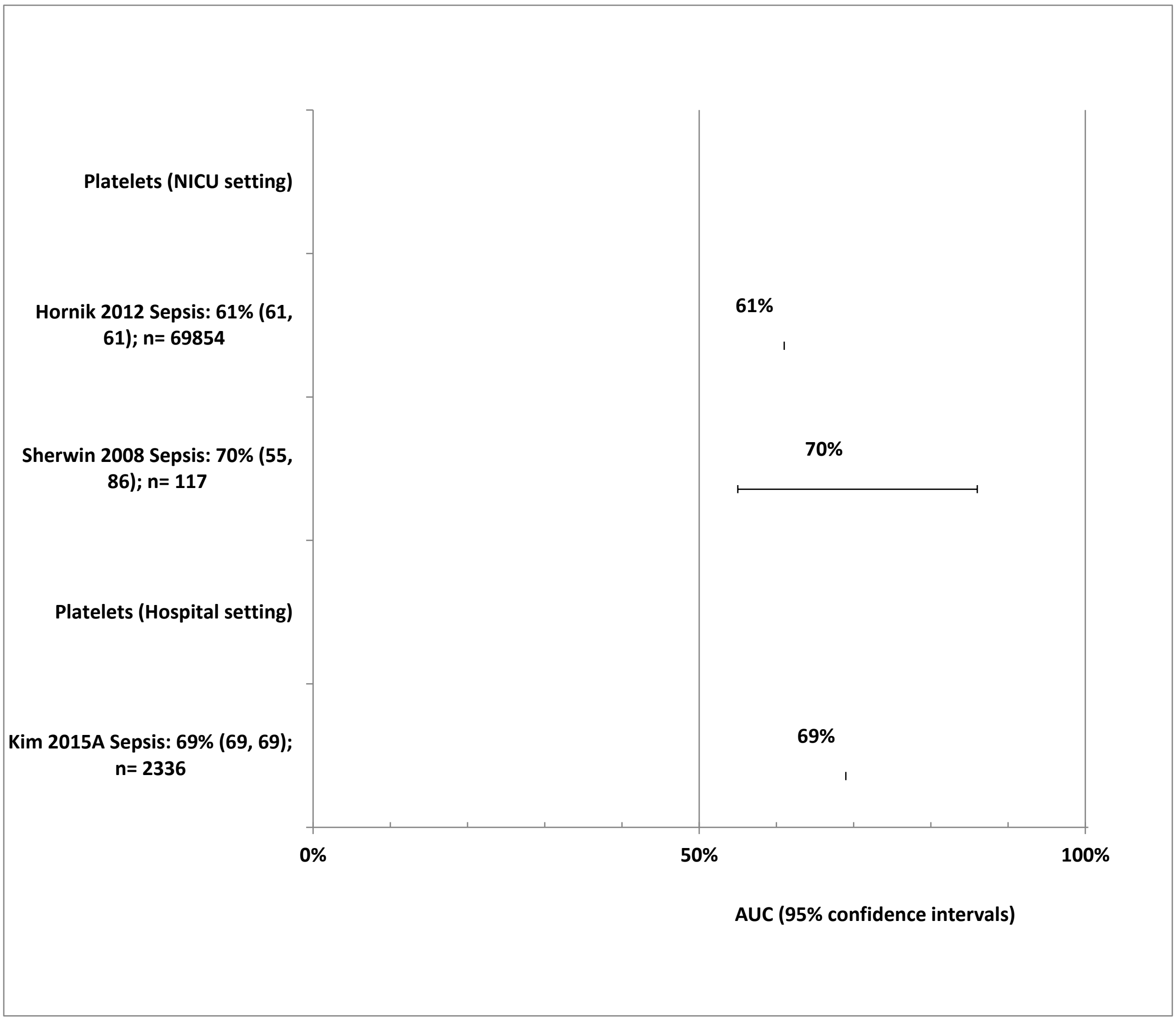
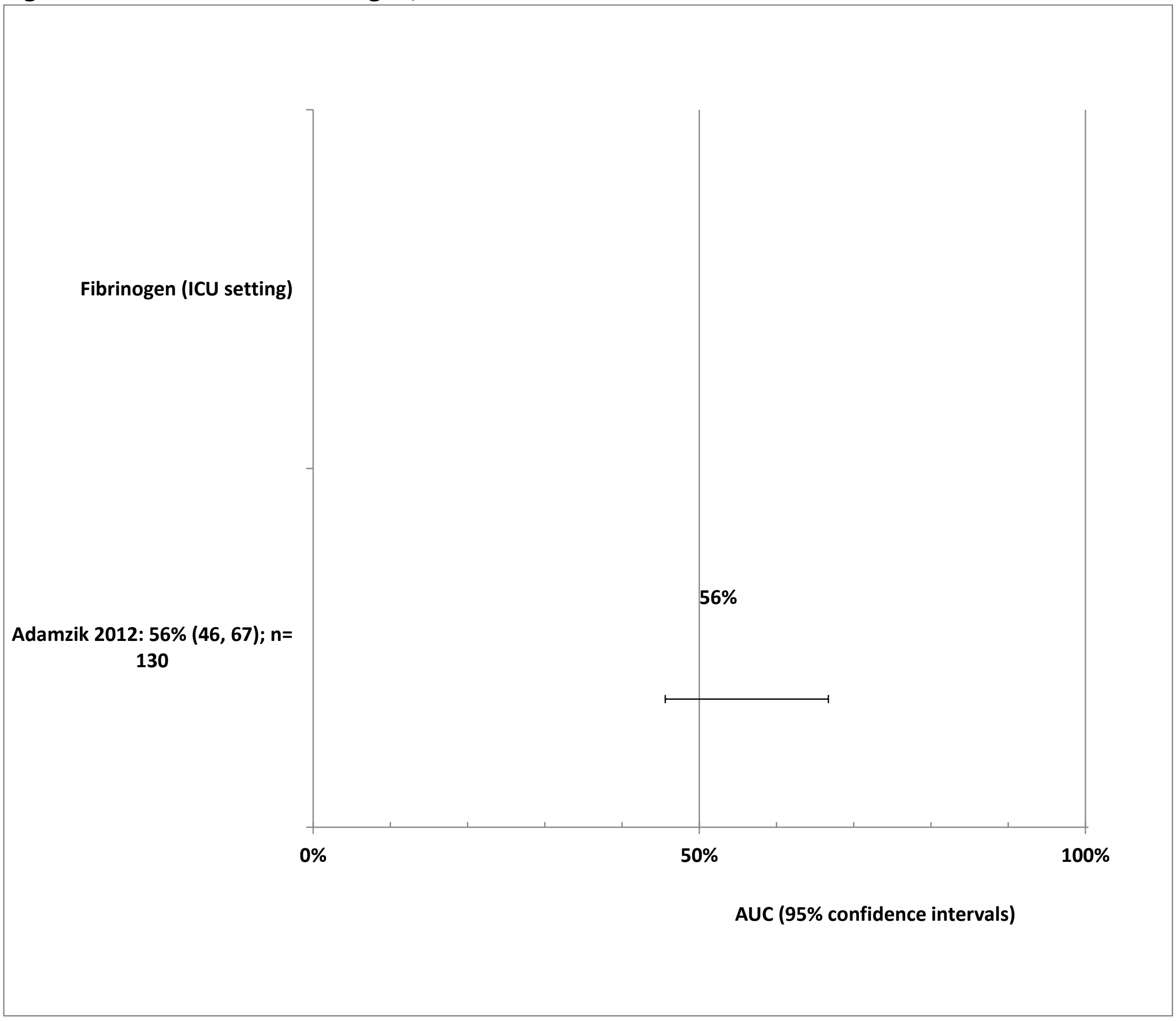


Figure 129: AUC for platelets to diagnose sepsis, severe sepsis and septic shock (divided by setting), neonates



K.3.34 Fibrinogen, adults

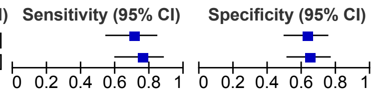
Figure 130: AUC for fibrinogen, adults



K.3.35 Fibrinogen, children

Figure 131: Sensitivity and specificity for fibrinogen (20% increase), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baez 2011. ICU. Post op sepsis. [24 hrs]	29	23	12	39	0.71 [0.54, 0.84]	0.63 [0.50, 0.75]
Baez 2011. ICU. Post op sepsis. [48 hrs]	31	22	10	40	0.76 [0.60, 0.88]	0.65 [0.51, 0.76]



K.3.36 Fibrinogen, neonates

None.

K.3.37 Thrombin time, adults

Figure 132: Odds ratio for prothrombin time (≥18.4 seconds), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Shorr 2008. Unknown setting. Mortality	0.6366	0.1588		1.89 [1.38, 2.58]

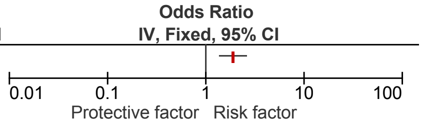


Figure 133: AUC for thrombin time (divided by setting), adults

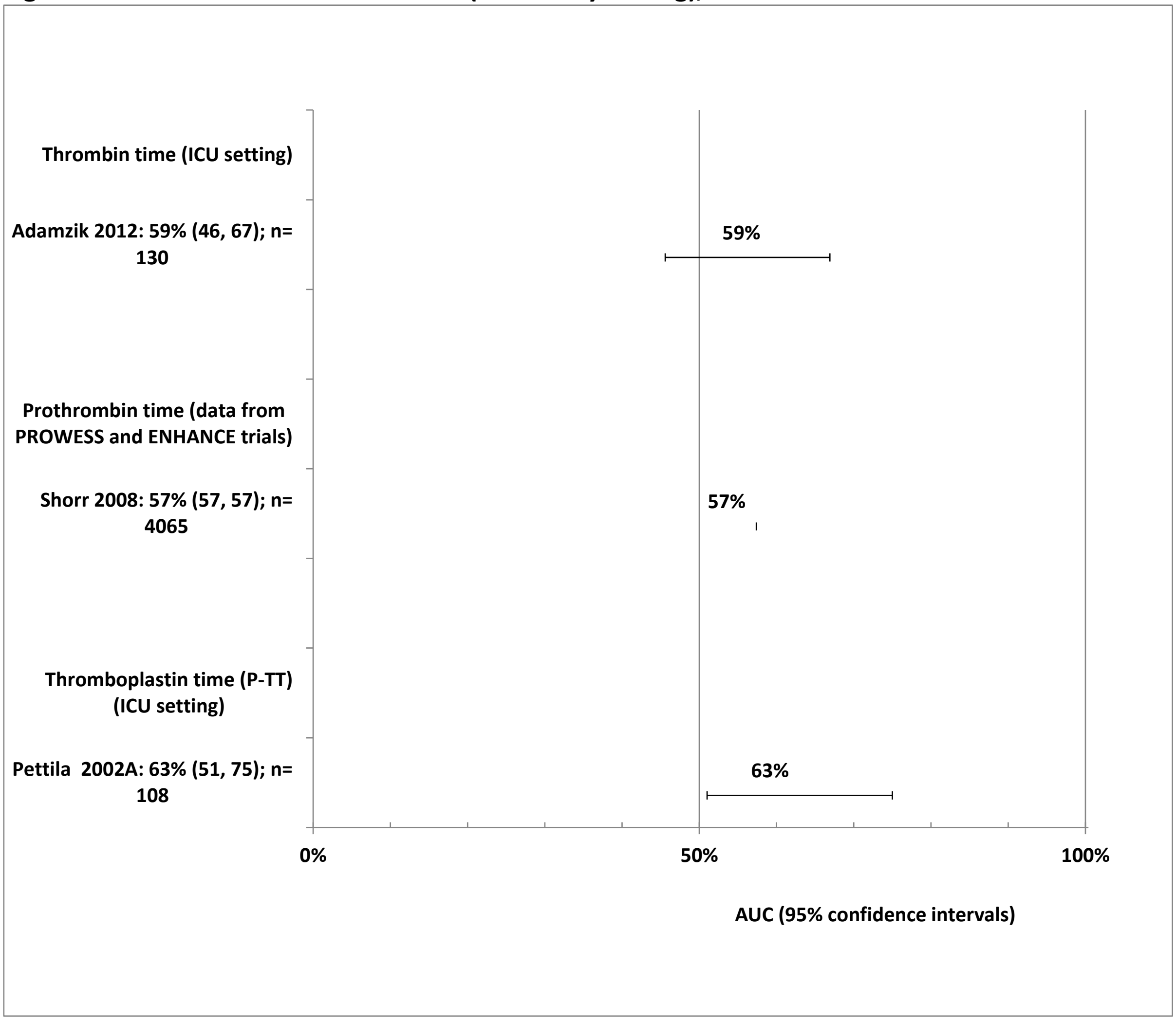
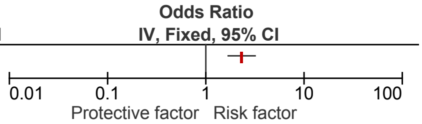


Figure 134: Odds ratio for anti-thrombin III (<53%), adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Shorr 2008. Unknown setting. Mortality	0.8416	0.1609		2.32 [1.69, 3.18]



K.3.38 Thrombin time, children

None.

K.3.39 Thrombin time, neonates

None.

K.3.40 Bilirubin, adults

None.

K.3.41 Bilirubin, children

None.

K.3.42 Bilirubin, neonates

None.

K.3.43 Combination of tests, adults

Figure 135: Sensitivity and specificity for bands (>10%) and WBC ($>12x10^9/l$), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cavallazzi 2010. ICU. Infection	11	3	31	100	0.26 [0.14, 0.42]	0.97 [0.92, 0.99]

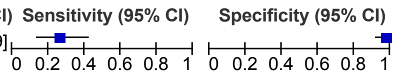


Figure 136: Sensitivity and specificity for CRP/albumin ratio (>5.09), adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2015B. ED. Mortality	115	188	73	294	0.61 [0.54, 0.68]	0.61 [0.56, 0.65]

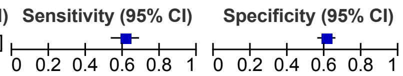


Figure 137: AUC for combination of tests (divided by combination and setting), adults

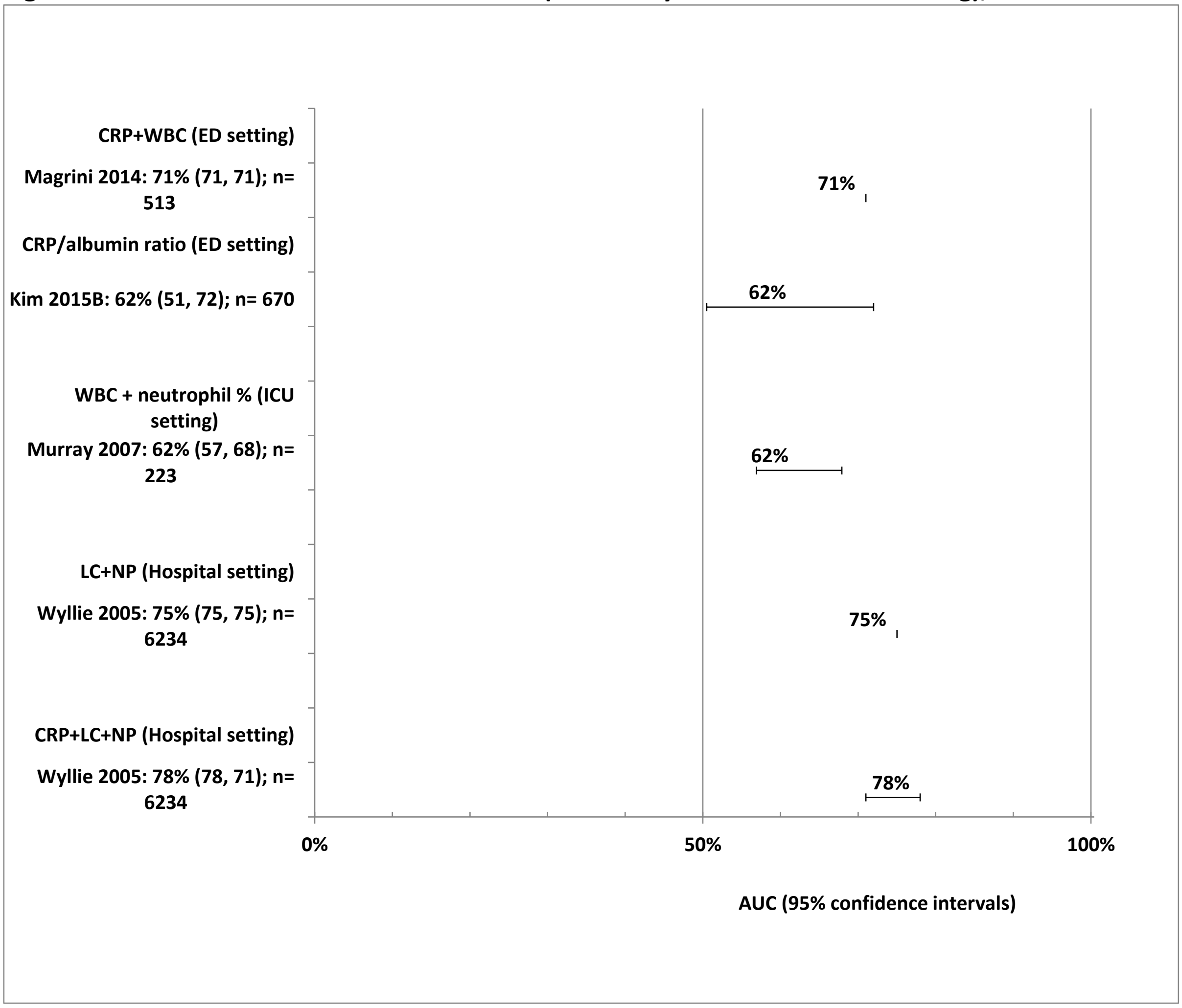


Figure 138: Odds ratio for CRP >100 mg/l and lactate <4.0 mmol/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Green 2011. Sepsis. ED. Suspected infection	0.6471	0.2287		1.91 [1.22, 2.99]

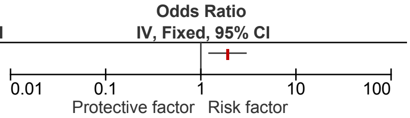


Figure 139: Odds ratio for CRP >100 mg/l and lactate ≥4.0 mmol/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Green 2011. Sepsis. ED. Suspected infection	2.5128	0.3033		12.34 [6.81, 22.36]

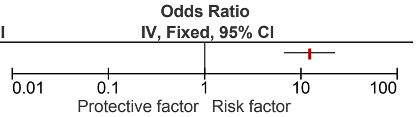
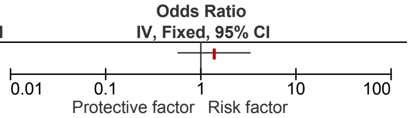


Figure 140: Odds ratio for CRP ≤100 mg/l and lactate ≥4.0 mmol/l, adults

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Green 2011. Sepsis. ED. Suspected infection	0.3221	0.4423		1.38 [0.58, 3.28]



K.3.44 Combination of tests, children

Figure 141: Sensitivity and specificity for CRP (>31mg/l) or WBC (>17.1x10[9]/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Isaacman 2002. ED.	22	95	7	132	0.76 [0.56, 0.90]	0.58 [0.51, 0.65]

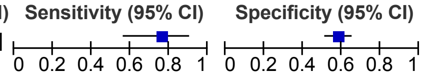


Figure 142: Sensitivity and specificity for CRP (>36mg/l) or ANC (>10.5x10[9]/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Isaacman 2002. ED.	23	114	6	114	0.79 [0.60, 0.92]	0.50 [0.43, 0.57]

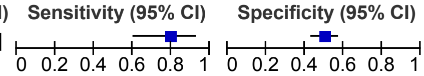


Figure 143: Sensitivity and specificity for CRP (>85mg/l) and ANC (>10x10[9]/l) or WBC (>15 x10[9]/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shaoul 2008. NICU. Positive blood culture.	42	233	8	143	0.84 [0.71, 0.93]	0.38 [0.33, 0.43]

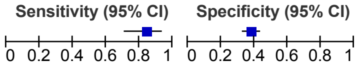
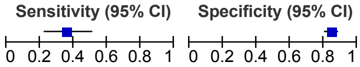


Figure 144: Sensitivity and specificity for CRP (>85mg/l) and ANC (>10x10[9]/l) and WBC (>15 x10[9]/l), children

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shaoul 2008. NICU. Positive blood culture.	18	58	32	317	0.36 [0.23, 0.51]	0.85 [0.80, 0.88]



K.3.45 Combination of tests, neonates

None.

K.4 Lactate

None.

