CQ2-3 (UnGRADE)

P: Patients who suspected infection/sepsis/septic shock
I: Gram stain
C: No intervention
O: Hospital mortality, length of ICU stay, serious adverse events, infectious complication, decrease blood pressure

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-2 (UnGRADE)

P: Patients with sepsis/septic shock (unknown focus)
I: Whole-body contrast CT examination
C: No CT examination
O: Mortality (28-days, hospital), length of ICU stay, contrast-induced nephropathy, risk of transfer

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ3-3 (UnGRADE)

P: Patients with sepsis (intra-abdominal infection)
I: Source control
C: No intervention
O: Mortality (28-days, hospital), length of ICU stay, length of hospital stay, complication due to intervention

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-4-1 (GRADE)

P: Patients with severe infected pancreatic necrosis
I: Early source control (within 48-72 hours)
C: Late source control (After 12 days)
O: Mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious	not serious	not serious	serious	none	14/25 (56.0%)	3/11 (27.3%)	**RR 2.05** (0.74 to 5.73)	**286 more per 1,000** (from 71 fewer to 1000 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-4-2 (GRADE)

P: Septic patients due to infected pancreatic necrosis
I: Minimum invasive source control
C: Invasive source control
O: Mortality (6 month, 3 year, 10 year), length of ICU stay, length of hospital stay, complication due to intervention

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (6M)												
2	randomised trials	serious	not serious	not serious	very serious	none	17/94 (18.1%)	13/92 (14.1%)	**RD 0.04** (-0.06 to 0.15)	**40 more per 1,000** (from 48 fewer to 211 more)	⨁◯◯◯ very Low	CRITICAL
Mortality (3Y)												
1	randomised trials	serious	not serious	not serious	very serious	none	8/43 (18.6%)	7/45 (15.6%)	**RD 0.03** (-0.16 to 0.19)	**31 more per 1,000** (from 82 fewer to 313 more)	⨁◯◯◯ very Low	CRITICAL
Mortality (10Y)												
1	randomised trials	serious	not serious	not serious	very serious	none	13/43 (30.2%)	9/45 (20.0%)	**RD 0.10** (-0.08 to 0.28)	**102 more per 1,000** (from 56 fewer to 434 more)	⨁◯◯◯ very Low	CRITICAL
Complication (6M)												
2	randomised trials	serious	serious	not serious	serious	none	22/94 (23.4%)	39/92 (42.4%)	**RD -0.19** (-0.45 to 0.06)	**187 fewer per 1,000** (from 305 fewer to 55 more)	⨁◯◯◯ very Low	CRITICAL
Length of ICU stay												
2	randomised trials	serious	serious	not serious	not serious	none	94	92	-	**MD 19.74 day more** (from 20.84 fewer to 60.31 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
2	randomised trials	serious	serious	not serious	not serious	none	94	92	-	**MD 7.76 day fewer** (from 27.86 fewer to 12.34 more)	⨁⨁◯◯ Low	Important

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-5 (UnGRADE)

P: Septic patients due to acute obstructive pyelonephritis
I: Source control
C: No intervention
O: Mortality (28-days, hospital), length of ICU stay, length of hospital stay, complication due to intervention

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-6 (UnGRADE)

P: Septic patients due to necrotizing soft tissue infection
I: Debridement
C: No intervention
O: Mortality (28-days, hospital), length of ICU stay, length of hospital stay, complication due to intervention

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-7 (UnGRADE)

P: Septic patients due to catheter related blood stream infection
I: Catheter removal
C: No intervention
O: Mortality (28-days, hospital), length of ICU stay, length of hospital stay, complication due to intervention

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ3-8 (UnGRADE)

P: Septic patients with empyema/ bronchopleural fistula/ pleurisy/ parapneumonic effusion
I: Source control
C: No intervention
O: Mortality (28-days, hospital), length of ICU stay, length of hospital stay, complication due to intervention

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ4-4 (UnGRADE)

P: Patients who suspected sepsis/ septic shock/ severe infection
I: Discontinuation of antimicrobial drugs when culture negative is found
C: Continuation of antimicrobial drugs after culture negative is found
O: Mortality, length of hospital stay, infection

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ4-6 (GRADE)

P: Patients with sepsis/ septic shock
I: Administration of antimicrobial drugs within 1 hour
C: Administration of antimicrobial drugs after 1 hour
O: Mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7	Observational study	very serious	not serious	not serious	not serious	none	1994/6458 (30.9%)	5411/16556 (32.7%)	**RR 0.97** (0.93 to 1.02)	**10 fewer per 1,000** (from 23 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

CQ4-7 (GRADE)

P: Patients with sepsis/ septic shock
I: Continuous infusion of beta-lactam antibiotic
C: Intermittent infusion of beta-lactam antibiotic
O: Mortality, clinical cure, side effect, drug-resistant bacterium, achieved target blood concentration

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	randomised trials	serious	not serious	not serious	serious	none	88/420 (21.0%)	112/424 (26.4%)	**RR 0.74** (0.49 to 1.12)	**69 fewer per 1,000** (from 135 fewer to 32 more)	⨁⨁◯◯ Low	CRITICAL
Clinical cure												
9	randomised trials	serious	not serious	not serious	not serious	Publication bias was suggested	245/443 (55.3%)	209/443 (47.2%)	**RR 1.24** (1.02 to 1.51)	**113 more per 1,000** (from 9 more to 241 more)	⨁⨁◯◯ Low	CRITICAL
Side effect												
3	randomised trials	serious	not serious	not serious	not serious	none	42/342 (12.3%)	43/349 (12.3%)	**RR 1.00** (0.67 to 1.48)	**0 fewer per 1,000** (from 41 fewer to 59 more)	⨁⨁⨁◯ Moderate	CRITICAL
Drug-resistant bacterium												
1	randomised trials	serious	not serious	not serious	serious	none	2/96 (2.1%)	4/102 (3.9%)	**RR 0.53** (0.10 to 2.83)	**18 fewer per 1,000** (from 35 fewer to 72 more)	⨁⨁◯◯ Low	CRITICAL
Achieved target blood concentration												
2	randomised trials	serious	not serious	not serious	not serious	none	71/90 (78.9%)	29/87 (33.3%)	**RR 2.35** (1.71 to 3.22)	**450 more per 1,000** (from 237 more to 740 more)	⨁⨁⨁◯ Moderate	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ4-8 (GRADE)

P: Patients with sepsis/ septic shock
I: De-escalation
C: Not de-escalation
O: Mortality (90-day, 28-day, longest observation period), superinfection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (90-day)												
1	randomised trials	serious	not serious	not serious	very serious	none	18/59 (30.5%)	13/57 (22.8%)	**RR 1.34** (0.72 to 2.47)	**78 more per 1,000** (from 64 fewer to 335 more)	⨁◯◯◯ Very low	CRITICAL
Superinfection												
1	randomised trials	serious	not serious	not serious	serious	none	6/57 (27.1%)	6/57 (10.5%)	**RR 2.58** (1.08 to 6.12)	**166 more per 1,000** (from 8 more to 539 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (longest observation period)												
13	observational study	serious	serious	not serious	not serious	none	229/1337 (17.1%)	544/2298 (23.7%)	**RR 0.66** (0.52 to 0.83)	**80 fewer per 1,000** (from 114 fewer to 40 fewer)	⨁◯◯◯ Very low	CRITICAL
Mortality (28-day)												
2	observational study	serious	serious	not serious	serious	none	15/244 (6.1%)	45/261 (17.2%)	**RR 0.48** (0.12 to 1.84)	**90 fewer per 1,000** (from 152 fewer to 145 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ4-9 (GRADE)

P: Patients with sepsis/ septic shock
I: Procalcitonin guided discontinuation
C: Not use procalcitonin guide
O: Mortality (28-day, hospital), recurrence of sepsis, duration of administration of antibacterial drugs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28-day)												
5	randomised trials	serious	not serious	not serious	not serious	none	320/1434 (22.3%)	379/1433 (26.4%)	**RR 0.84** (0.74 to 0.96)	**42 fewer per 1,000** (from 69 fewer to 11 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (Hospital)												
9	randomised trials	serious	not serious	not serious	not serious	none	256/1197 (21.4%)	321/1225 (26.2%)	**RR 0.81** (0.70 to 0.93)	**50 fewer per 1,000** (from 79 fewer to 18 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Recurrence of sepsis												
4	randomised trials	serious	not serious	not serious	serious	none	7/126 (5.6%)	6/135 (4.4%)	**RR 1.19** (0.40 to 3.55)	**8 more per 1,000** (from 27 fewer to 113 more)	⨁⨁◯◯ Low	CRITICAL
Duration of administration of antibacterial drugs												
3	randomised trials	serious	serious	not serious	serious	none	120	111	-	**MD 1.16 day fewer** (from 2.33 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

CQ4-10 (GRADE)

P: Patients with sepsis/ septic shock, Infectious patients who treated in ICU
I: Short-term antibiotic therapy (1 week)
C: Long-term antibiotic therapy (more than 1 week)
O: Mortality (28-day, longest observational period), clinical cure, recurrence of sepsis, drug-resistant bacterium

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28-day)												
3	randomised trials	not serious	not serious	not serious	serious	none	63/396 (15.9%)	61/408 (15.0%)	**RR 1.08** (0.77 to 1.52)	**12 more per 1,000** (from 34 fewer to 78 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (Longest observational period)												
4	randomised trials	serious	not serious	not serious	serious	none	73/512 (14.3%)	70/517 (13.5%)	**RR 1.08** (0.80 to 1.46)	**11 more per 1,000** (from 27 fewer to 62 more)	⨁⨁◯◯ Low	CRITICAL
Clinical cure												
2	randomised trials	serious	not serious	not serious	serious	none	135/195 (69.2%)	142/197 (72.1%)	**RR 0.93** (0.72 to 1.20)	**50 fewer per 1,000** (from 202 fewer to 144 more)	⨁⨁◯◯ Low	CRITICAL
Recurrence of sepsis												
3	randomised trials	serious	serious	not serious	serious	none	120/433 (27.7%)	89/429 (20.7%)	**RR 1.37** (1.00 to 1.89)	**77 more per 1,000** (from 0 fewer to 185 more)	⨁◯◯◯ Very low	CRITICAL
Drug-resistant bacterium												
2	randomised trials	serious	not serious	not serious	serious	none	49/127 (38.6%)	58/119 (48.7%)	**RR 0.73** (0.40 to 1.34)	**132 fewer per 1,000** (from 292 fewer to 166 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ5-1 (GRADE)

P: Patients with sepsis/ septic shock/ infection
I: Use of IVIG
C: Placebo or not use of IVIG
O: Mortality, length of ICU stay, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (All RCT)												
9	randomised trials	serious	not serious	serious	not serious	none	232/769 (30.2%)	271/709 (38.2%)	**RR 0.72** (0.58 to 0.90)	**107 fewer per 1,000** (from 161 fewer to 38 fewer)	⨁⨁◯◯ Low	CRITICAL
Mortality (Low RoB)												
3	randomised trials	not serious	not serious	serious	not serious	none	139/381 (36.5%)	131/364 (36.0%)	**RR 1.02** (0.84 to 1.23)	**7 more per 1,000** (from 58 fewer to 83 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of ICU stay												
4	randomised trials	serious	not serious	serious	not serious	none	233	202	-	**MD 1.1 day fewer** (from 5.44 fewer to 3.25 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events												
2	randomised trials	not serious	not serious	serious	very serious	none	15/371 (4.0%)	15/353 (4.2%)	**RR 0.97** (0.45 to 2.08)	**1 fewer per 1,000** (from 23 fewer to 46 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ5-2-1 (GRADE)

P: Septic patients due to streptococcal infection
I: Use of IVIG
C: Placebo or not use of IVIG
O: Mortality, length of ICU stay, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (STSS)												
1	randomised trials	not serious	not serious	serious	very serious	none	2/10 (20.0%)	4/11 (36.4%)	**RR 0.55** (0.13 to 2.38)	**164 fewer per 1,000** (from 316 fewer to 502 more)	⨁◯◯◯ Very low	CRITICAL
3	Observational study	very serious	not serious	serious	serious	none	11/58 (19.0%)	50/115 (43.5%)	**RR 0.42** (0.25 to 0.73)	**252 fewer per 1,000** (from 326 fewer to 117 fewer)	⨁◯◯◯ Very low	CRITICAL
Mortality (Study which use of CLDM)												
1	randomised trials	not serious	not serious	serious	very serious	none	1/8 (12.5%)	3/10 (30.0%)	**RR 0.42** (0.05 to 3.28)	**174 fewer per 1,000** (from 285 fewer to 684 more)	⨁◯◯◯ Very low	CRITICAL
4	observational study	serious	not serious	serious	serious	none	13/80 (16.3%)	29/95 (30.5%)	**RR 0.53** (0.30 to 0.94)	**143 fewer per 1,000** (from 214 fewer to 18 fewer)	⨁◯◯◯ Very low	CRITICAL
Sever adverse events												
1	randomised trials	not serious	not serious	serious	very serious	none	8/50 (16.0%)	11/50 (22.0%)	**RR 0.73** (0.32 to 1.65)	**59 fewer per 1,000** (from 150 fewer to 143 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ5-2-2 (UnGRADE)

P: Septic patients due to staphylococcus aureus
I: Use of IVIG
C: Placebo or not use of IVIG
O: Mortality, length of ICU stay, serious adverse events

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ6-1 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of echocardiography
C: Not use of echocardiography
O: Mortality (28-day), length of ICU stay

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28-day)												
1	randomised trials	serious	not serious	not serious	very serious	none	5/15 (33.3%)	3/15 (20.0%)	**RR 1.67** (0.48 to 5.76)	**134 fewer per 1,000** (from 104 fewer to 952 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
1	randomised trials	serious	not serious	not serious	very serious	none	15	15	-	**MD 0.3 day fewer** (from 4.46 fewer to 3.86 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-2 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of EGDT
C: Not use of EGDT
O: Mortality (28 or 30-day, 90-day), length of ICU stay, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
4	randomised trials	not serious	serious	not serious	not serious	none	403/1986 (20.3%)	425/2007 (21.2%)	**RR 0.96** (0.85 to 1.08)	**8 fewer per 1,000** (from 32 fewer to 17 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (90-day)												
3	randomised trials	not serious	not serious	not serious	not serious	none	461/1820 (25.3%)	470/1828 (25.7%)	**RR 0.98** (0.88 to 1.10)	**5 fewer per 1,000** (from 31 fewer to 26 more)	⨁⨁⨁⨁ High	CRITICAL
Length of ICU stay												
3	randomised trials	not serious	serious	not serious	not serious	none	1857	1880	-	**MD 0.22 day more** (from 0.13 fewer to 0.58 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												
3	randomised trials	not serious	serious	not serious	serious	none	109/1856 (5.9%)	105/1878 (5.6%)	**RR 1.02** (0.66 to 1.57)	**1 more per 1,000** (from 19 fewer to 32 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-3 (GRADE)

