Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Nishida O, Ogura H, Egi M, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016（J-SSCG2016）.
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SUPPLEMENTARY APPENDIX

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016（J-SSCG2016）

Nishida O, Ogura H, and others.

CONTENTS

CQ1-3

PICO

Patients (P): 1) Suspected septic critically ill patients in ICU 2) Suspected septic patients in ER or ward
Interventions (I): Using PCT, P-SEP, IL-6
Control (C): Not using these markers
Outcomes (O): Mortality, decision making about administration in out-patients setting, avoid an unnecessary treatments

Search terms

PCT
“procalcitonin”; “sepsis”, “sepsis syndrome”, “septicemia”, “infection”, “systemic inflammatory response syndrome”, and “SIRS”; and “sensitivity”, “specificity”, “predictive value”, “likelihood ratio”, “review”, “meta-analysis”, “false positive”, and “false negative”.

P-SEP
(“presepsin” or “soluble CD14 subtype” or “sCD14-ST”) AND (sepsis OR “bacterial infection” OR “systemic inflammatory response syndrome” OR “SIRS”)

IL-6
“sepsis” “infected” and “interleukin-6” or “IL-6”.

CRP
(1) type of study (“descriptive study” OR “diagnosis” OR “epidemiological study” OR “meta-analysis” OR “multicenter study” OR “prospective” OR “review-literature” OR “reproducibility” OR “test” OR “validation”); (2) site (“critical care” OR “hospital” OR “intensive care”); (3) subjects (“human”); (4) test (“C-reactive protein” OR “interferon” OR “interleukin” OR “procalcitonin” OR “white blood cell count” OR “sedimentation”) and (5) disease (“infection” OR “cross infection” OR “hospital acquired infection” OR “meningitis” OR “multiple organ dysfunction syndrome” OR “MODS” OR “pneumonia” OR “sepsis” OR “septicemia” OR “septic shock” OR “systemic inflammatory response syndrome” OR “SIRS”).

Body of the evidence

1) ICU setting

PCT

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./26	0	-1	0	0	-1	304	288-320	C	9
False negative	Obsr./26	0	-1	0	0	-1	96	80-112	C	8
True negative	Obsr./26	0	-1	0	0	-1	480	450-510	C	9
False positive	Obsr./26	0	-1	0	-1	-1	120	90-150	D	7

P-SEP

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./8	0	-1	0	0	0	344	316-364	B	9
False negative	Obsr./8	0	-1	0	0	0	56	36-84	B	8
True negative	Obsr./8	0	-1	0	0	0	468	408-510	B	9
False positive	Obsr./8	0	-1	0	-1	0	132	90-192	C	7

IL-6

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./3	0	-1	0	0	0	250	229-270	B	9
False negative	Obsr./3	0	-1	0	0	0	150	130-171	B	8
True negative	Obsr./3	0	-1	-1	0	0	449	415-481	C	9
False positive	Obsr./3	0	-1	-1	-1	0	151	119-185	D	7

CRP

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./7	-1	-1	0	0	0	280	220-328	C	9
False negative	Obsr./7	-1	-1	0	0	0	120	72-180	C	8
True negative	Obsr./7	-1	-1	-1	0	0	432	348-498	D	9
False positive	Obsr./7	-1	-1	-1	-1	0	168	102-252	D	7

2) ER or ward setting

PCT

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./26	0	-1	0	-1	-1	304	288-320	D	8
False negative	Obsr./26	0	-1	0	-1	-1	96	80-112	D	9
True negative	Obsr./26	0	-1	0	-1	-1	480	450-510	D	9
False positive	Obsr./26	0	-1	0	-1	-1	120	90-150	D	8

P-SEP

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./8	0	-1	0	-1	0	344	316-364	C	8
False negative	Obsr./8	0	-1	0	-1	0	56	36-84	C	9
True negative	Obsr./8	0	-1	0	-1	0	468	408-510	C	9
False positive	Obsr./8	0	-1	0	-1	0	132	90-192	C	8

IL-6

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./3	0	-1	0	-1	0	250	229-270	C	8
False negative	Obsr./3	0	-1	0	-1	0	150	130-171	C	9
True negative	Obsr./3	0	-1	-1	-1	0	449	415-481	D	9
False positive	Obsr./3	0	-1	-1	-1	0	151	119-185	D	8

CRP

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Value	95%CI	Strength	Importance
True positive	Obsr./7	-1	-1	0	-1	0	280	220-328	D	8
False negative	Obsr./7	-1	-1	0	-1	0	120	72-180	D	9
True negative	Obsr./7	-1	-1	-1	-1	0	432	348-498	D	9
False positive	Obsr./7	-1	-1	-1	-1	0	168	102-252	D	8

CQ2-1

PICO

Patients (P): Suspected bacteremia patients
Intervention (I): Timing of blood culture sampling
Control (C): none
Outcomes (O): Sensitivity, specificity, rate of contamination, proper use of antibiotics

Search terms

1. （blood culture［All Fields］ OR blood cultured［All Fields］ OR blood cultures［All Fields］）AND timing［All Fields］

CQ2-2

PICO

Patients (P): Septic and septic shock patients
Intervention (I): Method and timing of culture sampling
Control (C): none
Outcomes (O): Sensitivity, specificity, rate of contamination, proper use of antibiotics

Search terms

1. （ “bronchoalveolar lavage”［MeSH Terms］OR（“bronchoalveolar”［All Fields］AND “lavage”［All Fields］）OR “bronchoalveolar lavage”［All Fields］）OR（endotracheal［All Fields］AND aspiration［All Fields］）OR（“sputum”［MeSH Terms］OR “sputum”［All Fields］）AND（（“sepsis”［MeSH Terms］OR sepsis”［All Fields］）OR（“sepsis”［MeSH Terms］OR “sepsis”［All Fields］OR（“severe”［All Fields］AND “sepsis”［All Fields］）OR “severe sepsis”［All Fields］）OR（“shock, septic”［MeSH Terms］OR（“shock”［All Fields］AND “septic”［All Fields］）OR “septic shock”［All Fields］OR（“septic”［All Fields］AND “shock”［All Fields］））
2. （ “urine”［Subheading］OR“ urine”［All Fields］OR “urine”［MeSH Terms］）AND（“ethnology”［Subheading］OR “ethnology”［All Fields］OR “culture”［All Fields］OR “culture”［MeSH Terms］））AND（（“sepsis”［MeSH Terms］OR “sepsis”［All Fields］）OR（“sepsis”［MeSH Terms］OR “sepsis”［All Fields］OR（“severe”［All Fields］AND “sepsis”［All Fields］）OR “severe sepsis”［All Fields］）OR（“shock, septic”［MeSH Terms］OR（“shock”［All Fields］AND “septic”［All Fields］）OR “septic shock”［All Fields］OR（“septic”［All Fields］AND “shock”［All Fields］）））
3. “ cerebrospinal fluid”［Subheading］OR（“cerebrospinal”［All Fields］AND“ fluid”［All Fields］）OR“cerebrospinal fluid”［All Fields］OR “cerebrospinal fluid”［MeSH Terms］OR（“cerebrospinal”［All Fields］AND “fluid”［All Fields］））AND（（“sepsis”［MeSH Terms］OR “sepsis”［All Fields］）OR（“sepsis”［MeSH Terms］OR “sepsis”［All Fields］OR（“severe”［All Fields］AND “sepsis”［All Fields］）OR “severe sepsis”［All Fields］）OR（“shock, septic”［MeSH Terms］OR（“shock”［All Fields］AND “septic”［All Fields］）OR “septic shock”［All Fields］OR（“septic”［All Fields］AND “shock”［All Fields］）））

CQ2-3

PICO

Patients (P): Septic and septic shock patients
Intervention (I): Gram stain
Control (C): none
Outcomes (O): Sensitivity, specificity, avoidance of an unnecessary antibiotics, avoidance of a necessary antibiotics

Search terms

1. （Gram’s［All Fields］OR Gram［All Fields］）AND（(“staining and labeling”［MeSH Terms］OR （“staining”［All Fields］AND “labeling”［All Fields］）OR “staining and labeling”［All Fields］OR “stain”［All Fields］）OR（“staining and labeling［”MeSH Terms］OR（ “staining［”All Fields］AND “labeling”［All Fields］）OR “staining and labeling”［All Fields］OR “staining”［All Fields］））AND（(“sepsis”［MeSH Terms］OR “sepsis”［All Fields］）OR （“sepsis”［MeSH Terms］OR “sepsis”［All Fields］OR （“severe”［All Fields］AND “sepsis”［All Fields］）OR “severe sepsis”［All Fields］）OR （“shock, septic”［MeSH Terms］OR（“shock”［All Fields］AND“septic”［All Fields］）OR “septic shock”［All Fields］OR （“septic”［All Fields］AND “shock”［All Fields］）））

CQ3-1

PICO

Patients (P): Septic patients, septic shock patients
Intervention (I): To use image diagnosis
Control (C): Not to use image diagnosis
Outcome (O): Mortality

Search terms

1. （（（（（（infection）OR infectious）OR abcess））AND（（（site）OR focus）OR foci）OR source））AND（（（“systematic”［Filter］）AND “review”［Filter］））OR（（“randomized controlled trial”［Filter］）OR “meta analysis”［Filter］））AND（（sepsis）OR septic shock））AND（（radiography）OR imaging）
2. （（（（（（（（（“rhoentgenocephalometric” OR“ rhoentgenograms”OR “rhoentgenography” OR “rhoentgenomorphological” OR “rhoentgenotomography” OR“rhoentogram”））OR “echo”）OR “ultrasound”）OR“scinti”）OR “magnetic/resonance tomographies”）OR computed tomography））AND（（（（infection）OR infectious）OR abcess））AND（（（（site）OR focus）OR foci）OR source））AND（（sepsis）OR septic shock））AND（（（“systematic”［Filter］）AND “review”［Filter］））OR（（“randomized controlled trial”［Filter］）OR “meta analysis”［Filter］））
3. （（（（sepsis）OR septic shock）AND randomized controlled trials）AND infection）AND diagnosis AND human AND imaging

CQ3-2

PICO

Patients (P): Septic patients, septic shock patients
Intervention (I): to use contrast enhanced computed tomography
Control (C): Not to use contrast enhanced computed tomography
Outcome (O): Mortality

Search terms

1. （（ （（“Tomography Scanners, X-Ray Computed” ［Mesh］ OR “Tomography, Emission-Computed” ［Mesh］ OR“Tomography, Spiral Computed” ［Mesh］ OR“Tomography, Emission-Computed, Single-Photon” ［Mesh］ OR “X-Ray Microtomography” ［Mesh］ OR“Multidetector Computed Tomography” ［Mesh］）） AND （(sepsis） OR septic shock)） AND （（((“systematic” ［Filter］) AND “review” ［Filter］)) OR ((“randomized controlled trial” ［Filter］) OR “meta analysis” ［Filter］))) AND (((((infection) OR infectious) OR abcess)) AND ((((site) OR focus） OR foci） OR source))
2. （ sepsis OR septic shock） AND （infection AND diagnosis） AND （meta-analysis ［pt］ OR systematic ［sb］ OR review ［pt］） AND human AND computed tomography AND contrast enhanced computed tomography
3.（（ ((contrast-induced nephropathy） AND septic shock） AND severe sepsis） AND RCT） AND meta analysis
4. （（ ((contrast-induced nephropathy） AND septic shock） AND severe sepsis） AND RCT） AND meta analysis

CQ4-1

PICO

Patients (P): Septic patients caused by intra-abdominal infection who received laparotomy
Intervention (I): Early intervention
Control (C): Late intervention
Outcomes (O): Mortality, length of ICU, hospital stay, complication

Search terms

1. Search (((((((((severe sepsis OR septic shock))) AND (((intra-abdominal infection OR intraabdominal infection OR abdominal infection OR peritonitis OR perforation OR gastrointestinal perforation OR diffuse peritonitis)AND ((surgery OR surgical OR drainage OR source control) AND (timing OR time OR delay OR duration OR interval)))) AND ((mortality OR length of ICU stay OR length of hospital stay OR complication)))) NOT ((animals OR murine OR rat OR pig))) NOT (((aortic aneurysm OR trauma OR hysterectomy OR vaginal OR cesarean)))) NOT (((case report OR review)))) AND english[la]

Body of the evidence

							The numbers of persons at risk (outcome rate)											
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	Obs./1	-1		-1	-1		54	5	9.2	51	39	76.5	OR	0.031	0.010-0.097	C	9	1)

1) Subjects of this study were patients who received re-laparotomy.

CQ4-2

PICO

1) Timing
Patients (P): Septic patients caused by infected necrotizing pancreatitis
Intervention (I): Late intervention
Control (C): Early intervention
Outcomes (O): Mortality, length of ICU, hospital stay, complication
2) Treatment
Patients (P): Septic patients caused by infected necrotizing pancreatitis
Intervention (I): Treatment 1
Control (C): Treatment 2
>>> Minimally invasive step-up approach vs. Open necrosectomy
>>> Endoscopic transgastric necrosectomy vs. Surgical necrosectomy
Outcomes (O): Mortality, length of ICU, hospital stay, complication

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality	RCT/3	-1	-1	-1	-1	-1										C	9
Timing of treatment (Late : >12days vs Early 48-72hr)							25	14	56	11	3	27.2	OR	0.29	0.063-1.39		
Minimally invasive step-up approach (A) vs Open							45	31	69	43	17	40	RR	1.2	0.48-3.01		
Endoscopic transgastric necrosectomy (C) vs Surgical							10	4	40	10	1	10	RD (relative difference)	0.3	-0.08-0.6		
Length of ICU stay	RCT/1	-1		-1	-1		45	Median 11	Range 0-111	43	Median 9	Range 0-281			P=0.26	C	7
Length of hospital stay	RCT/1	-1		-1	-1		45	Median 60	Range 1-247	43	Median 50	Range 1-287			P=0.53	C	3
Complication	RCT/2	-1	0	-1	-1	0										B	5
A vs B (MOF and complication)							45	19	42	43	5	12	RR	0.28	0.11-0.67		
A vs B (Intra-abdominal bleeding)							45	10	22	43	7	16	RR	0.73	0.31-1.75		
A vs B (perforation)							45	10	22	43	6	14	RR	0.63	0.25-1.58		
C vs D (MOF)							10	5	50	10	0	0	RD	0.50	0.12-0.76		
C vs D (Intra-abdominal bleeding)							10	0	0	10	0	0	RD				
C vs D (perforation)							10	2	20	10	0	0	RD	0.20	-0.11-0.51		
C vs D (pancreatic fistula)							10	7	70	10	1	10	RD	0.60	0.17-0.81		

CQ4-3

PICO

Patients (P): Septic patients who received intravascular catheter
Intervention (I): To remove catheter
Control (C): Not to remove catheter
Outcomes (O): Mortality, ICU-free survival days, length of ICU stay, infective complication

Search terms

1. search ((((((sepsis OR septic shock OR ICU)) AND "catheter removal") AND (length of stay OR mortality)) AND english[la]) NOT ((animals OR murine OR rat OR pig))) NOT ((case report OR review))
2. search (((((sepsis OR severe sepsis OR septic shock)) AND catheter removal) AND Randomized Controlled Trial) AND Humans) AND English

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality	RCT/1	-1		-2	0		32	8	25.0	32	10	31.3	OR	0.73	0.25-2.19	D	9

CQ4-4

PICO

Patients (P): Septic patients caused by obstructive pyelonephritis
Intervention (I): Early source control
Control (C): Without early source control
Outcomes (O): Mortality, length of ICU stay

Search terms

1. (((((obstructed OR infected kidney OR urosepsis OR obstruction OR obstructive pyelonephritis OR pyonephrosis))) AND (sepsis OR septic shock)) AND (decompression OR stent or nephrostomy)) NOT (animals OR murine OR rat OR pig) NOT (case report OR review) AND english[la]
2. ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infection"[All Fields]) OR "urinary tract infection"[All Fields]) OR urosepsis[All Fields] AND ("drainage"[MeSH Terms] OR "drainage"[All Fields]) AND (Randomized Controlled Trial[ptyp]) AND english[la]

CQ4-5

PICO

Patients (P): Septic patients caused by necrotizing soft tissue infection
Intervention (I): Early surgical intervention
Control (C): Without early surgical intervention
Outcomes (O): Mortality, length of ICU stay

Search terms

1. (((Necrotizing Soft Tissue Infection) AND (severe sepsis OR septic shock)) AND (mortality OR length of ICU stay)) AND (operation OR drainage OR surgical OR open OR incision OR ultrasonographically OR ultrasonographic OR needle)
2. ((("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]) OR ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields])) AND ("drainage"[MeSH Terms] OR "drainage"[All Fields])) AND ((("Systemic Inflammatory Response Syndrome"[Mesh] OR "Systemic Inflammatory Response Syndrome"[TW] OR sepsis[TW] OR septic[TW]) AND ((("skin"[MeSH Terms] OR "skin"[All Fields]) OR (soft[All Fields] AND ("tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields]))) AND ("infection"[MeSH Terms] OR "infection"[All Fields])) OR ("necrotising fasciitis"[All Fields] OR "fasciitis, necrotizing"[MeSH Terms] OR ("fasciitis"[All Fields] AND "necrotizing"[All Fields]) OR "necrotizing fasciitis"[All Fields] OR ("necrotizing"[All Fields] AND "fasciitis"[All Fields])))) AND (("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh:noexp] OR randomly[TIAB] OR trial[TI]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) OR (Meta-Analysis[PT] OR systematic[SB])))

CQ5-1

PICO

Patients (P): Septic patients or Septic shock patients
Intervention (I): Administration of antibiotics within 1 hour
Control (C): Administration of antibiotics after more than 1 hour
Outcome (O): Mortality

Search terms

1. timing AND (antimicrobial OR Antibiot*) AND sepsis AND (empiric OR initial)
2. ((((septic shock) OR (severe sepsis) OR (sepsis))) AND ((antibacterial agents) OR (antibiotics))) AND (randomized or randomised)
3. (sepsis OR septic) AND (antibacterial OR antibiotics) AND (timing OR (period of time)) AND randomized

CQ5-2

PICO

Patients (P): Septic patients or Septic shock patients
Intervention (I): Antibiotic combination therapy
Control (C): Antibiotic monotherapy
Outcome (O): Mortality, development of bacterial resistance, nephrotoxicity

Search terms

1. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) AND combination[All Fields] AND ("antimicrobial"[All Fields] OR "beta-lactam"[All Fields] OR "beta lactam"[All Fields]) AND ((Randomized Controlled Trial[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp]) AND English[lang])
2. (sepsis OR critically ill) AND (antibiotic monotherapy OR antibiotic combination therapy) AND (meta-analysis[pt] OR systematic[sb] OR review[pt]) AND (english[la] OR japanese[la]) AND hasabstract[tw]
3. (sepsis OR critically ill) AND (antibiotic monotherapy OR antibiotic combination therapy) AND (randomized controlled trial[pt]) AND (english[la] OR japanese[la]) AND hasabstract[tw]

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality (same beta lactam)	RCT/13	-1	0	0	-1	0	716	76	10.6	715	80	11.2	RR	0.97	073-1.30	B	9
Mortality (other beta lactam)	RCT/31	-1	0	0	-1	0	2175	197	9.1	1971	222	11.3	RR	0.85	0.71-1.01	B	9
Development of bacterial	RCT/9	-1	0	-1	-1	0	716	28	3.9	654	29	4.4	RR	0.88	0.54-1.45	B	6
Nephrotoxicity	RCT/46	-1	0	0	-1	0	2709	64	2.4	2560	228	8.9	RR	0.3	0.23-0.39	B	4

CQ5-3

PICO

Patients (P): Septic patients or Septic shock patients who have risk factors of candida infection
Intervention (I): Antifungal therapy (+)
Control (C): Antifungal therapy (-)
Outcome (O): Mortality, complication

Search terms

1. (sepsis OR "septic shock") AND ("antifungal agents" OR "antifungal therapy") AND ("candida" OR "candidemia" OR "invasive candidiasis") AND (timing OR "risk factor" OR score OR beta-d glucan) AND (randomized controlled trial[ptyp] OR randomized OR randomised OR randomly OR "meta-analysis"[ptyp] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR systematic[sb] OR "systematic review") NOT (Trials[jo] OR Animals OR case reports[ptyp])
2. ((((("intensive care"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields])) OR ((("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) OR ("sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("severe"[All Fields] AND "sepsis"[All Fields]) OR "severe sepsis"[All Fields]))) AND (("mycoses"[MeSH Terms] OR "mycoses"[All Fields] OR "mycosis"[All Fields]) OR ("antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR ("antifungal"[All Fields] AND "agents"[All Fields]) OR "antifungal agents"[All Fields] OR ("antifungal"[All Fields] AND "agent"[All Fields]) OR "antifungal agent"[All Fields]))) AND ((Randomized Controlled Trial[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp]) AND "humans"[MeSH Terms] AND English[lang])
3. ((((("intensive care"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields])) OR ((("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) OR ("sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("severe"[All Fields] AND "sepsis"[All Fields]) OR "severe sepsis"[All Fields]))) AND (("mycoses"[MeSH Terms] OR "mycoses"[All Fields] OR "mycosis"[All Fields]) OR ("antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR ("antifungal"[All Fields] AND "agents"[All Fields]) OR "antifungal agents"[All Fields] OR ("antifungal"[All Fields] AND "agent"[All Fields]) OR "antifungal agent"[All Fields]))) AND ((Randomized Controlled Trial[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp]) AND "humans"[MeSH Terms] AND English[lang])

4. (antifungal or candida) and (sepsis or septic) and (clinical trial)

5. (antifungal OR candida) and (sepsis OR septic) and (clinical trial) and (appropriate OR empiric OR initial) (sepsis OR septic) AND (antibacterial OR antibiotics) AND (timing OR (period of time)) AND randomized

CQ5-4

PICO

Patients (P): Septic patients
Intervention (I): Prolonged or continuous administration of beta lactams
Control (C): Intermittent administration of beta lactams
Outcome (O): Mortality, rate of target attainment

Search terms

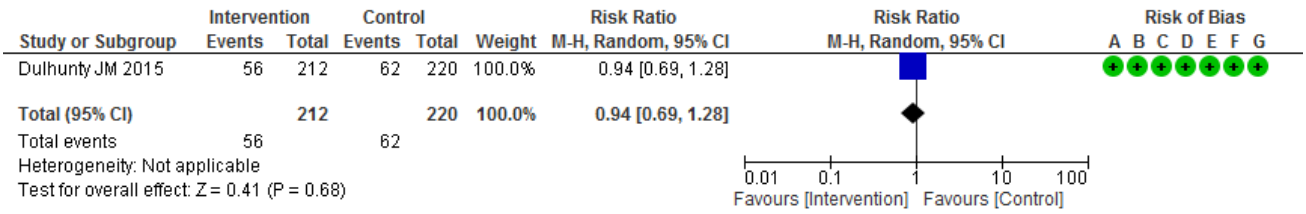
1. (((((((carbapenem OR carbapenems OR meropenem OR imipenem OR “imipenem- cilastatin” OR “imipenem/cilastatin” OR doripenem OR piperacillin/tazobactam OR cefepime OR ceftriaxone OR beta lactams[MeSH Terms]) AND (extended OR prolonged OR continuous OR discontinuous OR intermittent OR short OR bolus OR intravenous) AND (duration OR infusion OR administration OR interval OR dosing) AND (sepsis[MeSH Terms] OR sepsis OR "critically ill”))) AND ((randomized) OR randomised OR randomly)))))

Body of the evidence

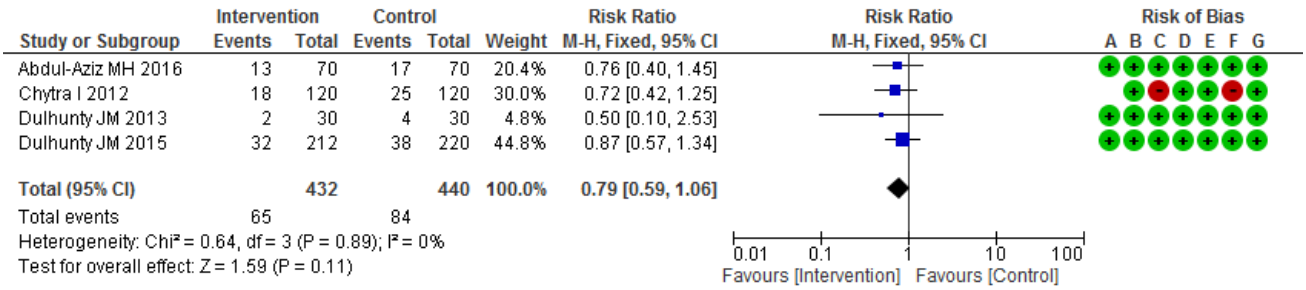
							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance
90-day mortality	RCT/1	0		0	0		220	62	28.2	212	56	26.4	RR	0.94	0.69-1.28	C	7
ICU mortality	RCT/4	0	0	0	0	-1	440	84	19.1	432	65	15.0	RR	0.79	0.59-1.06	B	7
Hospital mortality	RCT/3	-1	0	0	0	-1	370	90	24.3	362	68	18.8	RR	0.78	0.59-1.03	B	9
Target attainment	RCT/2	0	-2	-1	0	-1	74	42	56.8	79	73	92.4	RR	1.88	0.89-3.98	C	7

Results of meta-analysis

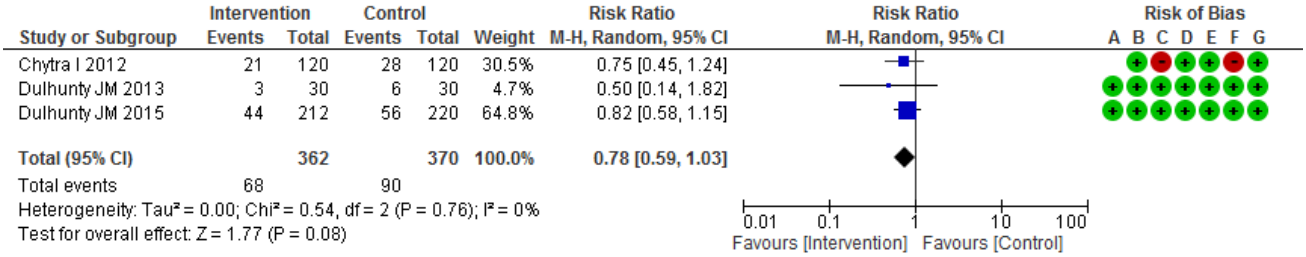
1. 90-day mortality



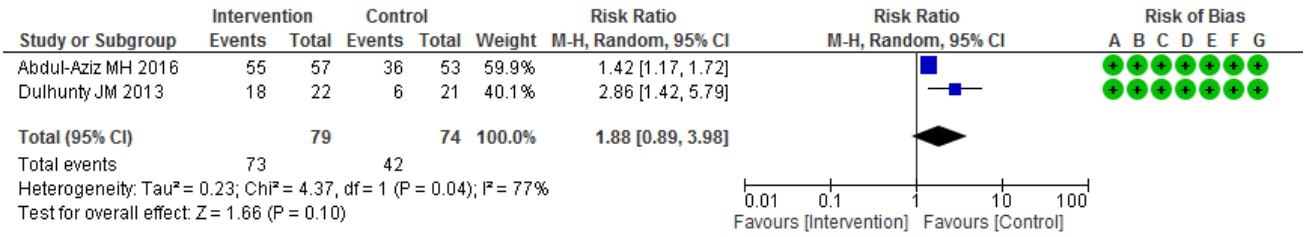
2. ICU mortality



3. Hospital mortality



4. Rate of target attainment



CQ5-5

PICO

Patients (P): Septic patients or septic shock patients
Intervention (I): De-escalation (+)
Control (C): De-escalation (-)
Outcome (O): Mortality, rate of superinfection

Search terms

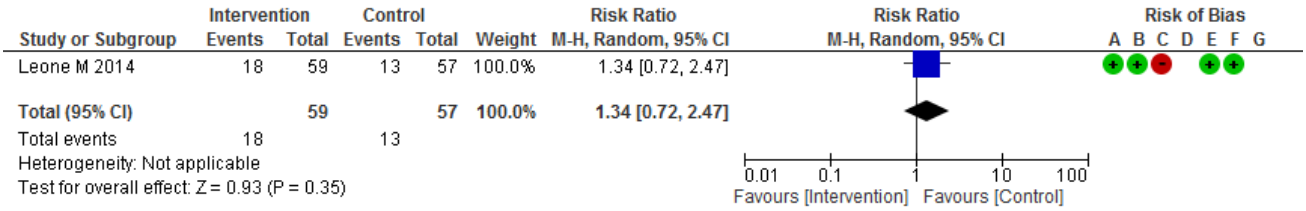
1. (((((((sepsis) OR septic)) OR critical ill OR critically)) AND escalation)) AND (((randomized) OR randomised) OR randomly)
2. ((((intensive care OR critical ill OR sepsis or septic)) AND ((de-escalation) OR escalation)) AND (antibacterial OR antibiotic)) AND (randomized OR randomised OR randomly)