K.5 Serum creatinine

Figure 145: Serum creatinine level increase per 0.1 mg/dl: 28-day mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Leedahl 2014. Septic shock ICU	-0.1278	0.055		0.88 [0.79, 0.98]

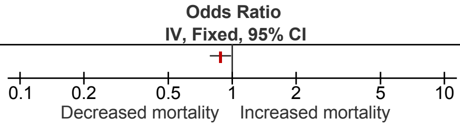


Figure 146: Initial serum creatinine >3.0 mg/dl: in-hospital mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Shmuely 2000. Bacteraemia ED	0.5306	0.2707		1.70 [1.00, 2.89]

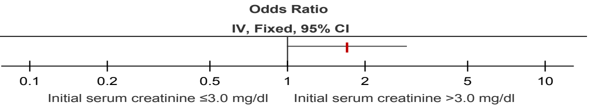


Figure 147: Initial serum creatinine >0.7 mg/dl: in-hospital mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Shapiro 2010. Suspected sepsis ED	0.239	0.3999		1.27 [0.58, 2.78]

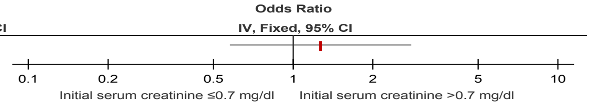
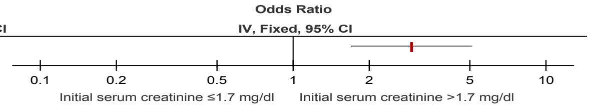


Figure 148: Initial serum creatinine >1.7 mg/dl: in-hospital mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Shapiro 2010. Suspected sepsis ED	1.0784	0.2795		2.94 [1.70, 5.08]



K.6 Disseminated intravascular coagulation (DIC)

Figure 149: 28-day mortality (multivariable analysis)

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
1.1.1 Multivariable analysis			
Gando 2008.DIC	0.2013	0.1007	1.22 [1.00, 1.49]
Gando 2013.Severe sepsis	0.2484	0.0594	1.28 [1.14, 1.44]
Ogura 2014.Severe sepsis	0.5499	0.2347	1.73 [1.09, 2.75]

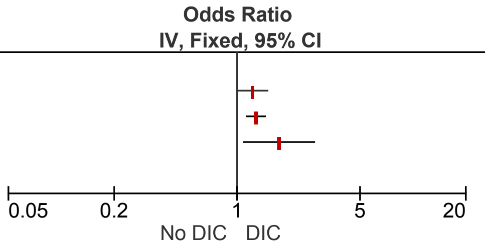
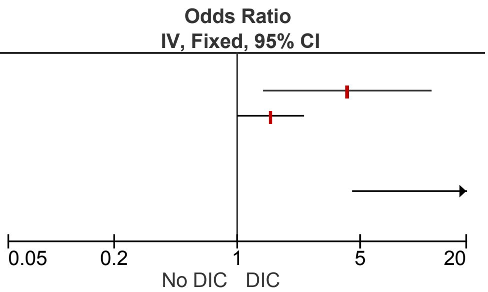


Figure 150: In-hospital mortality (multivariable and univariable analyses)

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
1.2.1 Multivariable analysis			
Gando 2007.SIRS/sepsis	1.441	0.557	4.22 [1.42, 12.59]
Ogura 2014.Severe sepsis	0.4357	0.2182	1.55 [1.01, 2.37]
1.2.2 Univariable analysis			
Gando 2007A.SIRS/sepsis	3.7013	1.1161	40.50 [4.54, 360.98]



K.7 Antimicrobial treatment

Figure 151: Mortality: <1 hour versus >1 hour, adult population

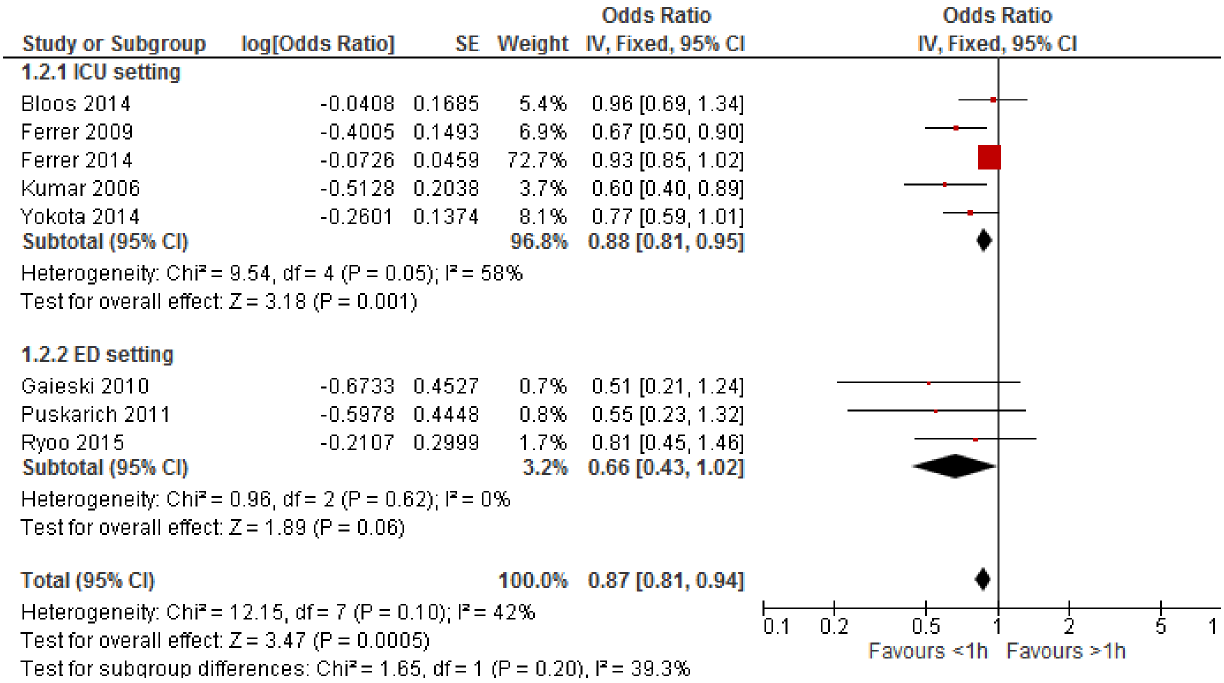


Figure 152: Mortality <2 hours versus >2 hours, adult population

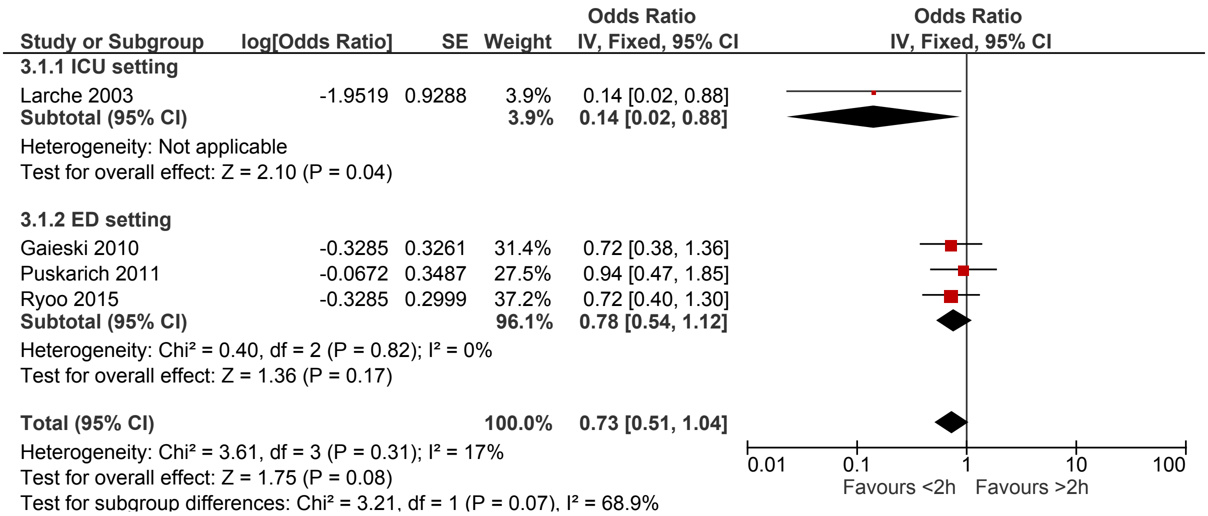


Figure 153: Mortality <3 hours versus >3 hours

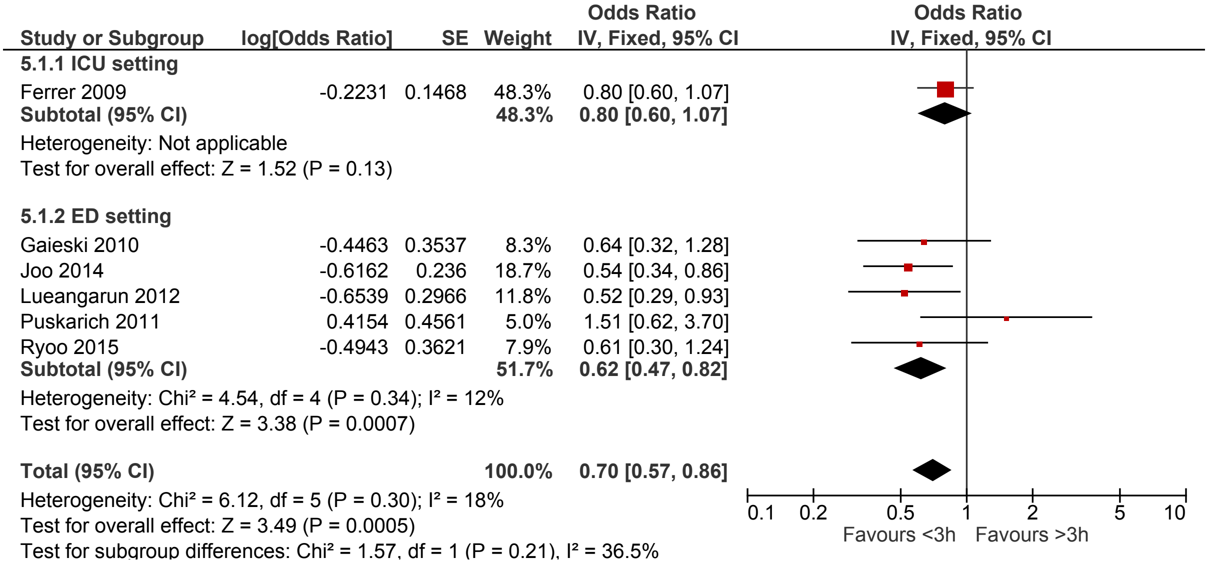


Figure 154: Mortality <4 hours versus >4 hours

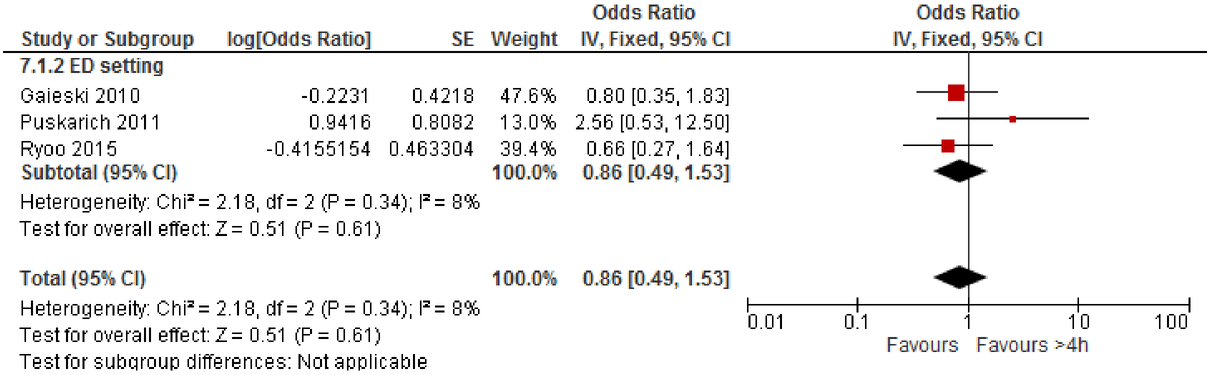


Figure 155: Mortality <5 hours versus >5 hours

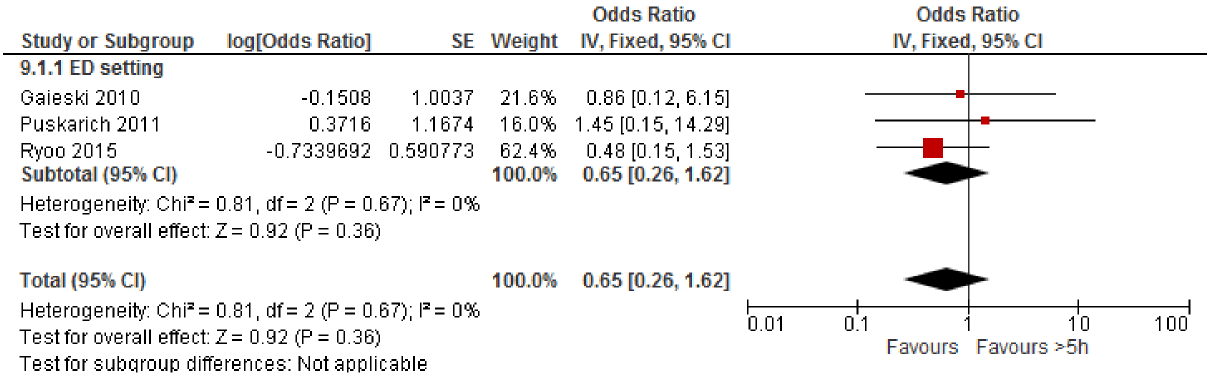
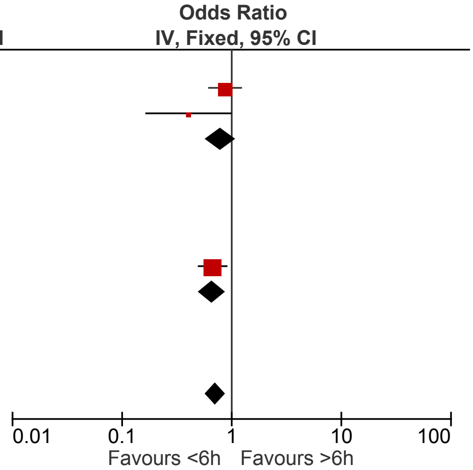


Figure 156: In-hospital mortality <6 hours versus >6 hours

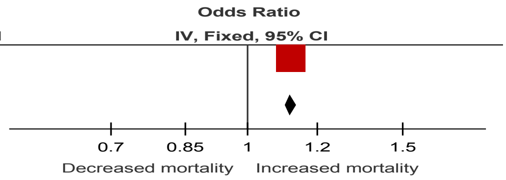
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
10.1.1 ICU setting				
Ferrer 2009	-0.1393	0.1728	40.2%	0.87 [0.62, 1.22]
Nygard 2014	-0.9088	0.4525	5.9%	0.40 [0.17, 0.98]
Subtotal (95% CI)			**46.1%**	**0.79 [0.57, 1.08]**
Heterogeneity: Chi² = 2.52, df = 1 (P = 0.11); I² = 60%				
Test for overall effect: Z = 1.47 (P = 0.14)				
10.1.2 ED setting				
Menendez 2012	-0.4005	0.1493	53.9%	0.67 [0.50, 0.90]
Subtotal (95% CI)			**53.9%**	**0.67 [0.50, 0.90]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.68 (P = 0.007)				
Total (95% CI)			**100.0%**	**0.72 [0.58, 0.90]**
Heterogeneity: Chi² = 3.08, df = 2 (P = 0.21); I² = 35%				
Test for overall effect: Z = 2.97 (P = 0.003)				
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%				



K.7.1 Hourly treatment delay

Figure 157: In-hospital mortality for hourly treatment delay

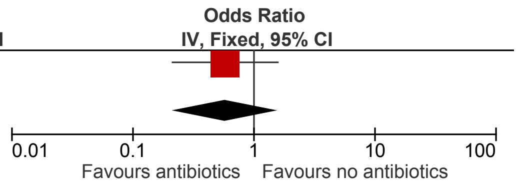
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Kumar 2006	0.1124	0.0073	100.0%	1.12 [1.10, 1.14]
Total (95% CI)			**100.0%**	**1.12 [1.10, 1.14]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 15.40 (P < 0.00001)				



K.7.2 Parenteral antibiotics prior to admission to hospital

Figure 158: Mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Cartwright 1992	-0.5473	0.5112	100.0%	0.58 [0.21, 1.58]
Total (95% CI)			**100.0%**	**0.58 [0.21, 1.58]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.07 (P = 0.28)				



K.7.3 PICU setting, paediatric population

Figure 159: PICU mortality: <1 hour versus >1 hour

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Weiss 2014	-0.5125	0.7971	100.0%	0.60 [0.13, 2.86]
Total (95% CI)			**100.0%**	**0.60 [0.13, 2.86]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.64 (P = 0.52)				

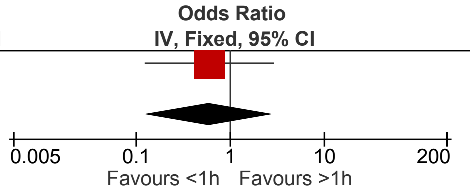


Figure 160: PICU mortality: <2 hours versus >2 hours

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Weiss 2014	-0.8867	0.6059	100.0%	0.41 [0.13, 1.35]
Total (95% CI)			**100.0%**	**0.41 [0.13, 1.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)

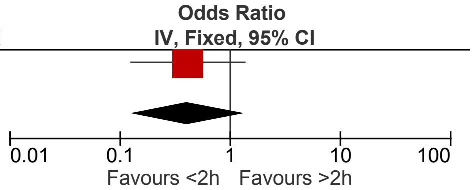


Figure 161: PICU mortality: <3 hours versus >3 hours

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Weiss 2014	-1.3665	0.575	100.0%	0.25 [0.08, 0.79]
Total (95% CI)			**100.0%**	**0.25 [0.08, 0.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)

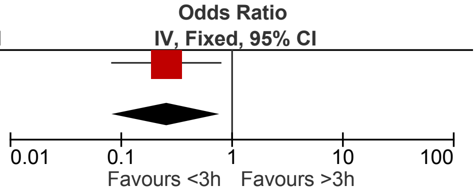
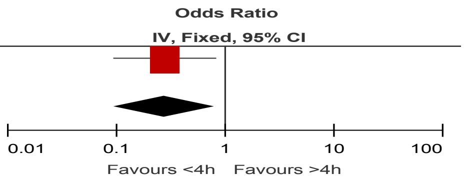


Figure 162: PICU mortality: <4 hours versus >4 hours

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Weiss 2014 (univariable)	-1.2801	0.5475	100.0%	0.28 [0.10, 0.81]
Total (95% CI)			**100.0%**	**0.28 [0.10, 0.81]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.34 (P = 0.02)



K.8 IV fluid administration

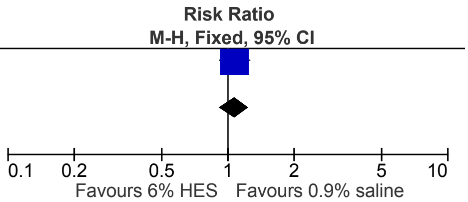
K.8.1 6% HES versus 0.9% saline in adults with sepsis

K.8.1.1 Mortality at 28 days

Figure 163: Mortality at 90 days

Study or Subgroup	6% HES Events	6% HES Total	0.9% saline Events	0.9% saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Myburgh 2012	248	976	224	945	100.0%	1.07 [0.92, 1.25]
Total (95% CI)		**976**		**945**	**100.0%**	**1.07 [0.92, 1.25]**
Total events	248		224			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)



K.8.2 Crystalloid versus colloid plus crystalloid in adults with severe sepsis

K.8.2.1 Mortality at 28 days

Figure 164: Hospital mortality

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid + crystalloid Events	Colloid + crystalloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McInthyre 2007A	101	235	121	258	100.0%	0.92 [0.75, 1.12]
Total (95% CI)		**235**		**258**	**100.0%**	**0.92 [0.75, 1.12]**
Total events	101		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						

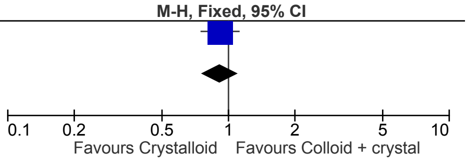
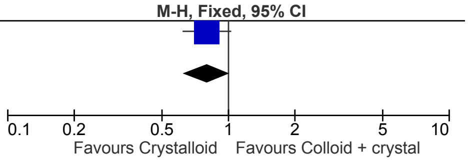


Figure 165: ICU mortality

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid + crystalloid Events	Colloid + crystalloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McInthyre 2007A	72	235	99	258	100.0%	0.80 [0.62, 1.02]
Total (95% CI)		**235**		**258**	**100.0%**	**0.80 [0.62, 1.02]**
Total events	72		99			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						

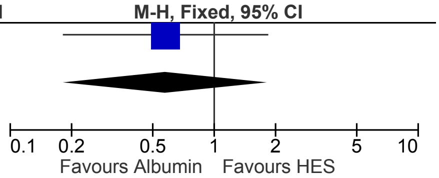


K.8.3 20% albumin versus 6% HES in adults with severe sepsis

K.8.3.1 Mortality at 28 days

Figure 166: 28-day mortality

Study or Subgroup	Albumin Events	Albumin Total	Colloid - HES Events	Colloid - HES Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dolecek 2009	4	30	6	26	100.0%	0.58 [0.18, 1.83]
Total (95% CI)		**30**		**26**	**100.0%**	**0.58 [0.18, 1.83]**
Total events	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						



K.8.4 4% albumin versus 0.9% Sodium Chloride BP in adults with severe sepsis

K.8.4.1 Mortality at 28 days

Figure 167: 28-day mortality (univariate analysis)

Study or Subgroup	Albumin Events	Albumin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SAFE 2011	185	603	217	615	100.0%	0.87 [0.74, 1.02]
Total (95% CI)		**603**		**615**	**100.0%**	**0.87 [0.74, 1.02]**
Total events	185		217			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						

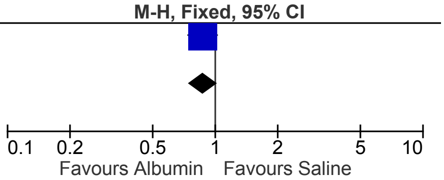
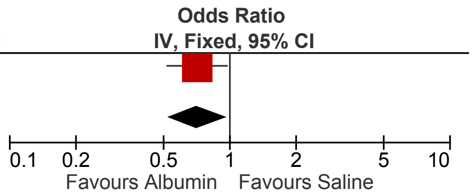


Figure 168: 28-day mortality (multivariate analysis)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
SAFE 2011	-0.3425	0.1589	100.0%	0.71 [0.52, 0.97]
Total (95% CI)			**100.0%**	**0.71 [0.52, 0.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.16 (P = 0.03)



Note: adjusted OR

K.8.5 Albumin versus crystalloids in adults with sepsis

K.8.5.1 Mortality at 28 days

Figure 169: Mortality

	Albumin		Crystalloids			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Patel 2014	710	1937	763	1941	100.0%	0.93 [0.86, 1.01]
Total (95% CI)		**1937**		**1941**	**100.0%**	**0.93 [0.86, 1.01]**
Total events	710		763			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)

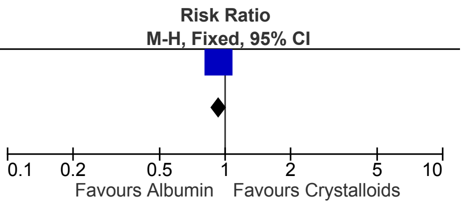
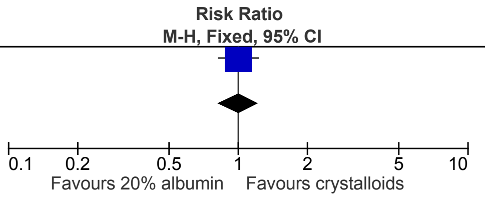