P: Patients with sepsis/ septic shock
I: Early use of vasopressor with initial fluid resuscitation
C: Only initial fluid resuscitation
O: Mortality (28 day, 90-day or longest observational period), serious adverse events (pulmonary edema, myocardial ischemia)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
2	randomised trials	not serious	serious	not serious	serious	none	27/204 (13.2%)	35/204 (17.2%)	**RR 0.77** (0.49 to 1.22)	**39 fewer per 1,000** (from 88 fewer to 38 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (90-day or longest observational period)												
2	randomised trials	not serious	not serious	not serious	serious	none	39/203 (19.2%)	41/202 (20.3%)	**RR 0.95** (0.64 to 1.40)	**10 fewer per 1,000** (from 73 fewer to 81 more)	⨁⨁◯◯ Low	CRITICAL
Pulmonary edema												
2	randomised trials	not serious	not serious	not serious	serious	none	23/205 (11.2%)	44/204 (21.6%)	**RR 0.52** (0.33 to 0.82)	**104 fewer per 1,000** (from 145 fewer to 39 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Myocardial ischemia												
2	randomised trials	not serious	not serious	not serious	very serious	none	7/205 (3.4%)	4/204 (2.0%)	**RR 1.74** (0.52 to 5.86)	**15 more per 1,000** (from 9 fewer to 95 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-4 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of lactate or lactate clearance
C: Not use of lactate or lactate clearance
O: Mortality (28 or 30 day, 90-day), length of ICU stay, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
5	randomised trials	not serious	serious	not serious	serious	none	204/738 (27.6%)	230/741 (31.0%)	**RR 0.80** (0.57 to 1.14)	**62 fewer per 1,000** (from 133 fewer to 43 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (90-day)												
2	randomised trials	not serious	serious	not serious	serious	none	156/383 (40.7%)	163/389 (41.9%)	**RR 0.95** (0.65 to 1.38)	**21 fewer per 1,000** (from 147 fewer to 159 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
3	randomised trials	not serious	not serious	not serious	serious	none	542	542	-	**MD 0.03 day more** (from 0.66 fewer to 0.72 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse event (SOFA score after 72 hours)												
3	randomised trials	not serious	serious	not serious	serious	none	487	492	-	**MD 0.04 more** (from 0.88 fewer to 0.96 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-7 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of crystalloid solution and albumin
C: Use of only crystalloid solution
O: Mortality (28 or 30 day), length of ICU stay, serious adverse events (lung injury score)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
3	randomised trials	not serious	not serious	not serious	serious	none	187/622 (30.1%)	220/631 (34.9%)	**RR 0.87** (0.74 to 1.02)	**45 fewer per 1,000** (from 91 fewer to 7 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of ICU stay												
1	randomised trials	not serious	not serious	not serious	very serious	none	603	615	-	**MD 0.7 day more** (from 0.1 fewer to 1.5 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse event (Lung injury score)												
1	randomised trials	not serious	not serious	not serious	serious	none	12	12	-	**MD 0.75 more** (from 0.22 more to 1.28 more)	⨁⨁⨁◯ Moderate	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-8 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of colloid solution and albumin
C: Use of only crystalloid solution
O: Mortality (28 or 30 day, 90 day or longest observational period), length of ICU stay, serious adverse events (use of dialysis, bleeding)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
4	randomised trials	serious	not serious	not serious	not serious	none	409/1293 (31.6%)	400/1293 (30.9%)	**RR 1.03** (0.92 to 1.15)	**9 more per 1,000** (from 25 fewer to 46 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (90 day or longest observational period)												
3	randomised trials	serious	serious	not serious	not serious	none	498/1271 (38.8%)	490/1274 (38.5%)	**RR 1.05** (0.84 to 1.32)	**19 more per 1,000** (from 62 fewer to 123 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	serious	not serious	very serious	none	109	105	-	**MD 1.13 day fewer** (from 8.28 fewer to 6.03 more)	⨁◯◯◯ Very low	CRITICAL
Serious adverse event (Use of dialysis)												
4	randomised trials	not serious	not serious	serious	not serious	none	268/1933 (13.9%)	264/1958 (13.5%)	**RR 1.12** (0.82 to 1.53)	**16 more per 1,000** (from 24 fewer to 71 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse event (Bleeding)												
2	randomised trials	not serious	not serious	serious	very serious	none	67/498 (13.5%)	45/496 (9.1%)	**RR 1.46** (1.03 to 2.07)	**42 more per 1,000** (from 3 more to 97 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-9-1 (GRADE)

P: Septic shock patients without vasopressor (initial fluid resuscitation did not archive target mean blood pressure)
I: Use of noradrenaline as the first line drug
C: Use of dopamine as the first line drug
O: Mortality (28 or 30 day, 90 day or longest observational period), length of ICU stay, time to resolution of shock, organ ischemia, arrythmia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
5	randomised trials	serious	not serious	not serious	serious	none	326/670 (48.7%)	390/727 (53.6%)	**RR 0.90** (0.81 to 1.00)	**54 fewer per 1,000** (from 102 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
arrythmia												
2	randomised trials	serious	not serious	serious	not serious	none	153/939 (16.3%)	274/992 (27.6%)	**RR 0.60** (0.50 to 0.71)	**110 fewer per 1,000** (from 138 fewer to 80 fewer)	⨁⨁◯◯ Low	CRITICAL
Myocardial ischemia												
1	randomised trials	not serious	not serious	serious	serious	none	2/821 (0.2%)	19/858 (2.2%)	**RR 0.11** (0.03 to 0.47)	**20 fewer per 1,000** (from 21 fewer to 12 fewer)	⨁⨁◯◯ Low	IMORTANT
Limb ischemia												
1	randomised trials	not serious	not serious	serious	very serious	none	14/821 (1.7%)	12/858 (1.4%)	**RR 1.22** (0.57 to 2.62)	**3 m**ore **per 1,000** (from 6 fewer to 23 more)	⨁◯◯◯ Very low	IMORTANT
Mesenteric ischemia												
1	randomised trials	not serious	not serious	serious	very serious	none	6/821 (0.7%)	11/858 (1.3%)	**RR 0.57** (0.21 to 1.53)	**6** fewer **per 1,000** (from 10 fewer to 7 more)	⨁◯◯◯ Very low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-9-2 (GRADE)

P: Septic shock patients without vasopressor (initial fluid resuscitation did not archive target mean blood pressure)
I: Use of noradrenaline as the first line drug
C: Use of phenylephrine as the first line drug
O: Mortality (28 or 30 day, 90 day or longest observational period), length of ICU stay, time to resolution of shock, organ ischemia, arrythmia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
3	randomised trials	serious	not serious	not serious	very serious	none	27/52 (51.9%)	28/51 (54.9%)	**RR 0.95** (0.67 to 1.36)	**27 fewer per 1,000** (from 181 fewer to 198 more)	⨁◯◯◯ Very low	CRITICAL
arrythmia												
1	randomised trials	serious	not serious	not serious	very serious	none	2/9 (22.2%)	1/8 (12.5%)	**RR 1.78** (0.20 to 16.10)	**98 more per 1,000** (from 100 fewer to 1000 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-10-1 (GRADE)

P: Septic shock patients (initial fluid resuscitation and the first line vasopressor did not archive target mean blood pressure)
I: Use of adrenaline as the second line drug
C: Not use of adrenaline as the second line drug
O: Mortality (28 day, 90 day), time to resolution of shock, organ ischemia, arrythmia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
2	randomised trials	not serious	not serious	serious	very serious	none	80/191 (41.9%)	73/199 (36.7%)	**RR 1.13** (0.89 to 1.45)	**48 more per 1,000** (from 40 fewer to 165 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (90 day)												
1	randomised trials	not serious	not serious	serious	very serious	none	84/161 (52.2%)	85/169 (50.3%)	**RR 1.04** (0.84 to 1.28)	**20 more per 1,000** (from 80 fewer to 141 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	not serious	very serious	serious	none	191	199	-	**MD 1 day fewer** (from 2.98 fewer to 0.98 more)	⨁◯◯◯ Very low	CRITICAL
Arrythmia												
2	randomised trials	not serious	not serious	serious	very serious	none	37/191 (19.4%)	34/199 (17.1%)	**RR 1.13** (0.74 to 1.73)	**22 more per 1,000** (from 44 fewer to 125 more)	⨁◯◯◯ Very low	CRITICAL
Limb ischemia												
2	randomised trials	not serious	not serious	serious	very serious	none	5/191 (2.6%)	8/199 (4.0%)	**RR 0.70** (0.17 to 2.91)	**12 fewer per 1,000** (from 33 fewer to 77 more)	⨁◯◯◯ Very low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-10-2 (GRADE)

P: Septic shock patients (initial fluid resuscitation and the first line vasopressor did not archive target mean blood pressure)
I: Use of vasopressin as the second line drug
C: Not use of vasopressin as the second line drug
O: Mortality (28 day, 90 day), time to resolution of shock, organ ischemia, arrythmia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
4	randomised trials	serious	not serious	serious	serious	none	217/636 (34.1%)	218/624 (34.9%)	**RR 0.97** (0.84 to 1.13)	**10 fewer per 1,000** (from 56 fewer to 45 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (90 day)												
1	randomised trials	not serious	not serious	serious	serious	none	177/400 (44.3%)	194/392 (49.5%)	**RR 0.89** (0.77 to 1.04)	**54 fewer per 1,000** (from 114 fewer to 20 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
3	randomised trials	not serious	not serious	serious	serious	none	602	615	-	**MD 0.16 day more** (from 1.84 fewer to 2.17 more)	⨁⨁◯◯ Low	CRITICAL
Arrythmia												
3	randomised trials	not serious	not serious	serious	very serious	none	11/616 (1.8%)	14/601 (2.3%)	**RR 0.77** (0.33 to 1.81)	**5 fewer per 1,000** (from 16 fewer to 19 more)	⨁◯◯◯ Very low	CRITICAL
Myocardial **ischemia**												
2	randomised trials	not serious	not serious	serious	very serious	none	15/601 (2.5%)	9/586 (1.5%)	**RR 1.67** (0.56 to 4.96)	**10 more per 1,000** (from 7 fewer to 61 more)	⨁◯◯◯ Very low	IMORTANT
Limb ischemia												
3	randomised trials	not serious	not serious	serious	serious	none	20/616 (3.2%)	5/601 (0.8%)	**RR 3.66** (1.44 to 9.30)	**22 more per 1,000** (from 4 more to 69 more)	⨁⨁◯◯ Low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ6-11 (UnGRADE)

P: Septic shock patients with depression of cardiac function
I: Use of inotropic agents
C: Not use of inotropic agents
O: Mortality (28 day, 90 day), time to resolution of shock, complication (organ dysfunction, arrythmia)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ6-12 (GRADE)

P: Patients with sepsis/ septic shock
I: Use of beta-blocker for rate control
C: Standard medication
O: Mortality (28 or 30 day, 90 day), length of ICU stay, length of hospital stay, serious adverse events (bradycardia, hypotension, arrythmia, organ dysfunction)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
2	randomised trials	serious	not serious	very serious	serious	none	50/107 (46.7%)	104/137 (75.9%)	**RR 0.60** (0.48 to 0.75)	**304 fewer per 1,000** (from 395 fewer to 190 fewer)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
1	randomised trials	serious	not serious	not serious	serious	none	33	9	-	**MD 4 day fewer** (from 18.06 fewer to 10.06 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU treatment												
1	randomised trials	serious	not serious	serious	serious	none	30	30	-	**MD 4.1 day more** (from 1.8 more to 6.4 more)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (bradycardia)												
1	randomised trials	serious	not serious	serious	very serious	none	2/30 (6.7%)	0/30 (0.0%)	**RR 5.00** (0.25 to 99.95)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (Use of renal replacement therapy)												
1	randomised trials	serious	not serious	not serious	very serious	none	31/77 (40.3%)	32/77 (41.6%)	**RR 0.97** (0.66 to 1.42)	**12 fewer per 1,000** (from 141 fewer to 175 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ7-1 (GRADE)

P: Septic shock patients (initial fluid resuscitation and vasopressor did not archive target mean blood pressure)
I: Use of steroid (hydrocortisone)
C: Not use of hydrocortisone
O: Mortality, resolution of shock, serious adverse events, adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
9	randomised trials	not serious	not serious	very serious	not serious	none	917/3208 (28.6%)	982/3216 (30.5%)	**RR 0.93** (0.87 to 1.01)	**21 fewer per 1,000** (from 40 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (more than 90 day)												
5	randomised trials	not serious	not serious	serious	not serious	none	1019/2859 (35.6%)	1079/2857 (37.8%)	**RR 0.94** (0.88 to 1.01)	**23 fewer per 1,000** (from 45 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
Resolution of shock												
5	randomised trials	not serious	very serious	serious	not serious	none	2323	2338	-	**MD 31.53 hour fewer** (from 36.6 fewer to 26.46 fewer)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events												
3	randomised trials	not serious	not serious	serious	not serious	none	350/2651 (13.2%)	384/2662 (14.4%)	**RR 0.93** (0.84 to 1.03)	**10 fewer per 1,000** (from 23 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
Infection												
7	randomised trials	not serious	not serious	serious	not serious	none	584/2914 (20.0%)	559/2911 (19.2%)	**RR 1.04** (0.94 to 1.16)	**8 more per 1,000** (from 12 fewer to 31 more)	⨁⨁⨁◯ Moderate	CRITICAL
Gastrointestinal bleeding												
6	randomised trials	not serious	not serious	serious	not serious	none	80/1079 (7.4%)	73/1082 (6.7%)	**RR 1.09** (0.80 to 1.48)	**6 more per 1,000** (from 13 fewer to 32 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hyperglycemia												
4	randomised trials	not serious	not serious	serious	not serious	none	773/2722 (28.4%)	709/2723 (26.0%)	**RR 1.10** (1.05 to 1.15)	**26 more per 1,000** (from 13 more to 39 more)	⨁⨁⨁◯ Moderate	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ7-2 (GRADE)

P: Septic shock patients (initial fluid resuscitation and vasopressor did not archive target mean blood pressure)
I: Use of hydrocortisone and fludrocortisone
C: Use of only hydrocortisone or placebo
O: Mortality, resolution of shock, serious adverse events, adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
2	randomised trials	not serious	not serious	not serious	not serious	none	289/764 (37.8%)	335/776 (43.2%)	**RR 0.88** (0.78 to 0.99)	**52 fewer per 1,000** (from 4 fewer to 95 fewer)	⨁⨁⨁⨁ High	CRITICAL
Mortality (Long-term)												
3	randomised trials	not serious	not serious	not serious	not serious	none	478/1009 (47.4%)	548/1040 (52.7%)	**RR 0.90** (0.83 to 0.98)	**53 fewer per 1,000** (from 11 fewer to 90 fewer)	⨁⨁⨁⨁ High	CRITICAL
Resolution of shock												
1	randomised trials	not serious	not serious	not serious	serious	none	83/150 (55.3%)	64/149 (43.0%)	**RR 1.29** (1.02 to 1.63)	**124 more per 1,000** (from 9 more to 271 more)	⨁⨁⨁◯ Moderate	CRITICAL
Superinfection												
3	randomised trials	not serious	serious	not serious	serious	none	266/1009 (26.4%)	242/1039 (23.3%)	**RR 1.14** (0.85 to 1.51)	**33 more per 1,000** (from 35 fewer to 119 more)	⨁⨁◯◯ Low	CRITICAL
Gastrointestinal bleeding												
2	randomised trials	not serious	not serious	not serious	very serious	none	50/764 (6.5%)	53/775 (6.8%)	**RR 0.96** (0.66 to 1.39)	**3 fewer per 1,000** (from 23 fewer to 27 more)	⨁⨁◯◯ Low	CRITICAL
Hyperglycemia												
3	randomised trials	not serious	not serious	not serious	not serious	none	547/614 (89.1%)	520/626 (83.1%)	**RR 1.07** (1.03 to 1.12)	**58 more per 1,000** (from 25 more to 100 more)	⨁⨁⨁⨁ High	IMORTANT
Mental disorder												
3	randomised trials	not serious	not serious	not serious	very serious	none	0/150 (0%)	1/149 (0.7%)	**RR 0.33** (0.01 to 8.06)	**4 fewer per 1,000** (from 6 fewer to 47 more)	⨁⨁◯◯ Low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ7-3 (GRADE)