Body of the evidence

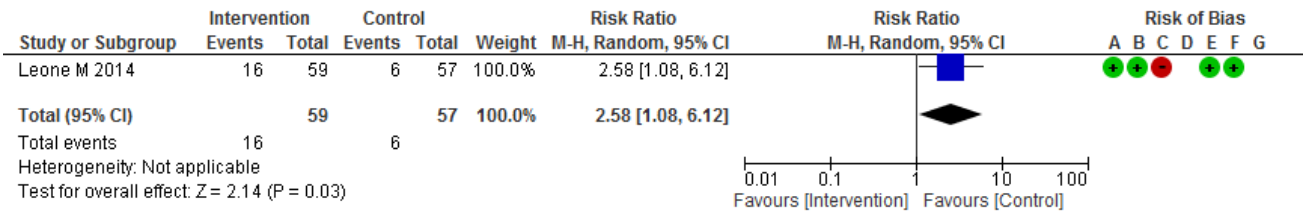
							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
90-day mortality	RCT/1	-1		0	0		57	13	22.8	59	18	30.5	RR	1.34	0.72-2.47	D	9
Superinfection	RCT/1	-1		-1	0		57	6	10.5	59	16	27.1	RR	2.58	1.08-6.12	D	7

Results of meta-analysis

1. 90-day mortality



2. Rate of superinfection



CQ5-6

PICO

Patients (P): Septic patients or septic shock patients
Intervention (I): Procalcitonin levels to guide antibiotic therapy (+)
Control (C): Procalcitonin levels to guide antibiotic therapy (-)
Outcome (O): Mortality, duration of antibiotic therapy

Search terms

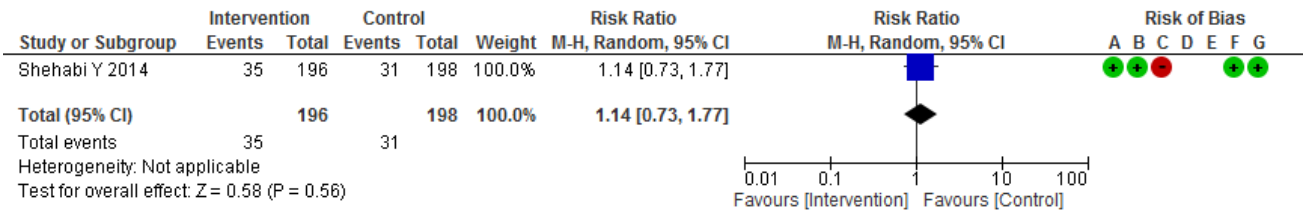
1. (sepsis OR septic OR ("intensive care" AND "bacterial infections")) AND (procalcitonin OR PCT OR "C reactive protein" OR "C-reactive protein" OR "soluble CD14 subtype" OR "presepsin") AND (antibacterial OR antibiotic OR antibiotics) AND ((mortality OR morbidity OR duration OR period OR stop OR stopped OR cessation) OR (algorithm OR guide OR guided)) AND (randomized OR randomised OR randomly) AND (english[la] OR japanese[la]) NOT (Review[ptyp] OR Meta-Analysis[ptyp] OR Trials[jo] OR Animals OR Case Reports[ptyp] OR Editorial[ptyp])

Body of the evidence

							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design/number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95 %CI	Strength	Importance
90-day mortality	RCT/1	-1		0	0		198	31	15.7	196	35	17.9	RR	1.14	0.73-1.77	C	7
ICU day mortality	RCT/3	-1	-1	0	0	-1	267	29	10.9	269	29	10.8	RR	0.86	0.40-1.87	B	7
Hospital mortality	RCT/4	-1	0	-1	0	0	122	26	21.3	126	21	16.7	RR	0.8	0.48-1.33	B	9
28-day mortality	RCT/4	-1	0	0	0	0	785	196	25.0	761	149	19.6	RR	0.84	0.72-0.98	B	5
60-day mortality	RCT/1	0		0	0		314	82	26.1	307	92	30.0	RR	1.15	0.89-1.48	C	5
Duration of antibiotic therapy	RCT/5	-1	0	-1	0	0								-1.99	-2.10 - 1.89	B	8

Results of meta-analysis

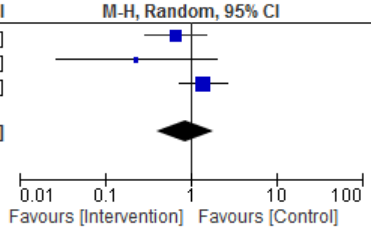
1. 90-day mortality

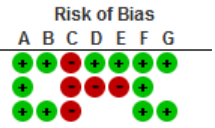


2. ICU mortality

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane D 2013	7	31	10	30	39.9%	0.68 [0.30, 1.55]
Deliberato RO 2013	1	42	4	39	11.0%	0.23 [0.03, 1.99]
Shehabi Y 2014	21	196	15	198	49.1%	1.41 [0.75, 2.66]
Total (95% CI)		**269**		**267**	**100.0%**	**0.86 [0.40, 1.87]**
Total events	29		29			

Heterogeneity: Tau² = 0.21; Chi² = 3.79, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 0.37 (P = 0.71)

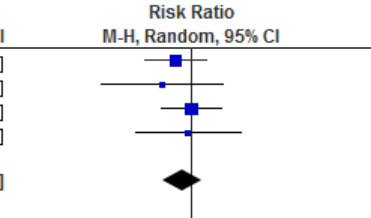


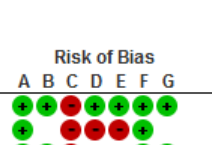


3. Hospital mortality

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane D 2013	7	31	10	30	38.0%	0.68 [0.30, 1.55]
Deliberato RO 2013	2	42	4	39	9.6%	0.46 [0.09, 2.39]
Nobre V 2007	9	39	9	40	39.3%	1.03 [0.46, 2.31]
Schroeder S 2009	3	14	3	13	13.0%	0.93 [0.23, 3.81]
Total (95% CI)		**126**		**122**	**100.0%**	**0.80 [0.48, 1.33]**
Total events	21		26			

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)

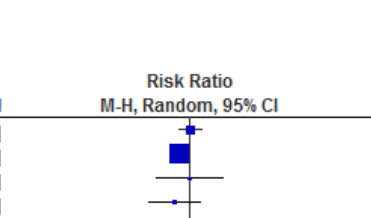




4. 28-day mortality

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bouadma L 2010	65	307	64	314	25.1%	1.04 [0.76, 1.41]
E de Jong 2016	149	761	196	785	66.8%	0.78 [0.65, 0.95]
Nobre V 2007	8	39	8	40	3.1%	1.03 [0.43, 2.46]
Svoboda P 2007	10	38	13	34	5.1%	0.69 [0.35, 1.36]
Total (95% CI)		**1145**		**1173**	**100.0%**	**0.84 [0.72, 0.98]**
Total events	232		281			

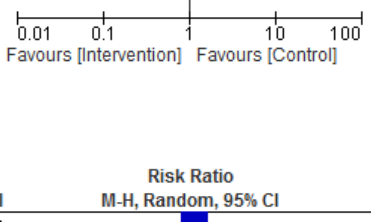
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)



5. 60-day mortality

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bouadma L 2010	92	307	82	314	100.0%	1.15 [0.89, 1.48]
Total (95% CI)		**307**		**314**	**100.0%**	**1.15 [0.89, 1.48]**
Total events	92		82			

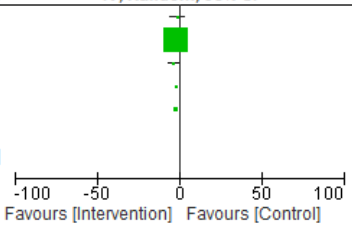
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)

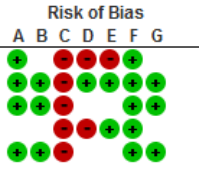


6. Duration of antibiotic therapy

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Deliberato RO 2013	10	9	42	11	10.7	39	0.1%	-1.00 [-5.32, 3.32]
E de Jong 2016	5	1	761	7	1.2	785	92.9%	-2.00 [-2.11, -1.89]
Nobre V 2007	6	7.8	39	9.5	7.8	40	0.1%	-3.50 [-6.94, -0.06]
Schroeder S 2009	6.6	1.1	14	8.3	0.7	13	2.4%	-1.70 [-2.39, -1.01]
Shehabi Y 2014	9	2.3	196	11	2.7	198	4.6%	-2.00 [-2.50, -1.50]
Total (95% CI)			**1052**			**1075**	**100.0%**	**-1.99 [-2.10, -1.89]**

Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 4 (P = 0.80); I² = 0%
Test for overall effect: Z = 36.86 (P < 0.00001)





CQ6-1

PICO

Patients (P): Septic patients/ Septic shock patients
Intervention (I): IVIG (+)
Control (C): Placebo or IVIG (-)
Outcome (O): Mortality, ICU mortality, length of ICU stay, complication

Search terms

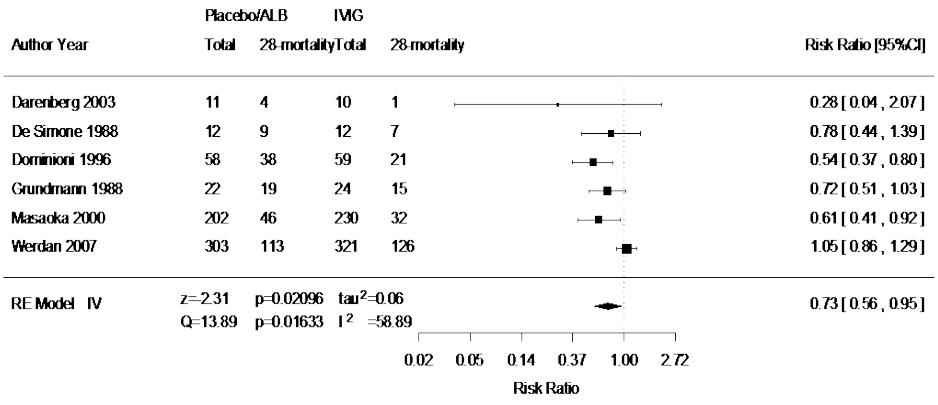
1. (sepsis or severe sepsis or septic shock or septicemia or septic) AND (immunoglobulin or IVIG or immuno globulin or immune globulin or IgG) AND (randomized controlled trial OR controlled clinical trial OR randomized clinical trial OR clinical trials OR randomly OR propensity OR observational) NOT (animals NOT humans)

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
All cause mortality	RCT/6	-1	0	0	-1	0	608	229	37.7%	656	202	30.8%	RR	0.73	0.56-0.95	C	9
ICU mortality	RCT/1	-1		0	-1		303	168	55.4%	321	126	39.3%	RR	0.71	0.60-0.84	D	7
Length of ICU stay	RCT/3	-1	0	0	-1	0	383			404			MD	-3.71	(-7.32)-(-0.09)	C	5
Complication	RCT/3	-1	0	-1	-1	0	372	6	1.6%	390	11	2.8%	RR	1.63	0.65-4.11	C	5

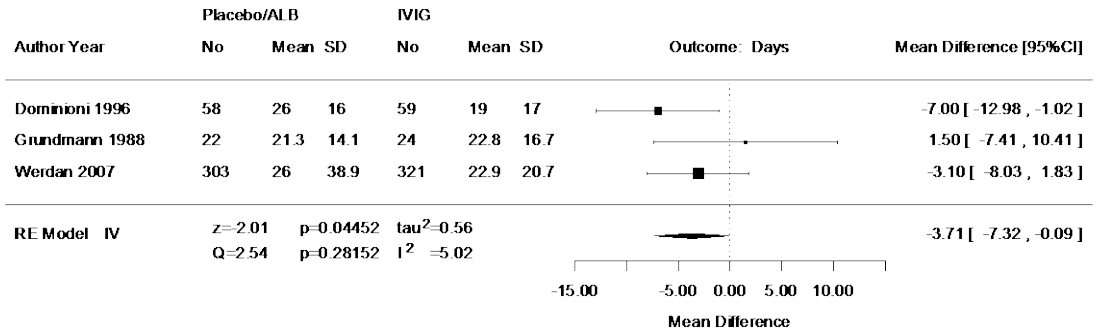
Results of meta-analysis

1. Mortality

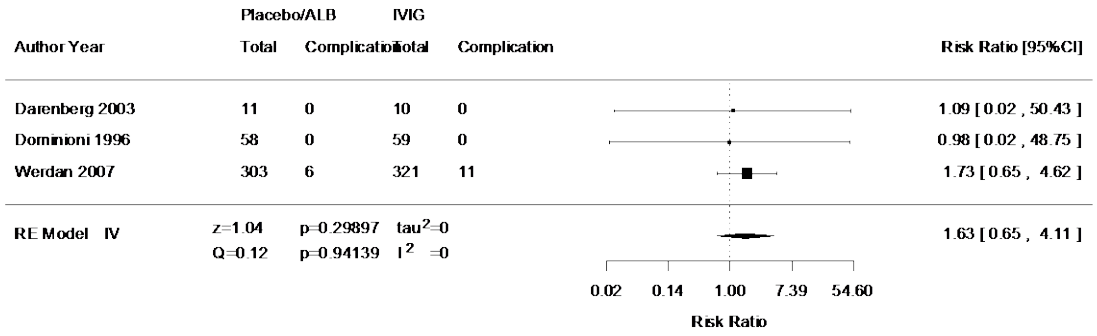


2. ICU mortality

3. Length of ICU stay



4. Complication



CQ7-1

PICO

Patients (P): Patients with septic and septic shock who treatment in accordance with SSCG without EGDT
Intervention (I): EGDT
Control (C): Standard treatment
Outcome (O): Mortality rate, time to shock reversal, ICU length of stay

Search terms

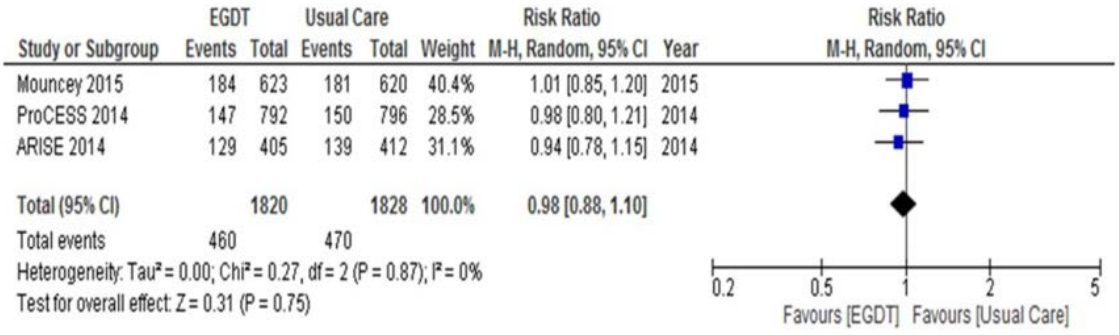
1. (sepsis or septic) and (goal directed therapy or goal directed resuscitation or EGDT or early goal directed therapy or goal oriented or central venous oxygen saturation) and (randomized or randomised or randomly)
2. (sepsis or septic) and (goal directed or goal-directed or EGDT or protocol) and (randomized or randomised or randomly)

Body of the evidence

							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance
90-day mortality rate	RCT/3	0	0	0	0	0	1828	470	25.71	1820	460	25.27	Risk Ratio	0.98	0.88-1.10	A	9
28-day mortality rate	RCT/2	0	0	0	0	0	1418	279	19.68	1417	272	19.20	Risk Ratio	0.98	0.84-1.13	A	9
Time to shock reversal	0																3
ICU length of stay	RCT/3	0	-1	0	0	0	1880			1857			Mean Differenc	0.27	-0.33-0.87	B	7

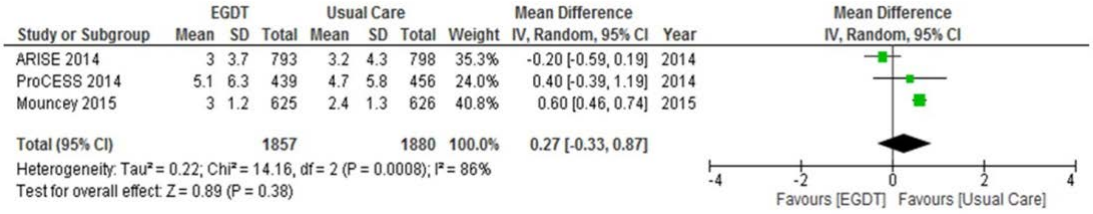
Results of meta-analysis

1. 90-day mortality rate



2. 28-day mortality rate

3. ICU length of stay



CQ7-2

PICO

Patients (P): Patients with septic shock and septic
Intervention (I): Initial high volume fluid resuscitation (+)
Control (C): Initial high volume fluid resuscitation (-)
Outcome (O): Mortality rate, complication rate, time to shock reversal, ICU length of stay

Search terms

1. (severe sepsis or septic shock) and (fluid resuscitation or fluid therapy) and (randomized or randomised or randomly)、
2. (sepsis or septic) and (fluid resuscitation or resuscitation volume or fluid volume or fluid balance) and (randomized or randomised or randomly)

CQ7-3

PICO

Patients (P): Patients with septic shock and septic
Intervention (I): Evaluation of cardiac function using echocardiography (+)
Control (C): Evaluation of cardiac function using echocardiography (-)
Outcome (O): 28-day mortality rate, complication rate, time to shock reversal, ICU length of stay

Search terms

1. (sepsis or septic*) and (arterial waveform or central venous pressure or *variation or echo* or *responsiveness or preload dependence) and (randomized or randomised or randomly)

CQ7-4

PICO

Patients (P): Patients with septic and septic shock
Intervention (I): Colloid
Control (C): Crystalloid
Outcome (O): Mortality rate, incidence of AKI, rate of RRT, transfusion rate of RBC and FFP

Search terms

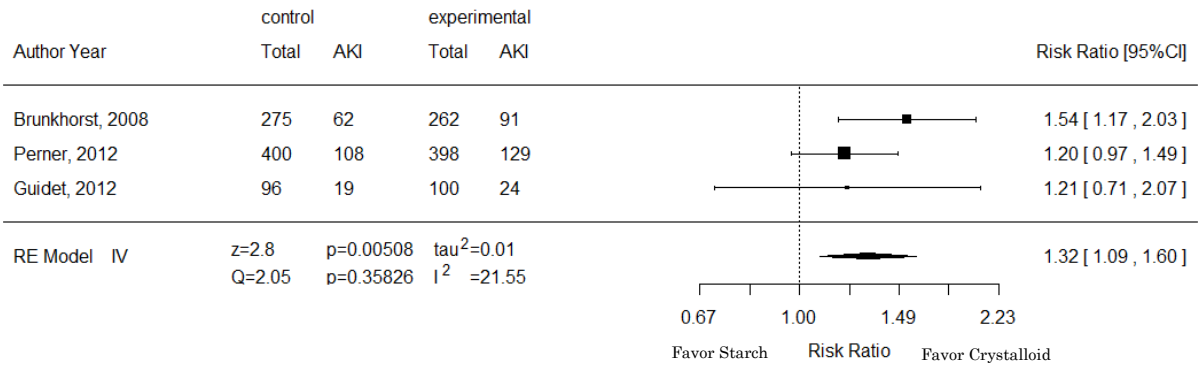
1. Sepsis or septic shock
2. Crystalloid or colloid

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
AKI	RCT/3	0	0	0	0	0	771	189	24.5	760	244	32.1	Risk Ratio	1.32	1.09-1.60	A	7
RRT	RCT/4	0	0	0	0	0	818	140	17.1	798	199	24.9	Risk Ratio	1.46	1.21-1.77	A	8
Transfusion rateof RBC	RCT/3	0	0	0	0	0	771	382	49.5	760	448	58.9	Risk Ratio	1.19	1.04-1.36	A	4
Transfusion rate of FFP	RCT/1	0		-1	0		400	96	24.0	398	113	28.4	Risk Ratio	1.18	0.94-1.49	D	4
ICU mortality rate	RCT/4	0	0	0	0	0	95	27	28.4	142	17	12.0	Risk Ratio	0.56	0.34-0.94	A	9
28-day mortality rate	RCT/4	0	0	-1	0	0	790	240	30.4	781	264	33.8	Risk Ratio	1.11	0.96-1.28	B	9
90-day mortality rate	RCT/4	0	0	0	0	0	1716	521	30.4	1736	596	34.3	Risk Ratio	1.14	1.04-1.26	A	9

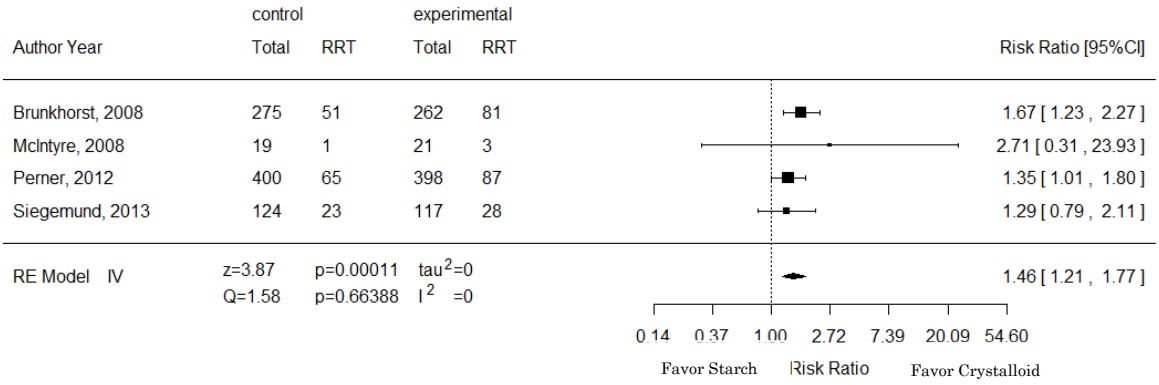
Results of meta-analysis

1. Incidence of AKI



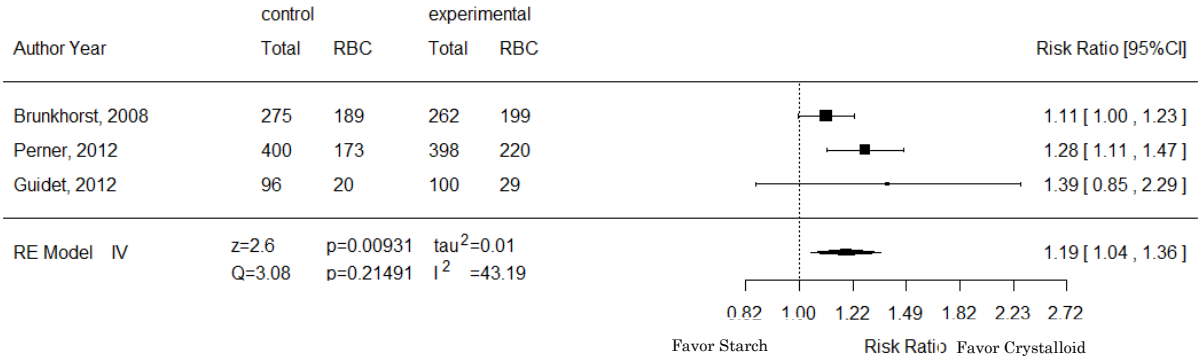
2.

Rate of RRT

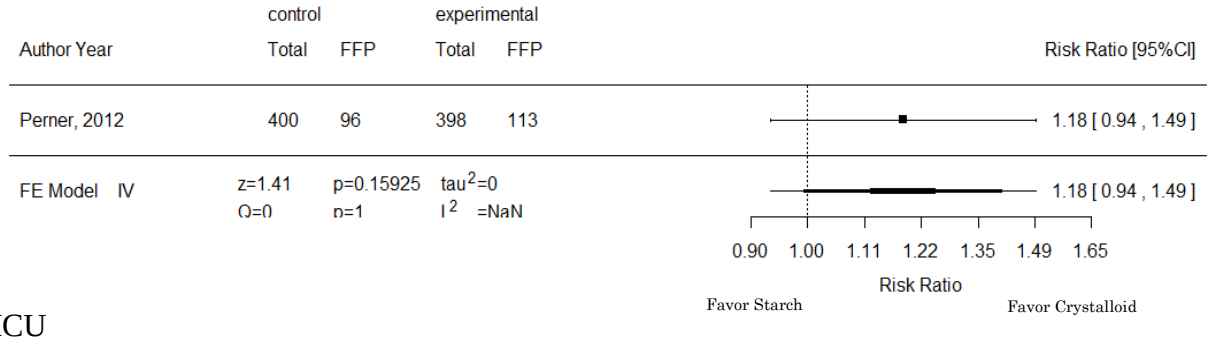


3. Transfusion rate of RBC

4.

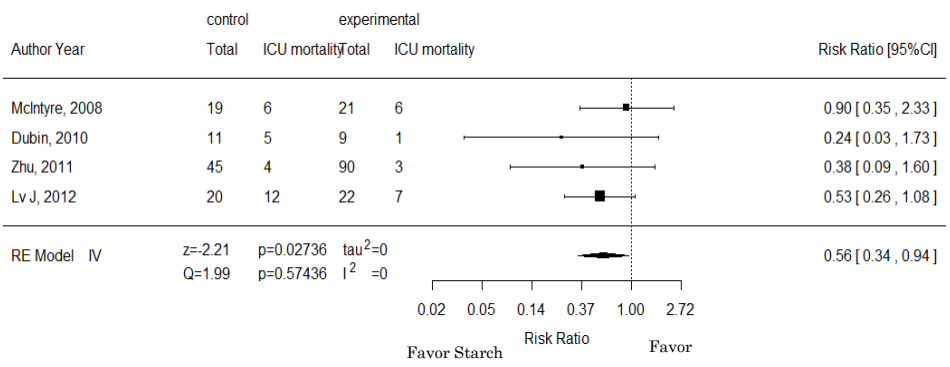


Transfusion rate of FFP

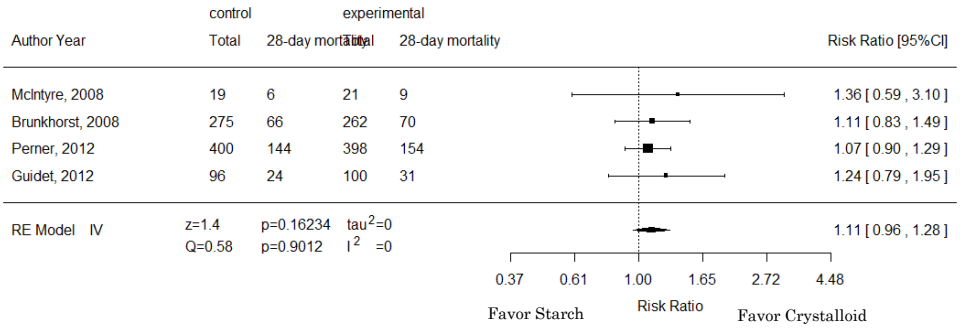


5. ICU

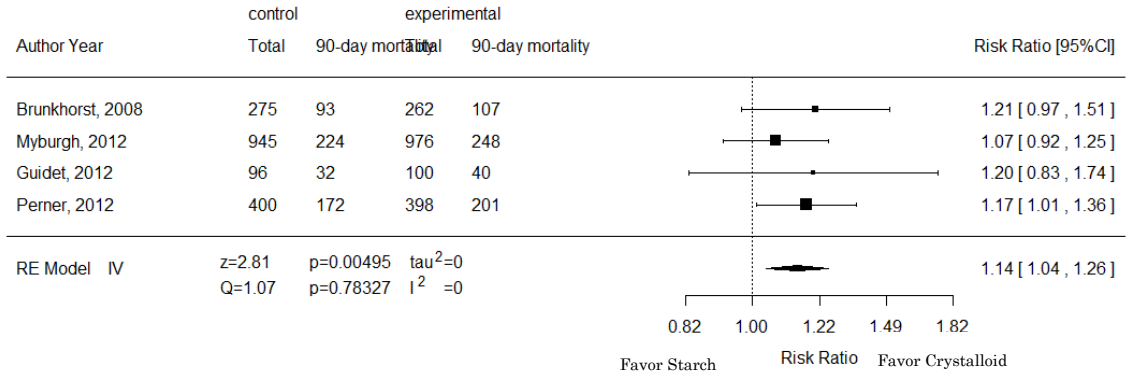
mortality rate



6. 28-day mortality rate



7. 90-day mortality rate



CQ7-5

PICO

Patients (P): Patients with septic shock
Intervention (I): Albumin (+)
Control (C): Albumin (-)
Outcome (O): Mortality rate, time to shock reversal, ICU length of stay

Search terms

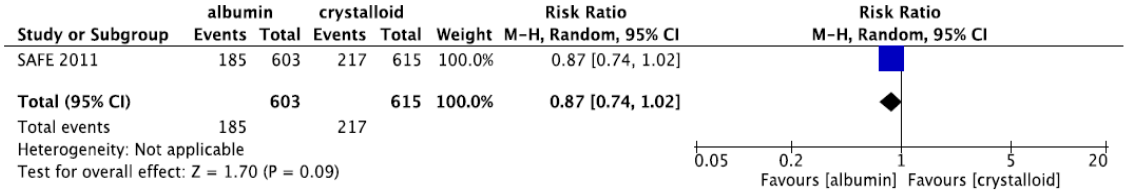
1. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) AND ("albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields]) AND (meta-analysis[pt] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR guideline[pt] OR systematic[sb]) AND "humans"[MeSH Terms] AND (english[la] OR japanese[la])
2. (sepsis OR "septic shock" OR "Severe sepsis") AND (albumin OR "albumin infusion")
Filter 1：meta-analysis OR randomized control trial
Filter 2：English OR Japanese
3. ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND ("body fluids"[MeSH Terms] OR ("body"[All Fields] AND "fluids"[All Fields]) OR "body fluids"[All Fields] OR "fluid"[All Fields]) AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]) AND ("albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields]) AND rct[All Fields]