Figure 170: 90-day mortality

	Albumin		Crystalloids			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
ALBIOS 2014	115	283	116	286	100.0%	1.00 [0.82, 1.22]
Total (95% CI)		**283**		**286**	**100.0%**	**1.00 [0.82, 1.22]**
Total events	115		116			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)



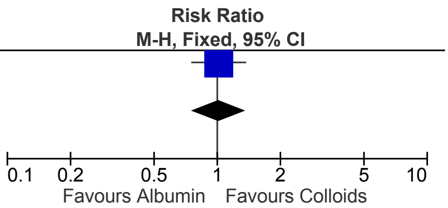
K.8.6 Albumin versus colloids in adults with sepsis

K.8.6.1 Mortality at 28 days

Figure 171: Mortality

	Albumin		Colloids			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Patel 2014	54	143	58	156	100.0%	1.02 [0.76, 1.36]
Total (95% CI)		**143**		**156**	**100.0%**	**1.02 [0.76, 1.36]**
Total events	54		58			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)



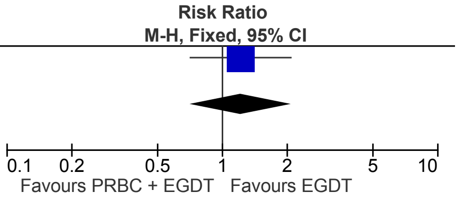
K.8.7 Packed red blood cells (PRBC) plus EGDT versus EGDT only in adults with septic shock

K.8.7.1 Mortality at 28 days

Figure 172: Hospital mortality

Study or Subgroup	PRBC + EGDT Events	PRBC + EGDT Total	EGDT Events	EGDT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fuller 2010	14	34	20	59	100.0%	1.21 [0.71, 2.08]
Total (95% CI)		**34**		**59**	**100.0%**	**1.21 [0.71, 2.08]**
Total events	14		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



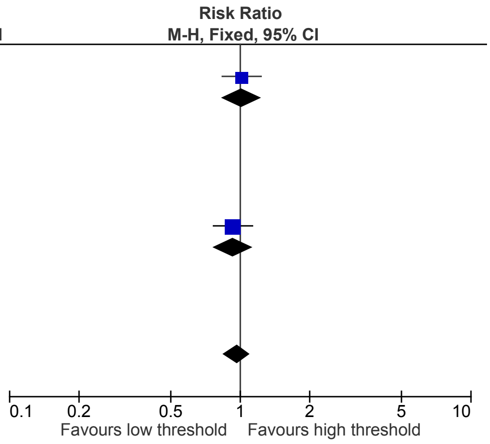
K.8.8 Red blood cells (RBC) for low threshold (≤7 g/dl) versus high threshold (≤9 g/dl) in adults with septic shock

K.8.8.1 Mortality at 28 days

Figure 173: 90-day mortality

Study or Subgroup	Low threshold Events	Low threshold Total	High threshold Events	High threshold Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 >70 years of age						
Holst 2014	93	173	98	185	42.4%	1.01 [0.84, 1.23]
Subtotal (95% CI)		**173**		**185**	**42.4%**	**1.01 [0.84, 1.23]**
Total events	93		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
11.1.2 70 years or younger						
Holst 2014	123	329	125	311	57.6%	0.93 [0.77, 1.13]
Subtotal (95% CI)		**329**		**311**	**57.6%**	**0.93 [0.77, 1.13]**
Total events	123		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**502**		**496**	**100.0%**	**0.97 [0.84, 1.11]**
Total events	216		223			

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%



K.8.9 0-2 litres versus 2-4 litres of fluid in adults with severe sepsis

K.8.9.1 Mortality at 28 days

Figure 174: Hospital mortality

Study or Subgroup	0-2L Events	0-2L Total	2-4L Events	2-4L Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McInthyre 2007A	97	210	82	186	100.0%	1.05 [0.84, 1.30]
Total (95% CI)		**210**		**186**	**100.0%**	**1.05 [0.84, 1.30]**
Total events	97		82			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)

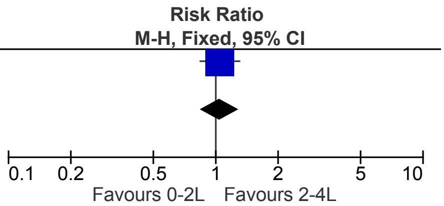
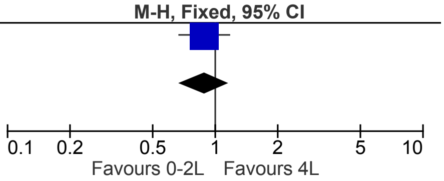


Figure 175: ICU mortality

	0-2L		2-4L			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
McInthyre 2007A	66	210	66	186	100.0%	0.89 [0.67, 1.17]	
Total (95% CI)		**210**		**186**	**100.0%**	**0.89 [0.67, 1.17]**	
Total events	66		66				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.85 (P = 0.39)							



K.8.10 0-2 litres versus >4 litres of fluids in adults with severe sepsis

K.8.10.1 Mortality at 28 days

Figure 176: Hospital mortality

	0-2L		>4L			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
McInthyre 2007A	97	210	45	100	100.0%	1.03 [0.79, 1.33]	
Total (95% CI)		**210**		**100**	**100.0%**	**1.03 [0.79, 1.33]**	
Total events	97		45				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.20 (P = 0.84)							

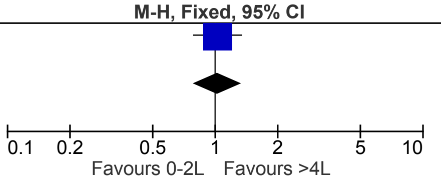
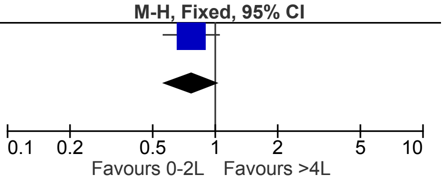


Figure 177: ICU mortality

	0-2L		>4L			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
McInthyre 2007A	66	210	41	100	100.0%	0.77 [0.56, 1.04]	
Total (95% CI)		**210**		**100**	**100.0%**	**0.77 [0.56, 1.04]**	
Total events	66		41				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.69 (P = 0.09)							



K.8.11 2-4 litres versus >4 litres of fluids in adults with severe sepsis

K.8.11.1 Mortality at 28 days

Figure 178: Hospital mortality

	2-4L		>4L			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
McInthyre 2007A	82	186	45	100	100.0%	0.98 [0.75, 1.28]	
Total (95% CI)		**186**		**100**	**100.0%**	**0.98 [0.75, 1.28]**	
Total events	82		45				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.15 (P = 0.88)							

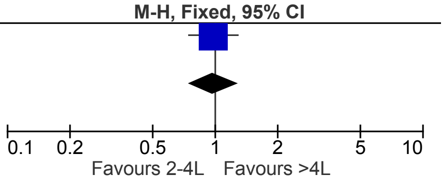
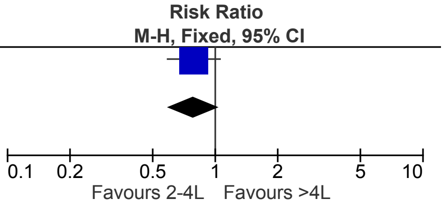


Figure 179: ICU mortality

Study or Subgroup	2-4L Events	2-4L Total	>4L Events	>4L Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McInthyre 2007A	66	186	45	100	100.0%	0.79 [0.59, 1.05]
Total (95% CI)		**186**		**100**	**100.0%**	**0.79 [0.59, 1.05]**
Total events	66		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						

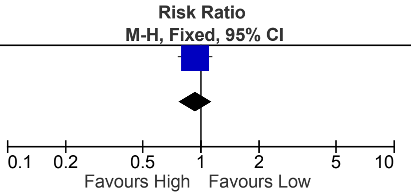


K.8.12 High volume (20-40 ml Ringer lactate/kg) versus low volume (20 ml Ringer lactate/kg) in children with septic shock

K.8.12.1 Mortality at 28 days

Figure 180: Cumulative 72-hour survival

Study or Subgroup	20-40ml RL per kg Events	20-40ml RL per kg Total	20ml RL per kg Events	20ml RL per kg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Santhanam 2008	52	74	55	73	100.0%	0.93 [0.77, 1.14]
Total (95% CI)		**74**		**73**	**100.0%**	**0.93 [0.77, 1.14]**
Total events	52		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						



K.9 Escalation of care

None.

K.10 Inotropic agents and vasopressors

K.10.1 Norepinephrine versus vasopressin for adults with septic shock

K.10.1.1 Mortality

Figure 181: 28-day mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Vasopressin Events	Vasopressin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Russell 2008	150	382	140	396	100.0%	1.11 [0.93, 1.33]
Total (95% CI)		**382**		**396**	**100.0%**	**1.11 [0.93, 1.33]**
Total events	150		140			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						

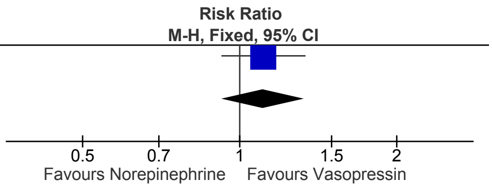


Figure 182: 90-day mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Vasopressin Events	Vasopressin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Russell 2008	188	379	172	392	100.0%	1.13 [0.97, 1.31]
Total (95% CI)		**379**		**392**	**100.0%**	**1.13 [0.97, 1.31]**
Total events	188		172			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						

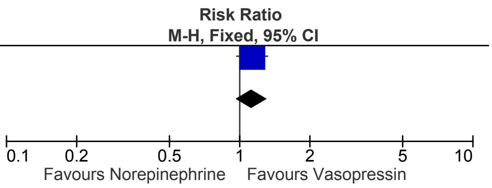
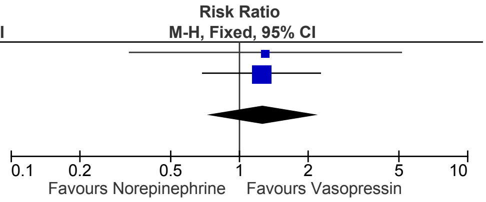


Figure 183: ICU mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Vasopressin Events	Vasopressin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lauzier 2006	3	10	3	13	24.6%	1.30 [0.33, 5.12]
Morelli 2009 (TERLIVAP)	10	15	8	15	75.4%	1.25 [0.69, 2.26]
Total (95% CI)		**25**		**28**	**100.0%**	**1.26 [0.72, 2.21]**
Total events	13		11			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						



K.10.1.2 Adverse events

Figure 184: Requiring renal replacement therapy

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Vasopressin Events	Vasopressin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morelli 2009 (TERLIVAP)	8	15	5	15	100.0%	1.60 [0.68, 3.77]
Total (95% CI)		**15**		**15**	**100.0%**	**1.60 [0.68, 3.77]**
Total events	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						

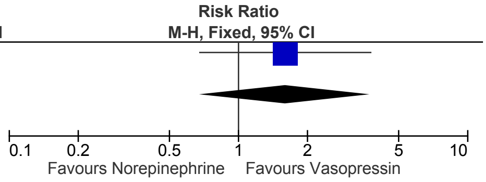
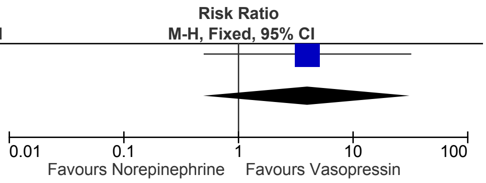


Figure 185: New onset of tachyarrhythmias

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Vasopressin Events	Vasopressin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morelli 2009 (TERLIVAP)	4	15	1	15	100.0%	4.00 [0.50, 31.74]
Total (95% CI)		**15**		**15**	**100.0%**	**4.00 [0.50, 31.74]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						



Note: this forest plot has a different scale

K.10.2 Norepinephrine versus dopamine for adults with septic shock

K.10.2.1 Mortality

Figure 186: 28-day mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Patel 2010	51	118	67	134	100.0%	0.86 [0.66, 1.13]
Total (95% CI)		**118**		**134**	**100.0%**	**0.86 [0.66, 1.13]**
Total events	51		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						

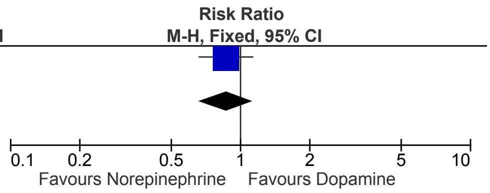


Figure 187: All-cause mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marik 1994	5	10	6	10	21.4%	0.83 [0.37, 1.85]
Mathur 2007	14	25	19	25	67.9%	0.74 [0.49, 1.11]
Ruokonen 1993	4	5	3	5	10.7%	1.33 [0.58, 3.09]
Total (95% CI)		**40**		**40**	**100.0%**	**0.82 [0.59, 1.15]**
Total events	23		28			

Heterogeneity: Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)

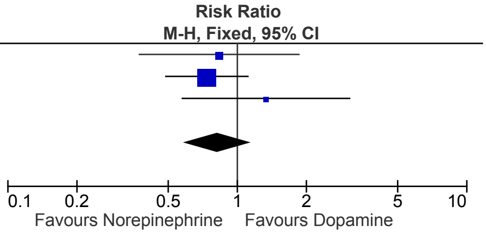
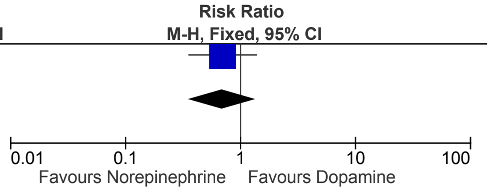


Figure 188: Hospital mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Martin 1993	7	16	10	16	100.0%	0.70 [0.36, 1.37]
Total (95% CI)		**16**		**16**	**100.0%**	**0.70 [0.36, 1.37]**
Total events	7		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)

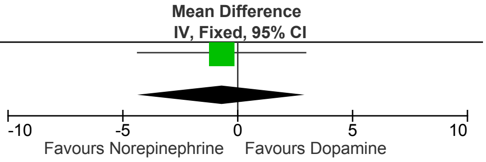


K.10.3 Duration of hospital stay

Figure 189: Length of stay in hospital

Study or Subgroup	Norepinephrine Mean	Norepinephrine SD	Norepinephrine Total	Dopamine Mean	Dopamine SD	Dopamine Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2010	13.5	13.3	118	14.2	16.3	134	100.0%	-0.70 [-4.36, 2.96]
Total (95% CI)			**118**			**134**	**100.0%**	**-0.70 [-4.36, 2.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)

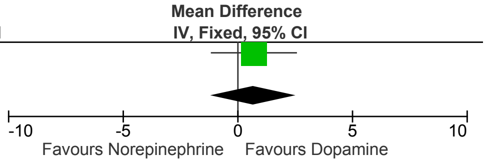


K.10.4 Duration of critical care stay

Figure 190: ICU length of stay

Study or Subgroup	Norepinephrine Mean	Norepinephrine SD	Norepinephrine Total	Dopamine Mean	Dopamine SD	Dopamine Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2010	7.5	7.6	118	6.8	7.3	134	100.0%	0.70 [-1.15, 2.55]
Total (95% CI)			**118**			**134**	**100.0%**	**0.70 [-1.15, 2.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)

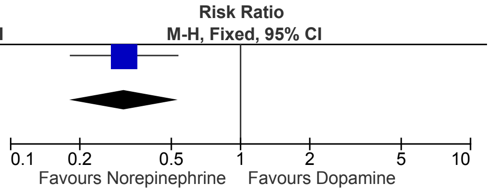


K.10.5 Adverse events

Figure 191: Incidence of arrhythmias

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Patel 2010	14	118	51	134	100.0%	0.31 [0.18, 0.53]
Total (95% CI)		**118**		**134**	**100.0%**	**0.31 [0.18, 0.53]**
Total events	14		51			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.25 (P < 0.0001)



K.10.6 Norepinephrine versus epinephrine for adults with septic shock

K.10.6.1 Mortality

Figure 192: 28-day mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Epinephrine Events	Epinephrine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Myburgh 2008	24	82	17	76	100.0%	1.31 [0.76, 2.24]
Total (95% CI)		**82**		**76**	**100.0%**	**1.31 [0.76, 2.24]**
Total events	24		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

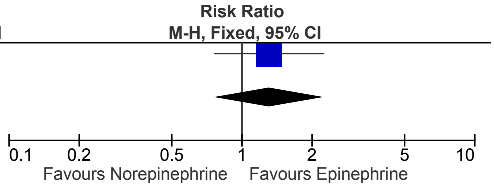
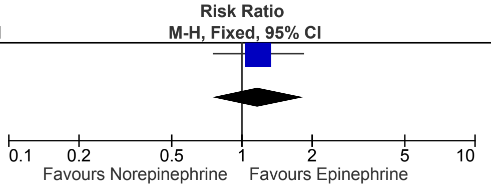


Figure 193: 90-day mortality

Study or Subgroup	Norepinephrine Events	Norepinephrine Total	Epinephrine Events	Epinephrine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Myburgh 2008	30	82	23	74	100.0%	1.18 [0.76, 1.83]
Total (95% CI)		**82**		**74**	**100.0%**	**1.18 [0.76, 1.83]**
Total events	30		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



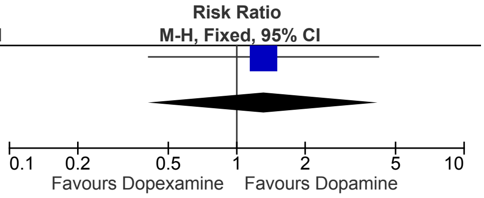
K.10.7 Dopexamine versus dopamine for adults with septic shock

K.10.7.1 Mortality at 28 days

Figure 194: 28-day mortality

Study or Subgroup	Dopexamine Events	Dopexamine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schmoelz 2006	5	20	4	21	100.0%	1.31 [0.41, 4.20]
Total (95% CI)		**20**		**21**	**100.0%**	**1.31 [0.41, 4.20]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



K.10.8 Norepinephrine plus dobutamine versus epinephrine for adults with septic shock

K.10.8.1 Mortality

Figure 195: 7-day mortality

Study or Subgroup	Norepi + dobutamine Events	Norepi + dobutamine Total	Epinephrine Events	Epinephrine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	34	169	40	161	100.0%	0.81 [0.54, 1.21]
Total (95% CI)		**169**		**161**	**100.0%**	**0.81 [0.54, 1.21]**
Total events	34		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

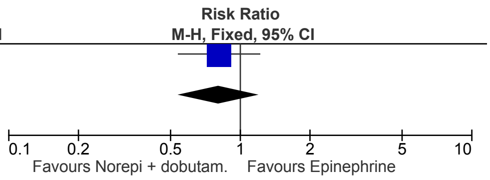


Figure 196: 14-day mortality

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	44	169	56	161	100.0%	0.75 [0.54, 1.04]
Total (95% CI)		**169**		**161**	**100.0%**	**0.75 [0.54, 1.04]**
Total events	44		56			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)

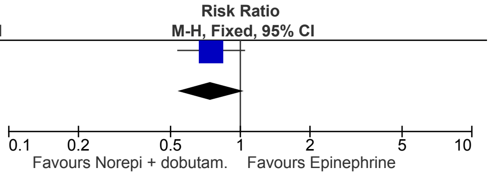


Figure 197: 28-day mortality

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	58	169	64	161	100.0%	0.86 [0.65, 1.14]
Total (95% CI)		**169**		**161**	**100.0%**	**0.86 [0.65, 1.14]**
Total events	58		64			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)

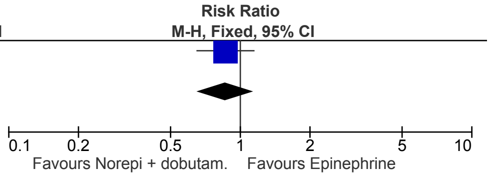


Figure 198: 90-day mortality

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	85	169	84	161	100.0%	0.96 [0.78, 1.19]
Total (95% CI)		**169**		**161**	**100.0%**	**0.96 [0.78, 1.19]**
Total events	85		84			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

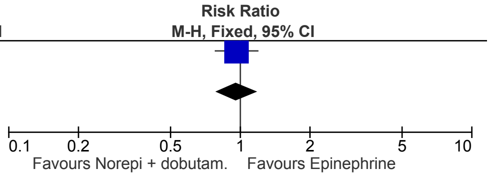


Figure 199: All-cause mortality

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Levy 1997	8	15	9	15	69.2%	0.89 [0.47, 1.67]
Seguin 2002	5	11	4	11	30.8%	1.25 [0.45, 3.45]
Total (95% CI)		**26**		**26**	**100.0%**	**1.00 [0.58, 1.71]**
Total events	13		13			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

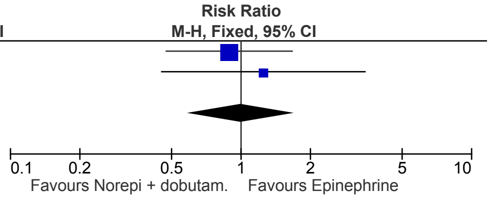


Figure 200: Mortality at discharge from the ICU

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	75	169	75	161	100.0%	0.95 [0.75, 1.21]
Total (95% CI)		**169**		**161**	**100.0%**	**0.95 [0.75, 1.21]**
Total events	75		75			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

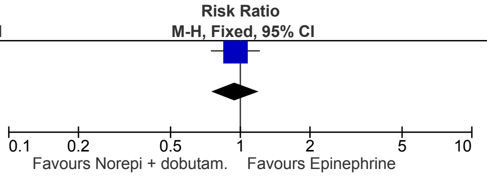
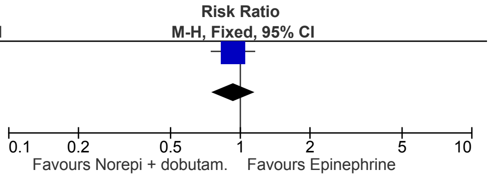


Figure 201: Mortality at discharge from the hospital

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	82	169	84	161	100.0%	0.93 [0.75, 1.15]
Total (95% CI)		**169**		**161**	**100.0%**	**0.93 [0.75, 1.15]**
Total events	82		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						