P: Septic patients without shock
I: Use of hydrocortisone
C: Not use of hydrocortisone or use of placebo
O: Mortality, progress to shock, serious adverse events, adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
3	randomised trials	serious	not serious	not serious	very serious	none	25/217 (11.5%)	26/220 (11.8%)	**RR 0.98** (0.59 to 1.63)	**2 fewer per 1,000** (from 48 fewer to 74 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (Long-term)												
2	randomised trials	not serious	not serious	not serious	serious	none	38/191 (19.9%)	33/191 (17.3%)	**RR 1.15** (0.76 to 1.76)	**2**6 more **per 1,000** (from 42 fewer to 131 more)	⨁⨁⨁◯ Moderate	CRITICAL
Progress to shock												
1	randomised trials	not serious	not serious	not serious	very serious	none	36/179 (20.1%)	39/170 (22.9%)	**RR 0.88** (0.59 to 1.31)	27 fewer **per 1,000** (from 94 fewer to 71 more)	⨁⨁◯◯ Low	CRITICAL
Infection												
1	randomised trials	not serious	not serious	not serious	serious	none	40/186 (21.5%)	32/189 (16.9%)	**RR 1.27** (0.84 to 1.93)	**46 more per 1,000** (from 27 fewer to 157 more)	⨁⨁⨁◯ Moderate	CRITICAL
Gastrointestinal bleeding												
1	randomised trials	not serious	not serious	not serious	very serious	none	3/186 (1.6%)	2/189 (1.1%)	**RR 1.52** (0.26 to 9.02)	**6** more **per 1,000** (from 8 fewer to 85 more)	⨁⨁◯◯ Low	CRITICAL
Hypernatremia												
1	randomised trials	not serious	not serious	not serious	very serious	none	10/186 (5.4%)	10/189 (5.3%)	**RR 1.02** (0.43 to 2.38)	**1 m**ore **per 1,000** (from 30 fewer to 73 more)	⨁⨁◯◯ Low	CRITICAL
Hyperglycemia												
1	randomised trials	not serious	not serious	not serious	not serious	none	169/186 (90.9%)	154/189 (81.5%)	**RR 1.12** (1.03 to 1.21)	**98 more per 1,000** (from 24 fewer to 171 more)	⨁⨁⨁⨁ High	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ8-1 (GRADE)

P: Septic shock patients
I: Red blood cell transfusion threshold of Hb less than 7 g/dl
C: Red blood cell transfusion threshold of Hb less than 10 g/dl
O: Mortality (90 day), ischemic organ injury

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (90 day)												
1	randomised trials	serious	not serious	not serious	serious	none	216/502 (43.0%)	223/496 (45.0%)	**RR 0.96** (0.83 to 1.10)	**18 fewer per 1,000** (from 76 fewer to 45 more)	⨁⨁◯◯ Low	CRITICAL
Ischemic events												
1	randomised trials	serious	not serious	not serious	serious	none	35/488 (7.2%)	39/489 (8.0%)	**RR 0.90** (0.58 to 1.39)	**8 fewer per 1,000** (from 33 fewer to 31 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ8-2 (UnGRADE)

P: Septic patients without shock
I: Red blood cell transfusion threshold of Hb less than 7 g/dl
C: Red blood cell transfusion threshold of Hb less than 10 g/dl
O: Mortality (Hospital), length of ICU stay, infection, serious adverse event (TRALI, anaphylaxis etc.)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ8-3 (UnGRADE)

P: Septic patients
I: Use of flesh frozen plasma
C: Not use of flesh frozen plasma
O: Mortality (Hospital), length of ICU stay, infection, serious adverse event (TRALI, anaphylaxis etc.)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ8-4 (UnGRADE)

P: Septic patients
I: Use of platelet
C: Not use of platelet
O: Mortality (Hospital), length of ICU stay, infection, serious adverse event (TRALI, anaphylaxis etc.)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ9-1 (GRADE)

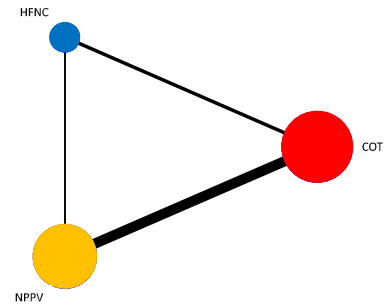
P: Septic patients
I: Higher SpO_2 target
C: Lower SpO_2 target
O: Mortality, organ dysfunction, infection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	not serious	not serious	serious	none	94/337 (27.9%)	75/336 (22.3%)	**RR 1.19** (0.83 to 1.70)	**42 more per 1,000** (from 38 fewer to 156 more)	⨁⨁⨁◯ Moderate	CRITICAL
Organ dysfunction												
1	randomised trials	not serious	not serious	not serious	serious	none	56/218 (25.7%)	41/216 (19.0%)	**RR 1.35** (0.94 to 1.92)	**66 more per 1,000** (from 11 fewer to 175 more)	⨁⨁⨁◯ Moderate	CRITICAL
Infection												
1	randomised trials	not serious	not serious	not serious	serious	none	50/218 (22.9%)	39/216 (18.1%)	**RR 1.27** (0.88 to 1.85)	**49 more per 1,000** (from 22 fewer to 153 more)	⨁⨁⨁◯ Moderate	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ9-2 (GRADE)

Mortality

Estimates of effects, confidence intervals, and certainly of the evidence for oxygen therapy in septic patients with acute respiratory failure.	
Frequency NMA-SoF table	
BENEFITS	
Patients or population: Septic patients with acute respiratory failure who need oxygen therapy Interventions: One of the following oxygen therapies: NPPV, HFNC, or COT Comparator (reference): One of the other therapies other than the therapy included in intervention Outcome: Short-term mortality Setting: In-hospital	**Network plot** 

Total studies: 19 Total Patients: 4,837		Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
			Without intervention	With intervention	Difference			
	NPPV (14 RCT; 2,359 participants)	0.88 (0.76 to 1.01) Network estimate	249 per 1000	219 per 1000	30 fewer per 1000 (60 fewer to 3 more)	⊕⊕◯◯ Low	2 (64.4)	-
	HFNC (5 RCT; 1,463 participants)	0.92 (0.80 to 1.07) Network estimate	306 per 1000	242 per 1000	65 fewer per 1000 (95 fewer to 28 more)	⊕⊕⊕◯ Moderate	1 (77.3)	-
	COT	Reference comparator	No estimable	No estimable	No estimable	-	3 (8.3)	-
	NPPV (3 RCT; 338 participants)	0.95 (0.78 to 1.16) Network estimate	157 per 1000	149 per 1000	8 fewer per 1000 (35 fewer to 25 more)	⊕⊕◯◯ Low	-	-
	HFNC	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Intubation

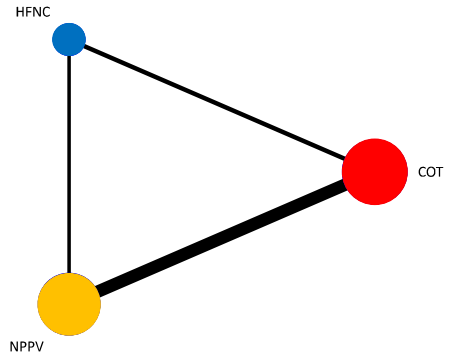
Estimates of effects, confidence intervals, and certainly of the evidence for oxygen therapy in septic patients with acute respiratory failure.

Frequency NMA-SoF table

BENEFITS

Patients or population: Septic patients with acute respiratory failure who need oxygen therapy
Interventions: One of the following oxygen therapies: NPPV, HFNC, or COT
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Intubation
Setting: In-hospital

Network plot



Total studies: 24 Total Patients: 4,261	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
NPPV (17 RCT; 2,506 participants)	0.81 (0.71 to 0.91) Network estimate	317 per 1000	257 per 1000	60 fewer per 1000 (92 fewer to 29 fewer)	⊕⊕◯◯ Low	2 (74.5)	-
HFNC (6 RCT; 1,563 participants)	0.79 (0.69 to 0.91) Network estimate	307 per 1000	243 per 1000	65 fewer per 1000 (95 fewer to 28 fewer)	⊕⊕⊕◯ Moderate	1 (74.7)	-
COT	Reference comparator	No estimable	No estimable	No estimable	-	3 (0.8)	-
NPPV (5 RCT; 584 participants)	1.02 (0.86 to 1.20) Network estimate	230 per 1000	235 per 1000	5 more per 1000 (32 fewer to 46 more)	⊕⊕◯◯ Low	-	-
HFNC	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Time to intubation

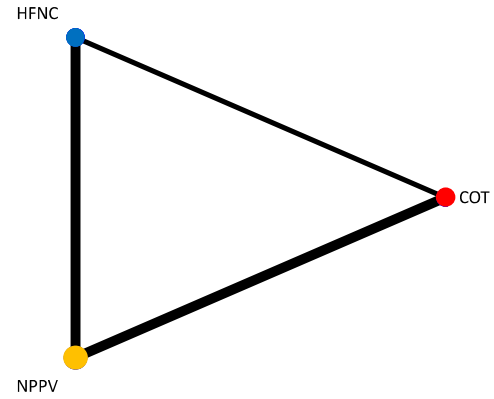
Estimates of effects, confidence intervals, and certainly of the evidence for oxygen therapy in septic patients with acute respiratory failure.

Frequency NMA-SoF table

BENEFITS

Patients or population: Septic patients with acute respiratory failure who need oxygen therapy
Interventions: One of the following oxygen therapies: NPPV, HFNC, or COT
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Time to intubation (hours)
Setting: In-hospital

Network plot



Total studies: 3 Total Patients: 606	Relative effect (95% CI)	Anticipated absolute effect (95% CI)		Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention			
NPPV (2 RCT; 284 participants)	-	The mean difference in time to intubation was 0 hours.	The mean difference in time to intubation was 0.53 higher (0.27 lower to 0.80 higher)	⊕⊕⊕⊕ High	2 (40.3)	-
HFNC (1 RCT; 200 participants)	-	The mean difference in time to intubation was 0 hours.	The mean difference in time to intubation was 1.15 higher (0.21 lower to 2.09 higher)	⊕⊕⊕⊕ High	1 (85.2)	-
COT	Reference comparator	No estimable	No estimable	-	3 (24.5)	-
NPPV (2 RCT; 432 participants)	-	The mean difference in time to intubation was 0 hours.	The mean difference in time to intubation was 0.62 lower (1.52 lower to 0.28 higher)	⊕⊕⊕◯ Moderate	-	-
HFNC	Reference comparator	No estimable	No estimable	-	-	-

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ9-3 (GRADE)

P: Septic patients
I: Lung protective ventilation
C: Conventional ventilation
O: Mortality, ventilator free days, barotrauma, ventilator associated pneumonia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	randomised trials	not serious	not serious	serious	not serious	none	446/1217 (36.6%)	482/1205 (40.0%)	**RR 0.91** (0.78 to 1.06)	**36 fewer per 1,000** (from 88 fewer to 24 more)	⨁⨁⨁◯ Moderate	CRITICAL
Ventilator free days												
3	randomised trials	not serious	serious	serious	serious	none	958	953	-	**MD 1.79 day higher** (from 0.62 lower to 4.2 higher)	⨁◯◯◯ Very low	CRITICAL
Barotrauma												
7	randomised trials	not serious	not serious	serious	very serious	none	71/1093 (6.5%)	79/1089 (7.3%)	**RR 0.89** (0.57 to 1.38)	**8 fewer per 1,000** (from 31 fewer to 28 more)	⨁◯◯◯ Very low	CRITICAL
Ventilator associated pneumonia												
1	randomised trials	serious	not serious	very serious	very serious	none	9/15 (60.0%)	6/13 (46.2%)	**RR 1.30** (0.63 to 2.67)	**138 more per 1,000** (from 171 fewer to 771 more)	⨁◯◯◯ Very low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ9-4 (GRADE)

P: Septic critically ill patients who need mechanical ventilation
I: High PEEP
C: Low PEEP
O: Mortality, ventilator free days, barotrauma, PaO_2/FiO_2 (Day 1 to 3), circulatory insufficient due to PEEP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7	randomised trials	not serious	not serious	serious	not serious	none	706/1815 (38.9%)	717/1842 (38.9%)	**RR 0.98** (0.86 to 1.12)	**8 fewer per 1,000** (from 54 fewer to 47 more)	⨁⨁⨁◯ Moderate	CRITICAL
Ventilator free days												
3	randomised trials	not serious	very serious	serious	not serious	none	827	827	-	**MD 0.45 day higher** (from 2.02 lower to 2.92 higher)	⨁◯◯◯ Very low	CRITICAL
Barotrauma												
6	randomised trials	not serious	serious	serious	very serious	none	122/1716 (7.1%)	101/1741 (5.8%)	**RR 1.08** (0.61 to 1.91)	**5 more per 1,000** (from 23 fewer to 53 more)	⨁◯◯◯ Very low	CRITICAL
PaO_2/FiO_2												
6	randomised trials	not serious	not serious	serious	not serious	none	1135	1174	-	**MD 57.71 higher** (from 35.13 higher to 80.3 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Circulatory insufficient due to PEEP												
1	randomised trials	serious	not serious	serious	not serious	none	174/501 (34.7%)	144/509 (28.3%)	**RR 1.23** (1.02 to 1.47)	**65 more per 1,000** (from 6 more to 133 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ9-5 (GRADE)

P: Patients who need mechanical ventilation
I: Protocol-directed weaning
C: Physician-directed weaning
O: Mortality, re-intubation (within 48-72 hours), ventilator free days, length of ICU stay

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
8	randomised trials	serious	not serious	not serious	very serious	none	104/640 (16.3%)	111/642 (17.3%)	**RR 0.94** (0.70 to 1.26)	**10 fewer per 1,000** (from 52 fewer to 45 more)	⨁◯◯◯ Very low	CRITICAL
Re-intubation												
7	randomised trials	serious	not serious	not serious	very serious	none	50/542 (11.1%)	59/539 (11.0%)	**RR 0.78** (0.45 to 1.37)	**24 fewer per 1,000** (from 61 fewer to 41 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
5	randomised trials	serious	not serious	not serious	serious	none	348	354	-	**MD 0.89 day lower** (from 2.73 lower to 0.95 higher)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ9-6 (GRADE)

Mortality

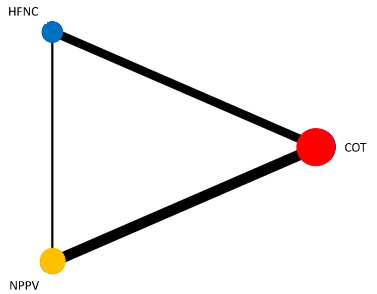
Estimates of effects, confidence intervals, and certainly of the evidence for oxygen therapy after extubation in patients recovering from sepsis

Frequency NMA-SoF table

BENEFITS

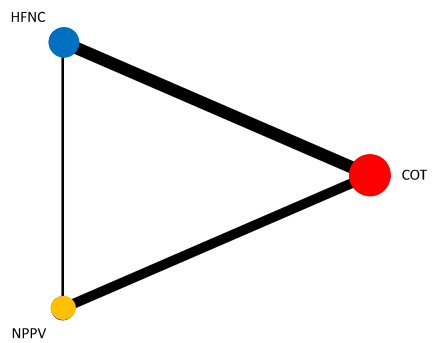
Patients or population: septic patients after extubation
Interventions: One of the following oxygen therapies: NPPV, HFNT, or COT
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Short-term mortality
Setting: In-hospital

Network plot



Total studies: 10 Total Patients: 2,190	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
NPPV (5 RCT; 784 participants)	0.70 (0.49 to 1.01) Network estimate	104 per 1000	73 per 1000	31 fewer per 1000 (53 fewer to 1 more)	⊕⊕⊕◯ Moderate	1 (91.8)	-
HFNT (4 RCT; 802 participants)	0.84 (0.58 to 1.21) Network estimate	75 per 1000	63 per 1000	12 fewer per 1000 (32 fewer to 16 more)	⊕⊕⊕◯ Moderate	2 (46.3)	-
COT	Reference comparator	No estimable	No estimable	No estimable	-	3 (11.8)	-
NPPV (1 RCT; 604 participants)	0.84 (0.62 to 1.12) Network estimate	269 per 1000	226 per 1000	43 fewer per 1000 (102 fewer to 32 more)	⊕⊕⊕◯ Moderate	-	-
HFNC	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Re-intubation