Body of the evidence

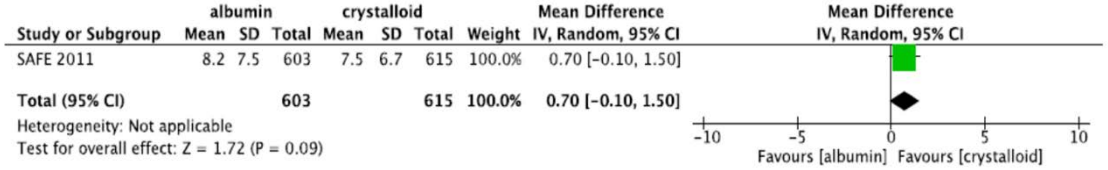
							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality rate	RCT/1	0		-1	-1		615	217	39.3	603	185	36.6	RR	0.87	0.74-1.02	C	9
Time to shock reversal	0																3
ICU length of stay	RCT/1	0		-1	-1		7.5	6.7		8.2	7.5		MD	0.7	-0.10 - 1.50	C	7

Results of meta-analysis

1. Mortality rate



2. ICU length of stay



CQ7-6

PICO

Patients (P): Patients with septic and septic shock
Intervention (I): Initial resuscitation using monitoring which evaluates fluid responsiveness
Control (C): Initial resuscitation not using monitoring
Outcome (O): 28-day mortality rate, complication rate, time to shock reversal, ICU length of stay

Search terms

1. (sepsis OR septic*) AND ((arterial waveform) or central (venous pressue) or *variation or echo* or *responsiveness or (preload dependence) AND (randomized OR randomised OR randomly)

Body of the evidence

1. SVV vs others

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	The numbers of persons at risk (outcome rate)						Type	Value	95%CI	Strength	Importance
							Control group			Intervention group							
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality rate	RCT/2	-1	0	-1	-1	0	58	18	31.03	60	12	20	RR	0.67	0.30-1.46	C	9
ICU length of stay	RCT/2	-1	0	-1	-1	0	58			60			MD	0.86	0.02-1.70	C	6
Time to shock reversal	RCT/1	-1		-1	0		30	2	1.41	30	2.3	3.1	MD	0.30	-0.92-1.52	D	6
Complication rate	RCT/1	-1		-1	-1		30	4	2.96	30	4	3.7	MD	0.00	-1.70-1.70	D	6
Duration of ventiration	RCT/2	-1	-1	-1	-1	0	58			60			MD	1.38	-4.08-6.85	C	6

2. PLR vs others

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	The numbers of persons at risk (outcome rate)						Type	Value	95%CI	Strength	Importance
							Control group			Intervention group							
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Short term mortality	RCT/4	0	0	-1	-1	0	162	45	27.8	160	40	25	RR	0.9	0.60-1.36	C	9
ICU length of stay	RCT/3	0	-1	0	-1	-1	121			119			MD	-0.3	-1.15 to 0.56	D	6
Ventilator-free days	RCT/2	0	0	-1	-1	-1	71			71			MD	1.92	-3.56 to 7.41	D	6
Time to shock reversal	RCT/2	0	0	-1	-1	0	71			71			MD	0.19	-0.79 to 1.17	C	6

3. Thermodilution vs others (CVP)

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	The numbers of persons at risk (outcome rate)						Type	Value	95%CI	Strength	Importance
							Control group			Intervention group							
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality rate	RCT/1	-1		-1	0		168	83	49.4	182	90	49.5	RR	1	0.81-1.24	C	9
ICU length of stay	RCT/1	-1		-1	0		168	9	5.9	182	7.5	8.2	MD	1.5	0.01-2.99	C	6
Time to shock reversal	RCT/1	-1		-1	0		168	14.5	18.5	182	19	19.3	MD	-4.5	(-8.46, -0.54)	C	6
Complication rate	RCT/1																
Duration of ventilation	RCT/1	-1		-1	0		168	6	6.7	182	5.5	6.7	MD	0.5	(-0.9, 1.9)	C	6

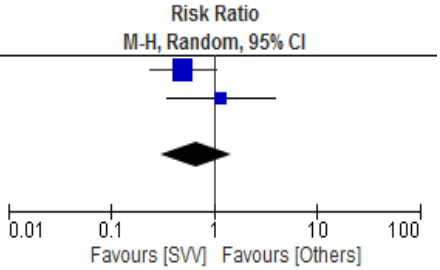
Results of meta-analysis

1. SVV vs others

A) Mortality rate

Study or Subgroup	SVV Events	SVV Total	Others Events	Others Total	Weight	Risk Ratio M-H, Random, 95% CI
Richard JC 2015	7	30	14	30	66.2%	0.50 [0.24, 1.06]
Xu Q 2014	5	30	4	28	33.8%	1.17 [0.35, 3.91]
Total (95% CI)		**60**		**58**	**100.0%**	**0.67 [0.30, 1.46]**
Total events	12		18			

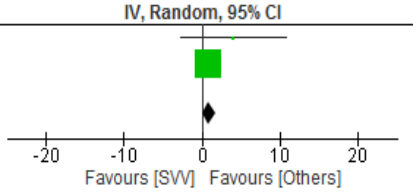
Heterogeneity: Tau² = 0.10; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.01 (P = 0.31)



B) ICU length of stay

Study or Subgroup	SVV Mean	SVV SD	SVV Total	Others Mean	Others SD	Others Total	Weight	Mean Difference IV, Random, 95% CI
Richard JC 2015	14	16.3	30	10	9.6	30	1.5%	4.00 [-2.77, 10.77]
Xu Q 2014	10.2	1.58	30	9.39	1.71	28	98.5%	0.81 [-0.04, 1.66]
Total (95% CI)			**60**			**58**	**100.0%**	**0.86 [0.02, 1.70]**

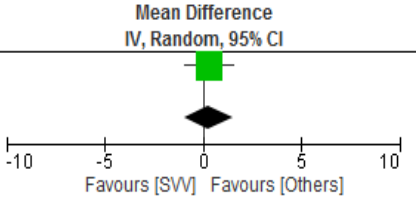
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)



C) Time to shock reversal

Study or Subgroup	SVV Mean	SVV SD	SVV Total	Others Mean	Others SD	Others Total	Weight	Mean Difference IV, Random, 95% CI
Richard JC 2015	2.3	3.1	30	2	1.41	30	100.0%	0.30 [-0.92, 1.52]
Total (95% CI)			**30**			**30**	**100.0%**	**0.30 [-0.92, 1.52]**

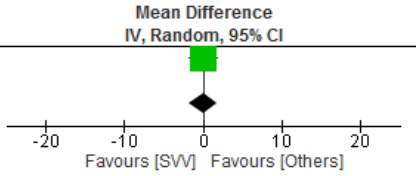
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)



D) Complication rate (pulmonary edema)

Study or Subgroup	SVV Mean	SVV SD	SVV Total	Others Mean	Others SD	Others Total	Weight	Mean Difference IV, Random, 95% CI
Richard JC 2015	4	3.7	30	4	2.96	30	100.0%	0.00 [-1.70, 1.70]
Total (95% CI)			**30**			**30**	**100.0%**	**0.00 [-1.70, 1.70]**

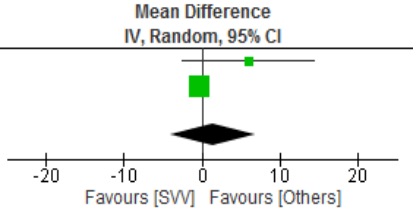
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



E) Duration of ventilation

Study or Subgroup	SVV Mean	SVV SD	SVV Total	Others Mean	Others SD	Others Total	Weight	Mean Difference IV, Random, 95% CI
Richard JC 2015	14	17.8	30	8	15.6	30	26.7%	6.00 [-2.47, 14.47]
Xu Q 2014	5.6	1.9	30	5.9	1.6	28	73.3%	-0.30 [-1.20, 0.60]
Total (95% CI)			**60**			**58**	**100.0%**	**1.38 [-4.08, 6.85]**

Heterogeneity: Tau² = 10.40; Chi² = 2.10, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.50 (P = 0.62)

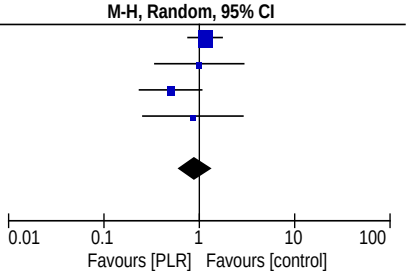


2. PLR vs others

A) Short term mortality rate

Study or Subgroup	Passive Leg Raising Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2015	23	41	20	41	52.7%	1.15 [0.76, 1.74]
Kuan 2015	6	61	6	61	13.0%	1.00 [0.34, 2.93]
Richard 2015	7	30	14	30	23.7%	0.50 [0.24, 1.06]
Xu 2014	4	28	5	30	10.5%	0.86 [0.26, 2.87]
Total (95% CI)		**160**		**162**	**100.0%**	**0.90 [0.60, 1.36]**
Total events	40		45			

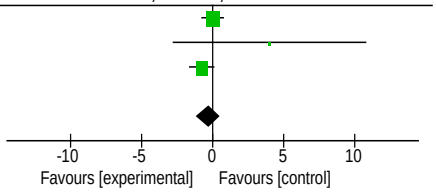
Heterogeneity: Tau² = 0.04; Chi² = 3.75, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.51 (P = 0.61)



B) ICU length of stay

Study or Subgroup	Passive Leg Raising Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kuan 2015	4	2.59	61	4	1.48	61	51.9%	0.00 [-0.75, 0.75]
Richard 2015	14	16.3	30	10	9.6	30	1.6%	4.00 [-2.77, 10.77]
Xu 2014	9.39	1.71	28	10.16	1.58	30	46.6%	-0.77 [-1.62, 0.08]
Total (95% CI)			**119**			**121**	**100.0%**	**-0.30 [-1.15, 0.56]**

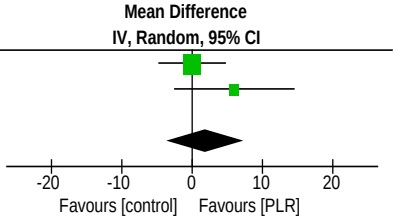
Heterogeneity: Tau² = 0.22; Chi² = 3.34, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.68 (P = 0.50)



C) Ventilator-free days

Study or Subgroup	Passive Leg Raising Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2015	5.5	9.1	41	5.5	12.4	41	67.9%	0.00 [-4.71, 4.71]
Richard 2015	14	17.8	30	8	15.6	30	32.1%	6.00 [-2.47, 14.47]
Total (95% CI)			**71**			**71**	**100.0%**	**1.92 [-3.56, 7.41]**

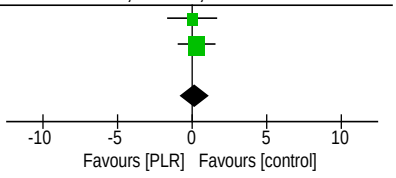
Heterogeneity: Tau² = 5.78; Chi² = 1.47, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 0.69 (P = 0.49)



D) Time to shock reversal

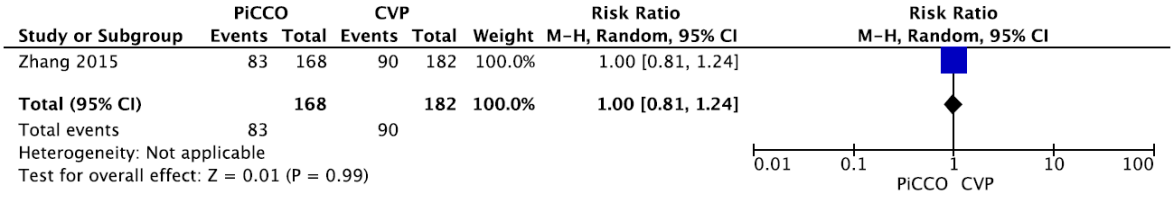
Study or Subgroup	Passive Leg Raising Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2015	4	4.44	41	4	2.96	41	35.9%	0.00 [-1.63, 1.63]
Richard 2015	2.3	3.11	30	2	1.41	30	64.1%	0.30 [-0.92, 1.52]
Total (95% CI)			**71**			**71**	**100.0%**	**0.19 [-0.79, 1.17]**

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)

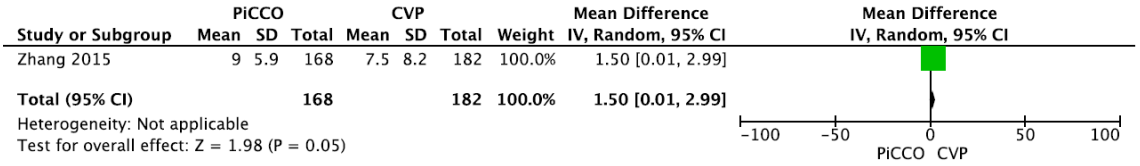


3. Thermodilution vs others (CVP)

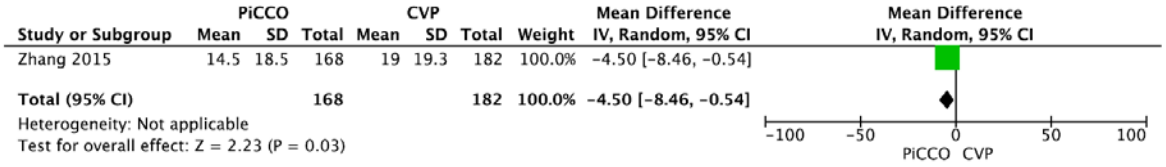
A) Mortality rate



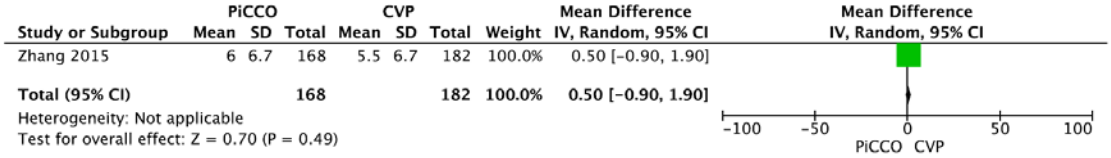
B) ICU length of stay



C) Time to shock reversal



D) Duration of ventilation



CQ7-7

PICO

Patients (P): Patients with septic and septic shock
Intervention (I): Evaluation of lactate (+)
Control (C): Evaluation of lactate (-)
Outcome (O): Mortality rate, complication rate, time to shock reversal, ICU length of stay

Search terms

1. ((systemic inflammatory response syndrome) or sepsis or (severe sepsis) or (septic shock)) and ((lactic acid) or (central venous oxygen saturation)) and (randomized or randomised or randomly)

CQ7-8

PICO

Patients (P): Patients with septic shock
Intervention (I): Evaluation of $S_{CV}O_2$
Control (C): Evaluation of lactate clearance
Outcome (O): Hospital mortality rate, hospital and ICU length of stay, complication rate

Search terms

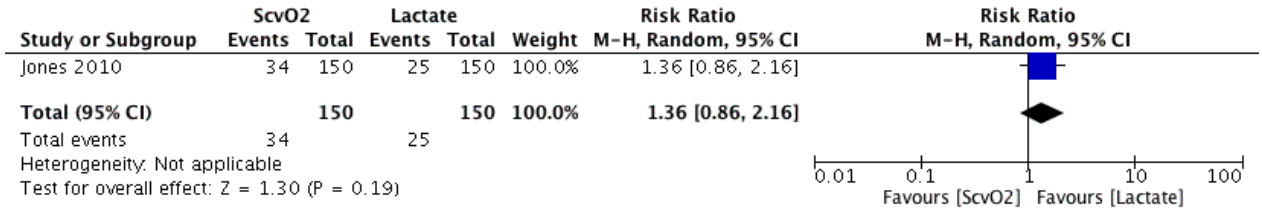
1. ((systemic inflammatory response syndrome) or sepsis or (severe sepsis) or (septic shock)) and ((lactic acid) or (central venous oxygen saturation)) and (randomized or randomised or randomly)

Body of the evidence

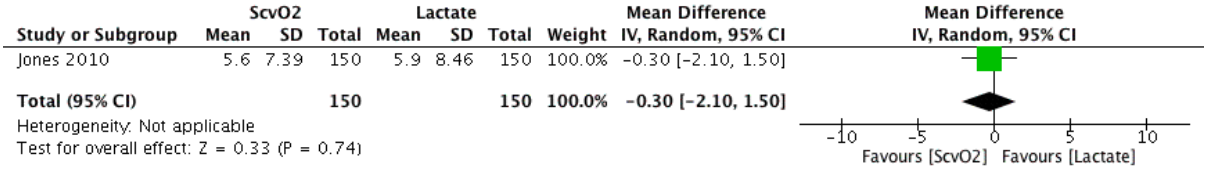
							The numbers of persons at risk (outcome rate)											
							Control group			Intervention group								
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	Comment
Hospital mortality rate	RCT/1	0		-1	0		150	25	17	150	34	23				D	9	
ICU length of stay	RCT/1	0		-1	0		150	5.9	8.46	150	5.6	7.39				D	6	mean, SD
Hospital length of stay	RCT/1	0		-1	0		150	11.4	10.89	150	12.1	11.68				D	6	mean, SD
Complication rate (Multiple organ failure)	RCT/1	0		-1	0		150	33	22	150	37	25				D	6	

Results of meta-analysis

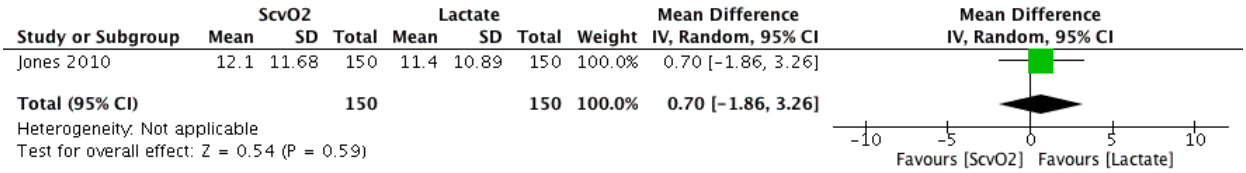
1. Hospital mortality rate



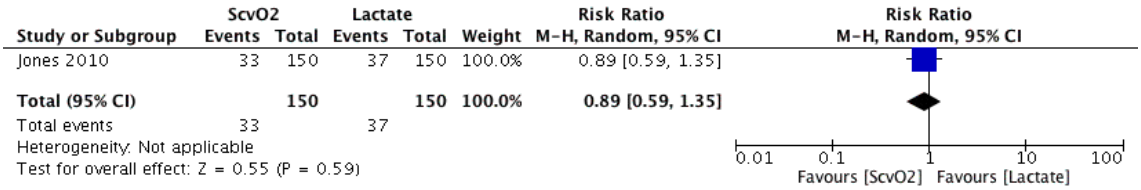
2. ICU length of stay



3. Hospital length of stay



4. Complication rate (multiple organ failure)



CQ7-9

PICO

Patients (P): Patients with septic shock
Intervention (I): Noradrenaline
Control (C): Dopamine
Outcome (O): 28-day mortality rate, time to shock reversal, ICU length of stay, complication rate

Search terms

1. (sepsis or septic shock) and (noradrenaline or norepinephrine)

Body of the evidence

Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	The numbers of persons at risk (outcome rate)						Type	Value	95%CI	Strength	Importance	Comment
							Control group			Intervention group								
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
28-day mortality	RCT/11	-1	0	0	0	0	886	450	50.8	832	376	45.2	RR	0.89	0.81-0.98	B	9	NE vs DOP
Recocery rate from shock																	7	
ICU length of stay	RCT/6	-2	0	-1	-1	0	804			782			Mean Differenc	1.01	-0.65-2.66	C	5	NE vs other
Complication	RCT/3	-2	0	-1	0	0	186	16	8.6	170	5	2.9	RR	0.34	0.14-0.84	C	7	NE vs DOP

CQ7-10

PICO

Patients (P): Patients with septic shock
Intervention (I): Adrenaline (+)
Control (C): Adrenaline (-)
Outcome (O): 28-day mortality rate, time to shock reversal, ICU length of stay, complication rate

Search terms

1. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) AND (("epinephrine"[MeSH Terms] OR "epinephrine"[All Fields] OR "adrenaline"[All Fields]) OR ("epinephrine"[MeSH Terms] OR "epinephrine"[All Fields])) AND (meta-analysis[pt] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR guideline[pt] OR systematic[sb]) AND "humans"[MeSH Terms] AND (english[la] OR japanese[la]) AND ("2010/12/16"[PDat]: "2015/12/14"[PDat])
2. (sepsis OR septic shock) AND (adrenaline OR epinephrine) AND (meta-analysis[pt] OR systematic[sb] OR review[pt]) AND humans[mh] AND (english[la] OR japanese[la]) AND hasabstract[tw]
3. (septic shock OR severe sepsis) AND (epinephrine OR norepinephrine) AND (systematic OR meta-analysis OR review) AND human

CQ7-11

PICO

Patients (P): Patients with septic shock using noradrenaline
Intervention (I): Vasopressin (+)
Control (C): Vasopressin (-)
Outcome (O): 28-day mortality rate, time to shock reversal, ICU length of stay, complication rate

Search terms

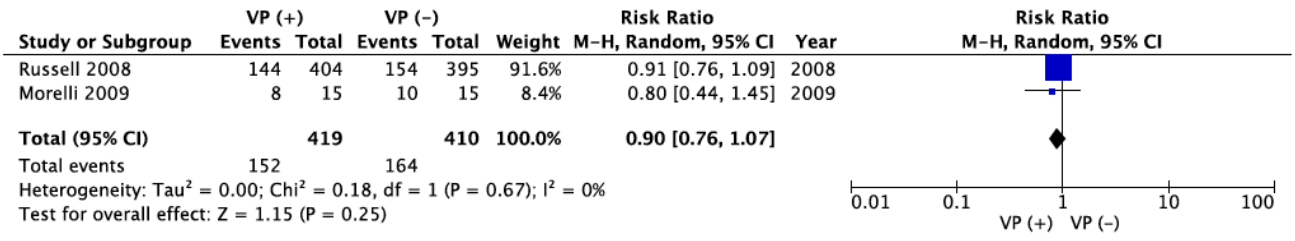
1. ((“epinephrine”[MeSH Terms] OR “epinephrine”[All Fields] OR “adrenalin”[All Fields]) OR ((“norepinephrine”[MeSH Terms] OR “norepinephrine”[All Fields] OR “noradrenalin”[All Fields]) OR ((“vasopressins”[MeSH Terms] OR “vasopressins”[All Fields] OR “vasopressin”[All Fields]) AND ((“sepsis”[MeSH Terms] OR “sepsis”[All Fields]) OR (“shock, septic”[MeSH Terms] OR (“shock”[All Fields] AND “septic”[All Fields]) OR “septic shock”[All Fields] OR (“septic”[All Fields] AND “shock” [All Fields])))) AND randomized controlled trial [pt]
2. ((systematic inflammatory response syndrome) or (sepsis) or (severe sepsis) or (septic shock)) and (noradrenaline or epinephrine or vasopressin) and (randomized or randomized or randomly))

Body of the evidence

							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	Comment
28-day mortality rate	RCT/2	0	0	-1	0	-1	410	164	40	419	152	36.28	RR	0.9	0.76-1.07	B	8	
Complication rate	RCT/2	0	0	-1	0	-1	397	44	11.08	411	42	10.22	RR	0.73	0.24-2.23	B	6	
Time to shock reversal	RCT/2	0			0	-1											6	
ICU length of stay	RCT/2	0	0	0	0	-1	410			419			MD	-0.95	-1.73, -0.17	C	5	mean=median, SD=range/4

Results of meta-analysis

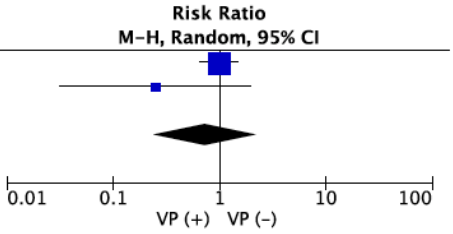
1. 28-days mortality rate



2. Complication rate

Study or Subgroup	VP (+) Events	Total	VP (−) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Russell 2008	41	396	40	382	78.2%	0.99 [0.65, 1.49]	2008
Morelli 2009	1	15	4	15	21.8%	0.25 [0.03, 1.98]	2009
Total (95% CI)		**411**		**397**	**100.0%**	**0.73 [0.24, 2.23]**	
Total events	42		44				

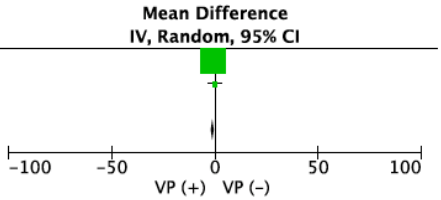
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 1.64$, df = 1 (P = 0.20); $I^2 = 39\%$
Test for overall effect: Z = 0.55 (P = 0.59)



3. ICU length of stay

Study or Subgroup	VP (+) Mean	SD	Total	VP (−) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Russell 2008	15	5.5	404	16	6	395	94.9%	−1.00 [−1.80, −0.20]	2008
Morelli 2009	17	5.5	15	17	4	15	5.1%	0.00 [−3.44, 3.44]	2009
Total (95% CI)			**419**			**410**	**100.0%**	**−0.95 [−1.73, −0.17]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 2.39 (P = 0.02)



CQ7-12

PICO

Patients (P): Patients with septic shock with reduction of cardiac function
Intervention (I): Dobutamine (+)
Control (C): Dobutamine (-)
Outcome (O): 28-day mortality rate, time to shock reversal, ICU length of stay, complication rate

Search terms

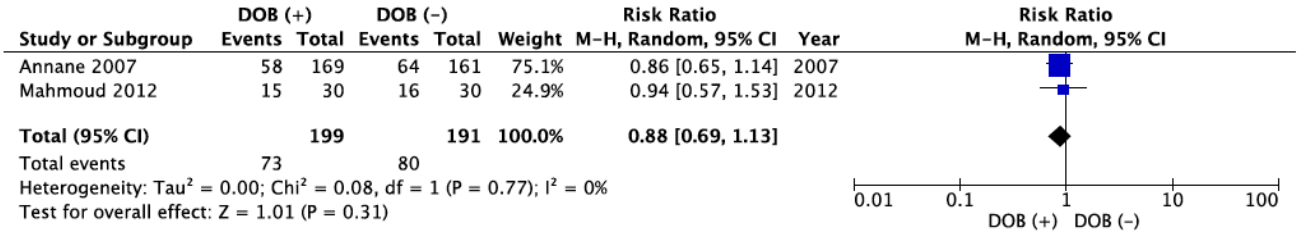
1. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("infection"[MeSH Terms] OR "infection"[All Fields])) AND ("dobutamine"[MeSH Terms] OR "dobutamine"[All Fields]) AND (("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) OR randomised[All Fields] OR randomly[All Fields])
2. (sepsis OR septic) AND dobutamine AND (randomized OR randomised OR randomly)

Body of the evidence

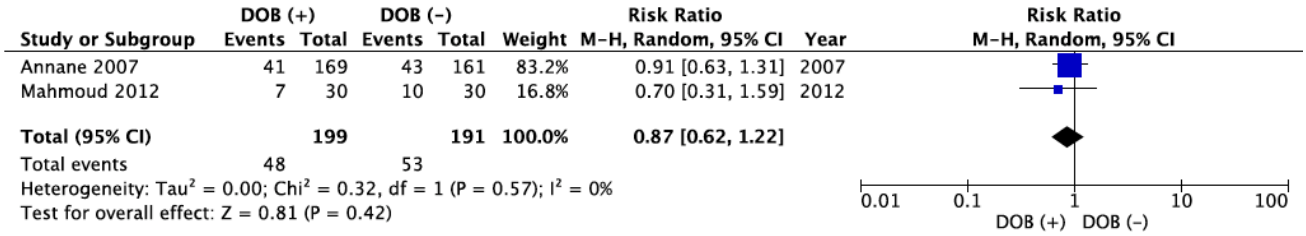
							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	Comment
28-day mortality rate	RCT/2	0	0	-1	-2	-1	191	80	41.88	199	73	36.68	RR	0.88	0.69-1.13	C	8	
Complication rate	RCT/2	0	0	-1	-2	-1	191	53	27.75	199	48	24.12	RR	0.87	0.62-1.22	C	6	
							The numbers of persons at risk (outcome rate)										
							Denominator	Mean	SD	Denominator	Mean	SD	Type	Value	95%CI			
Time to shock reversal	RCT/1	0			-2	-1	30	5	1.75	30	4	1.75	MD	-1.00	-1.89, -0.11	D	6	mean=median, SD=range/4
ICU length of stay	RCT/2	0	0	-1	-2	-1	191			199			MD	1.00	0.33, 1.67	C	4	mean=median, SD=range/4