K.10.8.2 Adverse events

Figure 202: Number of adverse events during catecholamine infusion

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	41	169	43	161	100.0%	0.91 [0.63, 1.31]
Total (95% CI)		**169**		**161**	**100.0%**	**0.91 [0.63, 1.31]**
Total events	41		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						

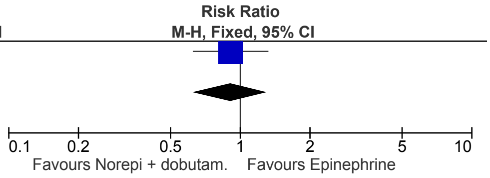
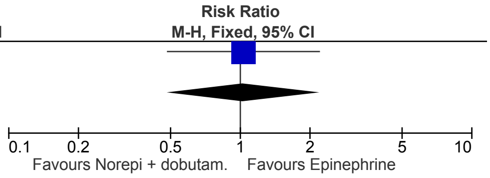


Figure 203: Number of adverse events after catecholamine infusion

Study or Subgroup	Norepi + dobutamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2007 (CATS)	13	169	12	161	100.0%	1.03 [0.49, 2.19]
Total (95% CI)		**169**		**161**	**100.0%**	**1.03 [0.49, 2.19]**
Total events	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						



K.10.9 Norepinephrine plus dopexamine versus epinephrine for adults with septic shock

K.10.9.1 Mortality

Figure 204: 28-day mortality

Study or Subgroup	Norepi + dopexamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Seguin 2006	2	12	3	10	100.0%	0.56 [0.11, 2.70]
Total (95% CI)		**12**		**10**	**100.0%**	**0.56 [0.11, 2.70]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						

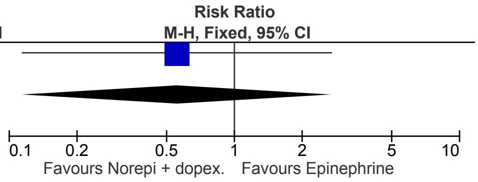
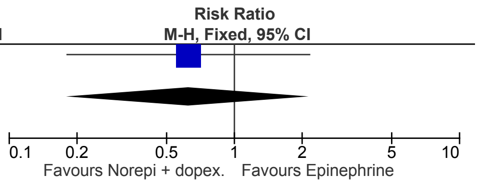


Figure 205: 90-day mortality

Study or Subgroup	Norepi + dopexamine Events	Total	Epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Seguin 2006	3	12	4	10	100.0%	0.63 [0.18, 2.16]
Total (95% CI)		**12**		**10**	**100.0%**	**0.63 [0.18, 2.16]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						



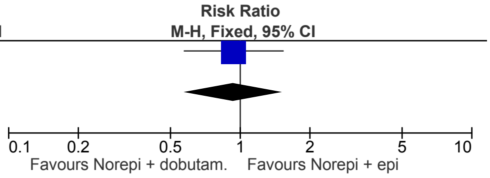
K.10.10 Norepinephrine plus epinephrine versus norepinephrine plus dobutamine for adults with septic shock

K.10.10.1 Mortality at 28 days

Figure 206: 28-day mortality

Study or Subgroup	Norepi + dobutamine Events	Total	Norepi + epi Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahmoud 2012	15	30	16	30	100.0%	0.94 [0.57, 1.53]
Total (95% CI)		**30**		**30**	**100.0%**	**0.94 [0.57, 1.53]**
Total events	15		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)



K.10.10.2 Number of organs supported

Figure 207: SOFA score at start

Study or Subgroup	Norepi + dobutamine Mean	SD	Total	Norepi + epi Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mahmoud 2012	15.2	6.4	30	14.4	5.9	30	100.0%	0.80 [-2.31, 3.91]
Total (95% CI)			**30**			**30**	**100.0%**	**0.80 [-2.31, 3.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)

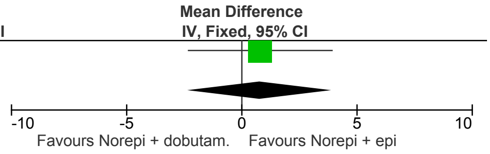


Figure 208: SOFA score at 24 hours

Study or Subgroup	Norepi + dobutamine Mean	SD	Total	Norepi + epi Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mahmoud 2012	14.6	6.1	30	13.9	6.2	30	100.0%	0.70 [-2.41, 3.81]
Total (95% CI)			**30**			**30**	**100.0%**	**0.70 [-2.41, 3.81]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

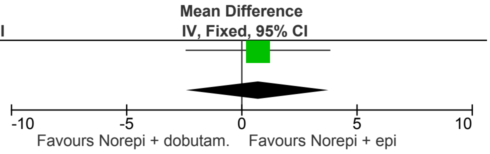


Figure 209: SOFA score at 48 hours

Study or Subgroup	Norepi + dobutamine Mean	SD	Total	Norepi + epi Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mahmoud 2012	14.4	6.3	30	13.8	5.9	30	100.0%	0.60 [-2.49, 3.69]
Total (95% CI)			**30**			**30**	**100.0%**	**0.60 [-2.49, 3.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

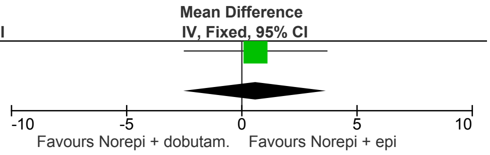


Figure 210: SOFA score at 72 hours

Study or Subgroup	Norepi + dobutamine Mean	SD	Total	Norepi + epi Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mahmoud 2012	14.1	7	30	13.5	6.1	30	100.0%	0.60 [-2.72, 3.92]
Total (95% CI)			**30**			**30**	**100.0%**	**0.60 [-2.72, 3.92]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

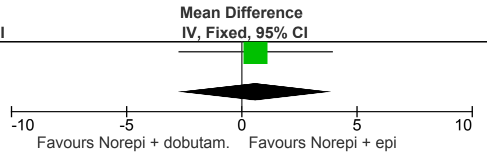
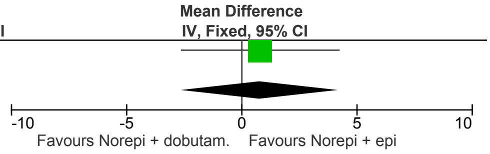


Figure 211: SOFA score at 96 hours

Study or Subgroup	Norepi + dobutamine Mean	SD	Total	Norepi + epi Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mahmoud 2012	13.5	6.9	30	12.7	6.6	30	100.0%	0.80 [-2.62, 4.22]
Total (95% CI)			**30**			**30**	**100.0%**	**0.80 [-2.62, 4.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

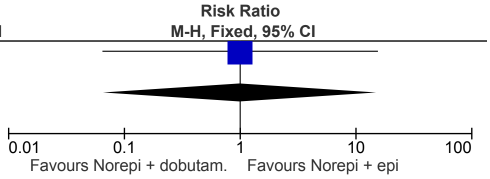


K.10.10.3 Adverse events

Figure 212: Acute coronary syndrome

Study or Subgroup	Norepi + dobutamine Events	Total	Norepi + epi Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahmoud 2012	1	30	1	30	100.0%	1.00 [0.07, 15.26]
Total (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.07, 15.26]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Note: this forest plot has a different scale

Figure 213: Arrhythmias

Study or Subgroup	Norepi + dobutamine Events	Total	Norepi + epi Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahmoud 2012	4	30	6	30	100.0%	0.67 [0.21, 2.13]
Total (95% CI)		**30**		**30**	**100.0%**	**0.67 [0.21, 2.13]**
Total events	4		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

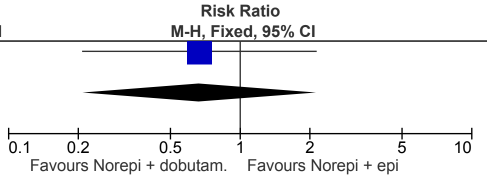


Figure 214: Cerebral stroke

Study or Subgroup	Norepi + dobutamine Events	Total	Norepi + epi Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahmoud 2012	0	30	0	30		Not estimable
Total (95% CI)		**30**		**30**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

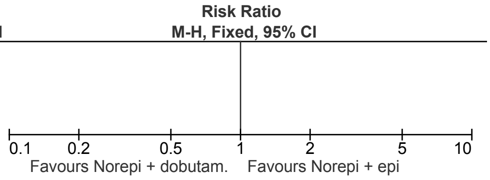
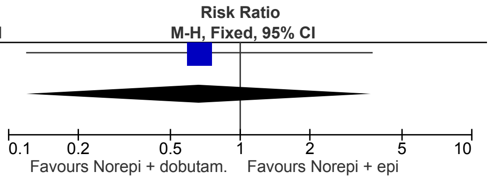


Figure 215: Limb ischaemia

Study or Subgroup	Norepi + dobutamine Events	Total	Norepi + epi Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahmoud 2012	2	30	3	30	100.0%	0.67 [0.12, 3.71]
Total (95% CI)		**30**		**30**	**100.0%**	**0.67 [0.12, 3.71]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)



K.11 Supplemental oxygen

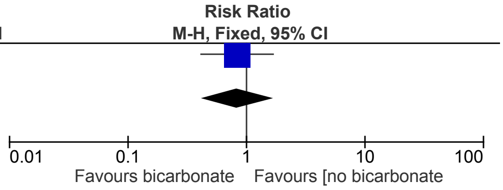
None.

K.12 Use of bicarbonate

Figure 216: Bicarbonate versus no bicarbonate in sepsis. 28-day mortality

Study or Subgroup	Bicarbonate Events	Bicarbonate Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Elsolh 2010	10	36	12	36	100.0%	0.83 [0.41, 1.68]
Total (95% CI)		**36**		**36**	**100.0%**	**0.83 [0.41, 1.68]**
Total events	10		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)



K.13 Early goal-directed therapy (EGDT)

K.13.1 The effect of EGDT versus a non-EGDT resuscitation strategy for people presenting to the ED with septic shock

K.13.1.1 Mortality

Figure 217: Primary mortality outcome of each study

Study or Subgroup	Favours EGDT Events	Favours EGDT Total	Favours Control Events	Favours Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISE Investigators 2014	147	792	150	796	28.6%	0.98 [0.80, 1.21]
Jones 2010	34	150	25	150	4.8%	1.36 [0.86, 2.16]
ProCESS Investigators 2014	92	439	167	902	20.9%	1.13 [0.90, 1.42]
ProMISe Investigators 2015	184	623	181	620	34.6%	1.01 [0.85, 1.20]
Rivers 2001	38	130	59	133	11.1%	0.66 [0.47, 0.91]
Total (95% CI)		**2134**		**2601**	**100.0%**	**1.01 [0.91, 1.12]**
Total events	495		582			

Heterogeneity: Chi² = 9.08, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 0.12 (P = 0.90)

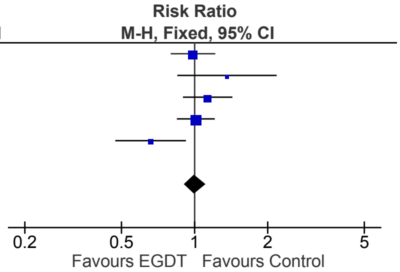
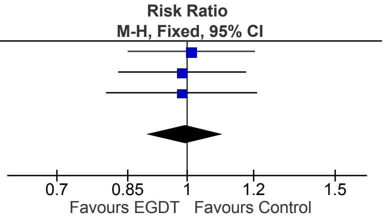


Figure 218: 90-day mortality

Study or Subgroup	Favours EGDT Events	Favours EGDT Total	Favours Control Events	Favours Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
ProMISe Investigators 2015	184	623	181	620	35.8%	1.01 [0.85, 1.20]	
ProCESS Investigators 2014	129	405	267	827	34.7%	0.99 [0.83, 1.17]	2014
ARISE Investigators 2014	147	792	150	796	29.5%	0.98 [0.80, 1.21]	2014
Total (95% CI)		**1820**		**2243**	**100.0%**	**1.00 [0.90, 1.11]**	
Total events	460		598				

Heterogeneity: Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)

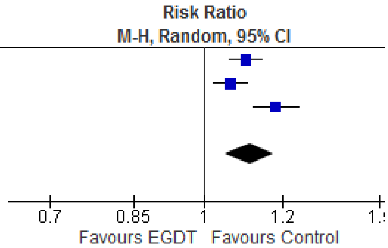


K.13.1.2 ICU Utilisation

Figure 219: ICU admission[a]

Study or Subgroup	Favours EGDT Events	Favours EGDT Total	Favours Control Events	Favours Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISE Investigators 2014	725	792	661	796	35.2%	1.10 [1.06, 1.14]
ProCESS Investigators 2014	401	439	774	902	34.8%	1.06 [1.02, 1.11]
ProMISe Investigators 2015	551	625	467	626	30.1%	1.18 [1.12, 1.25]
Total (95% CI)		**1856**		**2324**	**100.0%**	**1.11 [1.05, 1.18]**
Total events	1677		1902			

Heterogeneity: Tau² = 0.00; Chi² = 9.99, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 3.74 (P = 0.0002)

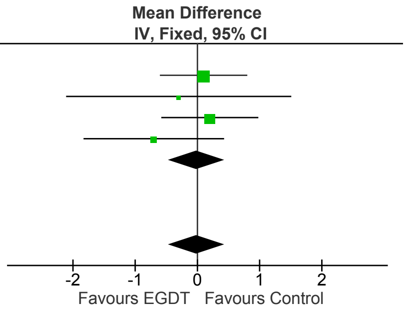


a: ICU admission refers to the rate of ICU admission from ED; 'favours EGDT means a lower ICU admission rate for the EGDT group and 'favours control' means a higher ICU admission rate for the EDGT group in the given trial.

Figure 220: ICU length of stay for patients admitted to ICU (days)

Study or Subgroup	Favours EGDT Mean	Favours EGDT SD	Favours EGDT Total	Favours Control Mean	Favours Control SD	Favours Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 New Subgroup								
ARISE Investigators 2014	4.9	7.2	725	4.8	5.9	661	42.8%	0.10 [-0.59, 0.79]
Jones 2010	5.6	7.39	150	5.9	8.46	150	6.3%	-0.30 [-2.10, 1.50]
ProCESS Investigators 2014	5.1	6.3	401	4.9	6.5	774	34.6%	0.20 [-0.57, 0.97]
ProMISe Investigators 2015	5.7	8.1	549	6.4	9.8	466	16.3%	-0.70 [-1.82, 0.42]
Subtotal (95% CI)			**1825**			**2051**	**100.0%**	**-0.02 [-0.47, 0.43]**
Heterogeneity: Chi² = 1.94, df = 3 (P = 0.58); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
Total (95% CI)			**1825**			**2051**	**100.0%**	**-0.02 [-0.47, 0.43]**

Heterogeneity: Chi² = 1.94, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable



K.14 Monitoring

None.

K.15 Patient education, information and support

None.

K.16 Training and education

None.

Appendix L: Excluded clinical studies

L.1 Scoring systems

Table 35: Studies excluded from the clinical review

Reference	Reason for exclusion
Adrie 2009[27]	Setting (ICU)
Acharya 2007[18]	Setting (ICU)
Ait-Oufella 2011[42]	Setting (ICU)
Alberti 2005[59]	Setting (ICU)
Alsous 2000[70]	Setting (ICU)
Anon 1999[1]	Not scoring tool
Arnell 1996[96]	Setting (ICU)
Arregui 1991[99]	Setting (ICU)
Artero 2010[101]	Setting (ICU)
Ausania 2015[106]	Not scoring tool
Bagshaw 2012[120]	Not scoring tool (biomarkers)
Bains 2012[131]	Not scoring tool
Bang 2005[138]	Not scoring tool
Barriere 1995[149]	Systematic review including ICU setting
Baumgartner 1992[157]	Setting (ICU)
Bassetti 2014[153]	Setting (ICU)
Bayer 2015[160]	Development of a new scoring system, not externally validated
Beck 2014[163]	Setting (ICU)
Behdad 2006[164]	Population
Bencosme 1996[169]	Setting (ICU)
Billeter 2009[189]	Outcomes not analysed for scoring tool
Bleeker 2001[192]	Not scoring tool
Boniatti 2011[212]	Setting (ICU)
Bonig 2000[213]	Setting (ICU)
Brunkhorst 2000[234]	Diagnostic accuracy of PCY, not a scoring system
Buist 2000[238]	Setting (ICU)
Byrne 1989[244]	Not scoring tool (theory behind the development of ASESPSIS)
Calle 2012[248]	Systematic review with different protocol
Calvano 1998[249]	Setting (surgical ICU)
Chan 2005[279]	Setting (ICU)
Charles 2008[285]	Setting (ICU)
Chawla 2007[288]	Setting (ICU)
Chen 2011[298]	Setting (ICU)
Chen 2006B[292]	Setting (ICU)
Chen 1994[291]	Setting (SICU)
Chen 2012[296]	Outcomes not analysed in relation to scoring tool
Close 2011[319]	Not scoring tool

Reference	Reason for exclusion
Coslovsky 2015[332]	Development of a new scoring system, not externally validated
Cook 1992[327]	Setting (ICU)
Couto-Alves 2013[334]	Setting (PICU)
Croce 1992[336]	Setting (post-trauma). Outcomes not analysed in relation to scores at admission
Dabar 2015[345]	Comparison
Dabhi 2014[346]	Setting (ICU)
Das 2014[353]	Setting and when scores taken (post-surgical)
De Azevedo 2015[357]	Setting (ICU)
Deleon 2005[363]	Setting (PICU)
Dellinger 1988[375]	Setting (ICU)
Derkx 1996 [378]	Setting (ICU)
Desai 2013[379]	Setting (MICU)
Eisen 2006[411]	Not scoring system
Elias 2015[416]	Setting (ICU)
Emparanza 1988[419]	Setting (PICU)
Escobar 2014[429]	Score immediately after birth (prior to hospital discharge)
Feng 2013[446]	Setting (ICU)
Flores 2001[461]	Setting (ICU)
Furtado 2012[472]	Setting (ICU)
Garcia Paez 2008[484]	Not scoring system
Giamarellos-Bourboulis 2012 [498]	Setting (ICU)
Gogos 2003[505]	Not scoring system
Goitein 1985[506]	Setting (PICU)
Granja 2013[516]	Setting (ICU)
Grozdanovski 2012[522]	Setting (ICU)
Hachimi-Idrissi 1998[543]	Setting (ICU)
Han 2006[550]	Narrative review
Henry 2015[561]	Setting (ICU)
Hillas 2010[572]	Setting (ICU)
Hoen 1993[578]	Not scoring system
Holme 2013[579]	Setting (NICU), population (neonates)
Inal 2009[597]	Setting (ICU)
Jaimes 2005[609]	Outcomes not analysed
Jiang 2015[622]	Setting (ICU)
Jones 2008[627]	Incorrect study design
Kaur 2014[643]	Setting (PICU)
Kellner 2013[647]	Setting (ICU)
Khwannimit 2009[657]	Setting (ICU)
Kumar 2003[691]	Setting (ICU included in outcome with ward)
Landesberg 2015[706]	No prognostic scores
Legall 1993[713]	Setting (ICU)
Lee 1993[716]	Setting (ICU)

Reference	Reason for exclusion
Maher 1989[759]	Setting (ICU)
Marra 2006a[774]	Setting (ICU)
Marshall 2014[776]	Narrative review
McGillicuddy 2009[791]	Not diagnostic accuracy of a scoring system
Mei 2007[796]	Not diagnostic accuracy of a scoring system
Mohan 2015[815]	Setting (ICU)
Moreno 1999[824]	Setting (ICU)
Naved 2011[842]	Setting (ICU)
Oda 2000[870]	Setting (ICU)
Paul 2006[904]	Development of a new scoring system, not externally validated
Paul 2007A[906]	Not mortality predictor
Pilz 1991[921]	Not a study
Pollock 1991[927]	Setting (PICU)
Pollock 1997[926]	Setting (PICU)
Presterl 1997[936]	Setting (ICU)
Que 2015[946]	Setting (ICU)
Rhee 2009[966]	Setting (ICU)
Richards 2011[967]	Setting (ICU)
Rixen 1996[974]	Setting (ICU)
LeGall1993[713]	Setting (ICU)
Rogy 1996[982]	Setting (surgical ICU)
Rosenberg 2002[987]	Setting (ICU)
Routsi 2007[989]	Setting (ICU)
Shapiro 2009[1025]	Not scoring tool
Silva 2001a[1038]	Setting (PICU)
Smith 2008[1047]	Systematic review with different protocol
Smith 2008B[1048]	Systematic review with different protocol
Tafelski 2015[1086]	Setting (ICU)
Tsai 2014 [1106]	Not a scoring tool
Ueda 2014[1116]	Setting (ICU)
Umscheid 2015[1119]	Development of a new scoring system, not externally validated
van de Voorde 2013 [1121]	Outcomes not analysed in relation to scoring tool
Vincent 2011 [1144]	Outcomes not analysed in relation to scores at admission
Vincent 2011A[1144]	Changes in score not analysed in regards to admission
Vincent 1996 [1143]	Not a study
Vincent 2003[1145]	Not a study
Viallon 2008[1141]	Not scoring tool
Wang 2010[1158]	Setting (ICU)
Wilson 1990[1172]	Setting (post-surgical). Outcomes not analysed in relation to scores at admission
Wong 2008[1179]	Setting (PICU)
Wong 2014[1180]	Setting (PICU)
Wunder 2004[1181]	Setting (ICU)

L.2 Signs and symptoms

Table 36: Studies excluded from the clinical review

Reference	Reason for exclusion
Aalto 2004[10]	No relevant outcomes and does not match review question (blood test)
Abrahamsen 2013[14]	No relevant outcomes
Abudu 2002[15]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Acosta 2012 [19]	Inappropriate study design (case control)
Adam 2013 [20]	Not a study
Adams 1993[22]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes) Incorrect study design (case-control study)
Adejuyigbe 2001[23]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Aebi 1996[29]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Ahkee 1997[34]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Ahn 2013A[37]	No relevant outcomes and does not match review question (blood test)
Aina-Mumuney 2007[40]	No relevant outcomes and does not match review question (foetal monitoring on neonatal outcomes) Incorrect study design (case-control study)
Akpede 1993[44]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Akpede 1994[43]	No relevant outcomes and does not match review question (prediction of meningitis in children with fever and seizure)
Al Jarousha 2008[46]	Incorrect study design (case-control study)
Alam 2014 [52]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Alberti 2005[59]	No relevant outcomes
Alexander 1998[61]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Alexander 1999[62]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Aliberti 2008[65]	No relevant outcomes and does not match review question (prediction of clinical failure related to CAP)
Aliberti 2015 [64]	No relevant outcomes and does not match review question
Almuneef 2000[67]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Altunhan 2011[71]	No relevant outcomes and does not match review question (diagnostic accuracy of PCT)
Alves 2010[73]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Alves 2011[72]	No relevant outcomes and does not match review question (no signs and symptoms considered)