Estimates of effects, confidence intervals, and certainly of the evidence for oxygen therapy after extubation in patients recovering from sepsis	
Frequency NMA-SoF table	
BENEFITS	
Patients or population: septic patients after extubation Interventions: One of the following oxygen therapies: NPPV, HFNT, or COT Comparator (reference): One of the other therapies other than the therapy included in intervention Outcome: Reintubation Setting: In-hospital	**Network plot** 

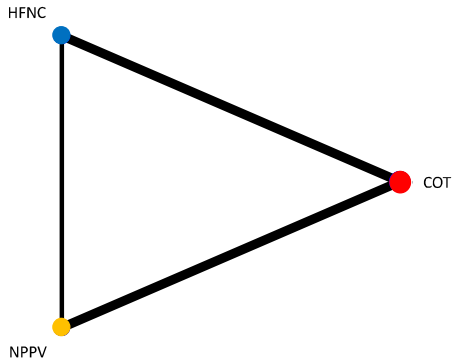
Total studies: 10 Total Patients: 2,130		Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
			Without intervention	With intervention	Difference			
●	NPPV (4 RCT; 664 participants)	0.52 (0.28 to 0.99) Network estimate	138 per 1000	72 per 1000	66 fewer per 1000 (99 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	2 (69.8)	-
●	HFNT (5 RCT; 862 participants)	0.49 (0.27 to 0.91) Network estimate	135 per 1000	66 per 1000	69 fewer per 1000 (99 fewer to 12 fewer)	⊕⊕◯◯ Low	1 (77.8)	-
●	COT	Reference comparator	No estimable	No estimable	No estimable	-	3 (2.8)	-
	NPPV (1 RCT; 604 participants)	1.07 (0.52 to 2.19) Network estimate	228 per 1000	244 per 1000	16 more per 1000 (109 fewer to 271 more)	⊕◯◯◯ Very low	-	-
	HFNC	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Respiratory failure

Estimates of effects, confidnce intervals, and certainly of the evidence for oxygen therapy after extubation in patients recovering from sepsis
Frequency NMA-SoF table
BENEFITS

Patients or population: septic patients after extubation
Interventions: One of the following oxygen therapies: NPPV, HFNT, or COT
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Respiratory failure
Setting: In-hospital

Network plot



Total studies: 5 Total Patients:1, 854	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
NPPV (2 RCT; 568 participants)	0.85 (0.58 to 1.24) Network estimate	188 per 1000	160 per 1000	28 fewer per 1000 (79 fewer to 45 more)	⊕⊕⊕◯ Moderate	1 (97.1)	-
HFNT (2 RCT; 682 participants)	0.61 (0.42 to 0.89) Network estimate	174 per 1000	106 per 1000	68 fewer per 1000 (101 fewer to 19 fewer)	⊕⊕⊕◯ Moderate	2 (42.1)	-
COT	Reference comparator	No estimable	No estimable	No estimable	-	3 (10.6)	-
NPPV (1 RCT; 604 participants)	1.39 (0.95 to 2.02) Network estimate	269 per 1000	374 per 1000	105 more per 1000 (13 fewer to 274 more)	⊕⊕⊕◯ Moderate	-	-
HFNC	Reference comparator	No estimable	No estimable	No estimable	-	-	-

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ10-1 (GRADE)

P: Critically ill patients under mechanical ventilation (sepsis, respiratory failure, heart failure, burn, major surgery)
I: Analgesia-first sedation protocol
C: Conventional management, hypnotic-based sedation protocol
O: Mortality, length of mechanical ventilation, ventilator free days, length of ICU stay, serious adverse event, delirium, agitation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious	not serious	serious	serious	none	119/511 (23.3%)	126/501 (25.1%)	**RR 0.93** (0.75 to 1.14)	**18 fewer per 1,000** (from 63 fewer to 35 more)	⨁⨁◯◯ Low	CRITICAL
Length of mechanical ventilation												
6	randomised trials	serious	serious	serious	serious	none	554	536	-	**MD 8.99 day lower** (from 20.66 lower to 2.68 higher)	⨁◯◯◯ Very low	CRITICAL
Ventilator free days												
1	randomised trials	not serious	not serious	serious	serious	none	55	58	-	**MD 4.2 day higher** (from 0.32 higher to 8.08 higher)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
6	randomised trials	serious	not serious	serious	serious	none	554	536	-	**MD 15.15 day lower** (from 26.08 lower to 4.22 lower)	⨁◯◯◯ Very low	CRITICAL
Serious complication												
7	randomised trials	not serious	not serious	serious	serious	none	47/647 (7.3%)	55/649 (8.5%)	**RR 0.85** (0.58 to 1.23)	**13 fewer per 1,000** (from 36 fewer to 19 more)	⨁⨁◯◯ Low	CRITICAL
Delirium												
1	randomised trials	serious	not serious	serious	serious	none	7/40 (17.5%)	9/39 (23.1%)	**RR 0.76** (0.31 to 1.84)	**55 fewer per 1,000** (from 159 fewer to 194 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ10-2 (GRADE)

P: Patients under mechanical ventilation
I: Propofol or dexmedetomidine
C: Benzodiazepine
O: Agitation, length of mechanical ventilation, length of ICU stay, mortality, accidental extubation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Agitation												
2	randomised trials	serious	not serious	not serious	serious	none	78/317 (24.6%)	99/315 (31.4%)	**RR 0.79** (0.62 to 1.01)	**66 fewer per 1,000** (from 119 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
Length of mechanical ventilation												
7	randomised trials	serious	serious	not serious	serious	none	668	546	-	**MD 1.56 day lower** (from 2.46 lower to 0.67 lower)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
11	randomised trials	serious	not serious	not serious	serious	none	816	698	-	**MD 2.06 day lower** (from 2.72 lower to 1.39 lower)	⨁⨁◯◯ Low	CRITICAL
Mortality												
10	randomised trials	serious	not serious	not serious	not serious	none	190/848 (22.4%)	157/725 (21.7%)	**RR 1.02** (0.85 to 1.23)	**4 more per 1,000** (from 32 fewer to 50 more)	⨁◯◯◯ Very low	CRITICAL
Accidental extubation												
3	randomised trials	serious	not serious	not serious	serious	none	20/179 (11.2%)	15/180 (8.3%)	**RR 1.37** (0.74 to 2.54)	**31 more per 1,000** (from 22 fewer to 128 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ10-3 (GRADE)

P: Patients under mechanical ventilation
I: Light sedation
C: Deep sedation
O: Length of mechanical ventilation, length of ICU stay, mortality, accidental extubation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Length of mechanical ventilation												
2	randomised trials	serious	not serious	not serious	serious	none	133	124	-	**MD 2.49 day lower** (from 4.43 lower to 0.54 lower)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
2	randomised trials	serious	not serious	not serious	serious	none	133	124	-	**MD 3.34 day lower** (from 6.09 lower to 0.60 lower)	⨁⨁◯◯ Low	CRITICAL
Mortality												
2	randomised trials	serious	not serious	not serious	serious	none	36/133 (27.1%)	39/124 (31.5%)	**RR 0.82** (0.57 to 1.19)	**57 fewer per 1,000** (from 135 fewer to 60 more)	⨁⨁◯◯ Low	CRITICAL
Accidental extubation												
1	randomised trials	serious	not serious	not serious	very serious	none	2/68 (2.9%)	4/60 (6.7%)	**RR 0.44** (0.08 to 2.32)	**37 fewer per 1,000** (from 61 fewer to 88 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ10-4 (GRADE)

P: Critically ill patients under mechanical ventilation (sepsis, respiratory failure, heart failure, burn, major surgery)
I: Dexmedetomidine, haloperidol, atypical antipsychotics, statin
C: Placebo
O: Mortality, cognitive disorder after ICU discharge, delirium, length of delirium (delirium free days), length of ICU stay, serious adverse event

Dexmedetomidine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	serious	not serious	not serious	serious	none	148/530 (27.9%)	164/531 (30.9%)	**RR 0.91** (0.76 to 1.09)	**28 fewer per 1,000** (from 74 fewer to 28 more)	⨁⨁◯◯ Low	CRITICAL
Cognitive disorder after ICU discharge (modified telephone interview for cognitive status: TICS-m)												
1	randomised trials	serious	not serious	serious	serious	none	221	213	-	**MD 4.7 higher** (from 3.78 higher to 5.62 higher)	⨁◯◯◯ Very low	CRITICAL
Length of delirium												
1	randomised trials	serious	not serious	not serious	very serious	none	50	50	-	**MD 0.2 day lower** (from 0.86 lower to 0.46 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium												
7	randomised trials	serious	serious	not serious	not serious	none	128/829 (15.4%)	247/829 (29.8%)	**RR 0.48** (0.32 to 0.72)	**155 fewer per 1,000** (from 203 fewer to 83 fewer)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events (acute coronary syndrome, pneumonia)												
2	randomised trials	serious	not serious	not serious	serious	none	3/130 (2.3%)	10/131 (7.6%)	**RR 0.31** (0.09 to 1.11)	**53 fewer per 1,000** (from 69 fewer to 8 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
5	randomised trials	serious	serious	not serious	serious	none	570	571	-	**MD 1.55 day lower** (from 3.82 lower to 0.72 higher)	⨁◯◯◯ Very low	IMPORTANT

Dexmedetomidine

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Haloperidol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7	randomised trials	not serious	not serious	serious	not serious	none	190/1199 (15.8%)	192/1172 (16.4%)	**RR 0.97** (0.81 to 1.16)	**5 fewer per 1,000** (from 31 fewer to 26 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of delirium												
3	randomised trials	not serious	not serious	serious	serious	none	174	173	-	**MD 0.02 higher** (from 0.23 lower to 0.27 higher)	⨁⨁◯◯ Low	CRITICAL
Delirium free days												
2	randomised trials	not serious	not serious	not serious	serious	none	803	777	-	**MD 0.66 lower** (from 1.42 lower to 0.11 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Delirium												
5	randomised trials	not serious	not serious	serious	serious	none	316/1093 (28.9%)	326/1066 (30.6%)	**RR 0.89** (0.70 to 1.13)	**34 fewer per 1,000** (from 92 fewer to 40 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events												
2	randomised trials	not serious	not serious	not serious	very serious	none	5/803 (0.6%)	6/777 (0.8%)	**RR 0.80** (0.24 to 2.66)	**2 fewer per 1,000** (from 6 fewer to 13 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
7	randomised trials	not serious	not serious	serious	not serious	none	1180	1153	-	**MD 0.07 lower** (from 0.26 lower to 0.11 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Haloperidol

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Atypical antipsychotics

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	serious	very serious	none	4/30 (13.3%)	6/36 (16.7%)	**RR 0.80** (0.25 to 2.57)	**33 fewer per 1,000** (from 125 fewer to 262 more)	⨁◯◯◯ Very low	CRITICAL
Length of delirium												
2	randomised trials	not serious	not serious	serious	serious	none	37	53	-	**MD 0.01 day higher** (from 1.13 lower to 1.16 higher)	⨁⨁◯◯ Low	CRITICAL
Delirium free days												
1	randomised trials	not serious	not serious	serious	very serious	none	30	36	-	**MD 3.73 higher** (from 1.01 lower to 8.47 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium												
2	randomised trials	not serious	not serious	serious	serious	none	14/114 (12.3%)	37/1113 (32.7%)	**RR 0.38** (0.22 to 0.66)	**203 fewer per 1,000** (from 255 fewer to 111 fewer)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
3	randomised trials	not serious	not serious	serious	serious	none	100	116	-	**MD 0.03 day lower** (from 0.67 lower to 0.61 higher)	⨁⨁◯◯ Low	IMPORTANT

Atypical antipsychotics

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	not serious	serious	none	30/71 (42.3%)	22/71 (31.0%)	**RR 1.36** (0.88 to 2.12)	**112 more per 1,000** (from 37 fewer to 347 more)	⨁⨁⨁◯ Moderate	CRITICAL
Cognitive disorder after ICU discharge												
1	randomised trials	very serious	not serious	serious	very serious	none	19/53 (35.8%)	29/77 (37.7%)	**RR 0.95** (0.60 to 1.51)	**19 fewer per 1,000** (from 151 fewer to 192 more)	⨁◯◯◯ Very low	CRITICAL
Delirium free days												
1	randomised trials	not serious	not serious	not serious	serious	none	71	71	-	**MD 1.1 lower** (from 4.74 lower to 2.54 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Delirium												
1	randomised trials	not serious	not serious	not serious	serious	none	66/71 (93.0%)	67/71 (94.4%)	**RR 0.99** (0.90 to 1.07)	**9 fewer per 1,000** (from 94 fewer to 66 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of ICU stay												
1	randomised trials	very serious	not serious	serious	serious	none	164	165	-	**MD 1 day higher** (from 0.84 lower to 2.84 higher)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	very serious	none	0/71 (0.0%)	0/71 (0.0%)	not estimate		⨁⨁◯◯ Low	CRITICAL

Statin

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ10-5 (GRADE)

P: Critically ill patients under mechanical ventilation (sepsis, respiratory failure, heart failure, burn, major surgery)
I: Dexmedetomidine, haloperidol, atypical antipsychotics
C: Placebo
O: Mortality, cognitive disorder after ICU discharge, delirium, length of delirium (delirium free days), length of ICU stay, serious adverse event

Dexmedetomidine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious	not serious	not serious	very serious	none	2/39 (5.1%)	0/32 (0.0%)	**RR 4.13** (0.21 to 82.95)	**0 more per 1,000** (from 0 fewer to 0 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
1	randomised trials	serious	not serious	not serious	very serious	none	39	32	-	**MD 1.37 day lower** (from 3.82 lower to 1.08 higher)	⨁◯◯◯ Very low	IMPORTANT

Dexmedetomidine

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Haloperidol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	not serious	serious	none	73/192 (38.0%)	63/184 (34.2%)	**RR 1.11** (0.85 to 1.45)	**38** more **per 1,000** (from 51 fewer to 154 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of delirium												
1	randomised trials	not serious	not serious	not serious	serious	none	192	184	-	**MD 0.34 day lower** (from 1.18 lower to 0.5 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Delirium free days												
1	randomised trials	not serious	not serious	not serious	very serious	none	192	184	-	**MD 0.33 day higher** (from 1.33 lower to 1.99 higher)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
1	randomised trials	not serious	not serious	not serious	very serious	none	192	184	-	**MD 0.33 day lower** (from 1.92 lower to 1.26 higher)	⨁⨁◯◯ Low	IMPORTANT

Haloperidol

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Atypical antipsychotics

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious	not serious	not serious	very serious	none	67/208 (32.2%)	66/202 (32.7%)	**RR 0.99** (0.75 to 1.30)	**3 fewer per 1,000** (from 82 fewer to 98 more)	⨁⨁◯◯ Low	CRITICAL
Length of delirium												
2	randomised trials	not serious	serious	not serious	serious	none	208	202	-	**MD 1.75 day lower** (from 4.31 lower to 0.81 higher)	⨁⨁◯◯ Low	CRITICAL
Delirium free days												
1	randomised trials	not serious	not serious	not serious	serious	none	190	184	-	**MD 1 day higher** (from 0.52 lower to 2.52 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	not serious	not serious	serious	none	208	202	-	**MD 1.1 day lower** (from 2.48 lower to 0.28 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Atypical antipsychotics

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ10-6 (GRADE)

P: Critically ill patients under mechanical ventilation (sepsis, respiratory failure, heart failure, burn, major surgery)
I: Improvement of sleep (sleeping mask, earplug, improvement of circadian rhythm), promotion of awaking (glasses, hearing aid, improvement of disorientation), relaxation
C: No intervention
O: Mortality, cognitive disorder after ICU discharge, delirium, length of delirium (delirium free days), length of ICU stay, serious adverse event