Results of meta-analysis

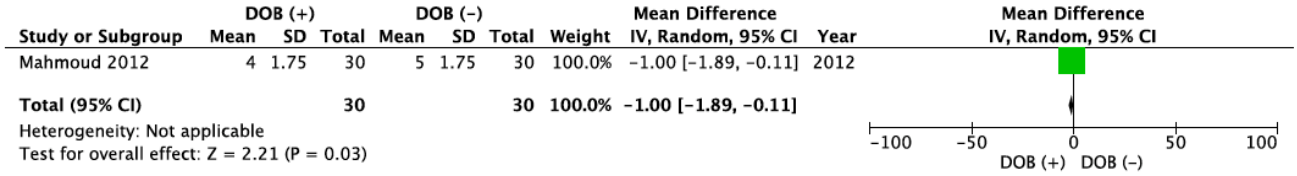
1. 28-day mortality rate



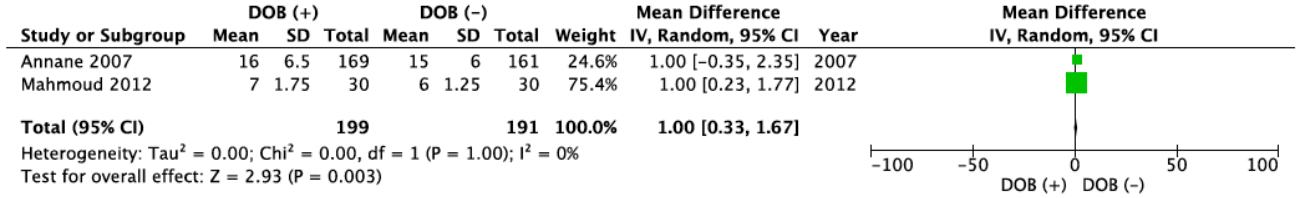
2. Complication rate



3. Time to shock reversal



4. ICU length of stay



CQ8-1

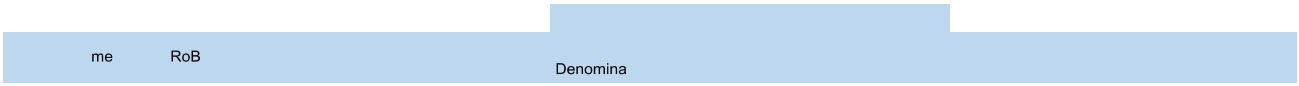
PICO

Patients (P): Patients with septic shock with an unsuccessful initial fluid resuscitation
Intervention (I): Administration of hydrocortisone
Control (C): No administration of hydrocortisone
Outcome (O): 28-day mortality rate, proportion of shock reversal by day 7, complication rates

Search terms

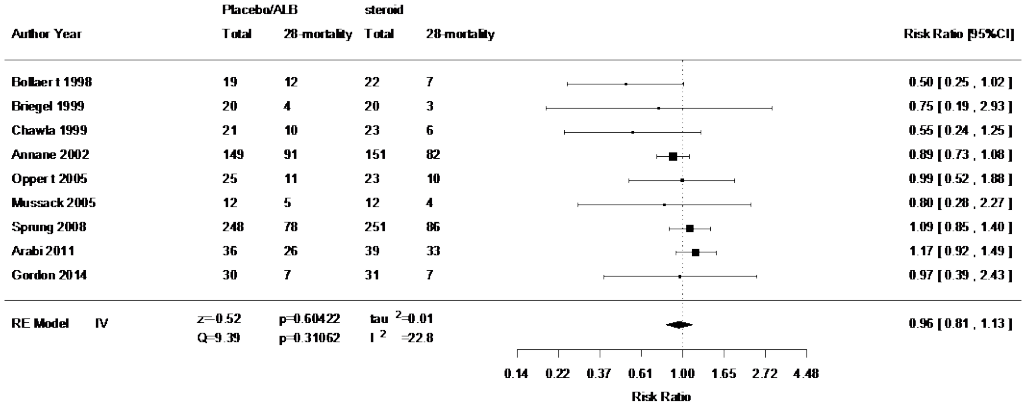
1. (sepsis OR severe sepsis OR septic shock) AND (glucocorticoid OR steroid OR hydrocortisone OR methylprednisolone) AND humans[mh] AND (English OR japanese) AND (meta-analysis OR systematic review OR practice guideline OR RCT) AND (English OR Japanes) AND (6 years)
2. ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields])) AND ("steroids"[MeSH Terms] OR "steroids"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields])
3. ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields])) AND ("steroids"[MeSH Terms] OR "steroids"[All Fields]) AND RCT[All Fields]

Body of the evidence

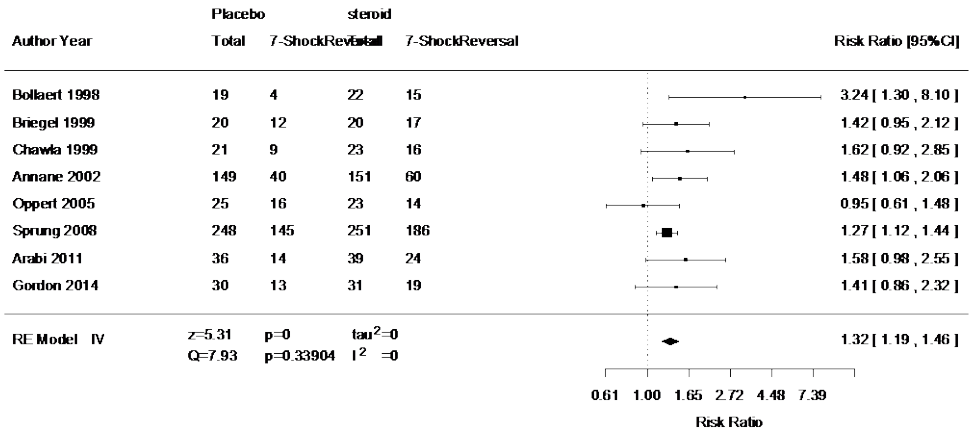


Results of meta-analysis

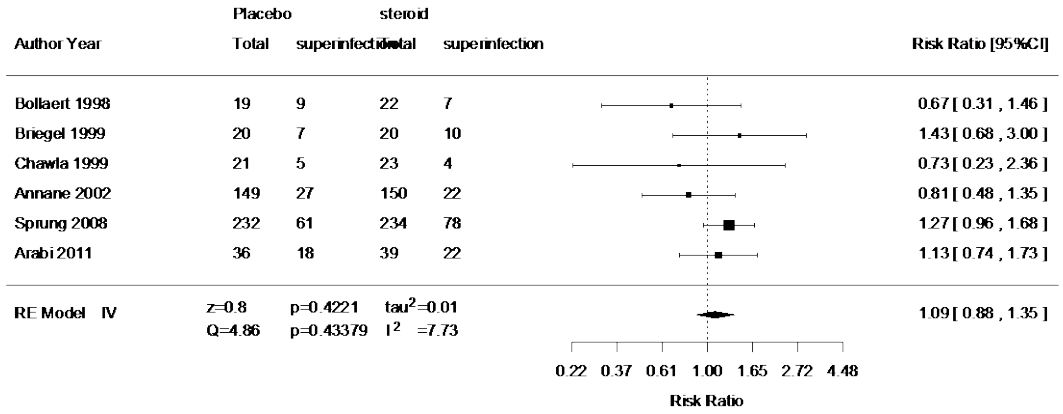
1. 28-day mortality rate



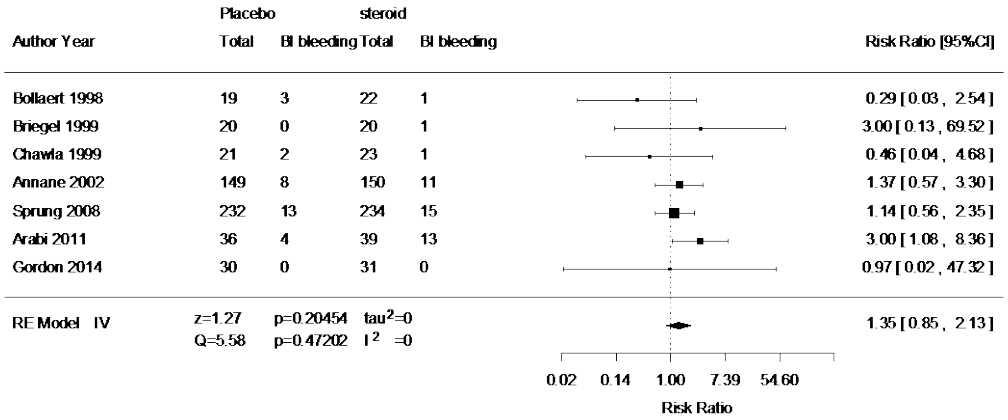
2. Proportion of shock reversal by day 7



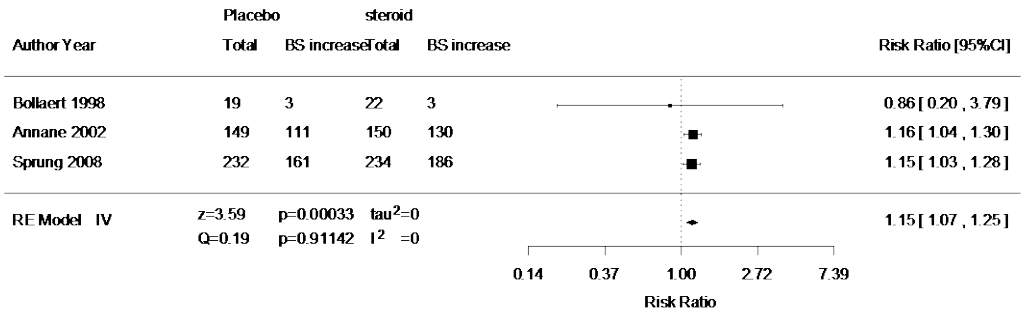
3. Infection



4. Gastrointestinal bleeding



5. Hyperglycemia



CQ8-2

PICO

Patients (P): Patients with septic shock
Intervention (I): Administration of corticosteroids earlier
Control (C): Administration of corticosteroids later
Outcome (O): 28-day mortality rate, proportion of shock reversal by day 7, complication rates

Search terms

1. （ sepsis OR severe sepsis OR septic shock） AND（ glucocorticoid OR steroid OR hydrocortisone ） AND timing AND humans［mh］ AND （english OR japanese） AND （(controlled clinical trial OR randomized controlled trial OR systematic OR meta-analysis)）

CQ8-3

PICO

Patients (P): Patients with septic shock
Intervention (I): Low dose and long term administration of corticosteroids
Control (C): High dose and short term administration of corticosteroids
Outcome (O): 28-day mortality rate, proportion of shock reversal by day 7, complication rates

Search terms

1. （ shock［MH］ OR septic［all fields］ OR septic［MH］OR septic［all fields］） AND （steroid ［MH］ OR steroid［all fields］ OR steroids［MH］ OR steroids［all fields］）AND（ dose［MH］ OR dose［all fields］ OR duration［MH］ OR duration［all fields］） AND randomizedcontrolled trial［pt］ AND humans［mh］ AND （english［la］ OR japanese［la］） AND abstract［tw］
2. （ “ shock, septic”［MeSH Terms］ OR （ “shock”［All Fields］ AND “septic”［All Fields］） OR “septic shock”［All Fields］ OR （“septic”［All Fields］ AND “shock”［All Fields］）） AND （“steroids”［MeSH Terms］ OR“steroids”［All Fields］ OR “steroid”［All Fields］）AND （“randomized controlled trial”［Publication Type］ OR“ randomized controlled trials as topic［”MeSH Terms］ OR “randomized controlled trial”［All Fields］OR “randomised controlled trial”［All Fields］）
3. R CT （“s e p t i c s h o ck”［A l l F i e l d s］ AND（（（（“steroids”［MeSH Terms］ OR “steroids”［All Fields］ OR“ steroid”［All Fields］）OR（ “adrenal cortex hormones”［Pharmacological Action］ OR “adrenal cortex hormones”［MeSH Terms］ OR （“adrenal”［All Fields］ AND “cortex”［All Fields］ AND “hormones”［All Fields］） OR “adrenal cortex hormones”［All Fields］ OR “corticosteroid”［All Fields］）） OR “hydrocortisone”［MeSH Terms］ OR“ hydrocortisone”［All Fields］））OR（ “glucocorticoids”［Pharmacological Action］OR “glucocorticoids”［MeSH Terms］ OR “glucocorticoids”［All Fields］ OR“ glucocorticoid”［All Fields］）） OR （“prednisolone”［MeSH Terms］ OR “prednisolone”［All Fields］））） AND （dose［All Fields］ OR duration［All Fields］） AND （Randomized Controlled Trial［ptyp］ AND “humans”［MeSH Terms］ AND （Japanese［lang］ OR English［lang］））

CQ8-4

PICO

Patients (P): Patients with septic shock
Intervention (I): Administration of hydrocortisone
Control (C): Administration of other steroids
Outcome (O): 28-day mortality rate, proportion of shock reversal by day 7, complication rates

Search terms

1.（（“shock, septic［”MeSH Terms］ OR“ septic shock［”All Fields］ ） OR（ “sepsis”［MeSH Terms］ OR“ sepsis”［All Fields］）） AND（ “steroids［”MeSH Terms］ OR“ steroid”［All Fields］ OR “methylprednisolone”［All Fields］ OR“hydrocortisone”［All Fields］ ） AND （(Meta-Analysis ［ptyp］ OR Randomized Controlled Trial［ptyp］） :“humans”［MeSH Terms］）
2.((“shock, septic”［MeSH Terms］ OR “septic shock”［All Fields］) OR （“sepsis”［MeSH Terms］ OR “sepsis”［All Fields］)） AND（“steroids”［MeSH Terms］ OR “steroid”［All Fields］ OR “methylprednisolone”［All Fields］ OR “hydrocortisone”［All Fields］） AND comparing
3. Intensive care /critically ill /infection / sepsis/ septic shock［Mesh/all field］) and（fludrocortisone / methylprednisolone /glucocorticoid /steroid ［Mesh/all field］) and（mortality /resuscitation /complication［Mesh/all field］)
4.（（“shock, septic”［MeSH Terms］ OR（ “shock”［All Fields］ AND “septic”［All Fields］) OR “septic shock”［All Fields］ OR （“septic”［All Fields］ AND “shock”［All Fields］)） OR （“sepsis”［MeSH Terms］ OR“sepsis”［All Fields］)） AND （“steroids”［MeSH Te r ms］ OR “s t e r o i d s”［A l l Fi e l d s］） AND ((Meta-Analysis［ptyp］ OR Randomized Controlled Tria［l ptyp］） AND“ 2010/07/28”［PDat］ :“ 2015/07/26”［PDat］ AND “humans”［MeSH Terms］)

CQ9-1

PICO

Patients (P): Septic shock patients
Intervention (I): Hemoglobin threshold of 7 g/dl for red-cell transfusion
Control (C): Hemoglobin threshold of 10 g/dl for red-cell transfusion
Outcome (O): 28-day mortality, incidence of organ failure

Search terms

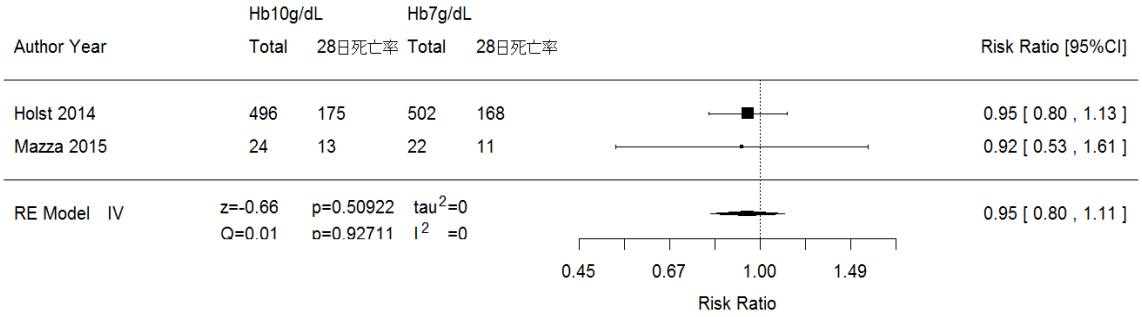
1. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields]))) AND ("erythrocytes"[MeSH Terms] OR "erythrocytes"[All Fields] OR ("red"[All Fields] AND "blood"[All Fields] AND "cell"[All Fields]) OR "red blood cell"[All Fields]) AND (("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) OR randomised[All Fields] OR randomly[All Fields])
2. (("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields])) OR ("sepsis"[MeSH Terms] OR "sepsis"[All Fields])) AND ("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields]) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms])

Body of the evidence

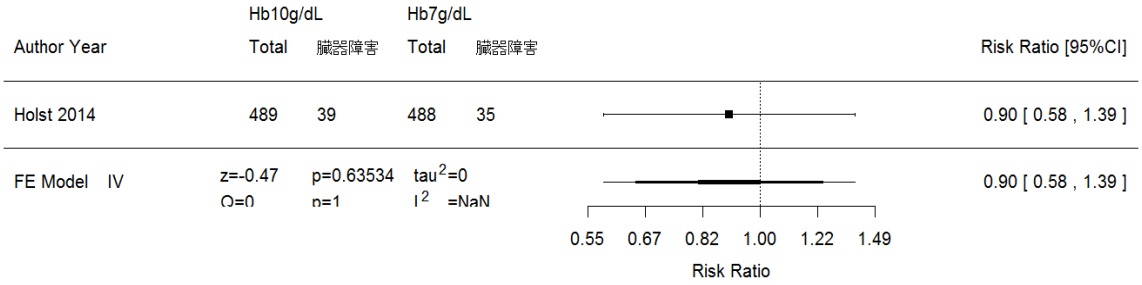
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
28-day mortality	RCT/2	0	0	0	-1	-1	520	188	36.2	524	179	34.2	RR	0.95	0.80-1.11	B	8
Organ failure	RCT/1	0		-1	-1		489	39	8.0	488	35	7.2	RR	0.9	0.58-1.39	C	6

Results of meta-analysis

1. 28-day mortality



2. Incidence of organ failure



CQ9-2

PICO

Patients (P): Septic patients
Intervention (I): FFP (+)
Control (C): FFP (-)
Outcome (O): 28-day mortality, incidence of organ failure

Search terms

1. （sepsis or septic shock） and (FFP or fresh frozen plasma)

CQ9-3

PICO

Patients (P): Septic patients
Intervention (I): Plt (+)
Control (C): Plt (-)
Outcome (O): 28-day mortality, incidence of organ failure

Search terms

1. （sepsis or septic shock） and (Platelet)

CQ12-1

PICO

Patients (P): Septic patients
Intervention (I): Diagnosis of AKI (+)
Control (C): Diagnosis of AKI (-)
Outcome (O): Mortality

Search terms

1. (KDIGO) AND (RIFLE OR AKIN)

CQ12-2

PICO

Patients (P): Septic AKI patients
Intervention (I): Early renal replacement therapy
Control (C): Late renal replacement therapy
Outcome (O): Mortality, length of ICU stay, requirement rate of HD

Search terms

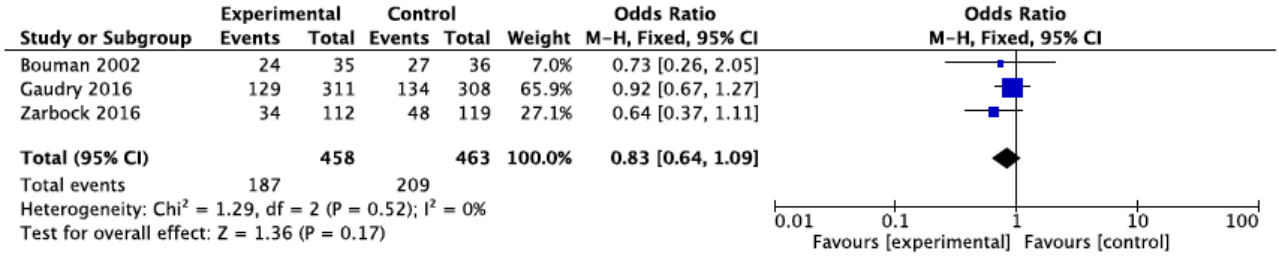
1. #1 and #2 and #3 and #4
#1(AKI): ((((("acute kidney injury"[MeSH Terms] OR (acute kidney failure[tw] OR acute renal failure[tw])) OR ((acute kidney injure[tw] OR acute kidney injuries[tw] OR acute kidney injury[tw] OR acute kidney injury,[tw]) OR (acute renal injuries[tw] OR acute renal injury[tw]))) OR ((acute kidney insufficiencies[tw] OR acute kidney insufficiency[tw]) OR (acute renal insufficiencies[tw] OR acute renal insufficiency[tw]))) OR acute tubular necrosis[tw]) OR (ARI[tw] OR AKI[tw] OR ARF[tw] OR AKF[tw] OR ATN[tw])
#2(RRT): renal replacement therapy[MeSH Terms] OR renal dialysis[MeSH Terms] OR(continuous hemofiltration[tw] OR continuous hemodiafiltration[tw] OR continuous hemodialysis[tw] OR continuous haemodialysis[tw] OR (CVVH[tw] OR CVVHDF[tw] OR CVVHD[tw] OR SCUF[tw] OR CRRT[tw] OR CHDF[tw] OR CHD[tw] OR CHF[tw] OR SLED[tw]) OR renal replacement therap*[tw] OR continuous ultrafiltration[tw]
#3(Timing): timing[TIAB] OR initiation[TIAB]
#4(RCT): ("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh: noexp] OR randomly[TIAB] OR trial[TI]) NOT (Animals[MH] NOT Humans[MH])
#5(English): English[LA]
2. (((intensive care)OR(critical care))AND((sepsis)OR(septic)) AND(acute kidney injury) AND ((renal replacement therapy) OR (hemodialysis) OR (hemofiltration) OR (hemodiafiltration)) AND (randomized)) AND (english)

Body of the evidence

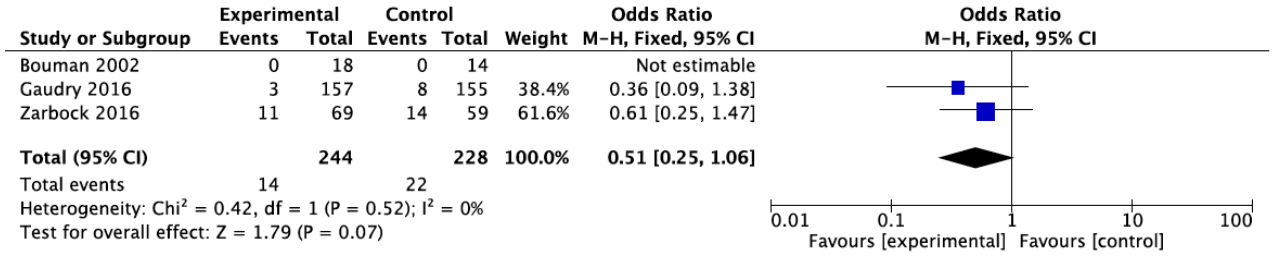
							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
28-day mortality	RCT/3	-2	-1	-2	-1	0	463	209	0.45	458	187	0.41	OR	0.83	0.64-1.09	C	9
Requirement of HD	RCT/2	-2	-1	-1	-1	0	228	22	0.10	244	14	0.06	OR	0.51	0.25-1.06	C	7

Results of meta-analysis

1. 28-day mortality



2. Requirement rate of HD (after day 60)



CQ12-3

PICO

Patients (P): Septic AKI patients
Intervention (I): Continuous RRT
Control (C): Intermittent RRT
Outcome (O): Mortality, length of ICU stay, requirement rate of HD, incidence of hypotension

Search terms

1. #1(AKI):(acute kidney[tw] OR acute renal[tw] OR acute nephr*[tw] OR acute glomer*[tw] OR acute dialysis[tw] OR acute tubul*[tw] OR "Acute Kidney Injury"[mh] OR kidney injur*[tiab] OR renal injur*[tiab] OR "Kidney Diseases/chemically induced"[mh] OR tubular injury[tiab] OR tubular necrosis*[tiab] OR tubular damage*[tiab] OR tubule damage*[tiab] OR nephrotox*[tiab] OR "Nephritis, Interstitial"[mh:noexp] OR tubulointerstitial nephritis[tiab] OR interstitial nephritis[tiab] OR kidney ischemi*[tiab] OR kidney ischaemi*[tiab] OR renal ischemi*[tiab] OR renal ischaemi*[tiab] OR induced kidney[tiab] OR induced renal[tiab] OR hemolytic uremi*[tiab] OR haemolytic uraemi*[tiab] OR "Hemolytic-Uremic Syndrome"[majr:noexp] OR aki[tiab] OR oliguri*[tw] OR anuri*[tw] OR anti-glomerular[tw] OR antiglomerular[tw] OR "Kidney Cortex Necrosis"[mh:noexp] OR pre-renal[tiab] OR prerenal[tiab] OR anti-gbm[tiab] OR obstructed kidney*[tiab] OR renal obstruction[tiab] OR obstructive nephropathy[tiab] OR obstructive uropathy[tiab] OR hepatorenal syndrome[tw] OR "Hemorrhagic Fever with Renal Syndrome"[majr:noexp] OR thrombotic thrombocytopeni*[tiab] OR thrombotic microangiopathy[tiab] OR "Acidosis/chemically induced"[mh] OR renal hypoperfusion[tiab] OR (worsening[tiab] AND renal[tiab]) OR improved renal function[tiab] OR (impair*[tiab] AND renal function[tiab]) OR azotemi*[tw] OR azotaemi*[tw] OR (renal[tiab] AND thrombosis[tiab]) OR (("Reperfusion Injury"[mh:noexp] OR ischemic injury[tiab] OR ischemia injury[tiab] OR ischaemic injury[tiab] OR ischaemia injury[tiab] OR ischemic reperfusion[tiab] OR ischemia reperfusion[tiab] OR ischaemic reperfusion[tiab] OR ischaemia reperfusion[tiab] OR critical care[tw] OR critically ill[tw] OR (critical*[tw] AND illness[tw]) OR sepsis[tw] or septic[tw] OR intensive care[tw] OR icu[tiab] OR tubular cell*[tiab] OR rhabdomyolysis[tw] OR thrombocytopeni*[tiab] OR life-threatening[tw] OR vasculit*[tw] OR polyarteritis[tw] OR cardiogenic shock[tiab] OR multiorgan dysfunction[tw] OR multi-organ dysfunction[tw] OR multiple organ dysfunction[tw] OR multiple organ failure[tw] OR multiorgan failure[tw] OR multi-organ failure[tw] OR polyangiitis[tw] OR (wegener*[tw] AND granulomatosis[tw]) OR "Blood Urea Nitrogen"[mh:noexp]) AND (kidney[tw] OR renal[tw] OR dialysis[tw] OR uremi*[tiab] OR uraemi*[tiab] OR dehydrat*[tw] OR creatinin*[tw])) OR (nephropath*[tw] AND (contrast medi*[tw] OR contrast induced[tw] OR

contrast agent*[tw] OR radiocontrast*[tw] OR iodinated[tw] OR crystal*[tw] OR cast[tw])) OR ((glomerulonephritis[tw] OR nephrit*[tiab]) AND (crescentic[tw] OR anca*[tiab] OR rapidly progressive[tiab] OR acute[tiab])) OR (("Kidney Diseases"[mh:noexp] OR renal insufficienc*[tw] OR renal failure[tw] OR renal function[tiab] OR renal impairment[tiab] OR glomerular filtration rate[tiab] OR ischemia-reperfusion injury[tiab]) AND ("Cardiovascular Surgical Procedures"[majr] OR "Cardiovascular Diseases"[mh:noexp] OR "Cardiovascular System/surgery"[majr] OR cardiac surg*[tw] OR (cardiopulmonary[tiab]) OR "Ischemia"[mh:noexp] OR "diagnostic imaging"[majr] OR "Contrast Media"[majr:noexp] OR "chemically induced"[sh] OR revers*[tiab] OR microangiopath*[tiab] OR cirrhosis[ti] OR "Substance-Related Disorders"[mh] OR "Neurologic Manifestations"[mh] OR preoperative*[tiab] OR pre-operative*[tiab] OR postoperative*[tiab] OR post-operative*[tiab])) OR ((injury[tw] OR ischemi*[tw] OR ischaemi*[tw] OR reperfusion[tw] OR contrast medi*[tw]) AND (renal tubul*[tiab] OR tubular[tiab])))]

#2(Therapy):((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

#3(English): English [LA]

#4(RRT): (((((renal replacement therapy[mh] OR renal dialysis[mh] OR hemodiafiltration[mh] OR hemofiltration[mh]))) OR (((contin*[tw] AND (dialy*[tw] OR hemodia*[tw] OR haemodia*[tw] OR hemofiltr*[tw] OR haemofiltr*[tw] OR hemodiafilt*[tw] OR haemodiafilt*[tw] OR filtrat*[tw] OR renal replacement therap*[tw] OR ultrafiltr*[tw] OR arteriovenous*[tw] OR venovenous*[tw])))) OR ((CVVHD[tw] OR CAVHD[tw] OR CVVHDF[tw] OR CAVHDF[tw] OR CVVHF[tw] OR CAVHF[tw] OR CRRT[tw] OR SCUF[tw] OR CVVH[tw] OR CAVH)))