Reference	Reason for exclusion
Ammann 2013 [75]	Setting not relevant.
Andersen 2004[78]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Andrews 2012[82]	Systematic review with different protocol
Angsuwat 2010 [84]	No analysis on relevant outcomes.
Anon 2007[3]	Abstract only
Antonow 1998 [86]	No relevant outcomes and does not match review question (inappropriate comparisons)
Ariffin 2002[92]	No relevant outcomes
Arsura 1998 [100]	No relevant outcomes and does not match review question (RDS). Sample size
Asiimwe 2015 [102]	No relevant analysis (no predictor analysis)
Ayoola 2003[112]	No relevant analysis.
Babay 2005[113]	No relevant outcomes and does not match review question (not a prognostic study; 8% of patients had sepsis)
Bagshaw 2007 [129]	No analysis on relevant outcomes. No relevant outcomes and does not match review question
Bagshaw 2008[126]	No relevant outcomes and does not match review question (sepsis as risk factor for acute kidney injury)
Bang 2005b[137]	No relevant analysis.
Barati 2013[141]	No relevant outcomes and does not match review question (diagnostic accuracy of brain natriuretic peptide)
Barie 2004[145]	No relevant outcomes and does not match review question (identification of source of infection)
Barnaby 2002[146]	No relevant outcomes
Bas 2011[151]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Baskaran 2008[152]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Bastos 1993[154]	Does not match review question (GCS as predictor of mortality in any non-traumatic ICU admission; 3% had sepsis)
Bayer 2015 [160]	No relevant analysis (no signs and symptoms analysed)
Bejan 2014A[166]	No relevant analysis.
Bekhof 2013[167]	Population does not match protocol (preterm infants)
Benito 2013[172]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests)
Bernstein 2007[181]	No relevant outcomes and does not match review question (diagnostic accuracy of PCT)
Bettiol 2012[182]	Cochrane review
Bettiol 2012[183]	Cochrane review
Beuchee 2009[184]	Population does not match protocol (preterm infants)
Bilavsky 2009 [187]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests)
Bilbault 2004[188]	Does not match review question (gene expression)
Bizzarro 2011 [190]	No relevant outcomes and does not match review question (RDS)
Bleeker 2007[191]	Does not match review question (diagnostic accuracy of a tool to predict bacteraemia)

Reference	Reason for exclusion
Bochicchio 2001[195]	Does not match review question (SIRS score to predict risk of infection)
Bochud 1994 [196]	Systematic review with different protocol
Boersma 1999[197]	Does not match review question (review on discriminant rules to predict mortality in patients with community acquired pneumonia)
Bogar 2006[198]	Does not match review question (diagnostic accuracy of PCT and leucocyte anti-sedimentation rate to predict bacteraemia)
Boland 1994[200]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Bonadio 1990[207]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Bonadio 1992[209]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests to predict serious bacterial infection)
Bonadio 1993[206]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Bonadio 1993B[210]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered, identification of pathogen)
Bonadio 1993C[208]	No relevant outcomes and does not match review question (diagnostic accuracy of Young Infant Observation Scale to predict infection)
Bonig 2000[213]	Does not match review question (blood tests)
Bonsu 2003[214]	Does not match review question (diagnostic accuracy of WBC to predict bacteraemia)
Boockvar 2013 [215]	No relevant outcomes and does not match review question (predictors of delirium)
Bossink 1998[220]	No relevant outcomes
Bossink 1999[217]	No relevant outcomes and does not match review question (development of model)
Bossink 2001[218]	No relevant outcomes
Bozzetti 1991[223]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Bressan 2012[228]	Does not match review question (diagnostic accuracy of PCT, CRP, WBC to predict serious bacterial infection)
Bressan 2012A[227]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Breuling 2015 [229]	No relevant analysis (no diagnostic accuracy data)
Brunkhorst 2000[234]	No relevant outcomes and does not match review question (diagnostic accuracy of PCT)
Byer 2006[242]	Does not match review question (prediction of hypotension or toxic shock syndrome in patients with fever and erythroderma)
Caksen 2000[245]	No relevant outcomes and does not match review question (distribution of patients according to symptoms for septic arthritis and osteomyelitis)
Caljouw 2011 [247]	No relevant outcomes and does not match review question
Carbonell 2008 [251]	No relevant outcomes and does not match review question
Carrieri 2003 [255]	No relevant outcomes and does not match review question
Chaboyer 2008[273]	Does not match review question (prediction of adverse events after discharge from ICU; sepsis: 22%)
Chan 2014[280]	No relevant outcomes and does not match review question (biomarker profiling for the prediction of neutropenic fever)

Reference	Reason for exclusion
Chassagne 1996[286]	Incorrect analysis (no data given to validate summary results)
Chen 1992 [289]	No relevant outcomes and does not match review question
Chen 2002[293]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Chen 2007[300]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Chen 2012B[299]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Chen 2014 [290]	No relevant outcomes and does not match review question
Chia 1991[303]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Chisti 2010[306]	Population not relevant (those with diarrhoea only in Bangladesh)
Chiu 1997[307]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Churgay 1994[311]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Chwals 1994[313]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests)
Clemmer 1992[318]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Coburn 2012 [321]	Systematic review with different protocol.
Comstedt 2009[325]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Corona 2004 [329]	No relevant outcomes and does not match review question
Craig 2010 [335]	Outcomes reported only in figure.
D'Orio 1990[342]	No relevant outcomes.
da Silvia 2007 [343]	No relevant outcomes and does not match review question (diagnostic accuracy of PCT)
Dalegrave 2012[347]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Damas 1997[350]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Daoud 1995 [352]	No relevant outcomes and does not match review question
Day 1992[356]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
de Macedo 2003[364]	No relevant outcomes.
De 2013[370]	No relevant outcomes and does not match review question (review traffic light system for predicting serious bacterial infections)
De2014[371]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests to predict serious bacterial infection)
Devaux 1992[383]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Dewhurst 2008[386]	Population does not match protocol (preterm infants)
Dickinson 2010[389]	Incorrect study design (narrative review)
Diepold 2008[390]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests: IL-6 and IL-8)
Dior 2014[393]	No relevant outcomes and does not match review question (maternal risk

Reference	Reason for exclusion
	factors on neonatal outcomes)
Dorio 1990[342]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Drewry 2013[398]	Incorrect study design (case-control study)
Drewry 2015 [399]	No relevant analysis (no predictor analysis)
Drvar 2013 [402]	No relevant outcomes and does not match review question
Dunser 2009[408]	No relevant outcomes reported
Dwyer 2011[409]	No relevant outcomes and does not match review question (diagnostic accuracy of prediction rules)
Ebersoldt 2007[410]	Systematic review with different protocol
Elbanks 1993[433]	No relevant outcomes and does not match review question
Elting 1992[418]	No relevant outcomes and does not match review question
Escobar 2000[428]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Fairchild 2010[437]	Incorrect study design (narrative paper)
Fairchild 2013A[436]	Incorrect study design (narrative paper)
Falguera 2009[439]	No relevant outcomes
Farley 1993[442]	No relevant outcomes and does not match review question
Fernandez-Perez 2005[447]	Review with different protocol
Fialkow 2006 [451]	No relevant outcomes and does not match review question
Figueroa-Damian 1999 [452]	No relevant outcomes and does not match review question
Filbin 2014 [453]	No relevant outcomes and does not match review question
Finfer 2004 [454]	No relevant outcomes and does not match review question
Fleming 2011[460]	Does not match protocol (no relevant analysis or outcomes)
Fok 1998 [463]	No relevant outcomes and does not match review question (RDS). Setting not relevant
Galanakis 2002[474]	No relevant outcomes and does not match review question (RDS)
Galetto-Lacour 2010[475]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests to predict serious bacterial infection)
Gallagher 1994[476]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Garra 2005[490]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Gavazzi 2005[491]	No relevant outcomes and does not match review question (no signs and symptoms considered)
George 1997 [492]	No relevant outcomes and does not match review question (predictors of delirium)
Ghiorghis 1992[496]	Incorrect study design (case-control study)
Gille-Johnson 2012[500]	No relevant outcome
Goerlich 2014[504]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Gogos 2003[505]	Does not match protocol (no relevant analysis or outcomes)
Goulet 2014[513]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Grander 2013[514]	Does not match review question (prediction of mortality from critical illness, 8% sepsis)

Reference	Reason for exclusion
Griffin 2005[518]	No relevant outcomes (results from multivariable analysis available in graphic form only)
Griffin 2007[519]	No relevant outcomes (results from multivariable analysis available in graphic form only)
Guo 2015 [534]	No relevant population (not people with sepsis)
Haj-Hassan 2011[545]	No relevant outcome
Hashavya 2001[556]	No relevant outcomes and does not match review question (blood test)
Hazan 2014[558]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests to predict serious bacterial infection)
Herbst 1997[564]	No relevant outcomes and does not match review question (maternal risk factors on neonatal outcomes)
Hernandez 2012[566]	No relevant outcomes and does not match review question (predictors of resuscitation)
Horeczko 2013[584]	No relevant outcomes and does not match review question
Housinger 1993 [588]	No relevant outcomes and does not match review question (blood test)
Hsiao 2006 [590]	Outcomes not relevant (no analysis)
Ireland 2014 [599]	No relevant outcomes and does not match review question (maternal predictors). Inappropriate comparison
Isfandiaty 2012[602]	No relevant outcomes and does not match review question (sepsis as a predictor of delirium)
Ismail 1997[604]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered; prediction of nosocomial bacteraemia)
Iwashyna 2012[605]	No relevant outcomes and does not match review question
Jacobs 1990A[607]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Jain 2003[610]	No relevant outcomes and does not match review question
Jeddi 2010[618]	No relevant outcomes and does not match review question (diagnostic accuracy of blood tests)
Juncal 2011[631]	No relevant outcomes
Karambin 2011 [638]	No relevant outcomes and does not match review question
Katsimpardi 2006[640]	Does not match review question (assessment of infectious complications in paediatric patients with acute lymphoblastic leukaemia)
Kayange 2010[644]	No relevant outcomes and does not match review question (inappropriate comparison)
Khaskheli 2013[652]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Khassawneh 2009[654]	No relevant outcomes and does not match review question (inappropriate comparison)
Khurana 2011[656]	No relevant outcomes and does not match review question
Kibuuka 2015[658]	Incorrect population (malaria population)
Kim 2011A[665]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Kimmoun 2013[669]	No relevant outcomes
Landesberg 2012[705]	No relevant outcomes
Lannergard 2009[707]	Does not match review question (evaluation of biomarkers as prognostic tools for the decision to stop antibiotic therapy or to investigate oral step-down therapy after an initial course of empiric intravenous cefuroxime or

Reference	Reason for exclusion
	a combination of cefuroxime and tobramycin)
Laterre 2005[710]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Laupland 2012[711]	No relevant outcomes
LeDoux 2000[714]	No relevant outcomes and does not match review question (effect of vasopressor therapy)
Lefrant 2010 [719]	No relevant outcomes and does not match review question (scoring tool)
Leichtle 2013[720]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Levy 2005[723]	No relevant outcomes and does not match review question
Liaw 1997[726]	No relevant outcomes and does not match review question
Lim 2012 [728]	Inappropriate population (pre-term infants)
Mann-Salinas 2013[765]	Incorrect study design (case-control study)
Mesquida 2012[801]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Metsvaht 2009 [803]	No relevant outcomes and does not match review question (antimicrobial)
Mikkelsen 2013 [808]	No relevant outcomes and does not match review question (development of ARDS in patients with sepsis)
Mitra 1993 [813]	Setting not relevant
Mobin 2012[814]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Nimri 2001[860]	No relevant outcomes and does not match review question (no signs and symptoms considered)
O'Leary 2015[865]	Incorrect population
Oostenbrink 2012[879]	No relevant outcomes
Ozalay 2006[889]	No relevant analysis
Papaioannou 2012[891]	No relevant outcomes reported
Piazza 2004 [920]	No relevant outcomes and does not match review question
Pontet 2003[928]	No relevant outcomes reported
Pope 2010[929]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Quach 2008 [944]	No relevant outcomes and does not match review question (scoring tool)
Rackoff 1996[947]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Ranes 2006[950]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Razzaq 2013[957]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Rehman 2014[959]	Incorrect study design (narrative study)
Ronco 1994 [983]	No analysis of relevant variables
Santolaya 2008[1000]	No relevant outcomes and does not match review question (prognostic value of blood tests)
Schultz 2013[1010]	No relevant outcomes reported
Sevastos 2008[1021]	No relevant outcomes and does not match review question
Shani 2008[1022]	No relevant outcomes and does not match review question (RDS)

Reference	Reason for exclusion
Shapiro 2009[1025]	Does not match protocol (sepsis scores)
Singh 2003[1043]	Population does not match protocol (preterm infants)
Sirvent 2013 [1044]	No relevant outcomes and does not match review question (scoring tool)
Smith 1997[1052]	No relevant outcomes and does not match review question (review to determine the rate of bacteraemia in women with pyelonephritis)
Sole-vidan 2011[1054]	No relevant outcomes and does not match review question
Somogyi-Zalud 2000 [1057]	No relevant outcomes and does not match review question
Spanos 2010[1062]	No relevant outcomes
Spruijt 2013[1064]	No relevant outcomes
Sprung 2006[1065]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Stathakis 2007[1066]	No relevant outcomes and does not match review question (no signs and symptoms considered, only blood markers)
Struelens 1991[1071]	Incorrect study design (case-control study)
Suchyta 1997[1079]	No relevant outcomes and does not match review question
Tayek 2012[1091]	Review with different protocol
Thai 2012[1095]	No relevant outcomes and does not match review question
Thompson 2009[1097]	Case study
Thompson 2010[1096]	Editorial
Torres 1991[1100]	Review with different protocol.
Toweill 2000[1102]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Tsering 2011[1110]	No relevant outcomes and does not match review question
Van den Bruel 2010[1123]	Systematic review
Vandissel 2005[1125]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Venugopal 2012[1139]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Vyles 2014[1150]	No relevant outcomes and does not match review question (no uni- or multi-variable analysis for signs and symptoms considered)
Wang 2009[1157]	No relevant outcomes and does not match review question (predicting mortality in patients with bacteraemia)
Waskerwitz 1981[1161]	No relevant outcomes and does not match review question (no signs and symptoms considered)
Wojkowskamach 2012[1176]	Inappropriate population (hospitalised LBW newborns)
Xi 2010[1182]	No relevant outcomes and does not match review question (inappropriate comparisons)
Yahav 2015[1186]	No relevant analysis (no analysis of predictors)
Yang 2013[1192]	No relevant outcomes and does not match review question (ARDS)
Yossuck 2002[1201]	Inappropriate population (newborn)
Yu 2011[1202]	No relevant outcomes and does not match review question (blood test)
Zaidi 1999[1204]	No relevant outcomes and does not match review question

L.3 Blood tests

Table 37: Studies excluded from the clinical review

Study	Exclusion reason
Abdollahi 2012[12]	Invalid country
Aboud 2010[13]	Case-control study
Adamik 2000[21]	Invalid diagnostic tests
Adhikari 1986[24]	Invalid outcomes
Adib 2012[25]	Invalid country
Agrawal 2008[32]	Invalid country
Agyeman 2011[33]	Invalid population
Ahmed 2005[35]	Invalid country
Ahn 2012[36]	Invalid diagnostic tests
Aikawa 2005[38]	Invalid population
Aimoto 2014[39]	Invalid population
Al 2011[47]	Invalid diagnostic tests
Alamgir 2006[55]	Invalid analysis
Albright 2015[60]	Invalid diagnostic tests
Al-Majali 2004[48]	Invalid country
Al-Nawas 1996[49]	Invalid outcomes
Al-Nawas 1996A[50]	Procalcitonin
Altunhan 2011[71]	Invalid country
Alves 2010[73]	Invalid diagnostic tests
Al-Zwaini 2009[51]	Invalid country
Ambalavanan 2005[74]	Invalid population
Anbar 1986[77]	Invalid outcomes
Ando 2012[79]	Invalid analysis
Anwer 2000[88]	Invalid country
Aquino 2012[90]	Invalid outcomes
Arkader 2006[93]	Invalid country
Arnalich 1999[95]	No prognostic or diagnostic data
Arnon 2007[98]	Invalid analysis
Aube 1992[105]	Published before 1999
Aydemir 2014[109]	Invalid country
Aydin 2013[111]	Invalid country
Aydin 2014[110]	Invalid country
Bakker 1996[132]	No data given
Balci 2003[133]	Invalid country
Ballot 2004[135]	Procalcitonin
Baorto 2001[140]	Invalid population
Barati 2008[143]	Procalcitonin
Barati 2015[142]	Invalid country
Baron 1989[148]	Invalid outcomes
Bates 1990[156]	Invalid outcomes
Becchi 2008[161]	Invalid outcomes
Bender 2008[171]	Procalcitonin
Benitz 1998[173]	Invalid setting
Benuck 1983[175]	Invalid outcomes
Berger 1995[176]	Invalid setting
Berkman 2009[179]	Invalid diagnostic tests
Bernstein 2007[181]	Invalid outcomes
Bhaandari 2014[185]	Invalid diagnostic tests
Bianchi 2004[186]	Invalid country

Bleeker 2001[192]	Invalid analysis
Blommendahl 2002[193]	Invalid population
Bloos 2014[194]	Narrative review
Bojic 2014[199]	Invalid country
Boskabadi 2010[216]	Case-control study
Bossink 1998[220]	Published before 1999
Bossink 1999A[219]	Invalid diagnostic tests
Bossink 2001[218]	Invalid outcomes
Brierley 2009[230]	Narrative review
Brodska 2009[231]	Procalcitonin
Broner 1990[233]	Invalid setting
Buck 1994[236]	Invalid population
Byl 1997[243]	Published before 1999
Caldas 2008[246]	Not English
Calvano 1998[249]	Invalid diagnostic tests
Carrol 2002[256]	Invalid population
Carrol 2002A[257]	Procalcitonin
Carrol 2005[258]	Invalid population
Casado-Flores 2006[261]	Invalid population
Cazalis 2013[267]	Invalid diagnostic tests
Cekmez 2011[269]	Invalid country
Celik 2010[270]	Invalid country
Chaaban 2009[272]	Invalid analysis
Chalupa 2011[275]	Invalid outcomes
Chan 1997[278]	Invalid population
Chan 2002[282]	Invalid country
Chan 2004[283]	Invalid country
Chan 2011[281]	Narrative review
Charles 2008[285]	Invalid outcomes
Chen 2010[297]	Narrative review
Chen 2014[294]	Invalid country
Chen 2014E[301]	Invalid country
Chen 2014F[295]	Invalid country
Chiesa 2000[304]	Procalcitonin
Chiesa 2003[305]	Invalid analysis
Claessens 2010[316]	Invalid population
Clec'h 2004[317]	Procalcitonin
Coggins 2013[323]	Invalid analysis
Collighan 2004[324]	Invalid diagnostic tests
Contenti 2015A[326]	Invalid diagnostic tests
Cortegiani 2014[331]	Invalid outcomes
Couto 2007[333]	Invalid diagnostic tests
Couto-Alves 2013[334]	Not relevant to review question
Craig 2010[335]	Invalid diagnostic tests
Da Silva 2007A[344]	Invalid population
Dalton 2012[349]	Invalid analysis
Davis 2015[354]	Invalid population
De 1998[369]	Invalid country
de Azevedo 2015[357]	Invalid country
De Blasi 2013[358]	Invalid study design
De Jager 2010[362]	Invalid study design
Debiane 2014[372]	Invalid population
Degroot 2014[361]	Invalid diagnostic tests

Dettmer 2015[381]	Invalid comparison
Devran 2012[385]	Invalid country
DeWerra 1997[368]	Published before 1999
Dhanalakshmi 2015[387]	Invalid country
Dierkes 2009[391]	Invalid diagnostic tests
Diez-Padrisa 2012[392]	Invalid country
Dornbusch 2003[394]	Procalcitonin
Draz 2013[396]	Invalid diagnostic tests
Drees 2012[397]	Invalid diagnostic tests
Drumheller 2012[401]	Invalid diagnostic tests
Du 2002[403]	Invalid outcomes
Du 2003[404]	Invalid country
Du 2014[405]	Invalid country
Elawady 2014[415]	Invalid country
El-Maghraby 2007[414]	Invalid country
Endo 2008[420]	Invalid analysis
Engel 1998[421]	Invalid diagnostic tests
Ersoy 2007[425]	Invalid outcomes
Escobar 2015[427]	Animal study
Fan 1989[440]	Invalid outcomes
Feng 2012[445]	Invalid country
Fisher 2000[456]	Invalid study design
Fleischhack 2000[458]	Invalid population
Fleischhack 2000A[459]	Invalid population
Galetto-Lacour 2010[475]	Invalid study design
Garcia 2007[485]	Invalid diagnostic tests
Garland 2003[487]	Invalid population
Gerdes 1987[494]	Invalid setting
Ghosh 2001[497]	Invalid country
Gille-Johnson 2012[500]	Invalid outcomes
Greenberg 1990[517]	Invalid outcomes
Gu 2015[523]	Invalid analysis
Guclu 2013[524]	Invalid study design
Guibourdenche 2002[526]	Invalid analysis
Guido 2012[529]	Invalid outcomes
Guillois 1994[530]	Invalid population
Gutovitz 2011[536]	Invalid comparison
Guven 2002[537]	Procalcitonin
Hall 2011[547]	Narrative review
Hanson 1983[551]	Invalid study design
Hariharan 2011[554]	Invalid outcomes
Hegadi 2015[559]	Invalid country
Hengst 2003[560]	Invalid study design
Heper 2006[562]	Invalid outcomes
Hermans 2012 [565]	Invalid outcomes
Hernandez-Bou 2015[568]	Invalid population
Herzum 2008[569]	Narrative review
Hisamuddin 2015[573]	Invalid country
Ho 2008[576]	Invalid population
Hoppensteadt 2014A[583]	Invalid diagnostic tests
Hoppensteadt 2015[582]	Invalid diagnostic tests
Hui 2012[592]	Invalid study design
Iba 2014[594]	Narrative review