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (longest observational period)												
4	randomised trials	serious	not serious	not serious	serious	none	80/447 (17.9%)	83/437 (19.0%)	**RR 0.92** (0.70 to 1.22)	**15 fewer per 1,000** (from 57 fewer to 42 more)	⨁⨁◯◯ Low	CRITICAL
Cognitive disorder after ICU discharge (MMSE)												
1	randomised trials	very serious	not serious	not serious	very serious	none	18	14	-	**MD 0.2 higher** (from 1.27 lower to 1.67 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium free days												
2	randomised trials	very serious	not serious	not serious	serious	none	404	395	-	**MD 0.01 day higher** (from 1.22 lower to 1.24 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium												
6	randomised trials	serious	serious	not serious	serious	none	156/510 (30.6%)	151/518 (29.2%)	**RR 0.85** (0.49 to 1.45)	**44 fewer per 1,000** (from 149 fewer to 131 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
5	randomised trials	very serious	not serious	not serious	serious	none	457	447	-	**MD 0.14 day lower** (from 1.06 lower to 0.79 higher)	⨁◯◯◯ Very low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ11-1 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: Furosemide
C: Placebo or standard treatment, no intervention
O: Mortality, renal replacement therapy, resolution of AKI, duration of AKI

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (hospital)												
6	randomised trials	not serious	not serious	serious	serious	none	124/338 (36.7%)	100/311 (32.2%)	**RR 1.12** (0.92 to 1.38)	**39 more per 1,000** (from 26 fewer to 122 more)	⨁⨁◯◯ Low	CRITICAL
Renal replacement therapy												
3	randomised trials	not serious	serious	serious	very serious	none	35/105 (33.3%)	29/101 (28.7%)	**RR 1.14** (0.64 to 2.04)	**40 more per 1,000** (from 103 fewer to 299 more)	⨁◯◯◯ Very low	CRITICAL
Resolution of AKI												
5	randomised trials	not serious	not serious	serious	serious	none	146/304 (48.0%)	158/298 (53.0%)	**RR 0.91** (0.78 to 1.05)	**48 fewer per 1,000** (from 117 fewer to 27 more)	⨁⨁◯◯ Low	IMPORTANT
Duration of AKI (duration of renal replacement therapy)												
3	randomised trials	not serious	not serious	serious	serious	none	234	229	-	**MD 0.67 day lower** (from 2.36 lower to 1.01 higher)	⨁⨁◯◯ Low	IMPORTANT
Hearing impairment												
3	randomised trials	not serious	not serious	serious	very serious	none	4/235 (1.7%)	2/230 (0.9%)	**RR 1.68** (0.34 to 8.22)	**6 more per 1,000** (from 6 fewer to 63 more)	⨁◯◯◯ Very low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ11-2 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: ANP
C: Placebo or standard treatment, no intervention
O: Mortality, renal replacement therapy, length of ICU stay, resolution of AKI, complication (hypotension)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (hospital)												
3	randomised trials	not serious	not serious	serious	serious	none	143/386 (37.0%)	139/393 (35.4%)	**RR 1.05** (0.84 to 1.31)	**18 more per 1,000** (from 57 fewer to 110 more)	⨁⨁◯◯ Low	CRITICAL
Renal replacement therapy												
3	randomised trials	not serious	serious	serious	serious	none	188/386 (48.7%)	206/393 (52.4%)	**RR 0.89** (0.70 to 1.14)	**58 fewer per 1,000** (from 157 fewer to 73 more)	⨁◯◯◯ Very low	CRITICAL
Resolution of AKI												
2	randomised trials	not serious	serious	serious	serious	none	130/357 (36.4%)	138/371 (37.2%)	**RR 1.05** (0.70 to 1.59)	**19 more per 1,000** (from 112 fewer to 219 more)	⨁◯◯◯ Very low	IMPORTANT
Hypotension												
3	randomised trials	not serious	serious	serious	not serious	none	217/386 (56.2%)	109/393 (27.7%)	**RR 2.06** (1.37 to 3.09)	**294 more per 1,000** (from 103 more to 580 more)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

CQ11-3 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: Dopamine
C: Placebo or standard treatment, no intervention
O: Mortality, renal replacement therapy, resolution of AKI, complication (arrythmia)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (hospital)												
1	randomised trials	not serious	not serious	not serious	serious	none	69/161 (42.9%)	66/163 (40.5%)	**RR 1.06** (0.82 to 1.37)	**24 more per 1,000** (from 73 fewer to 150 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (ICU)												
1	randomised trials	not serious	not serious	not serious	serious	none	53/161 (32.9%)	58/163 (35.6%)	**RR 0.93** (0.68 to 1.25)	**25 fewer per 1,000** (from 114 fewer to 89 more)	⨁⨁⨁◯ Moderate	CRITICAL
Renal replacement therapy												
1	randomised trials	not serious	not serious	not serious	very serious	none	35/161 (21.7%)	40/163 (24.5%)	**RR 0.89** (0.60 to 1.32)	**27 fewer per 1,000** (from 98 fewer to 79 more)	⨁⨁◯◯ Low	CRITICAL
Arrythmia												
1	randomised trials	not serious	not serious	not serious	very serious	none	53/161 (32.9%)	54/163 (33.1%)	**RR 0.99** (0.73 to 1.35)	**3 fewer per 1,000** (from 89 fewer to 116 more)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ11-4 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: Continuous renal replacement therapy
C: Intermittent renal replacement therapy
O: Mortality, dialysis dependence, composite outcome (mortality and dialysis dependence), complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	serious	not serious	serious	not serious	none	256/419 (61.1%)	262/419 (62.5%)	**RR 0.99** (0.89 to 1.10)	**6 fewer per 1,000** (from 69 fewer to 63 more)	⨁⨁◯◯ Low	CRITICAL
Dialysis dependence												
2	randomised trials	serious	not serious	serious	very serious	none	5/98 (5.1%)	8/103 (7.8%)	**RR 0.64** (0.22 to 1.87)	**28 fewer per 1,000** (from 61 fewer to 68 more)	⨁◯◯◯ Very low	CRITICAL
Composite outcome (mortality and dialysis dependence)												
1	randomised trials	serious	not serious	serious	very serious	none	34/70 (48.6%)	29/55 (52.7%)	**RR 0.92** (0.65 to 1.30)	**42 fewer per 1,000** (from 185 fewer to 158 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding												
2	randomised trials	serious	not serious	serious	very serious	none	16/297 (5.4%)	18/312 (5.8%)	**RR 0.94** (0.49 to 1.80)	**3 fewer per 1,000** (from 29 fewer to 46 more)	⨁◯◯◯ Very low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

CQ11-5-1 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: Stage 2
C: Stage 3 or classic absolute indications
O: Mortality, dialysis dependence, composite outcome (mortality and dialysis dependence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (Longest observational period)												
1	randomised trials	not serious	not serious	serious	serious	none	56/111 (50.5%)	83/119 (69.7%)	**RR 0.72** (0.58 to 0.90)	**195 fewer per 1,000** (from 293 fewer to 70 fewer)	⨁⨁◯◯ Low	CRITICAL
Dialysis dependence (Longest observational period)												
1	randomised trials	not serious	not serious	serious	very serious	none	4/55 (7.3%)	4/36 (11.1%)	**RR 0.65** (0.17 to 2.45)	**39 fewer per 1,000** (from 92 fewer to 161 more)	⨁◯◯◯ Very low	IMPORTANT
Mortality or dialysis dependence (Longest observational period)												
1	randomised trials	not serious	not serious	serious	serious	none	60/111 (54.1%)	87/119 (73.1%)	**RR 0.74** (0.60 to 0.91)	**190 fewer per 1,000** (from 292 fewer to 66 fewer)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

CQ11-5-2 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: Stage 3
C: Classic absolute indications
O: Mortality, dialysis dependence, composite outcome (mortality and dialysis dependence), complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious	not serious	not serious	not serious	none	293/547 (53.6%)	287/543 (52.9%)	**RR 1.02** (0.91 to 1.14)	**11 more per 1,000** (from 48 fewer to 74 more)	⨁⨁⨁⨁ High	CRITICAL
Bleeding												
2	randomised trials	very serious	not serious	not serious	serious	none	39/557 (7.0%)	51/550 (9.3%)	**RR 0.76** (0.51 to 1.13)	**22 fewer per 1,000** (from 45 fewer to 12 more)	⨁◯◯◯ Very low	CRITICAL
Dialysis dependence												
2	randomised trials	very serious	not serious	not serious	very serious	none	5/258 (1.9%)	11/265 (4.2%)	**RR 0.47** (0.16 to 1.34)	**22 fewer per 1,000** (from 35 fewer to 14 more)	⨁◯◯◯ Very low	IMPORTANT
Mortality or dialysis dependence												
2	randomised trials	very serious	not serious	not serious	not serious	none	293/550 (53.3%)	292/546 (53.5%)	**RR 1.00** (0.89 to 1.13)	**0 fewer per 1,000** (from 59 fewer to 70 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

CQ11-6 (GRADE)

P: Septic AKI patients/ Critically ill patients with AKI
I: High dose renal replacement therapy
C: Low dose renal replacement therapy
O: Mortality, dialysis dependence, composite outcome (mortality and dialysis dependence), complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	not serious	serious	not serious	none	644/1385 (46.5%)	623/1404 (44.4%)	**RR 1.05** (0.97 to 1.13)	**22 more per 1,000** (from 13 fewer to 58 more)	⨁⨁◯◯ Low	CRITICAL
Dialysis dependence												
3	randomised trials	serious	not serious	serious	not serious	none	494/1032 (47.9%)	468/1064 (44.0%)	**RR 1.05** (0.98 to 1.13)	**22 more per 1,000** (from 9 fewer to 57 more)	⨁⨁◯◯ Low	CRITICAL
Composite outcome (mortality and dialysis dependence)												
3	randomised trials	serious	not serious	serious	not serious	none	889/1382 (64.3%)	868/1404 (61.8%)	**RR 1.02** (0.98 to 1.07)	**12 more per 1,000** (from 12 fewer to 43 more)	⨁⨁◯◯ Low	CRITICAL
Hypophosphatemia												
2	randomised trials	serious	not serious	serious	not serious	none	560/1271 (44.1%)	457/1294 (35.3%)	**RR 1.35** (1.01 to 1.81)	**124 more per 1,000** (from 4 more to 286 more)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ11-7 (GRADE)

P: Septic patients
I: PMX-DHP
C: Not use of PMX-DHP, standard treatment
O: Mortality, adverse events, organ injury score (72 hours), catecholamine free days

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	very serious	not serious	serious	none	167/373 (44.8%)	138/359 (38.4%)	**RR 1.03** (0.68 to 1.58)	**12 more per 1,000** (from 123 fewer to 223 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
2	randomised trials	not serious	not serious	serious	not serious	none	93/343 (27.1%)	82/339 (24.2%)	**RR 1.07** (0.92 to 1.24)	**17 more per 1,000** (from 19 fewer to 58 more)	⨁⨁⨁◯ Moderate	CRITICAL
Organ injury score												
2	randomised trials	not serious	not serious	not serious	not serious	none	343	339	-	**MD 0.01 higher** (from 0.37 lower to 0.4 higher)	⨁⨁⨁⨁ High	IMPORTANT
Catecholamine free days												
1	randomised trials	serious	not serious	not serious	serious	none	119	113	-	**MD 1.8 day lower** (from 4.14 lower to 0.54 higher)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ12-1 (GRADE)

P: Patients in intensive care units
I: Enteral nutrition
C: Parental nutrition
O: Mortality, length of hospital stay, length of mechanical ventilation, infection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (90 day)												
4	randomised trials	serious	not serious	not serious	not serious	none	1015/2424 (41.9%)	962/2420 (39.8%)	**RR 1.05** (0.95 to 1.17)	**20 more per 1,000** (from 20 fewer to 68 more)	⨁⨁⨁◯ Moderate	CRITICAL
Length of hospital stay												
10	randomised trials	very serious	very serious	serious	serious	none	2767	2748	-	**MD 2.51 day lower** (from 4.78 lower to 0.24 lower)	⨁◯◯◯ Very low	CRITICAL
Length of mechanical ventilation												
4	randomised trials	very serious	very serious	not serious	serious	none	277	286	-	**MD 0.36 day lower** (from 0.93 lower to 0.2 higher)	⨁◯◯◯ Very low	CRITICAL
Sepsis (Blood stream infection)												
9	randomised trials	very serious	not serious	not serious	serious	none	51/1479 (3.5%)	82/1497 (5.5%)	**RR 0.66** (0.41 to 1.07)	**19 fewer per 1,000** (from 32 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL
Pneumonia (Ventilator associated pneumonia)												
8	randomised trials	serious	not serious	not serious	serious	none	150/1520 (9.9%)	181/1546 (11.7%)	**RR 0.85** (0.65 to 1.10)	**18 fewer per 1,000** (from 41 fewer to 12 more)	⨁⨁◯◯ Low	CRITICAL
Abdominal infection (Abdominal abscess, necrotizing pancreatitis)												
7	randomised trials	serious	not serious	not serious	not serious	none	48/1612 (3.0%)	100/1547 (6.5%)	**RR 0.39** (0.29 to 0.53)	**39 fewer per 1,000** (from 46 fewer to 30 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ12-2 (GRADE)

P: Critically ill patients who received catecholamine/ Hypotensive patients in intensive care units
I: Enteral nutrition
C: Parental nutrition
O: Mortality, length of hospital stay, serious adverse event, infection, serious intestinal complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Length of hospital stay												
1	randomised trials	serious	not serious	not serious	not serious	none	1202	1208	-	**MD 1 day lower** (from 2.42 lower to 0.42 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (90 day)												
1	randomised trials	not serious	not serious	not serious	not serious	none	530/1202 (44.1%)	507/1208 (42.0%)	**RR 1.05** (0.96 to 1.15)	**21 more per 1,000** (from 17 fewer to 63 more)	⨁⨁⨁⨁ High	CRITICAL
Intestinal pseudo-obstruction												
1	randomised trials	serious	not serious	not serious	serious	none	11/1202 (0.9%)	3/1208 (0.2%)	**RR 3.69** (1.03 to 12.93)	**7 more per 1,000** (from 0 fewer to 30 more)	⨁⨁◯◯ Low	CRITICAL
Intensive care unit acquired infection)												
1	randomised trials	serious	not serious	not serious	serious	none	173/1202 (14.4%)	194/1208 (16.1%)	**RR 0.90** (0.74 to 1.08)	**16 fewer per 1,000** (from 42 fewer to 13 more)	⨁⨁◯◯ Low	CRITICAL
Intestinal ischemia												
1	randomised trials	serious	not serious	not serious	very serious	none	19/1202 (1.6%)	5/1208 (0.4%)	**RR 3.82** (1.43 to 10.19)	**12 more per 1,000** (from 2 more to 38 more)	⨁◯◯◯ Very low	CRITICAL
Vomit												
1	randomised trials	serious	not serious	not serious	not serious	none	406/1202 (33.8%)	246/1208 (20.4%)	**RR 1.66** (1.46 to 1.87)	**134 more per 1,000** (from 94 more to 177 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Diarrhea												
1	randomised trials	serious	not serious	not serious	not serious	none	432/1202 (35.9%)	393/1208 (32.5%)	**RR 1.10** (0.99 to 1.23)	**33 more per 1,000** (from 3 fewer to 75 more)	⨁⨁⨁◯ Moderate	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ12-3 (GRADE)