#5(continuous, intermittent):continuous[All Fields] AND (intermittent[All Fields] OR sustained[All Fields] OR Extended[All Fields])

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Hospital mortality	RCT/7	-1	0	0	-1	1)	648	413	63.7	597	376	63	1)	1.01	0.92-1.12	B	9
Requirement of HD	RCT/3	-1	0	-1	-1	1)	79	66	83.5	82	70	85.4	1)	0.99	0.92-1.07	C	7

1) unevaluable

CQ12-4

PICO

Patients (P): Septic AKI patients who received RRT
Intervention (I): Quantity of blood purification; 40 ml/kg/hr, 20-25 ml/kg/hr
Control (C): Quantity of blood purification; 20-25 ml/kg/hr, 10-15 ml/kg/hr
Outcome (O): Mortality, length of ICU stay, requirement rate of HD, electrolyte disturbance (K,P)

Search terms

1. #1(AKI): (acute kidney[tw] OR acute renal[tw] OR acute nephr*[tw] OR acute glomer*[tw] OR acute dialysis[tw] OR acute tubul*[tw] OR "Acute Kidney Injury"[mh] OR kidney injur*[tiab] OR renal injur*[tiab] OR "Kidney Diseases/chemically induced"[mh] OR tubular injury[tiab] OR tubular necrosis*[tiab] OR tubular damage*[tiab] OR tubule damage*[tiab] OR nephrotox*[tiab] OR "Nephritis, Interstitial"[mh:noexp] OR tubulointerstitial nephritis[tiab] OR interstitial nephritis[tiab] OR kidney ischemi*[tiab] OR kidney ischaemi*[tiab] OR renal ischemi*[tiab] OR renal ischaemi*[tiab] OR induced kidney[tiab] OR induced renal[tiab] OR hemolytic uremi*[tiab] OR haemolytic uraemi*[tiab] OR "Hemolytic-Uremic Syndrome"[majr:noexp] OR aki[tiab] OR oliguri*[tw] OR anuri*[tw] OR anti-glomerular[tw] OR antiglomerular[tw] OR "Kidney Cortex Necrosis"[mh:noexp] OR pre-renal[tiab] OR prerenal[tiab] OR anti-gbm[tiab] OR obstructed kidney*[tiab] OR renal obstruction[tiab] OR obstructive nephropathy[tiab] OR obstructive uropathy[tiab] OR hepatorenal syndrome[tw] OR "Hemorrhagic Fever with Renal Syndrome"[majr:noexp] OR thrombotic thrombocytopeni*[tiab] OR thrombotic microangiopathy[tiab] OR "Acidosis/chemically induced"[mh] OR renal hypoperfusion[tiab] OR (worsening[tiab] AND renal[tiab]) OR improved renal function[tiab] OR (impair*[tiab] AND renal function[tiab]) OR azotemi*[tw] OR azotaemi*[tw] OR (renal[tiab] AND thrombosis[tiab]) OR (("Reperfusion Injury"[mh:noexp] OR ischemic injury[tiab] OR ischemia injury[tiab] OR ischaemic injury[tiab] OR ischaemia injury[tiab] OR ischemic reperfusion[tiab] OR ischemia reperfusion[tiab] OR ischaemic reperfusion[tiab] OR ischaemia reperfusion[tiab] OR critical care[tw] OR critically ill[tw] OR (critical*[tw] AND illness[tw]) OR sepsis[tw] or septic[tw] OR intensive care[tw] OR icu[tiab] OR tubular cell*[tiab] OR rhabdomyolysis[tw] OR thrombocytopeni*[tiab] OR life-threatening[tw] OR vasculit*[tw] OR polyarteritis[tw] OR cardiogenic shock[tiab] OR multiorgan dysfunction[tw] OR multi-organ dysfunction[tw] OR multiple organ dysfunction[tw] OR multiple organ failure[tw] OR multiorgan failure[tw] OR multi-organ failure[tw] OR polyangiitis[tw] OR (wegener*[tw] AND granulomatosis[tw]) OR "Blood Urea Nitrogen"[mh:noexp]) AND (kidney[tw] OR renal[tw] OR dialysis[tw] OR uremi*[tiab] OR uraemi*[tiab] OR dehydrat*[tw] OR creatinin*[tw])) OR (nephropath*[tw] AND (contrast medi*[tw] OR contrast induced[tw] OR

contrast agent*[tw] OR radiocontrast*[tw] OR iodinated[tw] OR crystal*[tw] OR cast[tw])) OR ((glomerulonephritis[tw] OR nephrit*[tiab]) AND (crescentic[tw] OR anca*[tiab] OR rapidly progressive[tiab] OR acute[tiab])) OR (("Kidney Diseases"[mh:noexp] OR renal insufficienc*[tw] OR renal failure[tw] OR renal function[tiab] OR renal impairment[tiab] OR glomerular filtration rate[tiab] OR ischemia-reperfusion injury[tiab]) AND ("Cardiovascular Surgical Procedures"[majr] OR "Cardiovascular Diseases"[mh:noexp] OR "Cardiovascular System/surgery"[majr] OR cardiac surg*[tw] OR (cardiopulmonary[tiab]) OR "Ischemia"[mh:noexp] OR "diagnostic imaging"[majr] OR "Contrast Media"[majr:noexp] OR "chemically induced"[sh] OR revers*[tiab] OR microangiopath*[tiab] OR cirrhosis[ti] OR "Substance-Related Disorders"[mh] OR "Neurologic Manifestations"[mh] OR preoperative*[tiab] OR pre-operative*[tiab] OR postoperative*[tiab] OR post-operative*[tiab])) OR ((injury[tw] OR ischemi*[tw] OR ischaemi*[tw] OR reperfusion[tw] OR contrast medi*[tw]) AND (renal tubul*[tiab] OR tubular[tiab])))

#2: English [LA]

#3(RRT): (((((renal replacement therapy[mh] OR renal dialysis[mh] OR hemodiafiltration[mh] OR hemofiltration[mh])))) OR (((contin*[tw] AND (dialy*[tw] OR hemodia*[tw] OR haemodia*[tw] OR hemofiltr*[tw] OR haemofiltr*[tw] OR hemodiafilt*[tw] OR haemodiafilt*[tw] OR filtrat*[tw] OR renal replacement therap*[tw] OR ultrafiltr*[tw] OR arteriovenous*[tw] OR venovenous*[tw])))))) OR ((CVVHD[tw] OR CAVHD[tw] OR CVVHDF[tw] OR CAVHDF[tw] OR CVVHF[tw] OR CAVHF[tw] OR CRRT[tw] OR SCUF[tw] OR CVVH[tw] OR CAVH)))

#4(dose): high-volume[All Fields] OR intensity[All Fields] OR high-dose[All Fields] OR dose [All Fields] OR doses[All Fields]

#5(RCT): ((randomized controlled trial[Publication Type] OR Controlled Clinical Trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) NOT Review[Publication Type])

2. (("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields]) AND ((((("intensive care"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields])) OR ("sepsis"[MeSH Terms] OR "sepsis"[All Fields])) OR ("shock, septic"[MeSH Terms] OR ("shock"[All Fields] AND "septic"[All Fields]) OR "septic shock"[All Fields] OR ("septic"[All Fields] AND "shock"[All Fields])))) AND ("renal replacement therapy"[MeSH Terms] OR ("renal"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "renal replacement therapy"[All Fields]) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Randomized Controlled Trial[ptyp] OR Multicenter Study[ptyp]) AND "humans"[MeSH Terms] AND English[lang])

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsi stency	Impreci sion	Indirec tness	Others	Control group			Intervention group			Type	Value	95%CI	Stren gth	Import ance
							Denom inator	Numer ator	(%)	Denom inator	Numer ator	(%)					
28-day mortality	RCT/8	-1	-1	-1	-1	0	1878	904	48.1	1963	904	46.1	RR	0.89	0.76-1.04	B	9
Requirement of HD	RCT/8	-1	-1	-1	-1	0	1878	710	37.8	1963	784	39.9	RR	1.12	0.95-1.31	B	7

CQ12-5

PICO

Patients (P): Septic shock patients
Intervention (I): PMX-DHP (+)
Control (C): PMX-DHP (-)
Outcome (O): Mortality, mean blood pressure, recovery rate from shock

Search terms

1. (((sepsis OR infection OR "septic shock" OR "systemic inflammatory response syndrome" OR SIRS OR "multiple organ dysfunction syndrome" OR MODS)) AND (PMX OR toraymyxin OR "endotoxin removal" OR "LPS removal" OR "endotoxin adsorption" OR "LPS adsorption" OR "polymyxin B immobilized" OR "polymyxin B hemoperfusion")) AND (RCT OR "randomized controlled" OR randomly)
2. (((((((“blood purification” OR “hemoperfusion” OR “hemoadsorption”))) AND ((“sepsis” OR “infection” OR “septic shock” OR “systemic inflammatory response syndrome” OR “SIRS” OR “multiple organ dysfunction syndrome” OR “MODS”))) AND ((“outcome” OR “intensive care unit” OR “ICU” OR “critically ill patients” OR “mortality” OR “prognosis”))) AND English[LA]) AND (("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh: noexp] OR randomly[TIAB] OR trial[TI]) NOT (Animals[MH] NOT Humans[MH]))) AND Search Sort by: PublicationDate Filters: Publication date from 2012/05/01

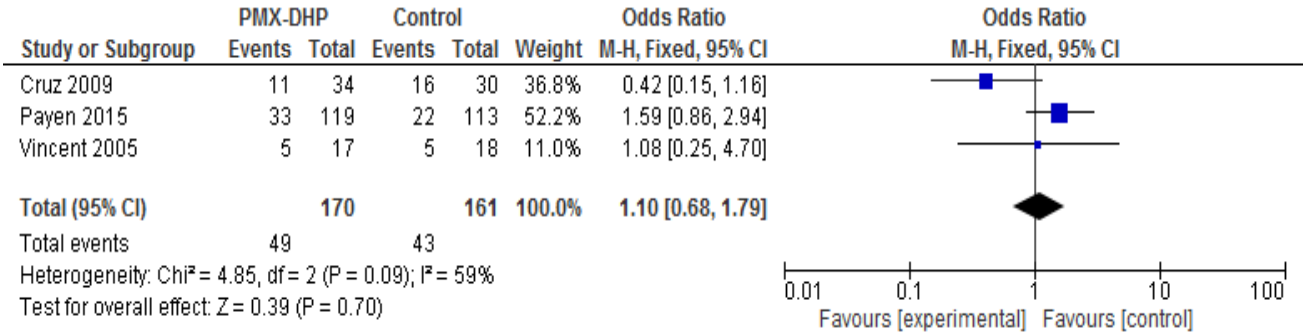
Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	RCT/ 3	-1	-1	-1	-1	0	161	43	26.7	170	49	28.8	OR	1.1	0.68, 1.79	C	9	
Change of mean BP	RCT/2	-1	-1	-2	-1	0	48			51			MD	4.59	[-1.71, 10.90]	D	7	1)

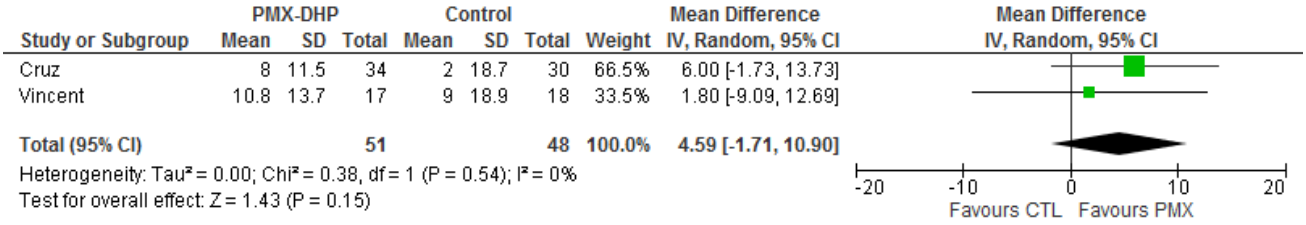
1) Change of mean BP was adopted 72 hr in Cruz (2009) study and 48 hr in Vincent (2005) study.

Results of meta-analysis

1. Mortality



2. Change of mean BP



CQ12-6

PICO

Patients (P): Septic AKI patients
Intervention (I): Furosemide (+)
Control (C): Furosemide (-)
Outcome (O): Mortality, requirement rate of HD

Search terms

1. (((((((("acute kidney injury"[MeSH Terms] OR (acute kidney failure[tw] OR acute renal failure[tw])) OR ((acute kidney injure[tw] OR acute kidney injuries[tw] OR acute kidney injury[tw] OR acute kidney injury,[tw]) OR (acute renal injuries[tw] OR acute renal injury[tw]))) OR ((acute kidney insufficiencies[tw] OR acute kidney insufficiency[tw]) OR (acute renal insufficiencies[tw] OR acute renal insufficiency[tw]))) OR acute tubular necrosis[tw]) OR (ARI[tw] OR AKI[tw] OR ARF[tw] OR AKF[tw] OR ATN[tw]))) AND ("Systemic Inflammatory Response Syndrome"[Mesh] OR "Systemic Inflammatory Response Syndrome"[TW] OR sepsis[TW] OR septic[TW]) AND ("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh: noexp] OR randomly[TIAB] OR trial[TI]) NOT (Animals[MH] NOT Humans[MH]) AND English[LA]) AND furosemide
2. ((((((((((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields] OR ""injury""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""failure""[All Fields]) OR ""kidney failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""failure""[All Fields]) OR ""renal failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""dysfunction""[All Fields]) OR ""renal dysfunction""[All Fields])) OR ((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields]))) OR (renal[All Fields] AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields]))) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiencies""[All Fields])

OR ""kidney insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiency""[All Fields]) OR ""kidney insufficiency""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""insufficiencies""[All Fields]) OR ""renal insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields])) OR (""kidney tubular necrosis, acute""[MeSH Terms] OR (""kidney""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields] AND ""acute""[All Fields]) OR ""acute kidney tubular necrosis""[All Fields] OR (""acute""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields]) OR ""acute tubular necrosis""[All Fields])) AND (""furosemide""[MeSH Terms] OR ""furosemide""[All Fields]) AND Randomized Controlled Trial[ptyp]

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	RCT/9	-2	0	-1	-1	0	423	119	28%	453	149	33%	RR	1.12	0.93-1.34	B	9	1)
Requirement rate of HD	RCT/9	-2	0	0	-1	0	284	84	30%	288	83	29%	RR	1.02	0.90-1.16	B	7	

1) Main population in these study was not patients with sepsis but patients with AKI.

CQ12-7

PICO

Patients (P): Septic AKI patients
Intervention (I): Dopamine (+)
Control (C): Dopamine (-)
Outcome (O): Mortality, requirement rate of HD, incidence of arrhythmia or ischemia (coronary, limbs, skin)

Search terms

1. ((((("Randomized Controlled Trial"[PT] OR "Controlled Clinical Trial"[PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh:noexp] OR randomly[TIAB] OR trial[TI]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND (acute kidney[tw] OR acute renal[tw] OR (acute nephrectomy[tw] OR acute nephritic[tw] OR acute nephritis[tw] OR acute nephrocalcinosis[tw] OR acute nephrolithiasis[tw] OR acute nephropathies[tw] OR acute nephropathy[tw] OR acute nephroses[tw] OR acute nephrosis[tw] OR acute nephrotoxicities[tw] OR acute nephrotoxicity[tw] OR acute nephrotoxicosis[tw]) OR (acute glomerulitis[tw] OR acute glomerulonephritis[tw] OR acute glomerulopathy[tw]) OR acute dialysis[tw] OR (acute tubular[tw] OR acute tubulitis[tw] OR acute tubulonephritis[tw] OR acute tubulonephrosis[tw] OR acute tubulopathy[tw]) OR "Acute Kidney Injury"[mh] OR (kidney injure[tiab] OR kidney injuries[tiab] OR kidney injury[tiab]) OR (renal injures[tiab] OR renal injuries[tiab] OR renal injury[tiab]) OR "Kidney Diseases/chemically induced"[mh] OR tubular injury[tiab] OR tubular necrosis[tiab] OR (tubular damage[tiab] OR tubular damages[tiab]) OR tubule damage[tiab] OR (nephrotox[tiab] OR nephrotoxcic[tiab] OR nephrotoxcicity[tiab] OR nephrotoxciity[tiab] OR nephrotoxcity[tiab] OR nephrotoxi[tiab] OR nephrotoxic[tiab] OR nephrotoxicant[tiab] OR nephrotoxicants[tiab] OR nephrotoxication[tiab] OR nephrotoxicicity[tiab] OR nephrotoxicidad[tiab] OR nephrotoxicities[tiab] OR nephrotoxicitiy[tiab] OR nephrotoxicity[tiab] OR nephrotoxicity'[tiab] OR nephrotoxicitywas[tiab] OR nephrotoxiciy[tiab] OR nephrotoxicologic[tiab] OR nephrotoxicological[tiab] OR nephrotoxicology[tiab] OR nephrotoxicoses[tiab] OR nephrotoxicosis[tiab] OR nephrotoxicpenicillium[tiab] OR nephrotoxics[tiab] OR nephrotoxicty[tiab] OR nephrotoxicy[tiab] OR nephrotoxigenic[tiab] OR nephrotoxiicity[tiab] OR nephrotoxim[tiab] OR nephrotoxin[tiab] OR nephrotoxins[tiab] OR nephrotoxis[tiab] OR nephrotoxiticity[tiab] OR nephrotoxitity[tiab] OR nephrotoxitiy[tiab] OR nephrotoxity[tiab] OR nephrotoxocity[tiab] OR nephrotoxoic[tiab]) OR "Nephritis, Interstitial"[mh:noexp] OR tubulointerstitial nephritis[tiab] OR interstitial nephritis[tiab] OR kidney ischemia[tiab] OR kidney ischaemia[tiab] OR renal ischemia[tiab] OR renal ischaemia[tiab] OR

induced kidney[tiab] OR induced renal[tiab] OR (hemolytic uremia[tiab] OR hemolytic uremic[tiab] OR hemolytic uremiclike[tiab]) OR (haemolytic uraemia[tiab] OR haemolytic uraemic[tiab]) OR "Hemolytic-Uremic Syndrome"[majr:noexp] OR aki[tiab] OR (oliguria[tw] OR oligurias[tw] OR oliguric[tw] OR oliguricanuric[tw] OR oligurics[tw] OR oligurie[tw]) OR (anuria[tw] OR anurian[tw] OR anuriaoliguria[tw] OR anurias[tw] OR anuric[tw] OR anuric'[tw] OR anurics[tw] OR anurid[tw] OR anurida[tw] OR anurie[tw] OR anurique[tw]) OR anti-glomerular[tw] OR antiglomerular[tw] OR "Kidney Cortex Necrosis"[mh:noexp] OR pre-renal[tiab] OR prerenal[tiab] OR anti-gbm[tiab] OR (obstructed kidney[tiab] OR obstructed kidneys[tiab]) OR renal obstruction[tiab] OR obstructive nephropathy[tiab] OR obstructive uropathy[tiab] OR hepatorenal syndrome[tw] OR "Hemorrhagic Fever with Renal Syndrome"[majr:noexp] OR (thrombotic thrombocytopenia[tiab] OR thrombotic thrombocytopenic[tiab]) OR thrombotic microangiopathy[tiab] OR "Acidosis/chemically induced"[mh] OR renal hypoperfusion[tiab] OR (worsening[tiab] AND renal[tiab]) OR improved renal function[tiab] OR ((impair[tiab] OR impairation[tiab] OR impaird[tiab] OR impaire[tiab] OR impaired[tiab] OR impaired'[tiab] OR impaired"[tiab] OR impaired's[tiab] OR impaired1[tiab] OR impairedby[tiab] OR impairedcell[tiab] OR impairedfasting[tiab] OR impairedin[tiab] OR impairedphysical[tiab] OR impaireds[tiab] OR impairement[tiab] OR impairement'[tiab] OR impairements[tiab] OR impairent[tiab] OR impairer[tiab] OR impairers[tiab] OR impaires[tiab] OR impairign[tiab] OR impairiment[tiab] OR impairing[tiab] OR impairm[tiab] OR impairmant[tiab] OR impairme[tiab] OR impairmed[tiab] OR impairmement[tiab] OR impairmen[tiab] OR impairment[tiab] OR impairment'[tiab] OR impairment"[tiab] OR impairment's[tiab] OR impairmentand[tiab] OR impairmentc[tiab] OR impairmentfugl[tiab] OR impairmentin[tiab] OR impairmentof[tiab] OR impairments[tiab] OR impairments'[tiab] OR impairmets[tiab] OR impairmint[tiab] OR impairmnent[tiab] OR impairness[tiab] OR impairnment[tiab] OR impairred[tiab] OR impairrment[tiab] OR impairs[tiab] OR impairs'[tiab]) AND renal function[tiab]) OR (azotemia[tw] OR azotemia'[tw] OR azotemial[tw] OR azotemias[tw] OR azotemic[tw] OR azotemic'[tw] OR azotemicas[tw] OR azotemics[tw]) OR (azotaemia[tw] OR azotaemia'[tw] OR azotaemic[tw] OR azotaemics[tw]) OR (renal[tiab] AND thrombosis[tiab]) OR (("Reperfusion Injury"[mh:noexp] OR ischemic injury[tiab] OR ischemia injury[tiab] OR ischaemic injury[tiab] OR ischaemia injury[tiab] OR ischemic reperfusion[tiab] OR ischemia reperfusion[tiab] OR ischaemic reperfusion[tiab] OR ischaemia reperfusion[tiab] OR critical care[tw] OR critically ill[tw] OR ((critical[tw] OR critical'[tw] OR critical'role[tw] OR criticalanalysis[tw] OR criticalbehaviorofthet[tw] OR criticalcut[tw] OR criticalexamination[tw] OR criticalexperimental[tw] OR criticalfor[tw] OR criticalin[tw] OR criticalincidentreportingsystems[tw] OR criticalist[tw] OR criticalists[tw] OR criticalities[tw] OR criticality[tw] OR criticality'[tw] OR criticall[tw] OR criticallike[tw] OR criticallity[tw] OR criticallly[tw] OR criticallncident[tw] OR critically[tw] OR criticalmediators[tw] OR criticalmix[tw] OR criticalness[tw] OR criticalpath[tw] OR criticalrole[tw] OR criticalroles[tw] OR criticals[tw] OR criticalsorb[tw] OR criticaltemperature[tw] OR criticalvirulence[tw] OR criticaly[tw] OR

criticalyl[tw]) AND illness[tw]) OR sepsis[tw] OR septic[tw] OR intensive care[tw] OR icu[tiab] OR (tubular cell[tiab] OR tubular celladenomas[tiab] OR tubular cells[tiab] OR tubular cellulose[tiab]) OR rhabdomyolysis[tw] OR (thrombocytopeni[tiab] OR thrombocytopenia[tiab] OR thrombocytopenia'[tiab] OR thrombocytopenia's[tiab] OR thrombocytopeniaabsent[tiab] OR thrombocytopeniae[tiab] OR thrombocytopenian[tiab] OR thrombocytopenias[tiab] OR thrombocytopenic[tiab] OR thrombocytopenica[tiab] OR thrombocytopenicpurpura[tiab] OR thrombocytopenics[tiab] OR thrombocytopenie[tiab] OR thrombocytopenisa[tiab]) OR life-threatening[tw] OR (vasculit[tw] OR vasculitc[tw] OR vasculite[tw] OR vasculiteles[tw] OR vasculites[tw] OR vasculiti[tw] OR vasculitic[tw] OR vasculitic'[tw] OR vasculitide[tw] OR vasculitides[tw] OR vasculitides'[tw] OR vasculitidic[tw] OR vasculitidies[tw] OR vasculitidis[tw] OR vasculitids[tw] OR vasculities[tw] OR vasculitiis[tw] OR vasculitique[tw] OR vasculitis[tw] OR vasculitis'[tw] OR vasculitisare[tw] OR vasculitisdagger[tw] OR vasculitise[tw] OR vasculitises[tw] OR vasculitislike[tw] OR vasculitities[tw] OR vasculititis[tw] OR vasculitits[tw] OR vasculitogenic[tw] OR vasculits[tw] OR vasculitude[tw] OR vasculitus[tw]) OR polyarteritis[tw] OR cardiogenic shock[tiab] OR multiorgan dysfunction[tw] OR multi-organ dysfunction[tw] OR multiple organ dysfunction[tw] OR multiple organ failure[tw] OR multiorgan failure[tw] OR multi-organ failure[tw] OR polyangiitis[tw] OR ((wegener[tw] OR wegener'[tw] OR wegener'granulomatosis[tw] OR wegener's[tw] OR wegenera[tw] OR wegeneri[tw] OR wegeneris[tw] OR wegeners[tw] OR wegeners'[tw] OR wegeners's[tw]) AND granulomatosis[tw]) OR "Blood Urea Nitrogen"[mh:noexp]) AND (kidney[tw] OR renal[tw] OR dialysis[tw] OR (uremia[tiab] OR uremia'[tiab] OR uremiacreatinine[tiab] OR uremias[tiab] OR uremic[tiab] OR uremic'[tiab] OR uremic's[tiab] OR uremica[tiab] OR uremicecms[tiab] OR uremici[tiab] OR uremiclike[tiab] OR uremics[tiab] OR uremictoxin[tiab] OR uremidiab[tiab] OR uremie[tiab] OR uremigenic[tiab] OR uremigenous[tiab] OR uremina[tiab] OR uremiogenic[tiab] OR uremix[tiab] OR uremization[tiab]) OR (uraemia[tiab] OR uraemia'[tiab] OR uraemias[tiab] OR uraemic[tiab] OR uraemic'[tiab] OR uraemica[tiab] OR uraemically[tiab] OR uraemics[tiab] OR uraemie[tiab] OR uraemization[tiab]) OR (dehydratable[tw] OR dehydrataion[tw] OR dehydratant[tw] OR dehydratase[tw] OR dehydratase'[tw] OR dehydratase1[tw] OR dehydrataseless[tw] OR dehydratases[tw] OR dehydratated[tw] OR dehydratation[tw] OR dehydratative[tw] OR dehydrate[tw] OR dehydratease[tw] OR dehydrated[tw] OR dehydrated'[tw] OR dehydrates[tw] OR dehydrathasis[tw] OR dehydratic[tw] OR dehydratin[tw] OR dehydrating[tw] OR dehydration[tw] OR dehydration'[tw] OR dehydration"[tw] OR dehydration's[tw] OR dehydration1[tw] OR dehydration14[tw] OR dehydration19[tw] OR dehydration20[tw] OR dehydration21[tw] OR dehydration29a[tw] OR dehydrationagents[tw] OR dehydrational[tw] OR dehydrationcurrent[tw] OR dehydrationin[tw] OR dehydrations[tw] OR dehydrationstress[tw] OR dehydrationwe[tw] OR dehydratisation[tw] OR dehydrative[tw] OR dehydratively[tw] OR dehydratization[tw] OR dehydrator[tw] OR dehydrators[tw]) OR (creatinin[tw] OR creatinina[tw] OR creatininaemia[tw] OR creatininaemias[tw] OR creatininaemic[tw] OR creatininal[tw] OR creatininase[tw] OR