Jain 2014[611]	Invalid country
James 1999[612]	Narrative review
Jansen 2009[614]	Invalid study design
Janum 2011[615]	Invalid outcomes
Jat 2011[617]	Invalid country
Jeschke 2013[620]	Invalid analysis
Jordan 2000[630]	Invalid diagnostic tests
Juutilainen 2011A[633]	Invalid population
Kasem 2012[639]	Procalcitonin
Katz 1992[641]	Invalid population
Keshet 2009[649]	Invalid population
Keßler 1994[650]	Invalid outcomes
Khassawneh 2007[653]	Invalid country
Kim 2013A[668]	Invalid outcomes
Kirschenbaum 2006[672]	Invalid outcomes
Kite 1988[673]	Invalid population
Kobayashi 2001[677]	Invalid outcomes
Kocabas 2007[678]	Invalid country
Kocazeybek 2003[679]	Invalid population
Kohli 1993[680]	Invalid country
Kohn 2001[681]	Invalid study design
Koksal 2007[682]	Invalid country
Kono 1999[684]	Invalid outcomes
Krediet 1992[686]	Invalid setting
Krishna 2000[688]	Invalid country
Kumar 2010[692]	Invalid country
Kushimoto 2007[696]	Invalid outcomes
Kyr 2007[697]	Invalid diagnostic tests
Laborada 2003[699]	Invalid diagnostic tests
Lacaze-Masmonteil 2014[700]	Invalid analysis
Laham 2014[701]	Invalid population
Lam 2008[702]	Invalid study design
Larsen 2011[709]	Invalid outcomes
Lee 2012A[715]	Invalid analysis
Leli 2014[721]	Procalcitonin
Lichtenstern 2012[727]	Narrative review
Luz Fiusa 2013[749]	Invalid country
Lyle 2013[750]	Narrative review
MacKay 2011A[753]	Invalid outcomes
Magudumana 2000[757]	Invalid population
Malik 2003[762]	Systematic review
Mannan 2010[767]	Invalid country
Manucha 2002[768]	Invalid country
Manzano 2010[769]	Procalcitonin
Manzon 2015[770]	Invalid diagnostic tests
Marecaux 1996[771]	Invalid outcomes
Martinez-Albarran 2009[780]	Invalid country
Marzouk 1993[781]	Invalid population
Mathers 1987[783]	Invalid setting
Mazur 1994[789]	Invalid outcomes
McKenzie 2009[792]	Invalid study design
Meidani 2013[797]	Cross-sectional study
Meisner 1998A[798]	Invalid population

Mencacci 2012[799]	Invalid diagnostic tests
Menon 2015[800]	Invalid country
Mimoz 1998[810]	Invalid outcomes
Mintegi 2009[811]	Invalid population
Mistry 2013[812]	Invalid population
Mokart 2005[817]	Inconsistencies regarding units of measurement
Montiel-Jarquin 2012[819]	Invalid country
Munoz 2004[832]	Procalcitonin
Murphy 2012A[834]	Invalid analysis
Mustafa 2005[836]	Invalid country
Mustard 1987[837]	Invalid population
Naher 2011[838]	Invalid country
Neely 1998[843]	Invalid setting
Neely 2004[844]	Invalid diagnostic tests
Ng 2004A[847]	Narrative review
Ng 2006[848]	Narrative review
Nijman 2011[859]	Invalid outcomes
Nijman 2013[858]	Invalid analysis
Nuntnarumit 2002[863]	Invalid country
Oberhoffer 1999[868]	Invalid outcomes
Oliveira 2008[877]	Invalid outcomes
Oliveira 2013[876]	Invalid comparison
Opal 2014[880]	Narrative review
Örtqvist 1995[885]	Invalid outcomes
Park 2014[896]	Invalid population
Park 2014B[894]	Invalid diagnostic tests
Pechorsky 2009[910]	Invalid outcomes
Peduzi 1992[911]	Invalid setting
Peltola 1983[913]	Invalid population
Pfitzenmeyer 1995[917]	Published before 1999
Pinilla 1998[922]	Invalid population
Povoa 1998[933]	Published before 1999
Povoa 2002[932]	Narrative review
Povoa 2005[934]	Invalid analysis
Qu 2015[943]	Invalid country
Ranzani 2013[951]	Invalid country
Raoofi 2014[952]	Procalcitonin
Rast 2015[953]	Invalid population
Ravishankar 2009[954]	Invalid study design
Ravishankaran 2011[955]	Invalid country
Reed 2013[958]	Invalid analysis
Resch 2003[963]	Invalid population
Riche 2003[968]	Invalid population
Riedel 2011[970]	Procalcitonin
Riedel 2012[969]	Procalcitonin
Rondina 201[984]	Invalid diagnostic tests
Rønnestad 1999[985]	Invalid analysis
Sakha 2008[995]	Invalid country
Samraj 2013[998]	Narrative review
Santolaya 2008[1000]	Invalid country
Sauer 2003[1003]	Invalid intervention
Schreiber 2013[1009]	Invalid outcomes
Schwarz 2000[1011]	Invalid analysis

Scott 2012[1013]	Invalid outcomes
Seigel 2012[1014]	Invalid outcomes
Shaw 1991[1026]	Case-control study
Shine 1985[1030]	Invalid analysis
Shorr 2010[1032]	Invalid analysis
Sierra 2007[1035]	Systematic review
Silveira 1999[1039]	Invalid population
Simms 1992[1040]	Invalid diagnostic tests
Sivula 2015[1045]	Invalid diagnostic tests
Somech 2000[1056]	Invalid outcomes
Sonawane 2014[1058]	Invalid country
Spasova 2005[1063]	Invalid outcomes
Steinbach 2007[1067]	Invalid population
Struelens 1988[1070]	Invalid outcomes
Su 2012B[1075]	Invalid country
Su 2014[1073]	Invalid country
Sucilathangam 2012[1080]	Invalid country
Suri 1991[1083]	Invalid country
Tegtmeyer 1992[1092]	Invalid outcomes
Toh 2003A[1098]	Invalid analysis
Tong 2015[1099]	Invalid diagnostic tests
Tsalik 2012[1107]	Inconsistencies regarding units of measurement
Tschaikowsky 2011[1109]	Invalid outcomes
Tugrul 2002[1113]	Invalid country
Turi 2013[1115]	Invalid diagnostic tests
Ueda 2014[1116]	Not relevant to review question
Ulla 2013[1118]	Invalid diagnostic tests
Van den Bruel 2011[1124]	Invalid study design
Vassiliou 2015A[1131]	Invalid diagnostic tests
Venkataseshan 2007[1135]	Invalid diagnostic tests
Ventetuolo 2008[1137]	Narrative review
Venugopal 2014[1138]	Narrative review
Verbakel 2014[1140]	Study protocol
Viallon 2008[1141]	Invalid diagnostic tests
Volante 2004[1147]	Narrative review
Wacharasint 2012[1151]	Invalid analysis
Waliullah 2010[1153]	Invalid country
Waliullah 2009[1155]	Invalid country
West 2012[1166]	Invalid country
Wilkinson 2009[1170]	Invalid outcomes
Xie 2013[1183]	Invalid diagnostic tests
Yan 2001[1190]	Invalid outcomes
Yentis 1995[1195]	Invalid analysis
Yilmaz 2003[1197]	Invalid outcomes
Yin 2011[1199]	Invalid outcomes
Zant 2014[1206]	Invalid population
Zarkesh 2015[1207]	Invalid country
Zimmerman 2010[1218]	Invalid outcomes

L.4 Lactate

Table 38: Studies excluded from the clinical review

Study	Reason for exclusion
Aitofella 2012[41]	AUC data but no sensitivity or specificity data
Berger 2013[178]	Hyperlactaemia was an outcome not a predictor
Bollaert 2003[205]	No diagnostic accuracy data; relativistic OR/RR data only
Breuling 2015[229]	No diagnostic accuracy data; relativistic OR/RR data only
Brodska 2013[232]	No diagnostic accuracy data; relativistic OR/RR data only
Casagandra 2015 [262]	AUC data but no sensitivity or specificity data
Chen 2014F [302]	Study conducted in non OECD country (China)
Cicarelli 2007[314]	Study conducted in a developing country (Brazil)
Contenti 2015[326]	No protocol outcomes
Gao 2014[483]	Study conducted in a developing country (China)
Giannazzo 2006[499]	No diagnostic accuracy data; relativistic OR/RR data only
Giulieri 2015 [502]	Target disease was community-acquired meningitis
Gwak 2015[538]	Target disease was community-acquired pneumonia
Hermans 2012[565]	AUC data but no sensitivity or specificity data
Hernandez 2012A[567]	No protocol outcomes
Hisamuddin 2012[574]	Study conducted in a developing country (Malaysia)
Howell 2007A[589]	No diagnostic accuracy data; relativistic OR/RR data only
Jansen 2011[613]	Non-systematic review with different inclusion criteria (prognostic value of lactate, non-sepsis specific)
Jones 2010[628]	No relevant to protocol
Kang 2011[636]	Wrong population
Kim 2015B[664]	Outcomes not relevant to this review
Kobayashi 2001[677]	No diagnostic accuracy data; relativistic OR/RR data only
Krishna 2009[689]	No protocol outcomes
Kung 2014[693]	No diagnostic accuracy data
Kung 2015[694]	AUC data but no sensitivity or specificity data
Lee 2008[717]	No diagnostic accuracy data; relativistic OR/RR data only
Li 2013A[725]	Li 2013A[725]
Liu 2015 [737]	Target condition was severe pneumonia, and country was non OECD (China)
Linder 2012[733]	No protocol outcomes
Lorente 2013[743]	No diagnostic accuracy data; relativistic OR/RR data only
Lorente 2014A[744]	No diagnostic accuracy data; relativistic OR/RR data only
Lorente 2014B[745]	No protocol outcomes
Lorente 2015A [745]	Not protocol biomarker
Lorente 2015 [742]	AUC data but no sensitivity or specificity data
Mallat 2014A[763]	No diagnostic accuracy data; relativistic OR/RR data only
Manzon 2015[770]	AUC data but no sensitivity or specificity data
Mato 2010[784]	No protocol outcomes
Matsumura 2014[786]	ICU population but did not have sepsis
Mesquida 2015[802]	No diagnostic accuracy data; relativistic OR/RR data only

Study	Reason for exclusion
Miguelbayarri 2012[806]	No diagnostic accuracy data; relativistic OR/RR data only
Mikkelsen 2009[807]	No diagnostic accuracy data; relativistic OR/RR data only
Muller 2000[828]	Target condition was sepsis – not a worsening of existing sepsis
Musikatavorn 2015 [835]	No diagnostic accuracy data
Nanda 2009[839]	No protocol outcomes
Nguyen 2010A[854]	No diagnostic accuracy data; relativistic OR/RR data only
Nguyen 2011[853]	Not relevant to the protocol
Ouillette 2014[888]	Case control study
Pandey 2014[890]	AUC data but no sensitivity or specificity data
Park 2014[896]	Study conducted in a developing country (South Korea)
Puskarich 2012A[942]	Insufficient data for analysis
Ryoo 2015[993]	No diagnostic accuracy data; relativistic OR/RR data only
Shapiro 2010[1023]	AUC data but no sensitivity or specificity data
Singer 2014[1041]	No diagnostic accuracy data
Singh2012A[1042]	Study did not evaluate lactate specifically
Song 2012[1059]	No diagnostic accuracy data; relativistic OR/RR data only
Suarezsantamaria 2010[1077]	AUC data but no sensitivity or specificity data
Tang 2015[1090]	No diagnostic accuracy data; relativistic OR/RR data only
Varpula 2005[1130]	No diagnostic accuracy data; relativistic OR/RR data only
Whittaker 2015[1168]	No diagnostic accuracy data; relativistic OR/RR data only
Zanaty 2012 [1205]	Study conducted in a developing country (Egypt)
Zhang 2014E[1209]	Study conducted in a developing country (China)

L.5 Serum creatinine

Table 39: Studies excluded from the clinical review

Study	Reason for exclusion
Badin 2011[116]	Not protocol biomarker
Bagshaw 2013[119]	Not protocol biomarker
Bagshaw 2010[124]	Not protocol biomarker
Bagshaw 2007[123]	No protocol outcomes
Bagshaw 2007[128]	Not protocol biomarker
Bagshaw 2006[122]	Not protocol biomarker
Bagshaw 2006[127]	Not protocol population
Basu 2011[155]	No protocol outcomes
Carbonell 2004 [250]	Not protocol biomarker
Cartinceba 2012[260]	SR with no protocol outcomes
Chawla 2005[287]	No outcomes of interest
De 2004[359]	Not protocol study type
Desouza 2014[367]	Study conducted in developing country
Dinardo 2013[388]	No protocol outcomes

Drey 2015[400]	No protocol outcomes
Elfarghali 2012[413]	No protocol outcomes
Glassford 2013[503]	No protocol outcomes
Guo 2011[533]	Study conducted in developing country
Hamzic-Mehmedbasic 2015 [549]	Study conducted in non-OECD country
Hoste 2003[586]	No protocol outcomes
Iglesias 2003[596]	Not protocol population
Kiers 2010[660]	No protocol outcomes
Mariano 2008[772]	Not protocol biomarker
Martensson 2010[777]	Not protocol biomarker
Martensson 2012[778]	No protocol outcomes
Mazulsunko 2004[788]	No protocol outcomes
Nejat 2010[845]	No protocol outcomes
Nie 2013[857]	Not protocol biomarker
Plataki 2011[924]	No protocol outcomes
Poukkanen 2013[931]	No protocol outcomes
Soni 2009[1060]	Not protocol population
Su 2011[1074]	Study conducted in developing country
Suh 2013[1081]	No protocol outcomes
Terzi 2014[1093]	No protocol outcomes
Vanmassenhove2013[1129]	Not protocol biomarker
Walshe 2009[1156]	No protocol outcomes
Waring 2011[1159]	SR with no protocol outcomes
Wheeler 2008[1167]	No protocol outcomes
Wong 2015[1178]	Not protocol biomarker
Yamashita 2014[1189]	Not protocol population
Yegenaga 2004[1194]	No protocol outcomes
Zhang 2015[1210]	Not protocol study type
Zhou [1217]	Study conducted in non OECD country

L.6 Disseminated intravascular coagulation (DIC)

Table 40: Studies excluded from the clinical review

Study	Reason for exclusion
Angstwurm 2006[83]	Not protocol study design
Brenner 2012[225]	Not protocol study design
Cauchie 2006[266]	Not protocol population
Dempfle 2004[377]	Not protocol study design
Ersoy 2007[425]	Not protocol risk factor
Gamper 2001[477]	Not protocol population
Gando 1999[480]	Not protocol study design
Gando 2002[479]	Not protocol study design
Gando 2006[478]	Not protocol study design
Gando 2009[481]	Not protocol study design

Study	Reason for exclusion
Gogos 2003[505]	Not protocol risk factor
Gomez 2007[509]	Not protocol risk factor
Guirgis 2014[531]	SR not protocol risk factor
Ha 2015[539]	Not protocol study design
Harbarth 2002[553]	Not protocol study design
Hayakawa 2007[557]	Not protocol study design
Hoppensteadt 2014 [581]	Not protocol study design
Iba 2015[595]	Not protocol study design
Ishimura 2014[603]	Not protocol study design
Jesmin 2013[621]	Not protocol risk factor
Keneka 2012[648]	Not protocol study design
Kienast 2006[659]	Not protocol study design
Kim 2014[662]	Not protocol risk factor
Kinasewitz 2005[671]	Not protocol study design
Kinasewitz 2004[670]	Not protocol study design
Kobayashi 2001[677]	Not protocol study design
Koyama 2014[685]	Not protocol risk factor
Kushimoto 2008[695]	Not protocol study design
Lavigne-Lissalde 2015[712]	Conference abstract
Lin 2006[732]	Not protocol study design
Lin 2008[731]	Not protocol study design
Lissaldelavigne 2008[734]	Not protocol study design
Madoiwa 2006[756]	Not protocol risk factor
Massion 2012[782]	Not protocol risk factor
Muller 2014[829]	Not protocol risk factor
Ogura 2014[872]	Not protocol study design
Oh 2010[873]	Not protocol study design
Okabayashi 2004[874]	Not protocol population
Ostrowski 2013[886]	Not protocol risk factor
Park 1999[897]	Not protocol study design
Park 2011[893]	Not protocol study design
Peigne 2013[912]	Not protocol study design
Saracco 2011[1001]	Not protocol study design
Sawamura 2009[1005]	Not protocol study design
Sawamura 2009[1004]	Not protocol study design
Seki 2013[1016]	Not protocol study design
Takahashi 2015[1087]	Not protocol study design
Voves 2006[1149]	Not protocol study design
Yamakawa 2013[1187]	Not protocol study design

L.7 Antimicrobial treatment

Table 41: Studies excluded from the clinical review

Reference	Reason for exclusion
Bagshaw 2009[121]	Not relevant outcomes
Band 2011[136]	Comparison does not match protocol (patients who presented to the ED by ambulance versus patients who arrived by alternative means)
Barochia 2010[147]	Setting does not match protocol (review on the use of bundles in patients with septic shock)
Beck 2014A[162]	Comparison does not match protocol (time to vasopressor initiation in patients with septic shock)
Behrendt 1999[165]	Comparison does not match protocol (appropriate therapy within 48 hours versus after 48 hours)
Degoricija 2006[373]	No relevant outcomes, comparison does not match protocol
Erbay 2009[423]	Comparison does not match protocol (appropriate treatment within 24 hours versus after 24 hours)
Gabram 1993[473]	No relevant outcomes, study population does not match protocol (trauma patients)
Garcia-Saenz 2002[486]	Full text not available. Not in English language.
Garnacho-Montero 2003[489]	Comparison does not match protocol (adequate versus non-adequate empirical antimicrobial therapy; no time to antibiotics)
Garnacho-Montero 2006[488]	Comparison does not match protocol (appropriate treatment within 24 hours versus after 24 hours)
Gordon 2005[512]	Comparison does not match protocol (not time to antibiotics)
Hanzelka 2013[552]	Setting does not match protocol (implementation of an EGDT protocol for cancer patients)
Hetem 2011[570]	Comparison does not match protocol (under 24 hours versus after 24 hours)
Hortmann 2014[585]	Comparison does not match protocol (time to antibiotics not analysed)
Houck 2004[587]	Study population does not match protocol (proportion of patients with sepsis not clearly mentioned)
Iscimen 2008[601]	No relevant outcomes and does not match review protocol
Irwin 2015[600]	No relevant outcome
Jacob 2012[606]	Wrong population
Kang 2003[634]	Comparison does not match protocol (under 24 hours versus after 24 hours)
Khan 2015[651]	No relevant intervention (over 24 hours)
Khatib 2006A[655]	Comparison does not match protocol (not early versus delayed treatment)
Kim 2012C[667]	Comparison does not match protocol (adequate versus inadequate treatment)
Ko 2015[676]	Setting does not match protocol (implementation of a door-to-antibiotics time)
Krediet 2003[687]	No relevant outcomes
Lin 2008[729]	Comparison does not match protocol (under 24 hours versus after 24 hours)
Lodise 2007[741]	Comparison does not match protocol (appropriate treatment up to 52

Reference	Reason for exclusion
	hours)
Lodise 2003[740]	Comparison does not match protocol (under 44.75 hours versus after 44.75 hours)
MacArthur 2004[752]	Comparison does not match protocol (adequate versus inadequate treatment)
MacRedmond 2010[755]	Setting does not match protocol (implementation of a sepsis management protocol)
Meehan 1997[795]	Study population does not match protocol (proportion of patients with sepsis not clearly mentioned)
Natarajan 2014[841]	No data reported
Nguyen 2006A[850]	Study design does not match protocol (review with different protocol)
Nguyen 2007B[851]	Setting does not match protocol (implementation of a sepsis bundle)
Nguyen 2010[849]	Study design does not match protocol
Nickerson 2009[856]	Comparison does not match protocol (median delay is 3 days)
Onder 2008[878]	Not relevant outcomes
Parish 2013[892]	Setting does not match protocol (assessing a nurse-led protocol)
Park 2013[895]	Comparison does not match protocol (adequate antimicrobial therapy within 3 days)
Paul 2010[905]	Study population does not match protocol (12% sepsis)
Paul 2010A[907]	Comparison does not match protocol (assesses appropriate antibiotics)
Pestana 2010[916]	No relevant outcomes, study population does not match protocol
Rehmani 2014[960]	Setting does not match protocol (assessing an antibiotic protocol)
Rodriguez-Pardo 2015[981]	No relevant outcomes, study population does not match protocol
Ronnestad 2005[986]	Study design does not match protocol (survey), not relevant (no info on antibiotics intervention)
Sainio 1995[994]	Not relevant review question
Schweizer 2010[1012]	Comparison does not match protocol (adequate versus inadequate treatment)
Shime 2010[1029]	Intervention does not match protocol (antibiotics up to 48 hours)
Shorr 2011[1031]	Comparison does not match protocol (appropriate therapy versus inadequate; no time to antibiotics)
Siddiqui 2009[1033]	Comparison does not match protocol (no comparison)
Siddiqui 2010[1034]	Cochrane review does not include RCT evidence
Silber 2003[1036]	Study population does not match protocol (proportion of patients with sepsis not clearly mentioned)
Sterling 2015[1068]	Unclear methodology
Strang 1992[1069]	Incorrect study design (survey data)
Studnek 2012[1072]	Setting does not match protocol (EGDT paper)
Sweet 2010[1084]	Setting does not match protocol (study assesses protocol and not timing of antibiotics)
Talmor 2008[1089]	Setting does not match protocol (EGDT paper)
The ProCESS Investigators 2014[937]	Setting does not match protocol (EGDT paper)
Tumbarello 2007[1114]	Comparison does not match protocol (examines inadequate antibiotics)
Uittenbogaard 2014[1117]	No relevant outcomes and does not match review protocol

Reference	Reason for exclusion
Vanparidon 2015[1126]	No relevant analysis (effect size per minute)
Venkatesh 2013[1136]	No relevant outcomes
Waterer 2006[1162]	Study population does not match protocol (no sepsis)
Yahav 2013[1185]	Review with different inclusion criteria (pneumonia population)
Zahar 2011[1203]	Comparison does not match protocol (appropriate treatment within 24 hours versus after 24 hours)