P: Critically ill patients in intensive care units
I: Early enteral nutrition (within 24-48 hours)
C: Late enteral nutrition
O: Mortality, length of hospital stay, serious adverse event, infection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
13	randomised trials	serious	not serious	not serious	serious	Publication bias was suspected	34/350 (9.7%)	47/359 (13.1%)	**RR 0.79** (0.52 to 1.19)	**27 fewer per 1,000** (from 63 fewer to 25 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (ICU)												
2	randomised trials	serious	not serious	not serious	serious	none	4/41 (9.8%)	5/39 (12.8%)	**RR 0.81** (0.27 to 2.39)	**24 fewer per 1,000** (from 94 fewer to 178 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (Hospital)												
2	randomised trials	serious	not serious	not serious	very serious	none	2/47 (4.3%)	1/48 (2.1%)	**RR 2.00** (0.19 to 20.90)	**21 more per 1,000** (from 17 fewer to 415 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
6	randomised trials	serious	serious	not serious	serious	none	118	115	-	**MD 0.38 day higher** (from 3.89 lower to 4.65 higher)	⨁◯◯◯ Very low	CRITICAL
Length of hospital stay												
5	randomised trials	serious	serious	not serious	serious	none	107	110	-	**MD 0.41 day higher** (from 2.71 lower to 3.53 higher)	⨁◯◯◯ Very low	CRITICAL
Pneumonia												
6	randomised trials	serious	not serious	not serious	serious	none	60/216 (27.8%)	83/225 (36.9%)	**RR 0.77** (0.53 to 1.11)	**85 fewer per 1,000** (from 173 fewer to 41 more)	⨁◯◯◯ Very low	CRITICAL
Bacteremia												
6	randomised trials	serious	not serious	not serious	serious	none	59/205 (28.8%)	38/149 (25.5%)	**RR 1.19** (0.73 to 1.94)	**48 more per 1,000** (from 69 fewer to 240 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ12-4 (GRADE)

P: Critically ill patients in intensive care units
I: Patients receive enteral nutrition less than their energy expenditure
C: Patients receive enteral nutrition as same as their energy expenditure
O: Mortality, length of hospital stay, serious adverse event, infection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
18	randomised trials	not serious	not serious	not serious	not serious	none	1277/6317 (20.2%)	1297/6262 (20.7%)	**RR 0.99** (0.89 to 1.10)	**2 fewer per 1,000** (from 23 fewer to 21 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (Hospital)												
10	randomised trials	not serious	serious	not serious	not serious	none	949/5312 (17.9%)	978/5269 (18.6%)	**RR 0.96** (0.83 to 1.12)	**7 fewer per 1,000** (from 32 fewer to 22 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
10	randomised trials	not serious	serious	not serious	not serious	none	3371	3357	-	**MD 0.35 day lower** (from 2.68 lower to 1.99 higher)	⨁⨁◯◯ Low	CRITICAL
Infection												
11	randomised trials	not serious	serious	not serious	not serious	none	751/3144 (23.9%)	810/3101 (26.1%)	**RR 0.99** (0.83 to 1.18)	**3 fewer per 1,000** (from 44 fewer to 47 more)	⨁⨁◯◯ Low	CRITICAL
Pneumonia												
10	randomised trials	not serious	not serious	not serious	serious	none	600/3935 (15.2%)	686/3843 (17.9%)	**RR 0.86** (0.72 to 1.02)	**25 fewer per 1,000** (from 50 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
Bacteremia												
9	randomised trials	not serious	not serious	not serious	not serious	none	460/5416 (8.5%)	491/5352 (9.2%)	**RR 0.94** (0.80 to 1.12)	**6 fewer per 1,000** (from 18 fewer to 11 more)	⨁⨁⨁◯ Moderate	CRITICAL
Catheter related blood stream infection												
5	randomised trials	not serious	not serious	not serious	very serious	Publication bias was suspected	19/816 (2.3%)	36/792 (4.5%)	**RR 0.59** (0.26 to 1.33)	**19 fewer per 1,000** (from 34 fewer to 15 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ12-5 (GRADE)

P: Critically ill patients in intensive care units
I: Use of supplemental parental nutrition
C: Not use of supplemental parental nutrition
O: Mortality, infection

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (90 day)												
1	randomised trials	not serious	not serious	not serious	very serious	none	17/60 (28.3%)	18/60 (30.0%)	**RR 0.94** (0.54 to 1.65)	**18 fewer per 1,000** (from 138 fewer to 195 more)	⨁⨁◯◯ Low	CRITICAL
Blood stream infection												
3	randomised trials	serious	serious	not serious	very serious	none	19/241 (7.9%)	22/263 (8.4%)	**RR 1.07** (0.26 to 4.50)	**6 more per 1,000** (from 62 fewer to 293 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory infection												
4	randomised trials	serious	not serious	not serious	serious	none	70/301 (23.3%)	98/323 (30.3%)	**RR 0.79** (0.53 to 1.16)	**64 fewer per 1,000** (from 143 fewer to 49 more)	⨁⨁◯◯ Low	CRITICAL
Urinary tract infection												
3	randomised trials	serious	not serious	not serious	very serious	none	24/265 (9.1%)	23/285 (8.1%)	**RR 1.31** (0.50 to 3.46)	**25 more per 1,000** (from 40 fewer to 199 more)	⨁◯◯◯ Very low	CRITICAL
Abdominal infection												
2	randomised trials	serious	not serious	not serious	very serious	none	12/205 (5.9%)	8/225 (3.6%)	**RR 2.47** (0.21 to 29.33)	**52 more per 1,000** (from 28 fewer to 1000 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ12-6 (GRADE)

P: Critically ill patients in intensive care units
I: Patients receive more than 1 g/kg/day of protein
C: Patients receive less than 1 g/kg/day of protein
O: Mortality, length of hospital stay, length of mechanical ventilation, duration of antimicrobial agents, ADL score, physical function, muscle volume

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious	not serious	serious	serious	none	65/366 (17.8%)	66/364 (18.1%)	**RR 0.98** (0.72 to 1.34)	**4 fewer per 1,000** (from 51 fewer to 62 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
5	randomised trials	serious	not serious	serious	not serious	none	369	364	-	**MD 2.36 day higher** (from 1.42 lower to 6.15 higher)	⨁⨁◯◯ Low	CRITICAL
Length of mechanical ventilation												
5	randomised trials	serious	not serious	serious	not serious	none	390	387	-	**MD 0.07 day higher** (from 0.02 lower to 0.16 higher)	⨁⨁◯◯ Low	CRITICAL
Duration of antimicrobial agent												
1	randomised trials	serious	not serious	serious	not serious	none	239	235	-	**MD 0.15 day higher** (from 0.07 higher to 0.23 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function												
3	randomised trials	serious	not serious	serious	serious	none	250	239	-	**MD 0.45 higher** (from 4.57 lower to 5.46 higher)	⨁◯◯◯ Very low	CRITICAL
Muscle volume												
2	randomised trials	serious	not serious	serious	serious	none	77	80	-	**MD 0.2 higher** (from 0.56 lower to 0.96 higher)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ12-7-1 (GRADE)

P: Critically ill patients in intensive care units
I: Use of vitamin C
C: Placebo or not use of vitamin C
O: Mortality, length of hospital stay, acute kidney injury

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
5	randomised trials	not serious	serious	not serious	serious	none	248/837 (29.6%)	246/809 (30.4%)	**RR 0.82** (0.57 to 1.17)	**55 fewer per 1,000** (from 131 fewer to 52 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (Hosiptal)												
7	randomised trials	serious	serious	not serious	serious	none	321/923 (36.2%)	317/875 (36.2%)	**RR 0.93** (0.71 to 1.23)	**25 fewer per 1,000** (from 105 fewer to 83 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
6	randomised trials	serious	not serious	not serious	not serious	none	717	677	-	**MD 0.58 day lower** (from 1.45 lower to 0.28 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Length of hospital stay												
5	randomised trials	serious	not serious	not serious	not serious	none	802	754	-	**MD 0.64 day higher** (from 1.24 lower to 2.52 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Acute kidney injury												
2	randomised trials	serious	not serious	not serious	serious	none	75/126 (59.5%)	75/122 (61.5%)	**RR 0.97** (0.82 to 1.15)	**18 fewer per 1,000** (from 111 fewer to 92 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ12-7-2 (GRADE)

P: Critically ill patients in intensive care units
I: Use of vitamin D
C: Placebo or not use of vitamin D
O: Mortality, length of hospital stay, hypercalcemia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 or 30 day)												
6	randomised trials	not serious	not serious	serious	serious	none	166/991 (16.8%)	161/975 (16.5%)	**RR 0.95** (0.70 to 1.28)	**8 fewer per 1,000** (from 50 fewer to 46 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (90 day)												
3	randomised trials	not serious	not serious	very serious	serious	none	132/584 (22.6%)	113/573 (19.7%)	**RR 1.14** (0.91 to 1.43)	**28 more per 1,000** (from 18 fewer to 85 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (Hospital)												
4	randomised trials	serious	not serious	serious	serious	none	78/317 (24.6%)	107/315 (34.0%)	**RR 0.72** (0.47 to 1.12)	**95 fewer per 1,000** (from 180 fewer to 41 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
6	randomised trials	not serious	serious	serious	not serious	none	358	337	-	**MD 0.24 day lower** (from 3.72 lower to 3.23 higher)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
9	randomised trials	serious	very serious	serious	not serious	none	948	938	-	**MD 0.32 day lower** (from 2.15 lower to 1.5 higher)	⨁◯◯◯ Very low	CRITICAL
Hypercalcemia												
5	randomised trials	not serious	serious	serious	very serious	none	15/637 (59.5%)	15/639 (2.3%)	**RR 0.70** (0.13 to 3.77)	**7 fewer per 1,000** (from 20 fewer to 65 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

CQ13-1 (GRADE)

P: Patients in intensive care unit
E: Glucometer (capillary blood)
C: Arterial blood gas analyzer (arterial/ venous blood), glucometer (arterial/ venous blood)
O: Mortality, infection, hypoglycemia, significantly outside the acceptable range

Arterial blood gas analyzer (arterial/ venous blood) vs glucometer (capillary blood)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucometer (capillary blood)	Blood gas analyzer (arterial/ venous blood)	Relative (95% CI)	Absolute (95% CI)		
Significantly outside the acceptable range												
3	observational study	not serious	not serious	not serious	not serious	none	79/1888 (4.2%)	2/912 (0.2%)	**RR 21.56** (6.15 to 75.57)	**45 more per 1,000** (from 11 more to 164 more)	⨁⨁⨁⨁ High	CRITICAL

Arterial blood gas analyzer (arterial/ venous blood) vs glucometer (arterial/ venous blood)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood gas analyzer (arterial/ venous blood)	Glucometer (arterial/ venous blood)	Relative (95% CI)	Absolute (95% CI)		
Significantly outside the acceptable range												
5	observational study	not serious	not serious	not serious	serious	none	3/1232 (0.2%)	38/3089 (1.2%)	**RR 0.18** (0.03 to 1.02)	**10 fewer per 1,000** (from 12 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Glucometer (arterial/ venous blood) vs glucometer (capillary blood)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucometer (capillary blood)	Glucometer (arterial/ venous blood)	Relative (95% CI)	Absolute (95% CI)		
Significantly outside the acceptable range												
8	observational study	not serious	not serious	not serious	not serious	none	249/2759 (9.0%)	164/3165 (5.2%)	**RR 2.11** (1.23 to 3.59)	**58 more per 1,000** (from 12 more to 134 more)	⨁⨁⨁⨁ High	CRITICAL

Arterial blood gas analyzer/ glucometer (arterial/ venous blood) vs glucometer (capillary blood)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucometer (capillary blood)	Blood gas analyzer/ glucometer (arterial/ venous blood)	Relative (95% CI)	Absolute (95% CI)		
Significantly outside the acceptable range												
3	observational study	not serious	not serious	not serious	not serious	none	79/1888 (4.2%)	30/3187 (0.9%)	**RR 5.12** (2.47 to 10.59)	**39 more per 1,000** (from 14 more to 90 more)	⨁⨁⨁⨁ High	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ13-2 (GRADE)

Mortality

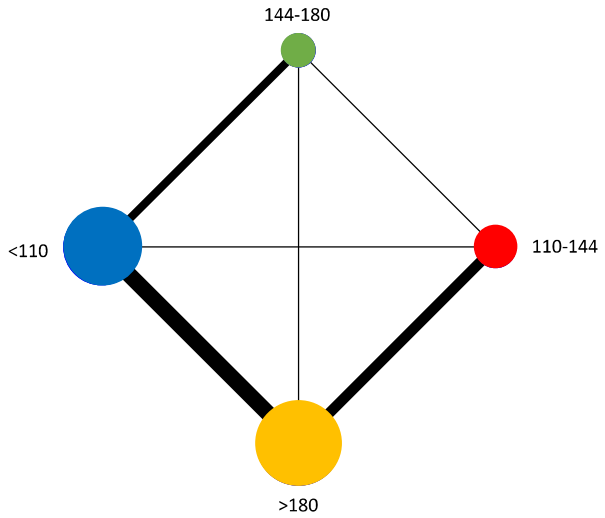
Estimates of effects, credible intervals, and certainly of the evidence for blood sugar level in septic patients.

Frequency NMA-SoF table

BENEFITS

Patients or population: septic patients
Interventions: One of the following oxygen therapies: <110, 110-144, 144-180, >180
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Short-term mortality
Setting: In-hospital

Network plot



Total studies: Total Patients:	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
>180 (12 RCT; 8,027 participants)	1.01 (0.95 to 1.08) Network estimate	432 per 1000	436 per 1000	4 more per 1000 (22 fewer to 35 more)	⊕⊕⊕⊕ High	4 (16.5)	-
144-180 (5 RCT; 7,323 participants)	0.90 (0.83 to 0.97) Network estimate	267 per 1000	240 per 1000	27 fewer per 1000 (45 fewer to 8 fewer)	⊕⊕⊕⊕ High	1 (81.0)	-

	110-144 (1 RCT; 90 participants)	0.88 (0.71 to 1.09) Network estimate	333 per 1000	293 per 1000	40 fewer per 1000 (100 fewer to 30 more)	⊕⊕⊕◯ Moderate	2 (77.4)	
	<110	Reference comparator	No estimable	No estimable	No estimable	-	3 (25.1)	-
	>180 (8 RCT; 884 participants)	1.14 (0.93 to 1.40) Network estimate	202 per 1000	230 per 1000	28 more per 1000 (14 fewer to 81 more)	⊕⊕⊕◯ Moderate	-	-
	144-180 (1 RCT; 20 participants)	1.01 (0.81 to 1.27) Network estimate	545 per 1000	551 per 1000	6 more per 1000 (104 fewer to 147 more)	⊕⊕⊕⊕ High		
	110-144	Reference comparator	No estimable	No estimable	No estimable	-	-	-
	>180 (1 RCT; 212 participants)	1.13 (1.02 to 1.25) Network estimate	10 per 1000	11 per 1000	1 more per 1000 (0 more to 3 more)	⊕⊕⊕◯ Moderate		
	144-180	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Infection

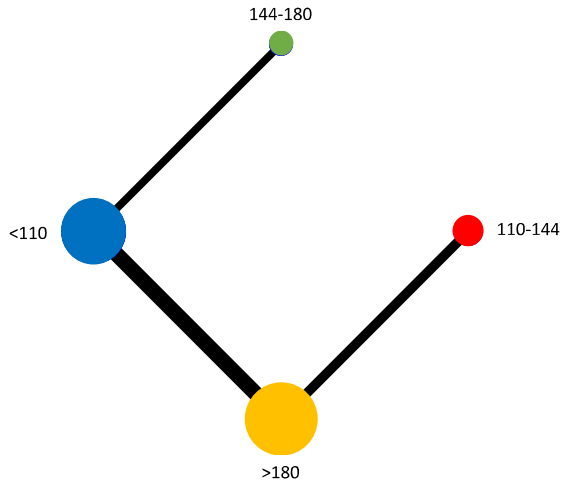
Estimates of effects, credible intervals, and certainly of the evidence for blood sugar level in septic patients.