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nephritoxic[tiab] OR nephritris[tiab] OR nephrits[tiab] OR nephritus[tiab])) AND (crescentic[tw] OR (anca[tiab] OR anca'[tiab] OR anca's[tiab] OR anca3[tiab] OR ancaassociated[tiab] OR ancac[tiab] OR ancac's[tiab] OR ancacontaining[tiab] OR ancacybp[tiab] OR ancad[tiab] OR ancadualfit[tiab] OR ancafit[tiab] OR ancagn[tiab] OR ancak[tiab] OR ancala[tiab] OR ancalar[tiab] OR ancalochloris[tiab] OR ancalomicrobium[tiab] OR ancam[tiab] OR ancamine[tiab] OR ancan[tiab] OR ancanegative[tiab] OR ancanthinurus[tiab] OR ancanthocephalans[tiab] OR ancantholysis[tiab] OR ancanthophiinae[tiab] OR ancanthophis[tiab] OR ancao[tiab] OR ancap[tiab] OR ancar1[tiab] OR ancarano[tiab] OR ancarboxaldehyde[tiab] OR ancardiaceae[tiab] OR ancardium[tiab] OR ancare[tiab] OR ancares[tiab] OR ancas[tiab] OR ancas'[tiab] OR ancash[tiab] OR ancashensis[tiab] OR ancashi[tiab] OR ancaspase[tiab] OR ancassociated[tiab] OR ancaster[tiab] OR ancathia[tiab]) OR rapidly progressive[tiab] OR acute[tiab])) OR (("Kidney Diseases"[mh:noexp] OR (renal insufficiencies[tw] OR renal insufficiency[tw] OR renal insufficiency,[tw]) OR renal failure[tw] OR renal function[tiab] OR renal impairment[tiab] OR glomerular filtration rate[tiab] OR ischemia-reperfusion injury[tiab]) AND ("Cardiovascular Surgical Procedures"[majr] OR "Cardiovascular Diseases"[mh:noexp] OR "Cardiovascular System/surgery"[majr] OR (cardiac surgeon[tw] OR cardiac surgeons[tw] OR cardiac surger[tw] OR cardiac surgeries[tw] OR cardiac surgery[tw] OR cardiac surgical[tw]) OR cardiopulmonary[tiab] OR "Ischemia"[mh:noexp] OR "diagnostic imaging"[majr] OR "Contrast Media"[majr:noexp] OR "chemically induced"[sh] OR (revers[tiab] OR revers'[tiab] OR reversa[tiab] OR reversability[tiab] OR reversable[tiab] OR reversably[tiab] OR reversacol[tiab] OR reversade[tiab] OR reversaible[tiab] OR reversal[tiab] OR reversal'[tiab] OR reversal's[tiab] OR reversaling[tiab] OR reversalis[tiab] OR reversality[tiab] OR reversally[tiab] OR reversalpotential[tiab] OR reversals[tiab] OR reversals'[tiab] OR reversan[tiab] OR reversant[tiab] OR reversants[tiab] OR reversati[tiab] OR reversbility[tiab] OR reversd[tiab] OR reverse[tiab] OR reverse'[tiab] OR reverse"[tiab] OR reversebly[tiab] OR reversecell[tiab] OR reversed[tiab] OR reversed'[tiab] OR reversedly[tiab] OR reversedorgans[tiab] OR reversedpattern[tiab] OR reversedphase[tiab] OR reversedwb[tiab] OR reversee[tiab] OR reverseflow[tiab] OR reversegenetic[tiab] OR reversely[tiab] OR reversely'[tiab] OR reverseosmosis[tiab] OR reversepassive[tiab] OR reversephase[tiab] OR reversephenomenon[tiab] OR reversepoled[tiab] OR reverseprotein[tiab] OR reverser[tiab] OR reversers[tiab] OR reversers'[tiab] OR reverses[tiab] OR reverses'[tiab] OR reversescreen[tiab] OR reversescreen2d[tiab] OR reversescreen3d[tiab] OR reverset[tiab] OR reverset3[tiab] OR reversetranscriptase[tiab] OR reversetranscription[tiab] OR reversetrendelenburg[tiab] OR reversetype[tiab] OR reversi[tiab] OR reversial[tiab] OR reversibe[tiab] OR reversibel[tiab] OR reversibile[tiab] OR reversibilities[tiab] OR reversibility[tiab] OR reversibility'[tiab] OR reversibilty[tiab] OR reversibily[tiab] OR reversibity[tiab] OR reversibiy[tiab] OR reversibl[tiab] OR reversible[tiab] OR reversible'[tiab] OR reversibleglycosuria[tiab] OR reversibles[tiab] OR reversibleydroureteronephrosis[tiab] OR reversiblity[tiab] OR reversiblly[tiab] OR reversibly[tiab] OR reversiblyforming[tiab] OR reversiby[tiab] OR reversiin[tiab] OR reversilbe[tiab] OR

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OR ischemiaxtime[tw] OR ischemic[tw] OR ischemic'[tw] OR ischemic"[tw] OR ischemic12322014[tw] OR ischemic1962715[tw] OR ischemica[tw] OR ischemical[tw] OR ischemically[tw] OR ischemicaly[tw] OR ischemicanoxic[tw] OR ischemiccomplications[tw] OR ischemicdysfunction[tw] OR ischemicen[tw] OR ischemicgin[tw] OR ischemichally[tw] OR ischemicheart[tw] OR ischemichypoxic[tw] OR ischemicized[tw] OR ischemick[tw] OR ischemiclegs[tw] OR ischemiclike[tw] OR ischemiclleart[tw] OR ischemicmitral[tw] OR ischemicoptic[tw] OR ischemicproliferative[tw] OR ischemics[tw] OR ischemicstroke[tw] OR ischemie[tw] OR ischemied[tw] OR ischemihc[tw] OR ischemin[tw] OR ischemina[tw] OR ischeminc[tw] OR ischemique[tw] OR ischemiques[tw] OR ischemis[tw] OR ischemisation[tw] OR ischemised[tw] OR ischemization[tw] OR ischemized[tw] OR ischemizing[tw]) OR (ischaemi[tw] OR ischaemia[tw] OR ischaemia'[tw] OR ischaemia4[tw] OR ischaemiae[tw] OR ischaemial[tw] OR ischaemias[tw] OR ischaemic[tw] OR ischaemic'[tw] OR ischaemica[tw] OR ischaemical[tw] OR ischaemically[tw] OR ischaemich[tw] OR ischaemiclike[tw] OR ischaemicmyocardial[tw] OR ischaemicnecrosis[tw] OR ischaemics[tw] OR ischaemicus[tw] OR ischaemie[tw] OR ischaemioc[tw] OR ischaemis[tw] OR ischaemisation[tw] OR ischaemising[tw] OR ischaemismall[tw] OR ischaemization[tw] OR ischaemized[tw]) OR reperfusion[tw] OR (contrast media[tw] OR contrast medias[tw] OR contrast mediated[tw] OR contrast medium[tw] OR contrast mediums[tw])) AND ((renal tubular[tiab] OR renal tubule[tiab] OR renal tubules[tiab] OR renal tubuli[tiab] OR renal tubulin[tiab] OR renal tubulitis[tiab] OR renal tubulogenesis[tiab] OR renal tubulointerstitium[tiab] OR renal tubulointerstitum[tiab] OR renal tubulonecrosis[tiab] OR renal tubulopathies[tiab] OR renal tubulopathy[tiab] OR renal tubulotoxicity[tiab] OR renal tubulus[tiab]) OR tubular[tiab]))) AND ("Systemic Inflammatory Response Syndrome"[Mesh] OR "Systemic Inflammatory Response Syndrome"[TW] OR sepsis[TW] OR septic[TW])) AND ("dopamine"[MeSH Terms] OR "dopamine"[All Fields]) AND English[la]

2. ((((((((((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields] OR ""injury""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""failure""[All Fields]) OR ""kidney failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""failure""[All Fields]) OR ""renal failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""dysfunction""[All Fields]) OR ""renal dysfunction""[All Fields])) OR ((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields]))) OR (renal[All Fields] AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields]

AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields]))) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiencies""[All Fields]) OR ""kidney insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiency""[All Fields]) OR ""kidney insufficiency""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""insufficiencies""[All Fields]) OR ""renal insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields])) OR (""kidney tubular necrosis, acute""[MeSH Terms] OR (""kidney""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields] AND ""acute""[All Fields]) OR ""acute kidney tubular necrosis""[All Fields] OR (""acute""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields]) OR ""acute tubular necrosis""[All Fields])) AND (""dopamine""[MeSH Terms] OR ""dopamine""[All Fields]) AND (Randomized Controlled Trial[ptyp] OR Clinical Trial[ptyp])AND hasabstract[tw]

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality	RCT/16	0	0	0	-1	0	686	105	15%	701	109	16%	RR	0.96	0.78-1.19	A	5
Requirement rate of HD	RCT/13	0	0	0	-1	0	610	93	15%	606	91	15%	RR	0.93	0.76-1.15	A	9
Arrhythmia, ischemia (coronary, limbs, skin)	RCT/18	0	-1	-1	-1	-1							RR	1.13	0.90-1.41	B	7

CQ12-8

PICO

Patients (P): Septic AKI patients
Intervention (I): ANP (+)
Control (C): ANP (-)
Outcome (O): Mortality, requirement rate of HD, incidence of hypotension

Search terms

1. ((((((((((natriuretic*[tw] AND (peptide*[tw] OR factor*[tw])))))) OR (((natriuretic*[tw] AND (peptide*[tw] OR factor*[tw])))))) OR atriopeptin*) OR anaritide*) OR urodilatin*) OR ((atrial natriuretic peptide*[tw] or ANP[tw] or ANF[tw]))) OR Atrial Natriuretic Factor[mh])) AND (((((("acute kidney injury"[MeSH Terms] OR (acute kidney failure[tw] OR acute renal failure[tw])) OR ((acute kidney injure[tw] OR acute kidney injuries[tw] OR acute kidney injury[tw] OR acute kidney injury,[tw]) OR (acute renal injuries[tw] OR acute renal injury[tw]))) OR ((acute kidney insufficiencies[tw] OR acute kidney insufficiency[tw]) OR (acute renal insufficiencies[tw] OR acute renal insufficiency[tw]))) OR acute tubular necrosis[tw]) OR (ARI[tw] OR AKI[tw] OR ARF[tw] OR AKF[tw] OR ATN[tw]))) AND (Meta-Analysis[PT] OR systematic[SB])
2. ((((((((((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields] OR ""injury""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""failure""[All Fields]) OR ""kidney failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""failure""[All Fields]) OR ""renal failure""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""dysfunction""[All Fields]) OR ""renal dysfunction""[All Fields])) OR ((""kidney""[MeSH Terms] OR ""kidney""[All Fields]) AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields])))) OR (renal[All Fields] AND (""injuries""[Subheading] OR ""injuries""[All Fields] OR ""wounds and injuries""[MeSH Terms] OR (""wounds""[All Fields] AND ""injuries""[All Fields]) OR ""wounds and injuries""[All Fields])))) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiencies""[All Fields]) OR ""kidney insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR

(""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""kidney""[All Fields] AND ""insufficiency""[All Fields]) OR ""kidney insufficiency""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields] OR (""renal""[All Fields] AND ""insufficiencies""[All Fields]) OR ""renal insufficiencies""[All Fields])) OR (""renal insufficiency""[MeSH Terms] OR (""renal""[All Fields] AND ""insufficiency""[All Fields]) OR ""renal insufficiency""[All Fields])) OR (""kidney tubular necrosis, acute""[MeSH Terms] OR (""kidney""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields] AND ""acute""[All Fields]) OR ""acute kidney tubular necrosis""[All Fields] OR (""acute""[All Fields] AND ""tubular""[All Fields] AND ""necrosis""[All Fields]) OR ""acute tubular necrosis""[All Fields])) AND (""atrial natriuretic factor""[MeSH Terms] OR (""atrial""[All Fields] AND ""natriuretic""[All Fields] AND ""factor""[All Fields]) OR ""atrial natriuretic factor""[All Fields] OR (""atrial""[All Fields] AND ""natriuretic""[All Fields] AND ""peptide""[All Fields]) OR ""atrial natriuretic peptide""[All Fields]) AND (Randomized Controlled Trial[ptyp] OR Clinical Trial[ptyp])

Body of the evidence

							The numbers of persons at risk (outcome rate)											
Outcome	Design /number	RoB	Inconsis tency	Imprecis ion	Indirectn ess	Others	Control group			Intervention group			Type	Value	95%CI	Streng th	Import ance	Comme nt
							Denomin ator	Numerat or	(%)	Denomin ator	Numerat or	(%)						
Mortality	RCT/9	-1	0	-1	-1	-1	533	161	30%	517	166	32%	RR	1.06	0.90-1.27	B	9	1)
Requirement rate of HD	RCT/9	-1	-1	0	-1	-1	556	278	50%	547	245	45%	RR	0.86	0.68-1.08	B	7	
Hypotension	RCT/9	-1	0	0	-1	-1	556	148	27%	547	266	49%	RR	1.69	1.29-2.22	A	5	

1) Main population was not patients with sepsis. We excluded studies of ANP use for prevention of AKI.

CQ13-1

PICO

Patients (P): Critically ill patients in the ICU
Intervention (I): Enteral nutrition (+)
Control (C): Enteral nutrition (-)
Outcome (O): Mortality, incidence of infection

Search terms

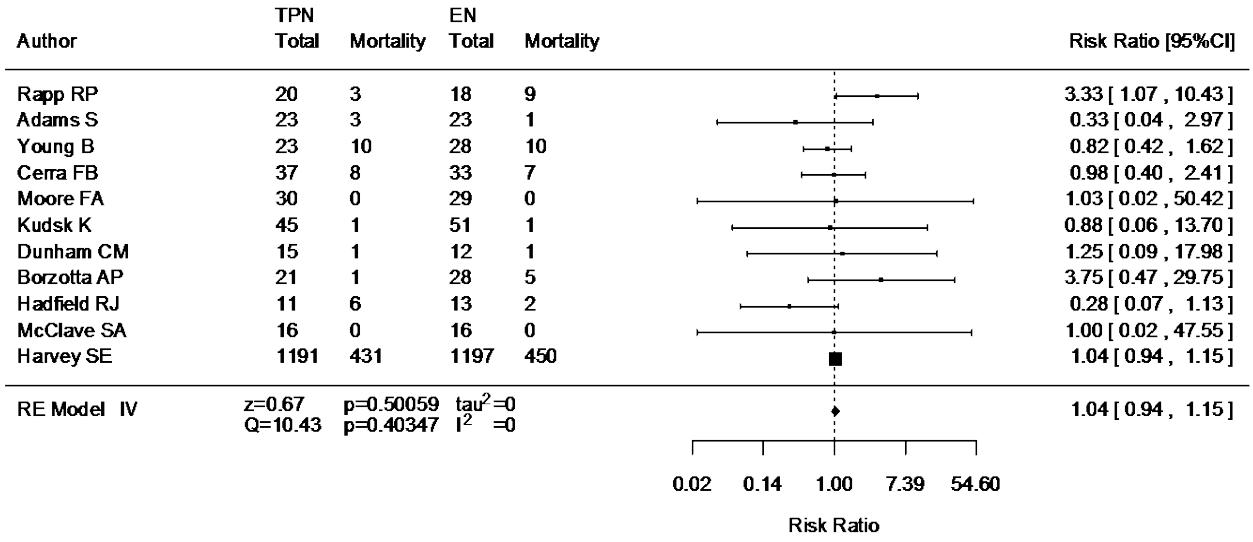
1. ((parenteral nutrition) AND (enteral nutrition) AND (randomized OR randomized OR randomly) OR (critically ill) OR (intensive care) OR (ICU) OR (sepsis)） OR (GI surgery) OR (abdominal surgery) OR (postoperative)

Body of the evidence

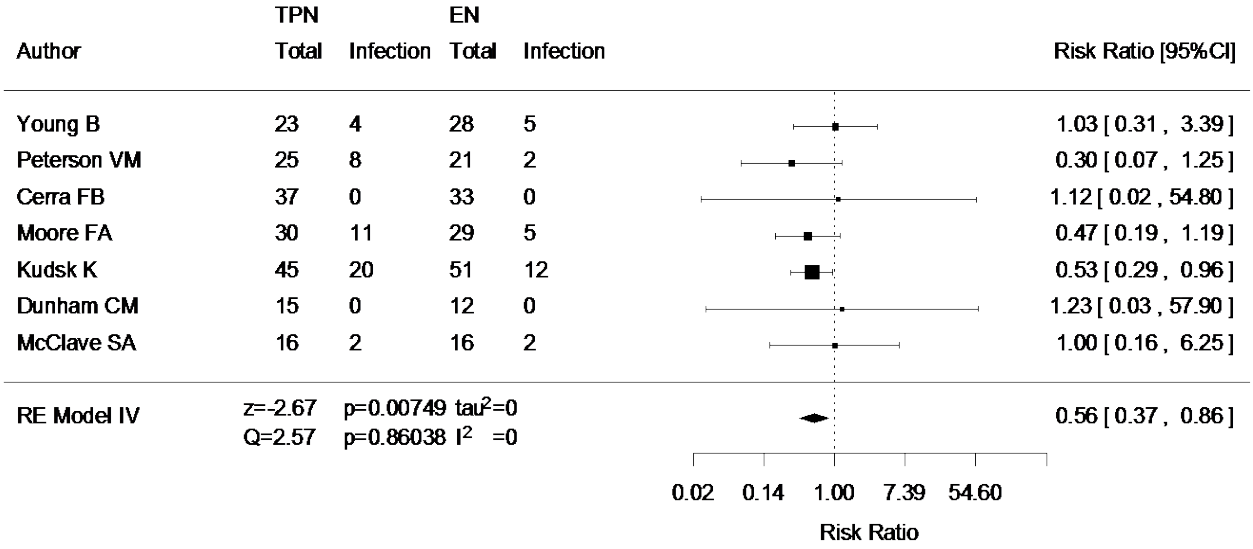
							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance
Mortality	RCT/11	-1	0	0	-1	0	1432	464	32	1448	486	34	RR	1.04	0.94-1.15	B	8
Incidence of infection	RCT/7	-1	0	0	-1	0	191	45	24	190	26	14	RR	0.56	0.37-0.86	B	9

Results of meta-analysis

1. Mortality



2. Incidence of infection



CQ13-2

PICO

Patients (P): Septic patients (Critically ill patients)
Intervention (I): Early enteral nutrition
Control (C): Late enteral nutrition
Outcome (O): Mortality, incidence of infection, ventilator days, length of ICU stay, length of hospital stay

Search terms

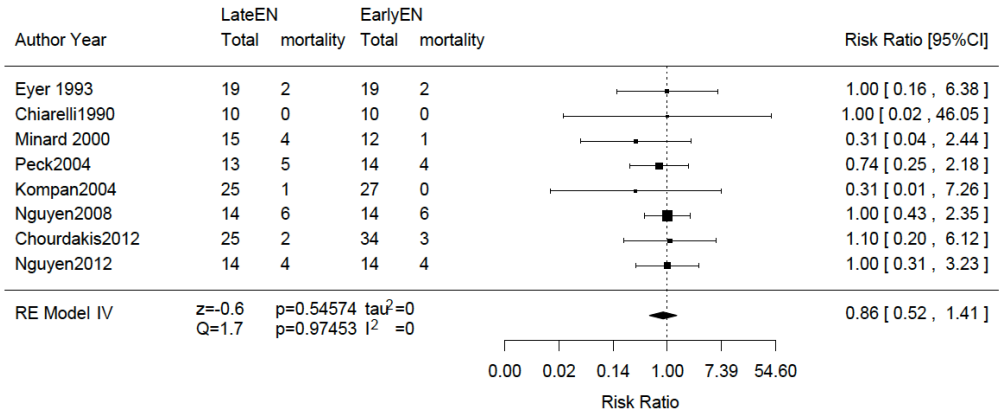
1. ((early enteral nutrition) and (sepsis or critically ill or intensive care))
2. (early or immediate) and (nutrition or feeding) and (enteral or jejunostomy) and (randomized or randomised) and (ICU or (intensive care) or (critically ill) or sepsis or septic)
3. ((((enteral feeding) OR enteral nutrition)) AND (((intensive) OR critically) OR critical)) AND (randomized OR randomised OR randomly)

Body of the evidence

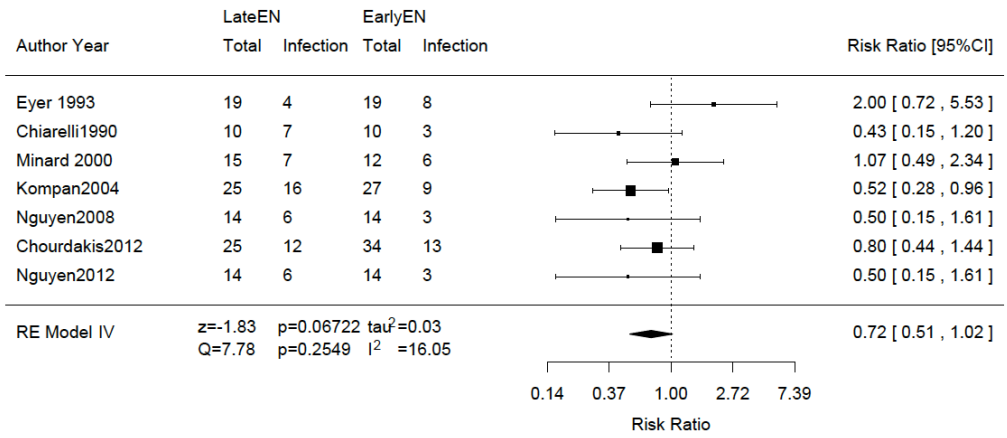
							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance
Mortality	RCT/8	-1	0	-1	-1	0	135	18	13	144	14	9.7	RR	0.86	0.52-1.41	C	9
Incidence of infection	RCT/7	-1	0	-1	-1	0	122	58	48	130	45	35	RR	0.72	0.51-1.02	C	9
Length of ICU stay	RCT/7	-1	-2	-1	-1	-1	125			134			MD	-1.69	[-5.25,1.88]	C	7
Length of hospital stay	RCT/4	-1	-2	-1	-1	-1	48			43			MD	-0.32	[-17.18 16.53]	C	7
Ventilation days	RCT/7	-1	-2	-1	-1	-2	110			107			MD	-1.16	[-4.82 2.49]	C	6

Results of meta-analysis

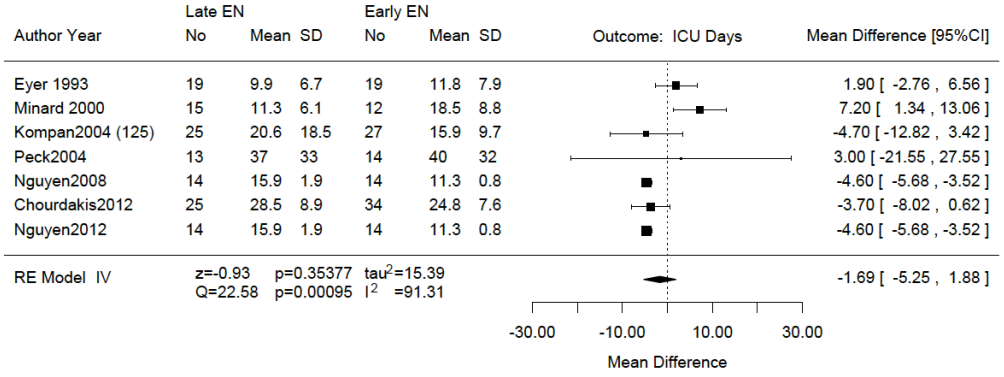
1. Mortality



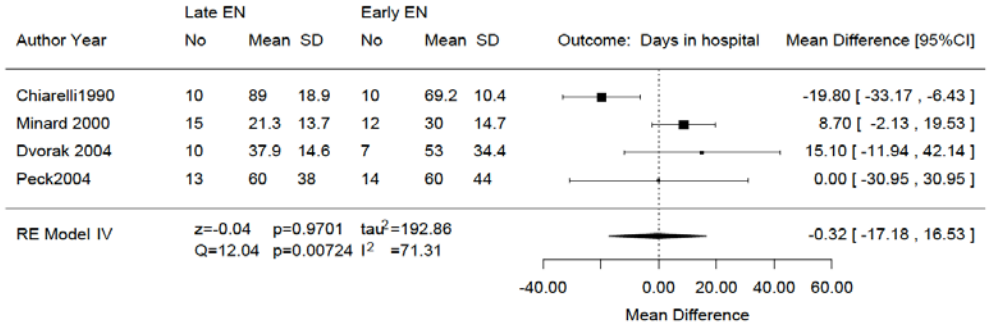
2. Incidence of infection



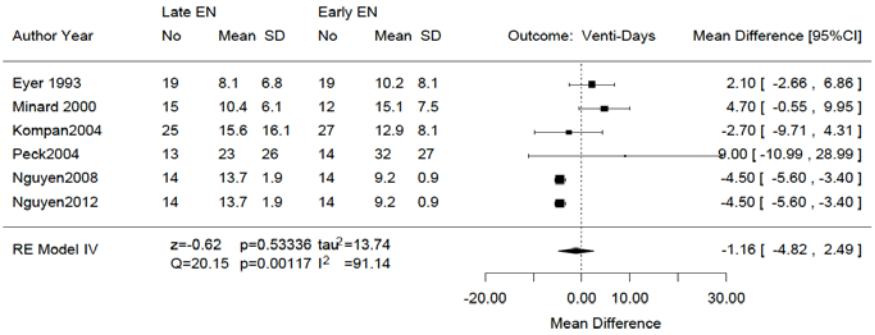
3. Length of ICU stay



4. Length of hospital stay



5. Ventilator days


Late EN
Early EN
Author Year
No Mean SD
No Mean SD
Outcome: Venti-Days
Mean Difference [95%CI]
Eyer 1993 19 8.1 6.8 19 10.2 8.1 2.10 [-2.66 , 6.86]
Minard 2000 15 10.4 6.1 12 15.1 7.5 4.70 [-0.55 , 9.95]
Kompan2004 25 15.6 16.1 27 12.9 8.1 -2.70 [-9.71 , 4.31]
Peck2004 13 23 26 14 32 27 9.00 [-10.99 , 28.99]
Nguyen2008 14 13.7 1.9 14 9.2 0.9 -4.50 [-5.60 , -3.40]
Nguyen2012 14 13.7 1.9 14 9.2 0.9 -4.50 [-5.60 , -3.40]
RE Model IV
z=-0.62 p=0.53336 tau²=13.74
Q=20.15 p=0.00117 I² =91.14
-1.16 [-4.82 , 2.49]
-20.00
0.00
10.00
30.00
Mean Difference

CQ13-3

PICO

Patients (P): Critically ill patients
Intervention (I): Underfeeding
Control (C): Full feeding
Outcome (O): Mortality, incidence of infection, ventilator days, length of ICU stay, length of hospital stay

Search terms

1. (critically ill or intensive care) and (enteral nutrition)

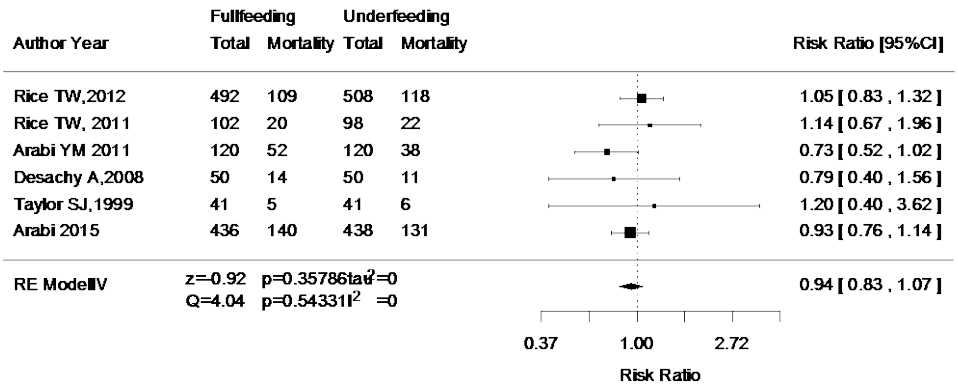
Body of the evidence

							The numbers of persons at risk (outcome rate)											
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	RCT/6	0	0	0	-1	0	1241	340	27.3	1255	326	26	RR	0.93	0.83-1.07	B	8	
Incidence of infection	RCT/3	-1	-2	-2	-1	0	589	227	38.5	587	226	38.5	RR	1.08	0.83-1.41	C	9	1)
Ventilator days	RCT/2	0	-1	-2	-1	-1							MD	-1.04	[-3.29~1.20]	C	7	
Length of ICU stay	RCT/2	0	0	-2	-1	-1							MD	-1.78	[-4.42~0.86]	C	7	
Length of hospital stay	RCT/2	0	0	-2	-1	-1							MD	-0.84	[-19.2~17.5]	C	7	
Incidence of VAP	RCT/4	-1	-1	-2	-1	0	1081	159	14.7	1095	158	14.4	RR	0.9	0.68-1.17	C	7	1)
CRRT rate	RCT/2	-1	0	0	-1	-1	516	68	13.2	526	44	8.36	RR	0.64	0.45-0.91	C	7	1)