L.8 IV fluid administration

Table 42: Studies excluded from the clinical review

Study	Exclusion reason
Abulebda 2014[16]	Incorrect interventions
Andre 2010[81]	Incorrect interventions
Andre 2011[80]	Incorrect interventions
Annane 2013[85]	Incorrect interventions
Apibunyopas 2014[89]	Paper not available
Arnold 2013[97]	No relevant outcome
Bagshaw 2013[125]	Not guideline condition
Bansal 2013[139]	Invalid inclusion criteria
Bayer 2011[159]	Incorrect interventions
Bayer 2012[158]	Incorrect interventions
Boldt 1995[202]	No relevant outcome
Boldt 1996[201]	Incorrect interventions
Boldt 1996[203]	Incorrect interventions
Boldt 1998[204]	Incorrect interventions
Boyd 2011[222]	Incorrect interventions
Brunkhorst 2008[235]	Incorrect interventions
Busund 1993[241]	Incorrect interventions
Cardoso 2010[252]	Incorrect interventions
Carlsen 2011[254]	Incorrect interventions
Casserly 2011[263]	Incorrect interventions
Castellanos-ortega 2010[264]	Incorrect interventions
Chang 2014[284]	No relevant outcome
Chen 2014[294]	Incorrect interventions
Chong 2014[308]	Incorrect interventions
Chopra 2011[309]	Incorrect interventions
Chuesakoolvanich 2007[310]	Not study design
Coen 2014[322]	Inappropriate comparison
Crowe 2010[339]	Inappropriate comparison
Cui 2012[341]	Not English
De oliveira 2008[366]	Inappropriate comparison
Delaney 2011[374]	Incorrect interventions
Dubin 2010[407]	No relevant outcome
El solh 2008[412]	Inappropriate comparison

Ernest 1999[424]	No relevant outcome
Estrada 2013[432]	Commentary
Fang 2008[441]	No relevant outcome
Femling 2014[443]	Incorrect interventions
Ferrer 2009[449]	Incorrect interventions
Finfer 2004[454]	Incorrect interventions
Ford 2012[465]	No relevant outcome
Fuller 2012[470]	No relevant outcome
Groeneveld 2011[521]	Incorrect interventions
Guidet 2012[528]	Incorrect interventions
Gurnani 2010[535]	Incorrect interventions
Haase 2013[541]	No relevant outcome
Haase 2013[540]	Incorrect interventions
Haase 2014[542]	Incorrect interventions
Holst 2013[580]	Study protocol
Jacob 2012[606]	Not study population
Jiang 2014[623]	Incorrect interventions
Jones 2007[625]	Inappropriate comparison
Karam 2011[637]	Incorrect interventions
Lee 2014[718]	Incorrect interventions
Lefrant 2010[719]	Incorrect interventions
Lin 2006[730]	Incorrect interventions
Liu 2013[736]	Incorrect interventions
Ma 2015[751]	Systematic review
Maitland 2011[760]	Not guideline condition
Malbrain 2014[761]	Not guideline condition
Miller 2013[809]	Incorrect interventions
Muller 2015[830]	Incorrect interventions
Murphy 2009[833]	Incorrect interventions
Nunes 2014[862]	No relevant outcome
Nurnberger 1999[864]	Incorrect interventions
O'neill 2012[866]	Incorrect interventions
Opiyo 2014[881]	Incorrect interventions
Orbegozo cortes 2014[882]	Not guideline condition
Parsons 2011[900]	Incorrect interventions
Patel 2013[901]	Incorrect interventions
Peake 2014[908]	Incorrect interventions
Perner 2012[915]	Incorrect interventions
Perner 2012[914]	Incorrect interventions
Purdy 1997[941]	No relevant outcome
Raghunathan 2014[948]	Incorrect interventions
Raza 2015[956]	Not review population
Reiter 2013[962]	Incorrect interventions
Rewari 2014[965]	Abstract only
Rinaldi 2013[971]	Incorrect interventions
Rivers 2001[973]	Incorrect interventions
Rochwerg 2014[979]	No relevant outcome
Rochwerg 2015[978]	Network meta-analysis with different study protocol
Rosland 2014[988]	Incorrect interventions

Serpa neto 2014[1020]	No relevant outcome
Smith 2012[1051]	Incorrect interventions
Surat 2014[1082]	Paper not available
Trof 2010[1103]	Inappropriate comparison
Upadhyay 2005[1120]	No relevant outcome
Vanparidon 2015[1126]	Invalid analysis
Veneman 2004[1134]	No relevant outcome
Wawrzeniak 2015[1163]	Inappropriate comparison
Wiedermann 2008[1169]	Incorrect interventions
Wittbrodt 2013[1175]	Incorrect interventions
Xu 2014[1184]	Incorrect interventions
Yang 2010[1191]	Not English
Yealy 2014[1193]	Incorrect interventions
Zhang 2015[1208]	Incorrect interventions
Zhong 2013[1213]	No relevant outcome

L.9 Escalation of care

Table 43: Studies excluded from the clinical review

Study	Exclusion reason
Alsolamy 2014[69]	Invalid intervention
Austin 2014[107]	Invalid population
Chamberlain 2015[277]	Invalid analysis
Esteban 2007[431]	Invalid comparison
Evans 2014[434]	Invalid population
Femling 2014[443]	Invalid comparison
Fendler 2012[444]	Invalid intervention
Jaderling 2013[608]	Invalid comparison
Junhasavasdikul 2013[632]	Invalid population
Robert 2000[975]	Invalid outcome
Takeyama 2012[1088]	Invalid intervention
Vinson 2014[1146]	Invalid intervention

L.10 Inotropic agents and vasopressors

Table 44: Studies excluded from this clinical review

Study	Exclusion reason
Acevedo 2009[17]	Abstract
Agrawal 2011[30]	No relevant outcome
Agrawal 2012[31]	Invalid study design
Albanese 2004[57]	No relevant outcome
Albanèse 2005[56]	Incorrect interventions

Study	Exclusion reason
Anantasit 2014[76]	Retrospective analysis of VASST trial
Anwar 2002[87]	Not available
Avni 2015[108]	Systematic review
Backer 2012[115]	Systematic review
Bahloul 2014[130]	Inappropriate comparison
Barton 1996[150]	No relevant outcome
Boulain 2009[221]	Invalid study design
Cardoso 2010[252]	Incorrect interventions
Cha 2004[271]	Not English
Daley 2013[348]	Invalid study design
Dunser 2009[408]	No relevant outcome
El solh 2008[412]	Incorrect interventions
Elmenesy 2008[417]	Not available
Gordon 2010[510]	Invalid study population
Gordon 2012[511]	No relevant outcome
Hall 2004[546]	Invalid study design
Klein 2006[674]	Not relevant setting
Kumar 2008[690]	Inappropriate comparison
Lampin 2012[704]	Inappropriate comparison
Levy 1999[722]	No relevant outcome
Levy 2005[723]	Inappropriate comparison
Lin 2006[730]	Inappropriate comparison
Lupei 2009[748]	Inappropriate comparison
Mark 2014[773]	Inappropriate comparison
Martin 2000[779]	Incorrect interventions
Matok 2005[785]	Incorrect interventions
Micek 2007[805]	Invalid study design
Moon 2010[820]	Not guideline condition
Morelli 2007[822]	Abstract
Morelli 2008[823]	Incorrect interventions
Morimatsu 2004[825]	Inappropriate comparison
Mullner 2004[831]	Cochrane review (outdated)
Oba 2014[867]	Systematic review
Obritsch 2004[869]	Inappropriate comparison
O'neill 2012[866]	Inappropriate comparison
Patel 2002[902]	No relevant outcome
Povoa 2009[935]	Inappropriate comparison
Prys-picard 2013[938]	Inappropriate comparison
Rodriguez-nunez 2006[980]	Incorrect interventions
Russell 2009[992]	Inappropriate comparison
Russell 2013[991]	Not review population
Sakr 2006[996]	Inappropriate comparison
Serpa neto 2012[1019]	Incorrect interventions

Study	Exclusion reason
Shapiro 2006[1024]	Incorrect interventions
Soong 2011[1061]	Inappropriate comparison
Tourneux 2008[1101]	Inappropriate comparison
Tsapenko 2013[1108]	Inappropriate comparison
Tsuneyoshi 2001[1111]	Invalid study design
Vasu 2012[1132]	Systematic review
Waechter 2014[1152]	Inappropriate comparison
Wilkman 2013[1171]	Inappropriate comparison
Yildizdas 2008[1196]	Incorrect interventions
Zhang 2015[1208]	Inappropriate comparison
Zhao 2012[1212]	Not English
Zhou 2013[1214]	Not English
Zhou 2014[1215]	Systematic review
Zhou 2015[1216]	Systematic review

L.11 Supplemental oxygen

Table 45: Studies excluded from the clinical review

Reference	Reason for exclusion
Alia 1999[63]	Inappropriate comparison (therapy with normal targeted value of oxygen delivery versus targeted oxygen delivery index)
Balk 2004[134]	Inappropriate study design (narrative paper)
Bellomo 2008[168]	Inappropriate study design (commentary)
Crone 1994[338]	Inappropriate study design (letter to the editor)
Duarte 2005[406]	Inappropriate study design (narrative review)
Erstad 1994[426]	Review with different protocol
Esen 1992 [430]	Inappropriate intervention (artificial ventilation)
Ferrer 200 [448]	Inappropriate population (acute hypoxemic respiratory failure) and incorrect comparison (non invasive ventilation versus oxygen using high concentration sources)
Freebairn 1997[466]	Inappropriate interventions (vecuronium or saline closed-loop infusion)
Ince 1999[598]	Review with different protocol
Matuschak 1997[787]	Review with different protocol
Rampal 2010[949]	Review with different protocol
Russell 1995[990]	Inappropriate study design (narrative review)
Textoris 2011 [1094]	Inappropriate intervention (local hospital protocol)
Vincent 1995[1142]	Inappropriate study design (narrative review)

L.12 Use of bicarbonate

Table 46: Studies excluded from the clinical review

Reference	Reason for exclusion
Kim 2013[663]	Population not relevant to review question (61% of patients had sepsis as cause of lactic acidosis; 67 % of the population received bicarbonate therapy)
Velissaris 2015[1133]	Literature review

L.13 Early goal-directed therapy (EGDT)

None.

L.14 Monitoring

Table 47: Studies excluded from the clinical review (use of scoring systems)

Reference	Reason for exclusion
Abbott 2015[11]	Intervention does not match protocol (not for monitoring: comparison of NEWS and PARS) Population does not match protocol (not sepsis specific: all patients admitted to the acute assessment unit)
Adshead 2009[28]	Incorrect study design (narrative article)
Akre 2010[45]	Intervention does not match protocol (not for monitoring: external validation or PEWS and calculation of median time from critical PEWS to rapid response team) Population does not match protocol (not sepsis specific: hospitalised paediatric patients, respiratory, infectious disease, cancer, cardiac, digestive)
Alam 2014A[53]	Intervention does not match protocol (not for monitoring: systematic review on ability of EWS to identify patients at risk of deterioration) Population does not match protocol (not sepsis specific: ED and ward patients)
Alam 2015[54]	Intervention does not match protocol (not for monitoring: validation of NEWS to predict adverse outcome) Population does not match protocol (not sepsis specific: all ED patients with an emergency severity index of 2 and 3 not triaged to the resuscitation room)
Albert 2011[58]	Intervention does not match protocol (not for monitoring: development of a modified EWS) Population does not match protocol (not sepsis specific: cardiac, respiratory, neurological, sepsis (1.3%))
Alrawi 2013 [68]	Intervention does not match protocol (not for monitoring: to assess ability of MEWS to predict mortality) Population does not match protocol (not sepsis specific: acutely ill nursing home residents)
Anon 2014B[9]	Incorrect study design (narrative article)
Armagan 2008[94]	Intervention does not match protocol (not for monitoring: validation of MEWS)

Reference	Reason for exclusion
	Population does not match protocol (not sepsis specific: all ED patients)
Ausania 2015[106]	Intervention does not match protocol (not for monitoring: multivariable analysis of risk factors associated with morbidity and mortality) Population does not match protocol (not sepsis specific: post-operative patients)
Bayer 2015[160]	Intervention does not match protocol (not for monitoring: development of a new scoring system, not externally validated) Population does not match protocol (not sepsis specific: all patients admitted to ED)
Bradman 2008[224]	Intervention does not match protocol (not for monitoring: to see if PEWS could determine at triage children who needed admission or who could be discharged at home) Population does not match protocol (not sepsis specific: all children attending the paediatric emergency department)
Badriyah 2014[117]	Intervention does not match protocol (not for monitoring: validation of NEWS) Population does not match protocol (not sepsis specific: all patients admitted to the medical assessment unit)
Breslin 2014[226]	Intervention does not match protocol (to establish that higher PEWS at time of ED disposition decision is associated with need for higher levels of care at ED disposition, not for monitoring) Population does not match protocol (not sepsis specific: ED patients)
Burch 2008[239]	Intervention does not match protocol (to evaluate the utility of MEWS as a triage tool, not for monitoring) Population does not match protocol (not sepsis specific: medical patients presenting to the ED)
Chaiyakulsil 2015[274]	Population does not meet protocol (not sepsis)
Cei 2009[268]	Intervention does not match protocol (to identify patients at risk of deterioration, not for monitoring) Population does not match protocol (not sepsis specific: all patients admitted to a medical ward)
Churpek 2013[312]	Intervention does not match protocol (to discuss risk scores for use on the general inpatient wards to predict mortality, ICU transfer and cardiac arrest, not for monitoring) Population does not match protocol (not sepsis specific: patients on general wards)
Cildir 2013[315]	Intervention does not match protocol (not for monitoring: to evaluate the ability of MEDS, MEWS and the Charlson comorbidity index (CCI) to predict prognosis in patients who are diagnosed in sepsis)
Corfield 2014[328]	Intervention does not match protocol (not for monitoring: to determine, in patients with sepsis, whether a single NEWS on ED arrival is a predictor of mortality, or ICU admission)
Correia 2014[330]	Intervention does not match protocol (not for monitoring: EWS score at -72h, -24h and -12h in patients transferred from the ward to the ER) Population does not match protocol (not sepsis specific: cardiovascular, respiratory, neurological, renal or other clinical reasons)
Dawes 2014[355]	Intervention does not match protocol (not for monitoring: ability of the Worthing PSS score, calculated using VitalPAC, to predict mortality.) Population does not match protocol (not sepsis specific: all patients admitted to the Acute Medical Unit)

Reference	Reason for exclusion
De Meester 2013A[365]	Intervention does not match protocol (monitoring for serious adverse events after ICU discharge) Population does not match protocol (not sepsis specific: surgical and medical ICU patients)
Ennis 2014[422]	Intervention does not match protocol (not for monitoring: evaluate the effectiveness of PEWS to early detect clinical deterioration) Population does not match protocol (not sepsis specific: acutely ill children in hospital)
Fairclough 2009[438]	Intervention does not match protocol (not for monitoring: use of MEWS to predict mortality in acute medical admission unit) Population does not match protocol (not sepsis specific: only 12% of patients had sepsis)
Finlay 2014[455]	Intervention does not match protocol (not for monitoring: MEWS to predict mortality) Population does not match protocol (not sepsis specific: general medical-surgical patients)
Friedman 2015[467]	Incorrect study design (narrative review)
Fuijkschot 2015[469]	Intervention does not match protocol (not for monitoring: PEWS to identify patients for PICU admission) Population does not match protocol (not sepsis specific: all patients receiving emergency medical interventions at the paediatric wards; all patients admitted to paediatric oncology ward)
Goldhill 2004[507]	Intervention does not match protocol (not for monitoring: physiological variables to predict mortality) Population does not match protocol (not sepsis specific: all patients in non-obstetric bed area)
Goldhill 2005[508]	Intervention does not match protocol (not for monitoring: physiological variables and Patient-At-Risk score to predict mortality) Population does not match protocol (not sepsis specific: outreach service database)
Griffiths 2012[520]	Incorrect study design (survey)
Haines 2006[544]	Intervention does not match protocol (not for monitoring: to develop and evaluate a clinical and physiologically based for identification of acutely ill children in ward areas) Population does not match protocol (not sepsis specific)
Hammond 2013[548]	Intervention does not match protocol (not for monitoring: to assess any change in combination or individual vital signs frequency before and after MEWS implementation) Population does not match protocol (not sepsis specific: ICU patients with three diagnostic groups: cardiovascular, respiratory and gastrointestinal)
Henry 2015[561]	Outcome does not match protocol (diagnostic accuracy data)
Ho 2013[577]	Intervention does not match protocol (not for monitoring: MEWS to predict mortality and ICU admission) Population does not match protocol (not sepsis specific: critically ill patients who require continuous ECG monitoring)
Holme 2013[579]	Intervention does not match protocol (not for monitoring: To design and validate an objective clinical scoring system to identify unwell neonates) Population does not match protocol (not sepsis specific: all neonates >35 weeks' gestation admitted to the NICU)
Jarvis 2015A[616]	Intervention does not match protocol (not for monitoring: use of NEWS

Reference	Reason for exclusion
	to calculate risk of death and adverse outcome) Population does not match protocol (not sepsis specific: all patients admitted to hospital)
Jo 2013[624]	Intervention does not match protocol (not for monitoring: to examine whether the predictive value of EWS could be improved by including rapid lactate levels, and to compare the modified EWS with the pre-existing risk scoring systems)
Kaul 2014[642]	Incorrect study design (survey)
Kellett 2012[645]	Intervention does not match protocol (not for monitoring: validation of an abbreviated Vitalpac Early Warning Score) Population does not match protocol (not sepsis specific: includes surgical patients, medical, cardiac, oncology, renal and stroke patients)
Kyriacos 2011[698]	Intervention does not match protocol (not for monitoring: review the validity of EWS/MEWS) Population does not match protocol (not sepsis specific: population not specified)
Lam 2006[703]	Intervention does not match protocol (not for monitoring: applicability of MEWS for the emergency department observation ward to predict serious outcome) Population does not match protocol (not sepsis specific: patients with cardiac or gastrointestinal symptoms, or dizziness)
Liu 2015[735]	Intervention does not match protocol (not for monitoring: validation of National EWS in emergency intensive care unit) Population does not match protocol (not sepsis specific: neurological, cardiovascular, respiratory, gastrointestinal and other diseases)
Ludikhuize 2012[747]	Intervention does not match protocol (not for monitoring: effectiveness of MEWS to predict cardiopulmonary arrest, ICU admission, death, emergency surgery) Population does not match protocol (not sepsis specific: patients on general wards)
Ludikhuize 2014[746]	Intervention does not match protocol (not for monitoring: implementation of a RRs protocol) Population does not match protocol (not sepsis specific: hospitalised patients)
Mandell 2015[764]	Population does not match protocol (not sepsis population)
Moseson 2014[826]	Intervention does not match protocol (not for monitoring: comparison of APACHE II, APACHE III, SAPS II, MEWS, REMS, PEDS to predict mortality) Population does not match protocol (not sepsis specific: critically ill patients admitted to the ICU with one of the following diagnosis category: respiratory, cardiovascular, infectious disease, neurology, gastrointestinal, other)
Oldroyd 2011[875]	Incorrect study design (narrative article)
Parshuram 2011[898]	Intervention does not match protocol (not for monitoring: before-and-after study to evaluate the effect of implementation of the Bedside PEWS) Population does not match protocol (not sepsis specific: all paediatric patients)
Parshuram 2011A[899]	Repeated measures analysis showed that the Bedside PEWS increased over the 24 hours before urgent ICU admission or code blue event from a baseline mean score of 5.3, 20-24h before clinical deterioration, to 8.4 in the last 4 h

Reference	Reason for exclusion
	Population does not match protocol (not sepsis specific: all paediatric patients, case-control study)
Patterson 2011[903]	Incorrect study design (survey)
Pearson 2011[909]	Incorrect study design (narrative article)
Prytherch 2010[939]	Intervention does not match protocol (not for monitoring: to develop a validated, paper-based, aggregate weighted track and trigger system (AWTTS) for the detection of patient deterioration) Population does not match protocol (not sepsis specific: database of acute medical admissions)
Reini 2012[961]	Intervention does not match protocol (not for monitoring: to assess ability of MEWS, SAPS III, and SOFSA to predict ICU mortality) Population does not match protocol (not sepsis specific: only 13% of participants had sepsis. ICU setting)
Seiger 2013[1015]	Intervention does not match protocol (not for monitoring: review to evaluate ability of PEWS to predict hospitalisation and ICU admission) Population does not match protocol (not sepsis specific: all children presenting to the ED with the following problems: trauma, gastrointestinal, FWS, dyspnea, wounds, neurologic, urinary tract problems, local infection/abscess, rash, ear, nose, throat, other)
Silcock 2015[1037]	Intervention does not match protocol (not for monitoring: validation of NEWS in identifying patients at risk of death or deterioration in the pre-hospital setting) Population does not match protocol (not sepsis specific: unselected pre-hospital patients)
Skaletzky 2012[1046]	Intervention does not match protocol (not for monitoring: validation of a modified PEWS) Population does not match protocol (not sepsis specific: all patients admitted to medical-surgical wards. Case-control study)
Smith 2013[1049]	Intervention does not match protocol (not for monitoring: evaluate the ability of NEWS to detect mortality and ICU admission) Population does not match protocol (not sepsis specific: patients admitted to the medical assessment unit)
Smith 2014[1050]	Intervention does not match protocol (not for monitoring: review on the validity of EWS) Population does not match protocol (not sepsis specific: medical and surgical inpatients)
So 2015[1053]	Intervention does not match protocol (to detect weather ED monitoring by MEWS is better than nurse clinical judgement in changing the patient's ED management plan) Population does not match protocol (not sepsis specific: all patients being held in the ED observation area because of access block to the following specialty wards: medical, general surgery, neurosurgery and clinical oncology)
Solevag 2013[1055]	Intervention does not match protocol (not for monitoring: to assess the correlation of modified PEWS results with other indicators of severe illness) Population does not match protocol (not sepsis specific: injury, congenital cardiovascular disease, acquired cardiovascular disease, neurological disease, renal disease including urinary tract infection, gastrointestinal disease, respiratory, other infection, miscellaneous including dehydration and diabetes ketoacidosis)

Reference	Reason for exclusion
Subbe 2001[1078]	Intervention does not match protocol (not for monitoring: validation of a modified EWS) Population does not match protocol (not sepsis specific: all medical emergency admissions admitted to the medical admissions unit)
Tafelski 2015[1086]	Intervention does not match protocol (not for monitoring: application of three different PIRO systems)
Tucker 2009[1112]	Intervention does not match protocol (not for monitoring: validation of PEWS) Population does not match protocol (not sepsis specific: most common diagnosis were asthma exacerbation, bronchiolitis and pneumonia)
Van Rooijen 2013[1127]	Intervention does not match protocol (not for monitoring: evaluation of the threshold value for the EWS on general wards) Population does not match protocol (not sepsis specific: all patients on medical and surgical wards)
Vorwerk 2009[1148]	Intervention does not match protocol (not for monitoring: to determine the efficacy of the abbreviated MEDS score (without neutrophil bands), and MEWS in predicting mortality in adult ED patients with sepsis)
Yoo 2015[1200]	Intervention does not match protocol (not for monitoring: to determine whether use of a combination of MEWS and lactate enhances prediction of ICU transfer and mortality in hospitalized patients with severe sepsis/septic shock)

L.15 Patient education, information and support

Table 48: Studies excluded from the clinical review

Reference	Reason for exclusion
Flynn 2012[462]	SR includes studies in wrong population
Higgins 2008[571]	Wrong population
Jeon 2012[619]	Wrong intervention
Obermann 2007[871]	Wrong intervention
Plowright 2013[925]	Wrong study type
Yamamoto 1997[1188]	Wrong intervention

L.16 Education and training

Table 49: Studies excluded from the clinical review

Reference	Reason for exclusion
Adler 2007[26]	Not relevant to review question
Allen 2011[66]	Not relevant to review question
Anon 2008[4]	Not relevant to review question
Anon 2005A[2]	Not relevant to review question
Anon 2007[3]	Comment
Anon 2008F[5]	Not relevant to review question
Anon 2010[6]	Not relevant to review question.