Frequency NMA-SoF table

BENEFITS

Patients or population: septic patients
Interventions: One of the following oxygen therapies: <110, 110-144, 144-180, >180
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Infection
Setting: In-hospital

Network plot



Total studies: Total Patients:	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
>180 (8 RCT; 6,104 participants)	1.15 (1.05 to 1.26) Direct estimate	167 per 1000	192 per 1000	25 more per 1000 (8 more to 43 more)	⊕⊕◯◯ Low	4 (12.2)	-
144-180 (3 RCT; 6,185 participants)	0.96 (0.86 to 1.07) Direct estimate	136 per 1000	131 per 1000	5 fewer per 1000 (19 fewer to 10 more)	⊕⊕◯◯ Low	3 (49.7)	-
110-144 (no direct comparison)	0.94 (0.75 to 1.16) Indirect estimate	no direct comparison	no direct comparison	no direct comparison	⊕◯◯◯ Very low	1 (83.2)	

	<110	Reference comparator	No estimable	No estimable	No estimable	-	2 (54.9)	-
	>180 (5 RCT; 485 participants)	1.23 (1.01 to 1.50) Direct estimate	269 per 1000	331 per 1000	62 more per 1000 (3 more to 135 more)	⊕⊕◯◯ Low	-	-
	144-180 (no direct comparison)	1.03 (0.80 to 1.31) Indirect estimate	no direct comparison	no direct comparison	no direct comparison	⊕⊕◯◯ Low		
	110-144	Reference comparator	No estimable	No estimable	No estimable	-	-	-
	>180 (no direct comparison)	1.20 (1.04 to 1.38) Indirect estimate	no direct comparison	no direct comparison	no direct comparison	⊕◯◯◯ Very low		
	144-180	Reference comparator	No estimable	No estimable	No estimable	-	-	-

Hypoglycemia

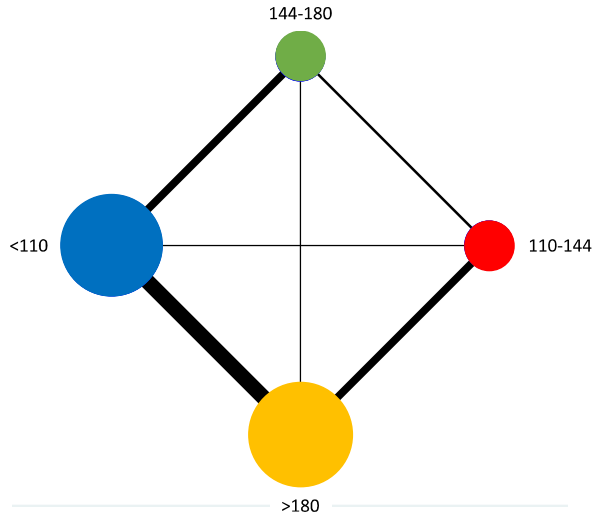
Estimates of effects, credible intervals, and certainly of the evidence for blood sugar level in septic patients.

Frequency NMA-SoF table

BENEFITS

Patients or population: septic patients
Interventions: One of the following oxygen therapies: <110, 110-144, 144-180, >180
Comparator (reference): One of the other therapies other than the therapy included in intervention
Outcome: Hypoglycemia
Setting: In-hospital

Network plot



Total studies: Total Patients:	Relative effect (95% CI)	Anticipated absolute effect (95% CI)			Certainly of the evidence	Ranking (SUCRA)	Interpretation of Findings
		Without intervention	With intervention	Difference			
>180 (12 RCT; 8,342 participants)	0.55 (0.50 to 0.60) Network estimate	188 per 1000	103 per 1000	85 fewer per 1000 (94 fewer to 75 fewer)	⊕⊕⊕⊕ High	2 (74.9)	-
144-180 (5 RCT; 7,331 participants)	0.17 (0.12 to 0.24) Network estimate	76 per 1000	13 per 1000	63 fewer per 1000 (67 fewer to 58 fewer)	⊕⊕◯◯ Low	1 (91.3)	-
110-144 (1 RCT; 90	1.10 (0.69 to 1.77)	134 per 1000	147 per 1000	13 more per 1000 (42 fewer to 103	⊕◯◯◯ Very low	3 (30.3)	

	participants)	Network estimate			more)			
	<110	Reference comparator	No estimable	No estimable	No estimable	-	4 (3.6)	-
	>180 (7 RCT; 730 participants)	0.50 (0.31 to 0.79) Network estimate	175 per 1000	88 per 1000	88 fewer per 1000 (121 fewer to 37 fewer)	⊕⊕◯◯ Low	-	-
	144-180 (1 RCT; 302 participants)	0.16 (0.09 to 0.27) Network estimate	79 per 1000	13 per 1000	66 fewer per 1000 (72 fewer to 58 fewer)	⊕⊕⊕◯ Moderate		
	110-144	Reference comparator	No estimable	No estimable	No estimable	-	-	-
	>180 (1 RCT; 212 participants)	3.17 (2.23 to 4.46) Network estimate	0 per 1000	0 per 1000	0 more per 1000 (0 more to 0 more)	⊕⊕⊕⊕ High		
	144-180	Reference comparator	No estimable	No estimable	No estimable	-	-	-

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ14-1 (GRADE)

P: Patients with sepsis/ septic shock/ infection
I: Use of antipyretic drugs/ cooling device
C: Use of placebo or no intervention
O: Mortality (hospital), length of ICU stay, serious adverse events, infectious complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (All RCT)												
7	randomised trials	serious	not serious	not serious	serious	none	208/752 (27.7%)	205/752 (27.3%)	**RR 1.08** (0.83 to 1.41)	**22 more per 1,000** (from 46 fewer to 112 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (Low RoB RCT)												
6	randomised trials	not serious	not serious	not serious	not serious	none	187/718 (26.0%)	197/721 (27.3%)	**RR 0.95** (0.81 to 1.11)	**14 fewer per 1,000** (from 52 fewer to 30 more)	⨁⨁⨁⨁ High	CRITICAL
Length of ICU stay												
2	randomised trials	serious	not serious	not serious	serious	none	446	443	-	**MD 0.26 day fewer** (from 0.99 fewer to 0.46 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse event												
2	randomised trials	serious	not serious	not serious	serious	none	9/569 (1.6%)	17/575 (3.0%)	**RR 0.56** (0.26 to 1.22)	**13 fewer per 1,000** (from 22 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL
Infectious complication												
3	randomised trials	serious	not serious	not serious	very serious	none	21/254 (8.3%)	29/256 (11.3%)	**RR 0.75** (0.38 to 1.48)	**28 fewer per 1,000** (from 70 fewer to 54 more)	⨁◯◯◯ Very low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ14-2 (unGRADE)

P: Sepsis or septic shock patients with hypothermia
I: Rewarming
C: No intervention
O: Mortality (hospital), length of ICU stay, serious adverse event, infectious complication, hypotension

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ15-3 (GRADE)

P: Septic DIC patients
I: Use of antithrombin
C: Use of placebo/ not use of antithrombin
O: Mortality, bleeding complication, resolution of DIC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious	not serious	not serious	serious	none	62/201 (30.8%)	86/193 (44.6%)	**RR 0.70** (0.57 to 0.87)	**134 fewer per 1,000** (from 192 fewer to 58 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Bleeding complication												
3	randomised trials	not serious	not serious	not serious	very serious	none	8/158 (5.1%)	7/163 (4.3%)	**RR 1.20** (0.45 to 3.19)	**9 more per 1,000** (from 24 fewer to 94 more)	⨁⨁◯◯ Low	CRITICAL
Resolution of DIC												
3	randomised trials	not serious	not serious	not serious	serious	none	32/54 (59.3%)	8/55 (14.5%)	**RR 3.39** (1.74 to 6.59)	**348 more per 1,000** (from 108 more to 813 more)	⨁⨁⨁◯ Moderate	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ15-4 (GRADE)

P: Septic DIC patients
I: Use of heparin
C: Use of placebo/ not use of heparin
O: Mortality, bleeding complication, resolution of DIC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	serious	not serious	not serious	very serious	none	12/127 (9.4%)	18/134 (13.4%)	**RR 0.57** (0.26 to 1.20)	**58 fewer per 1,000** (from 99 fewer to 27 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding complication												
1	randomised trials	serious	not serious	not serious	very serious	serious	5/105 (4.8%)	12/119 (10.1%)	**RR 0.48** (0.16 to 1.27)	**52 fewer per 1,000** (from 85 fewer to 27 more)	⨁◯◯◯ Very low	CRITICAL
Resolution of DIC												
1	randomised trials	serious	not serious	not serious	serious	none	20/22 (91%)	6/15 (40%)	**RR 0.11** (0.02 to 0.53)	**356 fewer per 1,000** (from 392 fewer to 188 fewer)	⨁⨁◯◯ Low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ15-5 (GRADE)

P: Septic DIC patients
I: Use of thrombomodulin
C: Use of placebo/ not use of thrombomodulin
O: Mortality, bleeding complication, resolution of DIC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	not serious	not serious	not serious	serious	none	156/725 (21.5%)	192/742 (25.9%)	**RR 0.84** (0.70 to 1.01)	**41 fewer per 1,000** (from 78 fewer to 3 more)	⨁⨁⨁◯ Moderate	CRITICAL
Bleeding complication												
3	randomised trials	serious	not serious	not serious	serious	none	44/813 (5.4%)	34/820 (4.1%)	**RR 1.30** (0.84 to 2.02)	**12 more per 1,000** (from 7 fewer to 42 more)	⨁⨁◯◯ Low	CRITICAL
Resolution of DIC												
2	randomised trials	serious	not serious	not serious	serious	none	40/92 (43.5%)	27/95 (28.4%)	**RR 1.45** (0.99 to 2.11)	**128 more per 1,000** (from 3 fewer to 315 more)	⨁⨁◯◯ Low	IMORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ15-6 (GRADE)

P: Septic DIC patients
I: Use of protease inhibitor
C: Use of placebo/ not use of protease inhibitor
O: Mortality, bleeding complication, resolution of DIC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	serious	not serious	not serious	very serious	none	14/45 (31.1%)	16/45 (35.6%)	**RR 0.89** (0.49 to 1.61)	**39 fewer per 1,000** (from 181 fewer to 217 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding complication												
1	randomised trials	serious	not serious	not serious	very serious	none	2/25 (8.0%)	6/25 (24.0%)	**RR 0.33** (0.07 to 1.50)	**161 fewer per 1,000** (from 223 fewer to 120 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ16-1 (unGRADE)

P: Patients with sepsis/ septic shock
I: Use of mechanical thromboprophylaxis
C: No intervention
O: Deep vein thrombosis, pulmonary embolism

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ16-2 (unGRADE)

P: Patients with sepsis/ septic shock
I: Use of UFH/ LMWH/ NOAC/ DOAC
C: No intervention
O: Deep vein thrombosis, pulmonary embolism

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ16-3 (unGRADE)

P: Patients with sepsis/ septic shock
I: Use of mechanical thromboprophylaxis or anticoagulant therapy until initiation of mobilization/ during hospital stay
C: Mechanical thromboprophylaxis or anticoagulant therapy was continued after initiation of mobilization/ hospital discharge
O: Deep vein thrombosis, pulmonary embolism

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ17-1 (GRADE)

P: Patients in intensive care units
I: Early mobilization
C: Not provide early mobilization
O: Mortality (hospital), length of hospital stay, the Medical Outcomes Study 36-Item Short Form Health Survey Physical Function scale (SF-36 PF) at 6 month, Medical Research Council (MRC) during hospital stay, Hospital Anxiety and Depression scale (HADS) at 6 month, Mini-Mental State Examination (MMSE) at 6 month, adverse event

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (Hospital)												
7	randomised trials	not serious	not serious	not serious	serious	none	64/466 (13.7%)	56/458 (12.2%)	**RR 1.12** (0.80 to 1.58)	**15 more per 1,000** (from 24 fewer to 71 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
10	randomised trials	serious	serious	serious	not serious	none	613	611	-	**MD 2.86 day lower** (from 5.51 lower to 0.21 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 PF at 6 month												
3	randomised trials	serious	serious	not serious	serious	none	119	122	-	**MD 4.65 higher** (from 16.13 lower to 25.43 higher)	⨁◯◯◯ Very low	CRITICAL
MRC during hospital stay												
3	randomised trials	serious	not serious	not serious	serious	none	97	99	-	**MD 4.84 higher** (from 0.36 higher to 9.31 higher)	⨁◯◯◯ Very low	CRITICAL
HADS at 6 month												
1	randomised trials	serious	not serious	not serious	serious	none	21	16	-	**MD 0.3 higher** (from 4.92 lower to 5.52 higher)	⨁◯◯◯ Very low	CRITICAL
MMSE at 6 month												
1	randomised trials	serious	not serious	not serious	serious	none	84	81	-	**MD 0.6 higher** (from 0.25 lower to 1.45 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
5	randomised trials	serious	serious	not serious	serious	none	13/358 (3.6%)	17/348 (4.9%)	**RR 0.71** (0.23 to 2.13)	**14 fewer per 1,000** (from 38 fewer to 55 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ17-2 (GRADE)

P: Patients in intensive care units
I: Passive joint exercise therapy
C: Not provide passive joint exercise therapy
O: Grip strength/ medical research council (MRC), 6 min walk test (6 MWD), functional independence measure (FIM), length of ICU/ hospital stay, length of mechanical ventilation, adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
MRC score												
3	randomised trials	serious	not serious	serious	serious	none	182	184	-	**MD 0.96 lower** (from 4.13 lower to 2.21 higher)	⨁◯◯◯ Very low	CRITICAL
6 MWD												
2	randomised trials	not serious	serious	serious	serious	none	84	89	-	**MD 10.5 m higher** (from 63.45 lower to 84.46 higher)	⨁◯◯◯ Very low	CRITICAL
FIM												
1	randomised trials	not serious	not serious	serious	serious	none	58	57	-	**MD 3 higher** (from 5.42 lower to 11.42 higher)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
4	randomised trials	serious	not serious	serious	serious	none	142	135	-	**MD 0.36 day higher** (from 1.79 lower to 2.51 higher)	⨁◯◯◯ Very low	CRITICAL
Length of hospital stay												
4	randomised trials	not serious	not serious	serious	serious	none	142	135	-	**MD 0.74 day higher** (from 3.68 lower to 5.15 higher)	⨁⨁◯◯ Low	CRITICAL
Length of mechanical ventilation												
4	randomised trials	serious	not serious	serious	serious	none	274	257	-	**MD 0.14 day higher** (from 1.03 lower to 1.31 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
3	randomised trials	serious	not serious	serious	very serious	none	9/216 (4.2%)	12/200 (6.0%)	**RR 0.70** (0.30 to 1.63)	**18 fewer per 1,000** (from 42 fewer to 38 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ17-3 (GRADE)

P: Patients in intensive care units
I: Neuromuscular electrical stimulation
C: Not provide neuromuscular electrical stimulation
O: ICU-AW at ICU discharge, MRC score at ICU discharge, length of mechanical ventilation, mortality (hospital), length of ICU stay

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
ICU-AW at ICU discharge												
1	randomised trials	serious	not serious	not serious	very serious	none	3/12 (25.0%)	4/16 (25.0%)	**RR 1.00** (0.27 to 3.66)	**0 fewer per 1,000** (from 183 fewer to 665 more)	⨁◯◯◯ Very low	CRITICAL
MRC score at ICU discharge												
1	randomised trials	serious	not serious	not serious	very serious	none	12	16	-	**MD 1.00 higher** (from 4.19 lower to 6.19 higher)	⨁◯◯◯ Very low	CRITICAL
Length of mechanical ventilation												
7	randomised trials	serious	not serious	not serious	very serious	none	132	130	-	**MD 1.56 day lower** (from 3.12 lower to 0.01 higher)	⨁◯◯◯ Very low	CRITICAL
Mortality (Hospital)												
5	randomised trials	serious	not serious	not serious	very serious	none	39/127 (30.7%)	40/124 (32.3%)	**RR 0.88** (0.46 to 1.68)	**39 fewer per 1,000** (from 174 fewer to 219 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
5	randomised trials	serious	serious	not serious	very serious	none	99	113	-	**MD 3.23 day higher** (from 3.35 lower to 9.81 higher)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