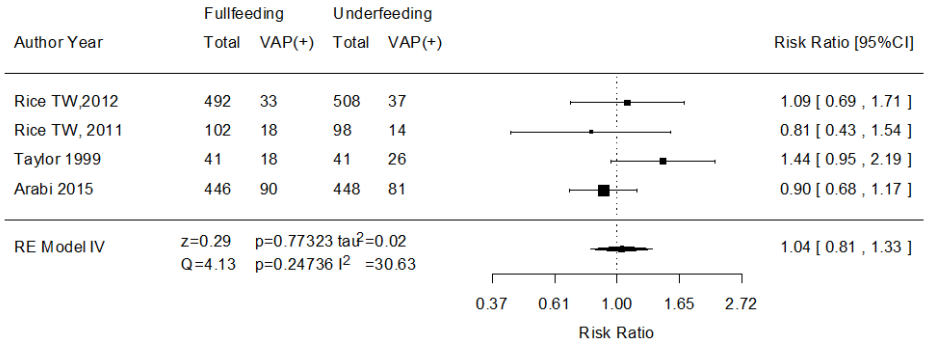
1) Open label

Results of meta-analysis

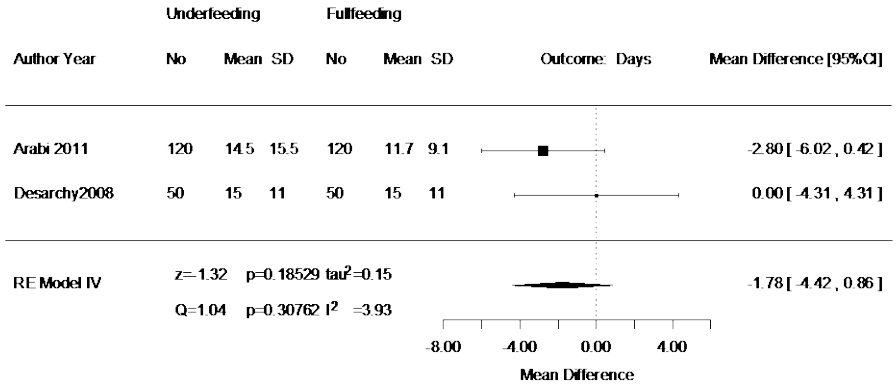
1. Mortality



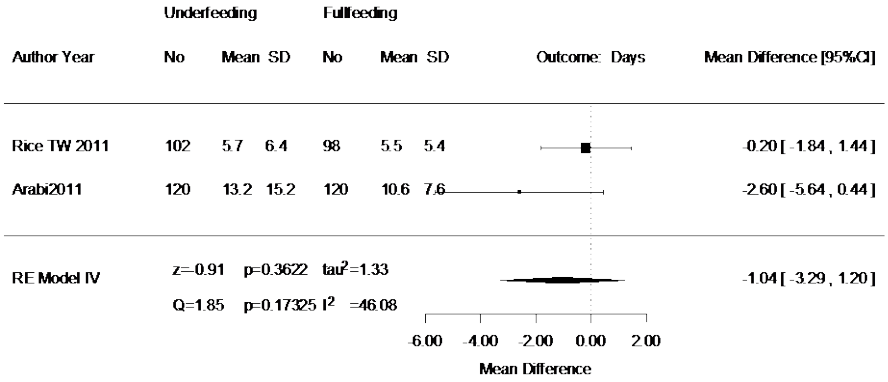
2. Incidence of VAP



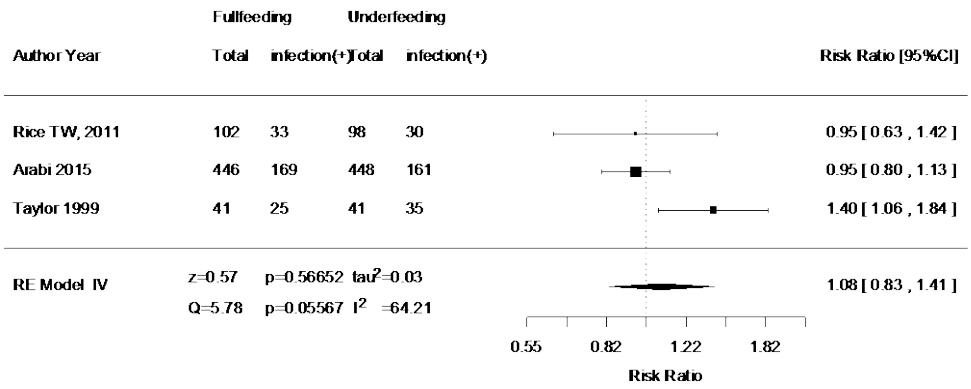
3. Length of ICU stay



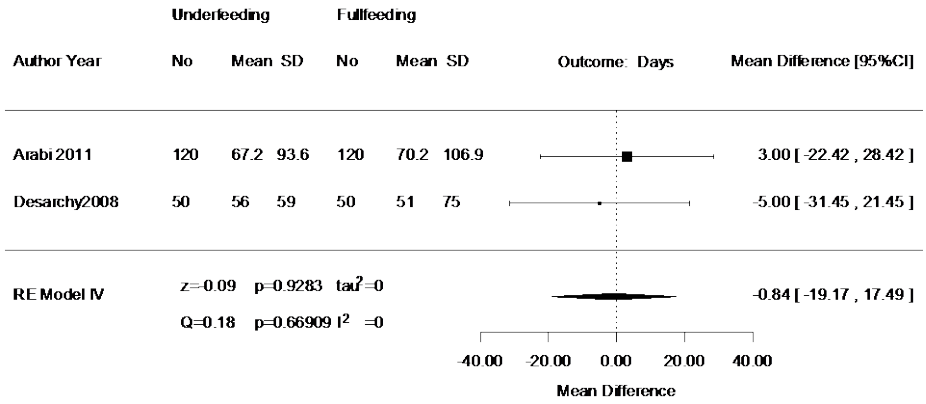
4. Ventilator days



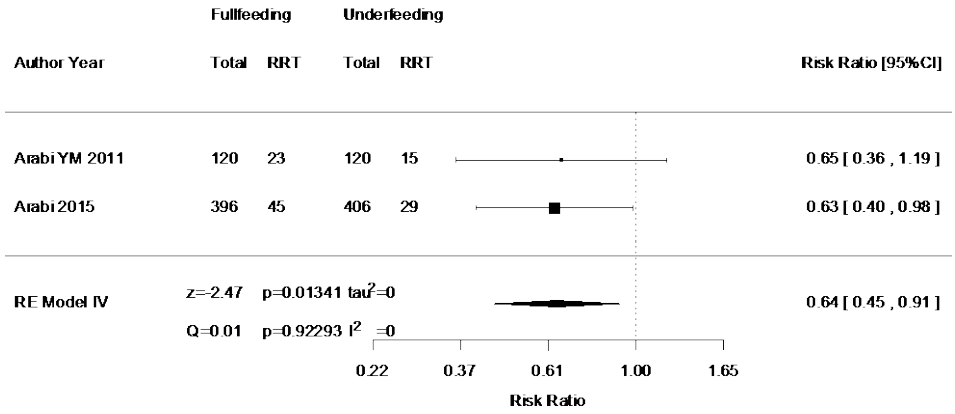
5. Incidence of infection



6. Length of hospital stay



7. CRRT rate



CQ13-4

PICO

Patients (P): Critically ill patients
Intervention (I): Parental nutrition within 1 week (+)
Control (C): Parental nutrition within 1 week (-)
Outcome (O): Mortality, incidence of blood stream infection, incidence of respiratory infection, incidence of urinary tract infection

Search terms

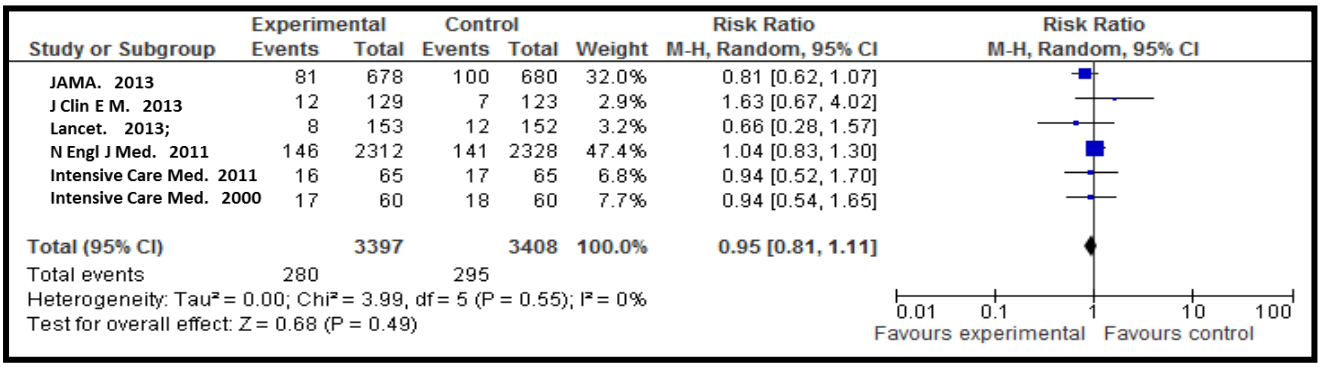
1. ((Parenteral) AND (randomized OR randomised) AND ((acute AND (ill OR illness)) OR (critically ill) OR (ICU) OR (sepsis) OR (intensive care))

Body of the evidence

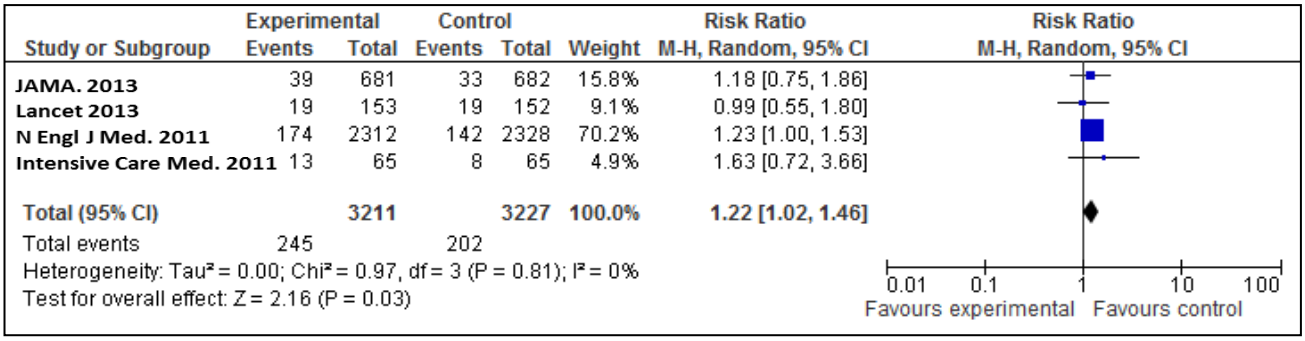
							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance
Mortality	RCT/9	-1	0	0	0	0	3408	295	8.7	3397	280	8.2	RR	1	0.81-1.11	C	8
Incidence of blood streaminfection	RCT/4	-1	0	0	0	0	3227	202	6.3	3211	245	7.6	RR	1.2	1.02-1.46	B	9
Incidence of respiratory infection	RCT/5	-1	-1	-1	0	0	3287	596	18	3271	651	20	RR	1.1	0.87-1.32	C	7
Incidence of urinary tract infection	RCT/5	-1	0	-1	0	0	3287	85	2.6	3271	96	2.9	RR	1.1	0.84-1.49	C	7

Results of meta-analysis

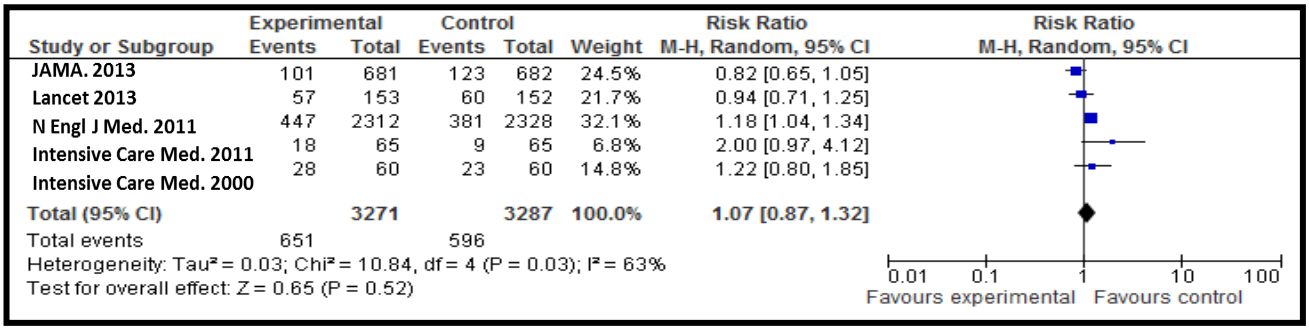
1. Mortality



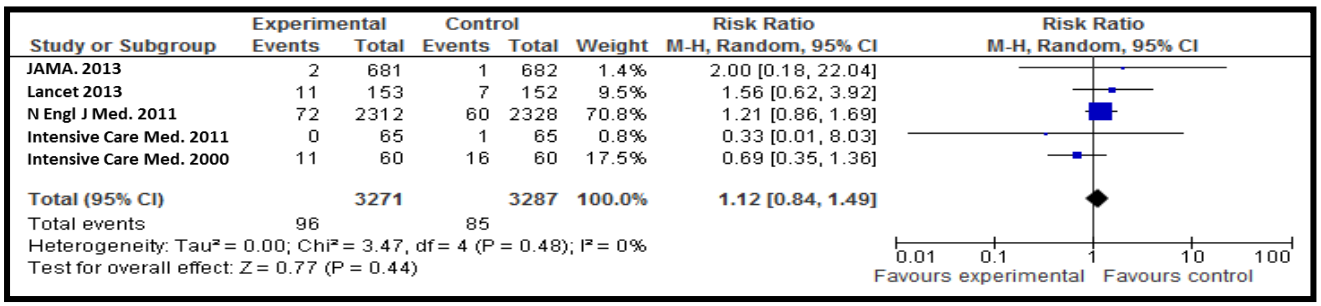
2. Incidence of blood stream infection



3. Incidence of respiratory infection



4. Incidence of urinary tract infection



CQ13-5

PICO

Patients (P): Critically ill patients
Intervention (I): Parental nutrition within 1 week (+)
Control (C): Parental nutrition within 1 week (-)
Outcome (O): Mortality, incidence of infection, ventilator days, length of ICU stay, length of hospital stay

Search terms

1. ((Parenteral) AND (randomized OR randomised) AND ((acute AND (ill OR illness)) OR (critically ill) OR (ICU) OR (sepsis) OR (intensive care))

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Mortality	RCT/1	−2		−1	−1		22	4	18.2	24	2	8.3				C	7
Incidence of catheter infection	RCT/1	−2		−1	−1		22	3	13.6	24	1	4.2				C	9
Incidence of pnuemonia	RCT/1	−2		−1	−1		22	6	27.3	24	2	8.3				C	8
Incidence of urinary tract infection	RCT/1	−2		−1	−1		22	2	9.1	24	0	0				C	8

CQ14-1　What is the optimal blood glucose target level in septic patients?

PICO

Patients (P): Septic patients or patients in the ICU
Intervention (I): Target blood glucose levels <110 mg/dL, 110–144 mg/dL, 144–180 mg/dL
Control (C): Target blood glucose levels >180 mg/dL
Outcome (O): Hospital mortality, incidence of infection, incidence of hypoglycemia

Search terms

1. (((critically ill OR ICU OR intensive care OR sepsis OR septic)) AND (glucose OR insulin)) AND (randomized OR randomised)
2. (((glucose) OR (insulin)) AND ((critically ill) OR (ICU) OR (intensive care) OR (sepsis))) AND randomized
3. glucose AND ((critically ill) OR (ICU) OR (intensive care)) AND randomized controlled trial[pt] AND humans[mh] AND (english[la] OR japanese[la]) AND hasabstract[tw]

Body of the evidence

1. Hospital mortality

	Direct evidence						Direct evidence			NMA			
Hospital mortality	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	OR	95%CI	Strength	OR	95%CrI	Strength	Importance
< 110 vs > 180	RCT/10	−1	−1	0	−1	−1	1	0.83−1.14	B (moderate)	0.91	0.77−1.14	B (moderate)	9
< 110 vs 110−144	RCT/0	No direct comparison								0.83	0.63−1.11	D (very low)	9
< 110 vs 144−180	RCT/3	0	0	0	−1	−1	1.14	0.83−1.47	B (moderate)	1.12	0.83−1.45	B (moderate)	9
110−144 vs 144−180	RCT/2	−1	0	−1	−1	−1	1.25	0.38−3.23	C (low)	1.33	0.83−2.04	D (very low)	9
110−144 vs > 180	RCT/5	−1	0	−1	−1	−1	1.11	0.77−1.59	B (moderate)	1.14	0.77−1.59	B (moderate)	9
144−180 vs > 180	RCT/0	No direct comparison								0.82	0.69−0.96	D (very low)	9

2. Infection

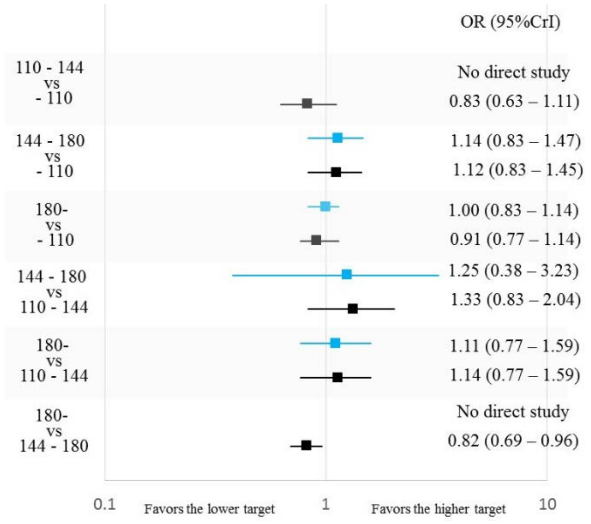
	Direct evidence						Direct evidence			NMA			
Infection	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	OR	95%CI	Strength	OR	95%CrI	Strength	Importance
< 110 vs > 180	RCT/5	−1	−1	0	−1	−1	0.83	0.38−2.00	B (moderate)	0.77	0.40−1.69	B (moderate)	6
< 110 vs 110−144	RCT/0	No direct comparison								1.1	0.71−1.80	D (very low)	6
< 110 vs 144−180	RCT/1	0		0	−1		1.05	0.21−5.56	C (low)	1.2	0.38−4.35	C (low)	6
110−144 vs 144−180	RCT/1	−1		−1	−1		1.25	0.20−8.33	C (low)	0.91	0.26−3.33	D (very low)	6
110−144 vs > 180	RCT/6	−1	−2	0	−1	0	0.56	0.24−1.30	C (low)	0.63	0.29−1.28	C (low)	6
144−180 vs > 180	RCT/0	No direct comparison								0.69	0.52−0.92	D (very low)	6

3. Hypoglycemia

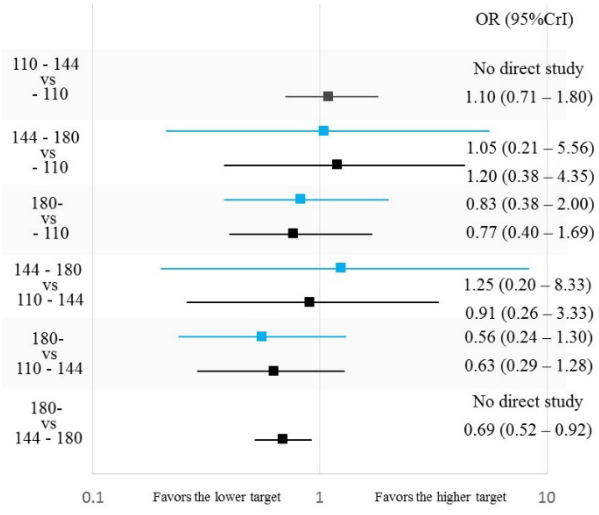
	Direct evidence						Direct evidence			NMA			
Hypoglycemia	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	OR	95%CI	Strength	OR	95%CrI	Strength	Importance
< 110 vs > 180	RCT/10	−1	−1	0	−1	0	6.25	3.70−11.36	B (moderate)	6.67	3.84−11.11	B (moderate)	9
< 110 vs 110−144	RCT/1	−1			−1					1	0.30−2.70	D (very low)	9
< 110 vs 144−180	RCT/3	0	−2	−1	−1	−1	5.88	2.00−14.93	C (low)	5.88	2.27−12.98	C (low)	9
110−144 vs 144−180	RCT/2	−1	0	−1	−1	−1	5.56	1.33−25.00	B (moderate)	5.88	2.08−18.18	C (low)	9
110−144 vs > 180	RCT/5	−1	0	−1	−1	0	8.33	2.27−38.46	B (moderate)	6.67	2.44−21.74	C (low)	9
144−180 vs > 180	RCT/0	No direct comparison								0.76	0.49−1.11	C (low)	9

Results of meta-analysis

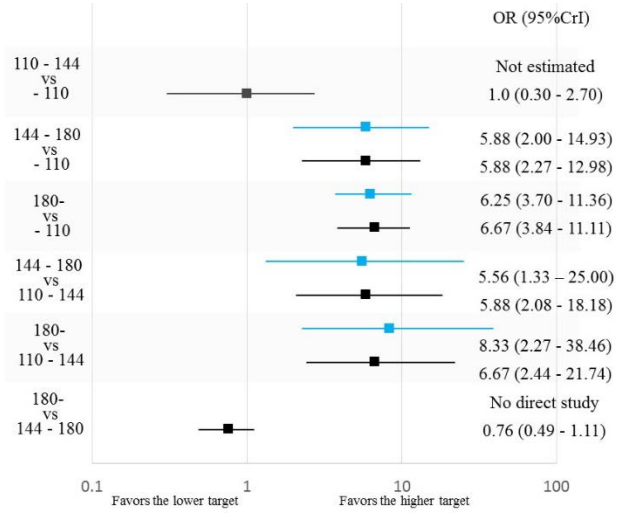
1. Hospital mortality



2. Infection



3. Hypoglycemia



CQ14-2

PICO

Patients (P): Septic patients or patients in the ICU
Intervention (I): Glucose meter (capillary blood), Glucose meter (arterial blood)
Control (C): Glucose meter (arterial blood)/ arterial blood gas analyzers (arterial blood), arterial blood gas analyzers (arterial blood)
Outcome (O): Error rate

Search terms

1. (sepsis OR septic OR intensive care OR critical care) AND (glucose OR sugar OR glycemic OR insulin) AND (bland altman OR agreement OR validation OR reliability OR accuracy correlation clarke grid OR bias)
2. (sepsis OR critically ill) AND (blood glucose measurements OR blood glucose estimation OR blood glucose analysis) AND (randomized controlled trial[pt]) AND (english[la] OR japanese[la]) AND hasabstract[tw]
3. ((Bland Altman) OR agreement OR validation OR reliability OR accuracy OR correlation OR (Clarke grid) OR bias)) AND (glucose OR sugar OR glycemic OR insulin) AND ((sepsis OR septic OR (intensive care) OR (critical care))

Body of the evidence

Comparison 1. Glucose meter (capillary blood) vs Arterial blood gas analyzers (arterial blood)

								The numbers of persons at risk (outcome rate)											
								Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Factors of improvement (Obs.)	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	comment
Error rate	Observational/3	-1	0	0	0	0	None	912	2	0.2	1888	79	4.2	OR	0.04	0.01-0.14	B	9	1)

Comparison 2. Glucose meter (capillary blood) vs Glucose meter (arterial blood)

								The numbers of persons at risk (outcome rate)											
								Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Factors of improvement (Obs.)	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	comment
Error rate	Observational/6	-1	0	0	0	0	None	2847	79	2.8	2501	204	8.2	OR	0.36	0.25-0.52	B	9	1)

Comparison 3. Glucose meter (arterial blood) vs Arterial blood gas analyzers (arterial blood)

								The numbers of persons at risk (outcome rate)											
								Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Factors of improvement (Obs.)	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	comment
Error rate	Observational/3	-1	-2	-1	0	-1	None	912	2	0.2	2275	28	1.2	OR	0.17	0.01-2.46	C	9	1)

1) Inoue S, et al. Crit Care. 2013;17:R48.

CQ15-1

PICO

Patients (P): Critically ill patients who have a fever
Intervention (I): Antipyretic treatment (+)
Control (C): Antipyretic treatment (-)
Outcome (O): Mortality, ICU-free survival days, length of ICU stay, incidence of infection

Search terms

1. ((Intensive care) or (critically ill) or (sepsis) or (critical care) or (ICU)) and (Randomized or randomised or randomly) and ((Cooling) or (antipyretic) or (ibuprofen) or (anti-pyretic) or (lornoxicam) or (cyclooxygenase) or (diclofenac) or (metamizol) or (propacetamol) or (paracetamol) or (acetaminophen)) AND (fever or febrile or temperature)

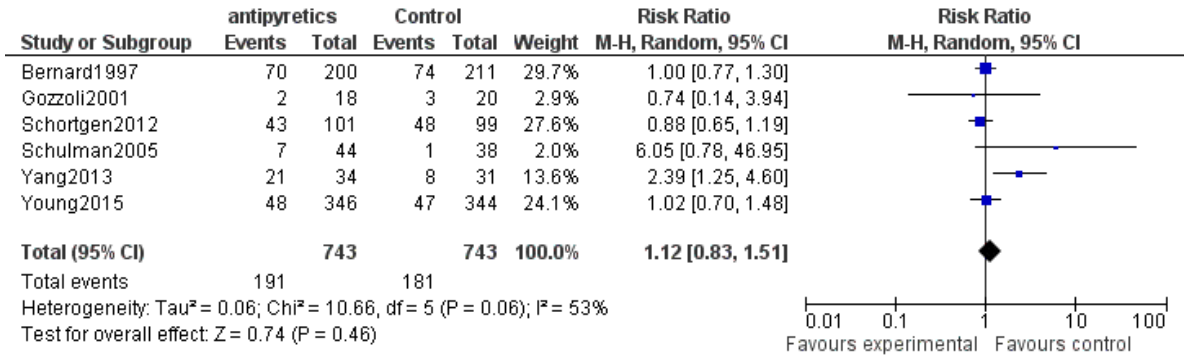
Body of the evidence

							The numbers of persons at risk (outcome rate)										
							Control group			Intervention group							
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Denominator	Numerator	(%)	Denominator	Numerator	(%)	Type	Value	95%CI	Strength	Importance	comment
Mortality	RCT/6	-1	-1	-1	0	-1	743	181	24.4%	743	191	25.7%	RR	1.12	0.83-1.51	C	9	
ICU free survival days	RCT/1	0		-1	0		344			347			MD	1	-0.38, 2.38	B	6	
Length of ICU stay	RCT/4	-1	0	0	0	0	501			510			MD	-0.04	-0.76, 0.68	B	6	
Incidence of infection																	6	1)

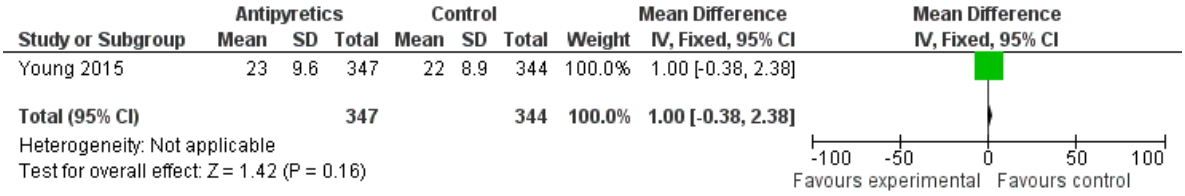
1) Free text.