Reference	Reason for exclusion
Anon 2010A[7]	Comment
Anon 2013D[8]	Comment
Arabi 2014[91]	Expert opinion
Assuncao 2010[103]	No detail about how training was carried out
Assuncao 2014[104]	No detail about how training was carried out
Austin 2014[107]	Not relevant to review question
Bach 1996[114]	Not relevant to review question.
Berger 2010[177]	Not education/training.
Bond 2013[211]	No detail about how training was carried out
Bridgewater 2014	Critical care nursing education/degree
Bruce 2011[793]	Protocol. Not on education/training
Buckley 2010[237]	Implementation of a protocol, not any details of training
Burney 2012[240]	Not relevant to review question
Baez 2013[118]	not relevant to review question/not enough details in paper
Barbieri 2013[144]	Quality improvement initiatives, do not explain specific training or education
Benczo 2004[170]	Not related to sepsis
Benson 2014[174]	Early recognition, not training
Berg 2013[180]	No details of how implemented/training
Capp 2011[464]	No details of training provided
Carlbom 2007[253]	Survey on barriers which may inform a training intervention but no training intervention
Casserly 2011[263]	Implementation of a Sepsis Intervention Programme, but no details on training
Chamberlain 2006[276]	Short summary
Carter 2007[259]	Outcomes not adequately measured
Castro2008[265]	Comparison of 2 intervention protocols, but no details on training
Chen 2013[1211]	Impact of an education programme on patient outcomes. Details of training and education programme not included
Coba 2011[320]	Outcomes not adequately measured
Croft 2014[337]	Not relevant to review question.
Cruz 2012[340]	Not relevant to review question.
Daniels 2010	No details of training provided
Daniels 2011[351]	States staff underwent training on sepsis 6 but no details of training provided
De Groot 2012[360]	No details of training provided.
Demmel 2010[376]	Not relevant to review question.
Desmond 2013[380]	Not relevant population.
Deutsch 2014[382]	Conference abstract
Devita 2007[384]	GDG ref. Comment on review
Fadale 2014[435]	Not relevant to review question. Training about vasopressor titration.
Fitzpatrick 2014[457]	Not relevant to review question. Wrong study design.
Fuchs 2015[468]	Conference abstract
Funk 2009[471]	Review proposes and discusses barriers and RRS but does not present actual results of effectiveness of these.

Reference	Reason for exclusion
Gannon 2011[482]	Not relevant to review question.
Gerber 2010[493]	Not relevant to review question.
Gerdtz2013[495]	GDG ref. Not relevant to review question
Girardis 2009[501]	Not relevant to review question. Development and implementation of a protocol. No details given on the training and education.
Granier 1998[515]	Not relevant to review question.
Greenspoon 1994	Implementation of a protocol.
Guerra 2013[525]	No detail about how training was carried out
Gultepe 2014[532]	Not relevant to review question
Harrigan 2006[555]	GDG ref. Not relevant to review question.
Herasevich 2011[563]	Not relevant to review question.
Hitti 2012[575]	No details of training provided.
Huggan 2011[591]	summary
Hurtado 2006[593]	summary of bundles in surviving sepsis campaign
Jeon 2012[619]	GDG ref. Not relevant to review question. Implementation of a protocol. No details given on the training and education.
Jones 1998[629]	Comment on sepsis and SIRS definitions
Jones 2014[626]	Not relevant to review question.
Kang 2012[635]	Not relevant to review question.
Kellie 2014[646]	Not relevant to review question.
Kim 2001[666]	Prevention of infection for HCP
Kim 1999[661]	Not relevant to review question.
Kleinpell 2014[675]	comment on SSC and bundles, not original research
Kollef 2010[683]	GDG ref. Not relevant to review question. Implementation of a protocol. No details given on the training and education.
Larosa 2012[708]	Not relevant to review question. No details given on the training and education.
Launay 2011	No details of training provided.
Levy 2010[724]	No detail about what was how training/education carried out.
Levy 2014	No detail about what was how training/education carried out.
Lobo 2005[739]	GDG ref. Prevention of catheter-related infections, not about raising awareness of identification/ management of sepsis
Lobo 2010[738]	Prevention of catheter-related infections, not about raising awareness of identification/ management of sepsis
Mackintosh 2012[754]	GDG ref. Not relevant to review question. Not about education/training
Mahavanakul 2012[758]	Not relevant to review question.
McGaughey 2010[790]	GDG ref. Wrong study design (protocol). Not relevant to review question. Not about education/training
Mann-Salinas 2014[766]	Description of sepsis in theory
Marshall 2009[775]	Conference abstract
Mckinley 2011[793]	Implemented protocol but no details of how implemented/training
McNally 2009[794]	Not relevant to review question.
Meyer 2013[804]	No training implementation/analysis
Mok 2014[816]	Not relevant to review question
Monette 2007[818]	Not relevant to review question.

Reference	Reason for exclusion
Moore 2009[821]	Sensitivity and specificity of sepsis screening protocol
Nassau 2003[840]	Summary/comment, not original research
Nelson 2011[846]	Not relevant to review question.
Nguyen 2014[855]	Not relevant to review question.
Nguyen 2009[852]	Not relevant to review question.
Noritomi 2014[861]	Protocol implementation. No detail about what was included/how training/education carried out
Orji 2007[884]	Not relevant to review question
Ottestad 2007[887]	Scores performance in identifying sepsis but not implementing any training
Patocka 2014	No details of training provided.
Phua 2012[918]	Not relevant to review question.
Phua 2013[919]	Not relevant to review question.
Plambech 2012[923]	Protocol implementation. No detail about what was included in the training.
Potter 2011[930]	Editorial article
Prasas 2010	Not relevant to review question.
Puntis 1991[940]	Prevention of catheter-related infections, not about raising awareness of identification/management of sepsis
Reuben 2006[964]	Not relevant to review question.
Rincon 2011[972]	No details of how implemented/training
Robson 2008[977]	Not relevant to review question.
Robson 2007[976]	Not relevant to review question.
Salluh 2008[997]	Not relevant to review question.
Santana 2008[999]	Prevention of catheter-related infections, not about raising awareness of identification/management of sepsis
Sarani 2008[1002]	Not relevant to review question
Sawyer 2011[1006]	Not training/education.
Scheer 2015[1007]	Conference abstract
Schramm 2011[1008]	Implementation of a protocol, not any details of training
Semelsberger 2009[1017]	Prevention of catheter-related infections, not about raising awareness of identification/management of sepsis
Seoane 2013[1018]	Implementation of a protocol, not any details of training
Shearer 2012[1027]	Not relevant to review question.
Sherertz 2000[1028]	GDG ref. Prevention of infection, not about raising awareness of identification/ management of sepsis
Smith 2012[1051]	Implementation of a protocol, not any details of training
Tromp 2009[1104]	No details of training.
Tromp 2010[1105]	Implementation of a protocol, not any details of training
Tromp 2011	Implementation of a protocol, not any details of training
Tafelski 2010[1085]	Not relevant to review question.
van Zanten 2014	No detail about what was how training/education carried out.
van Dijck 2009[1128]	Not relevant to review question.
Wallgren 2014[1154]	Implementation of two sepsis screening tools, not any details of training
Warren 2003[1160]	Specific sepsis prevention programme

Reference	Reason for exclusion
Weaver 2003[1164]	States what can be done but does not show results of it being done
Weinert 2008[1165]	General ICU not Sepsis
Wolbrink 2014[1177]	describes platform but no results of effect in practice
Winters 2013[1174]	GDG ref. Comment. No study undertaken
Winterbottom 2011[1173]	Implementation of bundle of care for managing patients with severe sepsis/septic shock. No details of education programme
Yilmaz 2007[1198]	Prevention of catheter-related infections, not about raising awareness of identification/management of sepsis
Yurkova 2011	No details of training provided.
Zaffar 2009	Not relevant to review question.
Zuhlke 2013[1219]	Public education, not health professionals.

Appendix M: Excluded health economic studies

M.1 Scoring systems

None.

M.2 Signs and symptoms

None.

M.3 Blood tests

None.

M.4 Lactate

None.

M.5 Serum creatinine

None.

M.6 Disseminated intravascular coagulation (DIC)

None.

M.7 Antimicrobial treatment

None.

M.8 IV fluid administration

Table 50: Studies excluded from the economic review

Reference	Reason for exclusion
GUIDET 2007 [527]	This study was selectively excluded due to a combination of applicability and methodological limitations. Health outcomes were not expressed as QALYs. Time horizon may not be sufficient to capture all benefits and costs if benefits persist beyond 5 years. The associated RCT (SAFE Study) is just 1 of 7 included studies in the clinical review, which also has limitations because the treatment effect used in the cost effectiveness paper is a post hoc analysis and the treatment effect in the severe sepsis group was not found to be significant.

M.9 Escalation of care

None.

M.10 Inotropic agents and vasopressors

None.

M.11 Supplemental oxygen

None.

M.12 Use of bicarbonate

None.

M.13 Early goal-directed therapy

None.

M.14 Monitoring

None.

M.15 Patient education, information and support

None.

M.16 Education and training

None.

Appendix N: Research recommendations

N.1 Epidemiological study on presentation and management of sepsis in England

Research question:

What is the incidence, presentation and management of sepsis in the United Kingdom?

Why this is important:

The lack of robust UK based epidemiological studies on the incidence and outcomes from sepsis have been clear throughout the guideline development process. A large epidemiological study to collect information about where sepsis is being treated, patient interventions and patient outcomes would provide population based statistics on epidemiology of sepsis which are necessary to support evaluation of interventions, planning of services and service redesign. The mortality and morbidity and service complexity associated with severe infection and sepsis, and the need to use broad spectrum antimicrobials to treat sepsis, justifies the cost required to set up such a study.

Criteria for selecting high-priority research recommendations:

PICO question	The questions that a registry could help answer are: What is the epidemiology of life threatening sepsis in the UK? How and where is life threatening sepsis treated? What important safety monitors need to be in place to capture unintended consequences? Would co-ordinated service evaluation linked to a Sepsis Registry lead to better patient care?
Importance to patients or the population	The interventions recognised in this guideline as a standard of care for sepsis require timely, coordinated, and robust healthcare services. Process and patient outcome improvement can only occur if based on standardised data systems that inform us of epidemiological, clinical and outcome trends. There is a lack of evidence to support any particular service improvement methodology in sepsis but coordinated efforts to provide longitudinal data on process and outcome would help with this.
Relevance to NICE guidance	Provide baseline data on impact of sepsis in UK population and help inform future guidance on effective service improvement methodologies
Relevance to the NHS	Will provide assurance of guideline implementation which (along with mechanisms such as CQUIN) will drive service improvement. Will provide measures of local and population based epidemiology to inform service design and resourcing.
National priorities	National Sepsis CQUIN NHS Ombudsman Report into Sepsis Sign up to Safety NHSE priorities
Current evidence base	There is a lack of current national sepsis statistics with poor coding of episodes of sepsis and limited knowledge of UK sepsis epidemiology
Equality	None Relevant
Study design	Service evaluation and audit Epidemiological primary research
Feasibility	Information governance and Caldicott issues will need to be addressed.

	Centralised registry will need to be funded in line with other similar databases.
Other comments	A variety of known local service evaluation and audit methods could be adapted for national use.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.2 A complex service evaluation of implementation of NICE Sepsis guideline

Research question:

What effect will the NICE Sepsis guideline have on patient care processes and outcome in the UK over the next 5 years?

Why this is important:

Implementation of the NICE Sepsis guideline will be a challenge to the NHS. A robust evaluation of how NHS service providers adhere to the recommended care processes and the effect of implementation needs to be carried out.

A complex evaluation is required to understand the effect of guidelines on services and on patient outcomes. Evaluation should include assessment of costs and cost effectiveness, the use of a universal audit tool for sepsis patient care that includes evaluation of pre-hospital and secondary care and monitoring of broad spectrum antibiotic use, development of multi-resistant organisms and incidence of antibiotic related infection such as C. Difficile.

Criteria for selecting high-priority research recommendations:

PICO question	What effect will the NICE Sepsis guideline have on patient care processes and outcome in the UK over the next 5 years?
Importance to patients or the population	The interventions recognised in this guideline as a standard of care for sepsis require timely, coordinated, and robust healthcare services. This is a complex intervention that needs assessment as such to allow changes to care to be monitored and evaluated to ensure improvement in care for people with sepsis.
Relevance to NICE guidance	Inform NICE of clinical effectiveness of guideline implementation and inform guideline updates.
Relevance to the NHS	Will provide information on guideline implementation which (along with mechanisms such as CQUIN) will drive service improvement.
National priorities	National Sepsis CQUIN NHS Ombudsman Report into Sepsis Sign up to Safety NHSE priorities
Current evidence base	Not applicable
Equality	None Relevant
Study design	Complex evaluation using the principles of process evaluation
Feasibility	Information governance and Caldicott issues will need to be addressed. The evaluation is feasible.
Other comments	
Importance	• High: the research is essential to inform NICE and local commissioners in gaps or difficulties in implementation of the guideline

N.3 Use of biomarkers to diagnose and initiate treatment

Research question:

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

Why this is important:

There is an urgent clinical need for accurate biomarkers of serious bacterial infection (SBI) which provide early diagnosis of SBI, and prompt clinical interventions to improve outcomes. The current tests used in the NHS (white cell count and C-reactive protein) are non-specific and not sensitive enough. Biomarker-guided initiation and termination of antibiotic therapy might be an effective strategy to reduce unnecessary antibiotic use and help prevent further multidrug resistance. The recent NICE Diagnostic Guidance (DG18) on Procalcitonin for diagnosing and monitoring sepsis has shown there is not enough evidence in this area.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults and children with suspected sepsis at triage in the UK Index test: PCT Comparison: CRP Outcomes: time to diagnosis of sepsis, antibiotic exposure (initiation of appropriate antibiotic therapy), duration of hospital stay, duration of ICU stay, adverse clinical outcomes (for example mortality, antibiotic-related adverse events)
Importance to patients or the population	The rapid and accurate determination of the presence or absence of systematic infection is important for patients' clinical outcomes and also to reduce unnecessary exposure to antibiotics.
Relevance to NICE guidance	Further research on PCT would provide a stronger evidence base in order for NICE to issue clear guidance for diagnosis of children, young people and adults with suspected sepsis
Relevance to the NHS	Antimicrobial stewardship is important for the NHS and accurate identification of the need for antibiotics would allow more targeted use of antibiotics. Better stratification of disease severity will reduce morbidity and mortality, and reduce NHS costs.
National priorities	National Sepsis CQUIN NHS Ombudsman Report into Sepsis Sign up to Safety NHSE priorities UK Five Year Antimicrobial Resistance Strategy 2013 to 2018
Current evidence base	The current evidence for PCT is is limited. The current evidence for CRP is considered in Chapter 8 of the full guideline.
Equality	There are no equality issues.
Study design	PCT and CRP would be evaluated by standard methods including specificities, sensitivities, receiver operator curves (ROCs) or area under the curves (AUC) for diagnosis of sepsis. Assessment of initiation of appropriate antibiotic therapy would be evaluated by hazard ratios, odds ratios and/or relative risk for duration of hospital stay, duration of ICU stay, and adverse clinical outcomes.
Feasibility	The study is feasible as currently CRP is routinely tested in people with suspected sepsis.
Other comments	The study may attract commercial funders in the diagnostics arena including companies developing novel PCT assays.

Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.4 Validation of clinical early warning scores in pre-hospital and emergency care settings

Research question:

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

Why this is important:

Delay in detecting and treating sepsis increases mortality. Early detection and appropriate management will reduce morbidity and mortality and will reduce NHS costs by reducing critical care admissions, inappropriate antimicrobial use and length of hospital stay. No high quality data exist on the validation or use of early warning scores in pre-hospital settings or in the emergency department settings. The use of scores might improve communication between pre-hospital settings and hospital settings and allow recognition of people who need more urgent assessment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: non-hospital based patients (both those totally managed in primary care and those who are transferred to secondary care), and patients managed in the emergency room with suspected sepsis in the UK. Intervention: (1) NEWS and (2) PEWS scores to direct care Comparison: No use of score to direct care Outcomes: referral rates, adverse clinical outcomes (for example mortality)
Importance to patients or the population	Timely diagnosis of sepsis and detection of worsening symptoms will improve patient outcomes.
Relevance to NICE guidance	Research would provide evidence to enable NICE to make recommendations on the use of NEWS and PEWS in the pre-hospital setting, emergency room or secondary care setting.
Relevance to the NHS	Prompt and early recognition of people with sepsis is critical to reducing morbidity and mortality and reducing NHS costs.
National priorities	NICE CG 50 Acutely ill patient in hospital: research recommendation re the sensitivity and specificity of track and trigger systems in various clinical settings NCEPOD Think Sepsis: recommends a standardised approach to vital signs monitoring in primary care, such as NEWS to help in the prioritisation of emergency care Ombudsman report 'Time to Kill': recommends the development of clinical tools highly predictive of sepsis to be used in primary care
Current evidence base	The development of the NICE guideline on sepsis found no evidence for use of validated tools in the pre-hospital or emergency room settings, and limited evidence in the emergency room and secondary care setting (chapter 6 of the guideline)
Equality	There are no equality issues.
Study design	Cluster randomised trial, or, if not feasible due to widespread NHS implementation following NCEPOD recommendation, observational score validation to establish: whether scores taken in primary/community care or the emergency room can differentiate patients requiring immediate escalation of care from those who can

	be managed less aggressively whether scores taken solely in the community can add to GPs or other health professional add to their assessments and clinical experience whether scores help communication between primary and secondary care and ambulances Whether scores in emergency room stings reduce the volume of empirical antimicrobial prescription, reduce critical care admissions, reduce length of stay or mortality
Feasibility	Baseline physiological measurements are already routinely taken in primary care but it is not usual practice to measure all the parameters and calculate a NEWS or PEWS score. It would require education and training of clinicians. In emergency room is feasible as baseline physiological measurements are routinely taken.
Other comments	
Importance	• High: The research is essential to inform future updates of key recommendations in the guideline.

N.5 Derivation of clinical decision rules in suspected sepsis

Research question:

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

Why this is important:

In primary care and emergency departments people with suspected sepsis are often seen by relatively inexperienced doctors. Many of these people will be in low and medium risk groups but evidence is lacking as to who can be sent home safely and who needs intravenous or oral antibiotics. The consequences of getting the decision making wrong can be catastrophic and therefore many patients are potentially over-investigated and admitted inappropriately. Current guidance is dependent on use of individual variables informed by low quality evidence.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults and children presenting to hospital with suspected sepsis in UK. Intervention: Derivation of history and physiological variables as well the application of diagnostic testing to be applied to patients fulfilling the inclusion criteria. Comparison: Normal practice/ guidelines. Outcome: diagnosis of sepsis, length of hospital stay, adverse clinical events (for example mortality)
Importance to patients or the population	Errors are still made with clinical decisions making in patients with suspected sepsis. Delays in initiating treatments can unfortunately lead to life-threatening consequences. Evidence based clinical decision rules would support safer decision making and improve patient safety
Relevance to NICE guidance	Would help to influence future guidelines in the moderate to low risk group.
Relevance to the NHS	Safer patient care. Cost reductions to allow early discharge of appropriate patients.
National priorities	Sepsis is high on the national agenda. Mortality rates are high and life-threatening treatments are occasionally omitted or delayed due to poor clinical decision making.
Current evidence base	The development of the NICE guideline on sepsis suggested that the current available evidence in this area is of poor quality and not fit for purpose.
Equality	None Relevant
Study design	Prognostic observational cohort study to identify risk factors for developing sepsis, and then validation of derived prediction tool in separate cohorts.
Feasibility	The research is feasible as comparable research has been achieved for other presentations, for example chest pains, DVTsGI Bleeds, headache, and head injuries
Other comments	The difficulty of diagnosing sepsis is the lack of an acceptable, recognised gold standard from which to work. Gold standard for a study may need to be developed by a Delphi method.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix O: NICE technical team

Name	Role
Sharon Summers-Ma	Guideline Lead
Martin Allaby	Clinical Advisor
Judith Thornton	Technical Lead (until November 2015)
Bhash Naidoo	Technical Lead (HE)
Caroline Keir	Guideline Commissioning Manager
Helen Dickinson	Guideline Coordinator
Gareth Haman	Editor
Rachel O'Mahony	Technical Lead (December 2015-present)
Laura Sadler	PIP Lead
Andrew Gyton	Project Manager

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