CQ18-1 (GRADE)

P: Pediatric patients with septic shock/ severe sepsis or organ injury due to infection
I: Use of clinical algorithms for initial resuscitation
C: Not use of clinical algorithms for initial resuscitation
O: Mortality, resolution of shock

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational study	very serious	not serious	not serious	serious	Residual confounding indicated pseudo effect.	2/27 (7.4%)	24/64 (37.5%)	**OR 0.13** (0.03 to 0.61)	**303 fewer per 1,000** (from 357 fewer to 107 fewer)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ18-7 (GRADE and unGRADE)

P: Pediatric patients with septic shock
I: Dopamine
C: Adrenaline/ Noradrenaline
O: Mortality, resolution of shock, length of ICU stay, serious adverse event

Dopamine vs Adrenaline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (28 day)												
2	randomized study	not serious	not serious	not serious	very serious	none	31/94 (33.0%)	18/86 (20.9%)	**RR 1.65** (0.71 to 3.82)	**136 more per 1,000** (from 61 fewer to 590 more)	⨁⨁◯◯ Low	CRITICAL
Resolution of shock within 1 hour												
1	randomized study	not serious	not serious	not serious	serious	none	4/31 (12.9%)	12/29 (41.4%)	**RR 0.31** (0.11 to 0.86)	**286 fewer per 1,000** (from 368 fewer to 58 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Vasoactive drug free-days												
1	randomized study	not serious	not serious	not serious	very serious	none	63	57	-	**MD 4.80 day lower** (from 8.44 lower to 1.16 lower)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
1	randomized study	not serious	not serious	not serious	serious	none	31	29	-	**MD 1.00 day lower** (from 3.95 lower to 1.95 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse event												
2	randomized study	not serious	not serious	not serious	very serious	none	25/94 (26.6%)	10/86 (11.6%)	**RR 2.08** (0.57 to 7.57)	**126 more per 1,000** (from 50 fewer to 764 more)	⨁⨁◯◯ Low	CRITICAL

Dopamine vs Adrenaline (GRADE)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Dopamine vs Noradrenaline (unGRADE)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ18-8 (GRADE)

P: Pediatric patients with septic shock/ vasodilation shock
I: Vasopressin
C: Noradrenaline or placebo
O: Mortality (hospital), Duration of resolution of shock, length of ICU stay, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	serious	not serious	serious	very serious	none	30/63 (47.6%)	25/60 (41.7%)	**RR 1.17** (0.60 to 2.26)	**60 more per 1,000** (from 130 fewer to 250 more)	⨁◯◯◯ Very low	CRITICAL
Duration of resolution of shock												
1	randomised trials	serious	not serious	serious	very serious	none	33	32	-	**MD 2.60 h higher** (from 49.95 lower to 55.15 higher)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
2	randomised trials	serious	not serious	serious	very serious	none	63	60	-	**MD 3.64 day lower** (from 9.82 lower to 2.53 higher)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events												
2	randomised trials	serious	not serious	serious	very serious	none	8/63 (12.7%)	5/60 (8.3%)	**RR 1.52** (0.53 to 4.36)	**40 more per 1,000** (from 60 fewer to 140 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ18-9 (GRADE)

P: Pediatric patients with septic shock (initial fluid resuscitation and catecholamines did not archive resolution of shock)
I: Steroid
C: Not use of steroid
O: Mortality (ICU), length of hospital stay, Duration of resolution of shock, length of mechanical ventilation, complication

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomised trials	serious	not serious	not serious	very serious	none	22/74 (29.7%)	27/81 (33.3%)	**RR 0.88** (0.50 to 1.39)	**40 fewer per 1,000** (from 167 fewer to 130 more)	⨁◯◯◯ Very low	CRITICAL
Length of hospital stay												
2	randomised trials	serious	not serious	not serious	not serious	none	El-Nawawy 2017: 11.4 ± 8.2 vs 8.2 ± 5.3 days Menon 2017: 10.7 [5.4, 25.9] vs 9.6 [7.1, 20.9] days				⨁⨁⨁◯ Moderate	CRITICAL
Duration of resolution of shock												
2	randomised trials	serious	not serious	serious	serious	none	El-Nawawy 2017: 60.0 ± 21.6 vs 139.2 ± 43.2 hours Menon 2017: 49.5 [26, 144] vs 70 [12, 269] hours				⨁◯◯◯ Very low	CRITICAL
Secondary infection												
2	randomised trials	serious	serious	not serious	very serious	none	7/42 (16.7%)	6/45 (13.3%)	**RR 1.31** (0.45 to 3.13)	**41 more per 1,000** (from 73 fewer to 284 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ18-10 (GRADE)

P: Hemodynamically stable pediatric critically ill patients
I: Lower red blood cell transfusion threshold
C: Higher red blood cell transfusion threshold
O: Mortality (hospital), length of ICU stay, length of hospital stay, length of mechanical ventilation, complication due to transfusion

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious	not serious	serious	very serious	none	17/391 (4.3%)	21/406 (5.2%)	**RR 0.89** (0.46 to 1.74)	**6 fewer per 1,000** (from 28 fewer to 30 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	serious	not serious	very serious	none	391	406	-	**MD 0.62 day lower** (from 1.76 lower to 0.51 higher)	⨁◯◯◯ Very low	CRITICAL
Length of mechanical ventilation												
2	randomised trials	not serious	serious	not serious	very serious	none	391	406	-	**MD 0.00 day higher** (from 0.84 lower to 0.84 higher)	⨁◯◯◯ Very low	CRITICAL
Complication due to transfusion												
1	randomised trials	not serious	not serious	not serious	very serious	none	97/320 (30.3%)	90/317 (28.3%)	**RR 1.10** (0.78 to 1.54)	**28 more per 1,000** (from 62 fewer to 153 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ18-11 (GRADE)

P: Pediatric patients with sepsis
I: Blood purification therapy
C: Not use of blood purification therapy
O: Mortality, length of ICU stay, length of mechanical ventilation, duration of resolution of shock, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious	not serious	not serious	very serious	none	10/25 (40.0%)	4/23 (17.4%)	**RR 3.17** (0.83 to 12.13)	**377 more per 1,000** (from 30 fewer to 1000 more)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

CQ18-12 (unGRADE)

P: Pediatric patients with severe sepsis/ septic shock or organ injury due to infection
I: Use of IVIG
C: Use of placebo or not use of IVIG
O: Mortality, duration of resolution of shock, length of mechanical ventilation, length of ICU stay, adverse effect

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CQ18-13 (GRADE)

P: Pediatric patients in intensive care unit
I: Strict glycemic management
C: Standard glycemic management
O: Mortality, length of ICU stay, length of mechanical ventilation, hypoglycemia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious	serious	not serious	serious	none	98/1928 (5.1%)	107/1995 (5.4%)	**RR 0.98** (0.73 to 1.31)	**1 fewer per 1,000** (from 14 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU stay												
3	randomised trials	not serious	serious	not serious	not serious	none	1533	1516	-	**MD 0.50 day lower** (from 0.52 lower to 0.48 lowerr)	⨁⨁⨁◯ Moderate	CRITICAL
Length of mechanical ventilation												
3	randomised trials	not serious	serious	not serious	not serious	none	1533	1516	-	**MD 0.30 day lower** (from 0.32 lower to 0.27 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Hypoglycemia												
5	randomised trials	not serious	serious	not serious	serious	none	185/1931 (9.6%)	39/2002 (1.9%)	**RR 6.37** (4.41 to 9.21)	**105 more per 1,000** (from 66 more to 166 more)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ20-2 (GRADE)

P: Septic patients/ Patients in intensive care units
I: Use of ICU diaries
C: Not use of ICU diaries
O: PTSD and ASD, Hospital Anxiety and Depression Scale (HADS), adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
PTSD and ASD (Patients)												
3	randomised trials	serious	not serious	not serious	serious	none	60/216 (27.8%)	71/208 (34.1%)	**RR 0.85** (0.64 to 1.12)	**51 fewer per 1,000** (from 123 fewer to 41 more)	⨁⨁◯◯ Low	CRITICAL
Anxiety (Patients, HADS score)												
2	randomised trials	serious	not serious	not serious	serious	none	189	184	-	**MD 0.82 lower** (from 2.45 lower to 0.82 higher)	⨁⨁◯◯ Low	CRITICAL
Depression (Patients, HADS score)												
2	randomised trials	serious	serious	not serious	serious	none	189	184	-	**MD 1.01 lower** (from 3.55 lower to 1.53 higher)	⨁◯◯◯ Very low	CRITICAL
PTSD and ASD (Family)												
2	randomised trials	serious	serious	not serious	very serious	none	148/324 (45.7%)	150/328 (45.7%)	**RR 0.88** (0.56 to 1.40)	**55 fewer per 1,000** (from 201 fewer to 183 more)	⨁◯◯◯ Very low	IMPORTANT
Anxiety (Family, HADS score)												
1	randomised trials	serious	not serious	not serious	serious	none	286	286	-	**MD 0** (from 0.73 higher to 0.73 higher)	⨁⨁◯◯ Low	IMPORTANT
Depression (Family, HADS score)												
1	randomised trials	serious	not serious	not serious	serious	none	286	286	-	**MD 0** (from 0.73 lower to 0.73 higher)	⨁⨁◯◯ Low	IMPORTANT

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ20-3 (GRADE)

P: Septic patients/ Patients in intensive care units
I: Use of physical restraints during ICU stay
C: Not use of physical restraints during ICU stay
O: Delirium, length of mechanical ventilation, length of ICU stay, unplanned removal, Patients and family/ medical staff feelings about physical restraint, alternative to physical restraint

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Delirium												
10	observational study	very serious	not serious	not serious	not serious	none	256/1351 (18.9%)	538/833 (64.6%)	**OR 0.09** (0.04 to 0.19)	**505 fewer per 1,000** (from 578 fewer to 389 fewer)	⨁⨁◯◯ Low	CRITICAL
Length of mechanical ventilation												
2	observational study	very serious	very serious	not serious	serious	none	430	702	-	**MD 0.8 day lower** (from 6.71 lower to 5.12 higher)	⨁◯◯◯ Very low	IMPORTANT
Length of ICU stay												
4	observational study	very serious	not serious	not serious	not serious	none	341	764	-	**MD 3.99 lower** (from 7.91 lower to 0.07 lower)	⨁⨁◯◯ Low	IMPORTANT
Unplanned removal												
5	observational study	very serious	serious	serious	not serious	none	100/2524 (4.0%)	244/2354 (10.4%)	**OR 0.36** (0.13 to 0.98)	**64 fewer per 1,000** (from 89 fewer to 2 fewer)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ20-4-1 (GRADE)

P: Septic patients/ Patients in intensive care units
I: Provide ventilation support
C: No intervention
O: Objective sleep

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Objective sleep												
5	randomized trials	serious	not serious	serious	serious	none	79	79	-	**MD 12.2 higher** (from 4.12 lower to 20.28 higher)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ20-4-2 (GRADE)

P: Septic patients/ Patients in intensive care units
I: Use of non-pharmacological sleep management (earplugs, eye-masks, music therapy)
C: Standard care
O: Subjective evaluation, objective sleep

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Subjective evaluation												
3	randomized trials	serious	serious	not serious	serious	none	68	68	-	**MD 1.5 higher** (from 1.11 higher to 1.9 higher)	⨁◯◯◯ Very low	CRITICAL
Objective sleep												
2	randomized trials	serious	not serious	not serious	serious	none	37	42	-	**MD 2.46 lower** (from 9.94 lower to 5.01 higher)	⨁⨁◯◯ Low	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ20-5 (GRADE)

P: Septic patients/ Patients in intensive care units/ Family
I: Family visiting restriction
C: No family visiting restriction
O: Delirium, length of ICU stay, depression (patients, family), anxiety (family), satisfaction (family), infection during ICU stay

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Infection during ICU stay												
2	randomised trials	serious	not serious	not serious	serious	none	50/951 (5.3%)	54/957 (5.6%)	**RR 0.93** (0.64 to 1.35)	**4 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁◯◯ Low	CRITICAL
Delirium												
2	randomised trials	serious	serious	not serious	very serious	none	161/865 (18.6%)	181/879 (20.6%)	**RR 0.67** (0.28 to 1.64)	**68 fewer per 1,000** (from 148 fewer to 132 more)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
1	randomised trials	serious	not serious	not serious	not serious	none	837	848	-	**MD 0.02 day lower** (from 0.15 lower to 0.09 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Satisfaction (Family)												
1	randomised trials	serious	not serious	not serious	not serious	none	493	483	-	**MD 13.5 higher** (from 10.87 higher to 16.13 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Depression (Family)												
1	randomised trials	serious	not serious	not serious	not serious	none	529	525	-	**MD 1.2 lower** (from 2 lower to 4 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Anxiety (Family)												
1	randomised trials	serious	not serious	not serious	not serious	none	529	525	-	**MD 1.6 lower** (from 2.3 lower to 0.9 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Depression (Patients)												
1	randomised trials	very serious	not serious	not serious	serious	none	115	111	-	**MD 0** (from 0 to 0)	⨁◯◯◯ Very low	CRITICAL

	JUDGEMENT						
PROBLEM	No	**Probably no**	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

CQ22-1 (GRADE)

P: Patients in intensive care units
I: Use of anti-ulcer drugs
C: Not use of anti-ulcer drugs or use of placebo
O: Gastrointestinal bleeding, mortality (hospital), pneumonia, Clostridioides difficile infection, serious adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Gastrointestinal bleeding (All RCT)												
28	randomised trials	serious	serious	not serious	not serious	none	202/3530 (5.7%)	285/2955 (9.6%)	**RR 0.50** (0.37 to 0.68)	**48 fewer per 1,000** (from 61 fewer to 31 fewer)	⨁⨁◯◯ Low	CRITICAL
Gastrointestinal bleeding (Low RoB RCT)												
14	randomised trials	not serious	serious	not serious	not serious	none	81/2558 (3.2%)	169/2326 (7.3%)	**RR 0.39** (0.25 to 0.62)	**44 fewer per 1,000** (from 54 fewer to 28 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia (Low RoB RCT)												
8	randomised trials	not serious	not serious	not serious	not serious	none	328/2244 (14.6%)	302/2042 (14.8%)	**RR 1.03** (0.89 to 1.19)	4 **more per 1,000** (from 16 fewer to 28 more)	⨁⨁⨁⨁ High	CRITICAL
Mortality (Low RoB RCT)												
8	randomised trials	not serious	not serious	not serious	not serious	none	593/2243 (26.4%)	562/2071 (27.1%)	**RR 1.01** (0.92 to 1.12)	**3 more per 1,000** (from 22 fewer to 33 more)	⨁⨁⨁⨁ High	CRITICAL
Serious adverse event												
7	randomised trials	not serious	not serious	not serious	serious	none	84/2156 (3.9%)	72/1987 (3.6%)	**RR 1.13** (0.83 to 1.54)	**5 m**ore **per 1,000** (from 6 fewer to 20 more)	⨁⨁⨁◯ Moderate	CRITICAL
Clostridioides difficile infection												
3	randomised trials	not serious	not serious	not serious	serious	none	21/1807 (1.2%)	28/1800 (1.6%)	**RR 0.75** (0.42 to 1.31)	**4 f**ewer **per 1,000** (from 9 fewer to 5 more)	⨁⨁⨁◯ Moderate	CRITICAL

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know