Results of meta-analysis

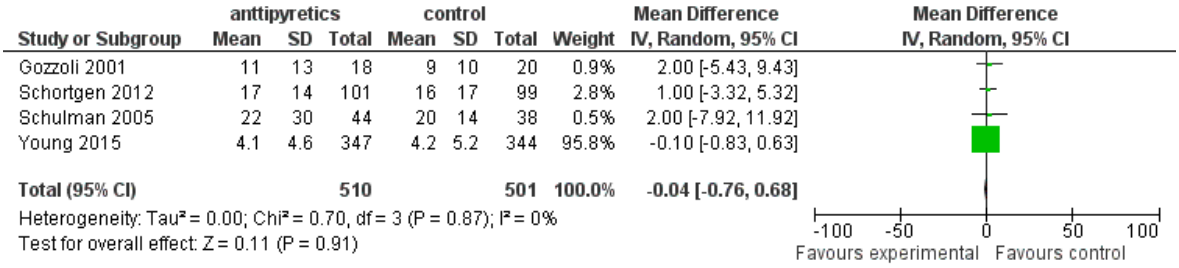
1. Mortality



2. ICU-free survival days



3. Length of ICU stay



4. Incidence of infection (Free text)

Schortgen 2012: 14 days after randomization

Cooling group 32.6/1,000 ICU days (95% CI, 32.3–32.9) vs Control group 23.8/1,000 ICU days (95% CI, 23.4–24.1), (OR, 1.37; 95% CI, 0.80–2.36)

Schulman 2005:

Antipyretic treatment group 4±6 times/patients vs Control group 3±2 times/patients (p=0.26)

CQ15-2

PICO

Patients (P): Septic patients with hypothermia
Intervention (I): Rewarming
Control (C): Permissive hypothermia
Outcome (O): Mortality, length of ICU stay

Search terms

1. (((((critically ill) OR severe illness)) OR ((intensive care) OR critical care))) AND (hypothermia and rewarming)
2. ((sepsis or septic) and (hypothermia or rewarming) and ("clinical trial" OR "controlled trial" OR randomized))
3. (sepsis) AND hypothermia

CQ16-1

PICO

Patients (P): Severe septic patients
Intervention (I): Diagnosis using JAAM DIC score
Control (C): Diagnosis not using JAAM DIC score
Outcome (O): Mortality

Search terms
1. JAAM DIC

CQ16-2

PICO

Patients (P): Sepsis induced DIC patients

Intervention (I): Recombinant human soluble thrombomodulin (+)

Control (C): Placebo or Recombinant human soluble thrombomodulin (-)

Outcome (O): Mortality, bleeding complication, recovery rate from DIC

Search terms

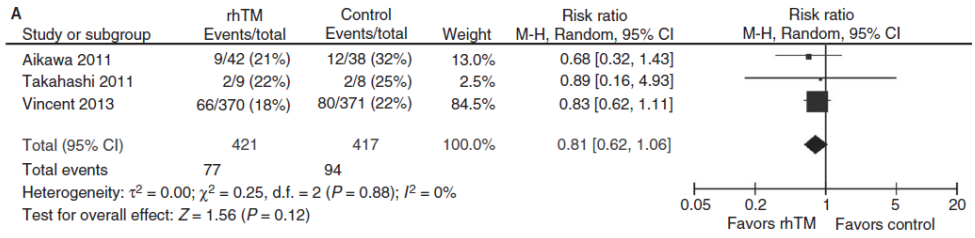
1. Disseminated intravascular coagulation AND random

Body of the evidence

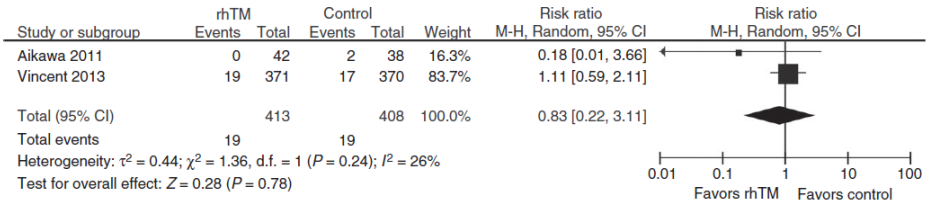
							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
28 days mortality	RCT/3	0	0	-1	0	0	417	94	22.5	421	77	18.3	RR	0.81	0.62-1.06	B	9
Bleeding complication	RCT/2	0	0	-2	0	0	408	19	4.7	413	19	4.6	RR	0.83	0.22-3.11	B	7
Recovery rate from DIC	RCT/3	0	0	-1	0	0	97	32	33	94	43	45.7	RR	1.28	0.93-1.75	B	4

Results of meta-analysis

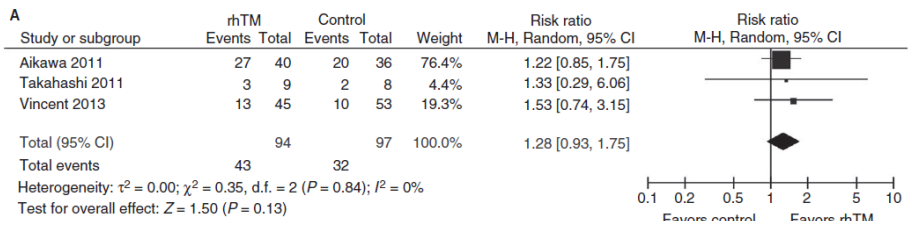
1. 28 days mortality



2. Bleeding complication



3. Recovery rate from DIC



CQ16-3

PICO

Patients (P): Sepsis induced DIC patients

Intervention (I): Antthrombin (+)

Control (C): Placebo or Antthrombin (-)

Outcome (O): 28 days mortality, bleeding complication, recovery rate from DIC

Search terms

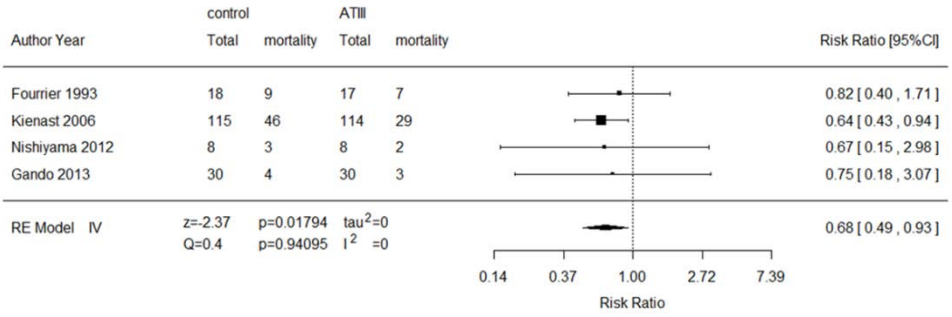
1. (Disseminated intravascular coagulation) AND (randomized or randomised)
2. dissemianted intravascular coagulation AND random

Body of the evidence

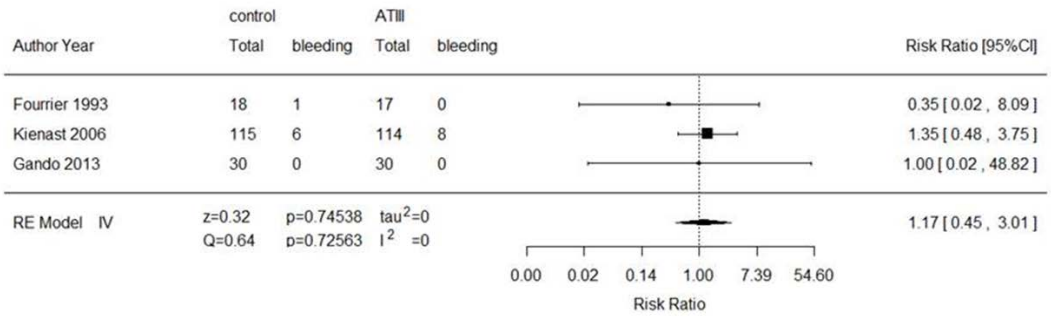
							The numbers of persons at risk (outcome rate)									
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
28 days mortality	RCT/4	-1	0	0	-1	0	171	62	36.3	169	41	24.3	RR	0.68	0.49-0.93	B	9
Bleeding complication	RCT/3	-1	0	-2	-1	0	163	7	4.3	161	8	5	RR	1.17	0.45-3.01	C	7
Recovery rate from DIC	RCT/2	-1	0	0	-1	0	48	12	25	44	26	59.1	RR	2.37	1.39-4.06	B	4

Results of meta-analysis

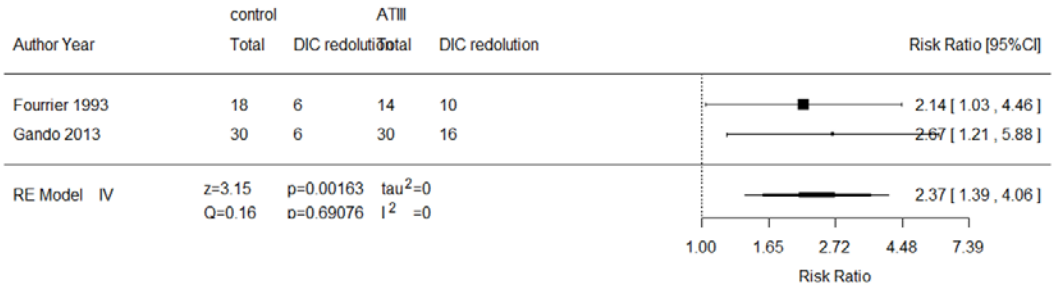
1. 28 days mortality



2. Bleeding complication



3. Recovery rate from DIC



CQ16-4

PICO

Patients (P): Sepsis induced DIC patients

Intervention (I): Protease inhibitor (+)

Control (C): Placebo or Protease inhibitor (-)

Outcome (O): 28 days mortality, bleeding complication, recovery rate from DIC

Search terms

1. (Disseminated intravascular coagulation) AND (randomized or randomised)
2. dissemianted intravascular coagulation AND random

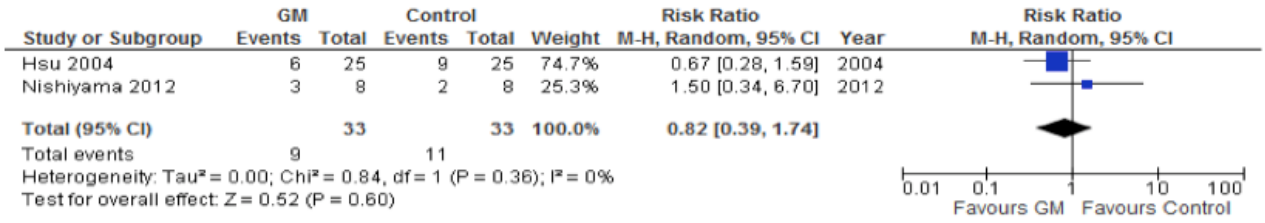
Body of the evidence

							The numbers of persons at risk (outcome rate)											
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
28 days mortality	RCT/2	-1	0	-2	0	0	33	11	33.3	33	9	27.3	RR	0.82	0.39-1.74	D	9	
Bleeding complication	RCT/0																7	1)
Recovery rate from DIC	RCT/0																4	1)

1) Included 2 RCTs did not evaluation this outcome.

Results of meta-analysis

1. 28 days mortality



CQ16-5

PICO

Patients (P): Sepsis induced DIC patients

Intervention (I): Heparin (+)

Control (C): Placebo or Heparin (-)

Outcome (O): 28 days mortality, bleeding complication, recovery rate from DIC

Search terms

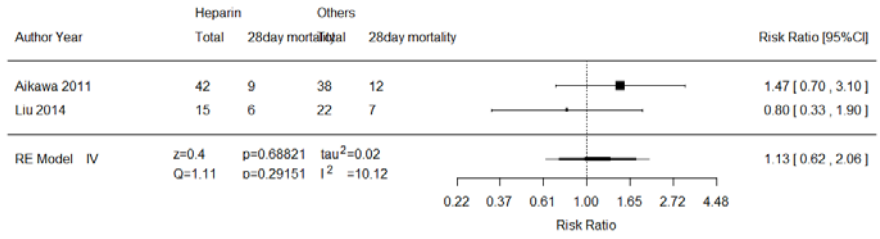
1. (Disseminated intravascular coagulation) AND (randomized or randomised)
2. dissemianted intravascular coagulation AND random

Body of the evidence

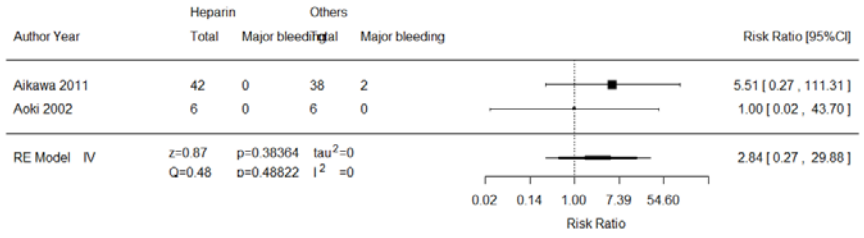
							The numbers of persons at risk (outcome rate)									
Outcome	Design /number	RoB	Inconsi stency	Impreci sion	Indirec tness	Othe rs	Control group			Intervention group			Type	Value	95%CI	Stren gth	Import ance
							Denomi nator	Numer ator	(%)	Denom inator	Numera tor	(%)					
28 days mortality	RCT/2	-1	-1	-2	-1	0	57	15	26.3	60	19	31.7	RR	1.13	0.62-2.06	D	9
Bleeding complication	RCT/2	-1	0	-2	-1	0	48	0	0.0	44	2	4.5	RR	2.84	0.27-29.88	D	7
Recovery rate from DIC	RCT/1	-1		-1	-1		40	27	67.5	36	20	55.6	RR	0.82	0.57-1.18	D	4

Results of meta-analysis

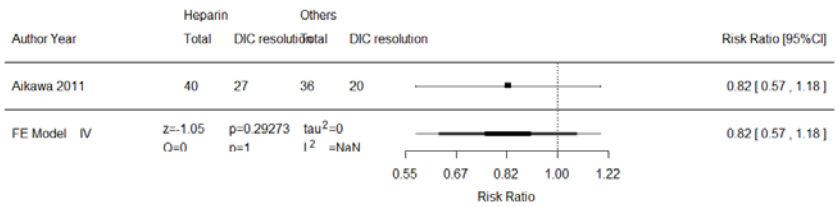
1. 28 days mortality



2. Bleeding complication



3. Recovery rate from DIC



CQ17-1

PICO

Patients (P): Septic patients
Intervention (I): Anticoagulation or Elastic stocking or Intermittent pneumatic compression (+)
Control (C): Anticoagulation or Elastic stocking or Intermittent pneumatic compression (-)
Outcome (O): Incidence of DVT, incidence of PE, complication rate

Search terms

1. (sepsis OR septic shock OR infection OR critical care OR intensive care OR acute ill) AND (venous thromboembolism OR deep venous thrombosis OR pulmonary embolism)

CQ17-2

PICO

Patients (P): Septic patients
Intervention (I): DVT diagnosis using specific method (clinical sign, D-dimer, imaging, et al.) (+)
Control (C): DVT diagnosis using specific method (clinical sign, D-dimer, imaging, et al.) (-)
Outcome (O): Mortality, incidence of PE

Search terms

1. (sepsis OR septic shock OR infection OR critical care OR intensive care OR acute ill) AND (venous thromboembolism OR deep venous thrombosis OR pulmonary embolism)

CQ18-1

PICO

Patients (P): Septic patients or critically ill patients in ICU
Intervention (I): Electrical muscle stimulation (+)
Control (C): Electrical muscle stimulation (-)
Outcome (O): Incidence of ICU-AW, muscle volume, duration of ventilation, length of ICU stay

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
Incidence of ICU-AW	RCT/1	0		-2	0		72	55	76.4	68	49	72.1	RR	0.94	0.78-1.15	C	9
Muscle volume	RCT/3	-2	-2	-2	0	-2	72			74			RR	0.93	0.51-1.35	C	6
Duration of ventiration																	4
Length of ICU stay																	4

CQ18-2

PICO

Patients (P): Septic patients or critically ill patients in ICU
Intervention (I): Early rehabilitation (+)
Control (C): Early rehabilitation (-)
Outcome (O): Incidence of ICU-AW, motor function, 6MWD, MRC, SF-36PF, EQ5D, HADS, duration of intubation, duration of ventilation

Search terms

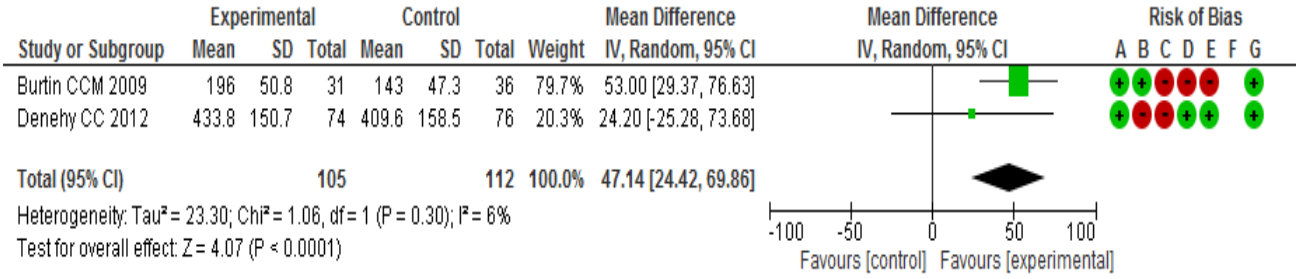
1. (((((((("critical ill"[tw] OR "critical illness"[tw] OR "critical care"[tw] OR "intensive care"[tw] OR "mechanical ventilation"[tw] OR "mechanical ventilated"[tw] OR "Postoperative care"[tw] OR sepsis OR "septic shock" OR "critical illness" OR infection)))) AND (((rehabilitation[tw] OR "physical therapy"[tw] OR physiotherapy[tw] OR exercise[tw] OR mobilization[tw] OR "mobility intervention"[tw] OR "Rehabilitation Nursing"[Mesh] OR "Physical and Rehabilitation Medicine"[Mesh] OR "Critical Illness/rehabilitation"[MAJR] OR "Activities of Daily Living"[Mesh] OR "Quality of Life"[tw] OR "Electrical muscle stimulation"[tw] OR "Stress Disorders, Post-Traumatic/prevention and control"[MAJR] OR fast-track[tw] OR "muscle training"[tw]))))) AND ("ICU-acquired weakness" OR "post-intensive care syndrome" OR "motor function" OR "Physical Functioning" OR "functional status" OR "physical function" OR "ventilator days" OR "quality of life" OR (walking OR walk) OR muscle OR psychological OR polyneuromyopathy' OR ("length of stay" OR "length of ICU stay" OR "length of hospital stay" OR "intubation period" OR "duration of mechanical ventilation") OR re-admission OR "functional outcome" OR dyspnea OR oxygenation OR "ventilator-associated pneumonia" AND (((randomized OR randomised OR randomly OR "Controlled Clinical Trial"[pt]))))) AND (((english[la] OR japanese[la])))) AND adult) NOT (((Review[ptyp] OR Meta-Analysis[ptyp] OR Trials[jo] OR Animals OR case reports[ptyp])))

Body of the evidence

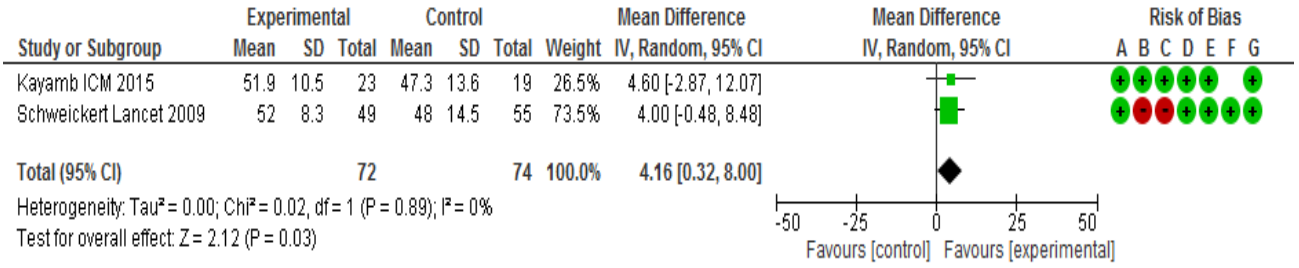
							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance
							Denominator	Numerator	(%)	Denominator	Numerator	(%)					
ICUAW (Incidence)	RCT/1	0		-2	0		55	39	70.9	49	28	57.1	RR	0.81	0.60-1.08	C	9
ICUAW (motor function)	RCT/2	-1	-1	-1	-1	-1							Hedge's g	0.46	0.13-0.78	C	5
ICUAW (6MWD)	RCT/2	-1	0	-1	-1	0							RR	47.14	24.42-69.86	C	8
ICUAW (MRC)	RCT/2	-1	0	-1	-1	0							RR	4.16	0.23-8.00	C	8
PICS (SP36-PF)	RCT/2	-1	-2	-2	-1	0							RR	-0.31	-5.78- 515	C	6
PICS (EQ5D)	RCT/1	-1		-2	-1								RR	5	-0.81-10.81	C	6
PICS (HAS/HADS)	RCT/2	-2	0	-2	-1	-1	33	10	30.3	38	7	18.4	RR	0.64	0.20-2.09	C	6
Duration of intubation	RCT/1	-2		-2	-2								RR	0.2	-1.91-2.31	C	5
Duration of ventilation	RCT/2	-1	-1	-1	-2	-1							RR	-2.29	-4.57-0.00	C	5

Results of meta-analysis

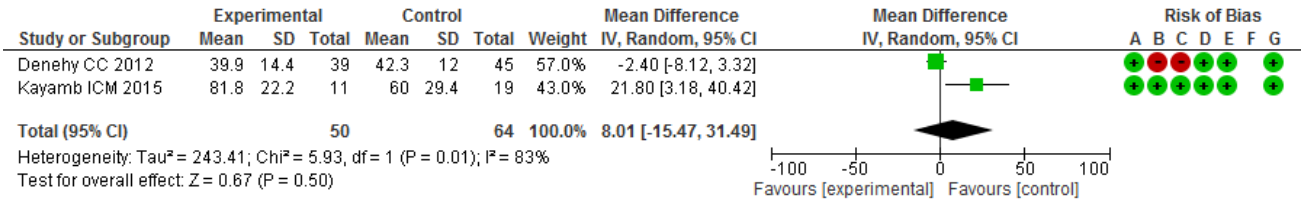
1. 6WMD



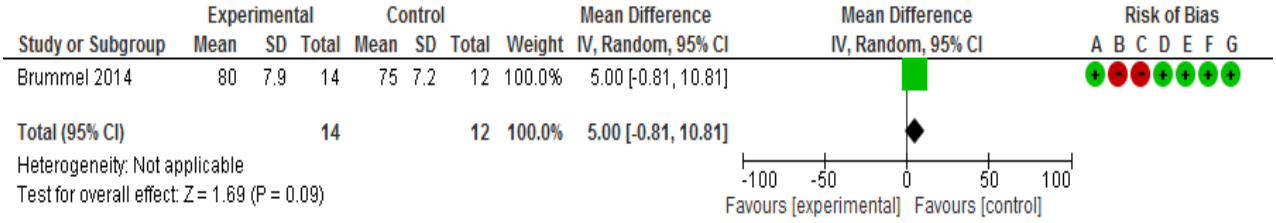
2. MRC



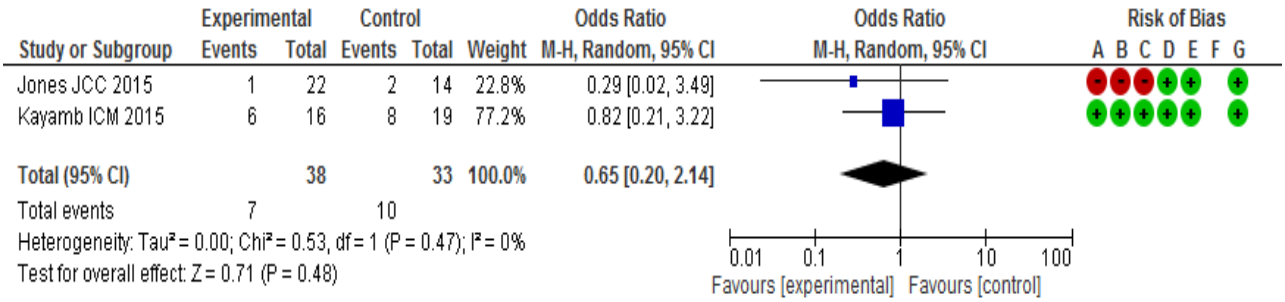
3. SF-36PF



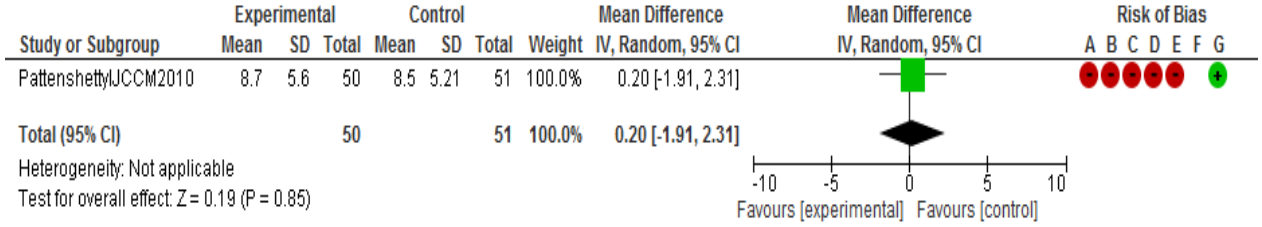
4. EQ5D



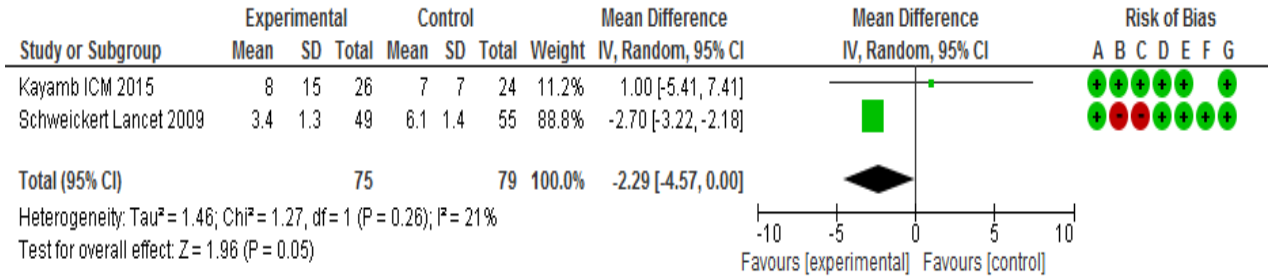
5. HADS



6. Duration of intubation



7. Duration of ventilation



CQ19-5

PICO

Patients (P): Pediatric septic patients
Intervention (I): Blood culture bottle for pediatrics
Control (C): Blood culture bottle for adults
Outcomes (O): Sensitivity, duration of administration and dose of antibiotics, complication rate

CQ19-6

PICO

Patients (P): Pediatric septic shock patients
Intervention (I): Particular cardiovascular agents
Control (C): Other cardiovascular agents
Outcomes (O): Mortality, length of ICU stay, complication rate

Search terms

1. (“sepsis” OR “severe sepsis” OR “septic shock” OR shock) AND (pediatric OR paediatric OR child* OR infant OR neonate) AND (Vasopressor OR Norepinephrine OR Vasopressin OR inotropic OR dobutamine OR dopamine OR vasodilator OR milrinone OR epinephrine OR levosimendan OR catecholamine OR amrinone OR terlipressin) AND (meta-analysis OR “randomized controlled trial”)

CQ19-7

PICO

Patients (P): Pediatric septic patients
Intervention (I): Hemodynamic management using CRT
Control (C): Hemodynamic management using other parameters
Outcomes (O): Mortality, organ failure after 24h (PELOD, MODS, et al.)

Search terms

Sepsis AND (pediatric OR children) AND (“capillary refill time” OR “capillary refill” OR CRT) AND (randomized OR randomized OR randomly OR review OR meta-analysis)

CQ19-8

PICO

Patients (P): Pediatric septic patients
Intervention (I): Hemodynamic management using $S_{CV}O_2$ or lactate
Control (C): Hemodynamic management using other parameters
Outcomes (O): Mortality, organ failure after 24h (PELOD, MODS, et al.)

Search terms

1. sepsis AND (pediatric OR children) AND (lactate OR “lactic acid” OR ScvO2 OR "central venous saturation" OR "central venous oxygen saturation") AND (randomized OR randomised OR randomly OR review OR meta-analysis)
2. (severe sepsis OR septic shock) AND (ScvO2 OR central venous oxygen saturation OR lactate) AND (child OR pediatric) AND (meta-analysis OR review OR clinical) AND (english[la] OR japanese[la])
3. (sepsis OR septic shock) AND (child OR children OR pediatric) AND (ScvO2 OR central venous oxygen saturation OR central venous saturation OR venous saturation OR lactate) AND randomized controlled trial[pt] AND (meta-analysis[pt] OR systematic[sb] OR review[pt]) AND humans[mh] AND (english[la] OR japanese[la]) AND has abstract[tw]

CQ19-9

PICO

Patients (P): Pediatric septic patients
Intervention (I): Hemoglobin threshold of 7 g/dL for red-cell transfusion
Control (C): Hemoglobin threshold of 9.5 g/dL for red-cell transfusion
Outcomes (O): Mortality, length of ICU stay

Search terms

1. SEARCH（((sepsis or severe sepsis or septic shock）AND （child or pediatrics)） AND（red blood cell transfusion）AND （controlled clinical trial OR meta-analysis OR randomized controlled trial OR systematic reviews）Filters : published in the last 5 years ; Humans ; English ; Child : birth-18 years

CQ19-10

PICO

Patients (P): Pediatric septic shock patients
Intervention (I): Steroid (+)
Control (C): Steroid (-)
Outcomes (O): Mortality, recovery rate from shock, complication

Search terms

1. ((("severe sepsis") OR "septic shock")) AND (((pediatric) OR child*) OR infant) ((((((steroid) OR corticosteroid) OR glucocorticoid) OR hydrocortisone) OR prednisolone) OR methylprednisolone) OR dexamethasone Filters: meta-analysis or systematic review or practice guideline or RCT, English or Japanese, Human, 5 years
2. ((((((sepsis) OR septic shock)) AND ((steroid) OR corticosteroid)) AND ((pediatric) OR neonate)) AND (((meta-analytic) OR systematic) OR review)) AND ((english) OR japanese)
3. ((((("severe sepsis") OR "septic shock")) AND (((pediatric) OR child*) OR infant))) AND (((((((steroid) OR corticosteroid) OR glucocorticoid) OR hydrocortisone) OR prednisolone) OR methylprednisolone) OR dexamethasone, Filters: Randomized Controlled Trial

Body of the evidence

							The numbers of persons at risk (outcome rate)										
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	RCT/1	-2		-2	-2		19	6	32.0	19	7	37.0	RR	1.17	0.48-2.83	D	9	
Recovery rate from shock	RCT/1	-2		-2	-2		19			19						D	6	1)
Complication	RCT/1	-2		-2	-2		19	1	5.0	19	2	11.0	RR	2	0.20-20.2	D	7	2)

1) This RCT reported duration of shock as median value; Intervention group 49.5 hr [26-144] vs Control group 70 hr [12-269] (P=0.65).
2) Bleeding and secondary infection.

CQ19-11

PICO

Patients (P): Pediatric septic shock patients
Intervention (I): Renal replacement therapy (+)
Control (C): Renal replacement therapy (-)
Outcomes (O): Mortality, duration of ventilation, complication

Search terms

1. SEARCH（（（sepsis OR severe sepsis OR septic shock）AND （children OR pediatric OR child OR infant OR newborn） AND （non renal indication OR renal replacement therapy OR hemofiltration OR hemodialysis OR PMX-DHP OR plasma exchange）） NOT （animals OR murine OR rat OR pig））AND（controlled clinical trial OR meta-analysis OR randomized controlled trial OR systematic reviews）AND English）

CQ19-12

PICO

Patients (P): Pediatric septic patients
Intervention (I): Intravenous immunoglobulin (+)
Control (C): Intravenous immunoglobulin (-)
Outcomes (O): Mortality, complication, length of hospital stay

Search terms

1. ((("severe sepsis") OR "septic shock")) AND (((pediatric) OR child*) OR infant) ((immunoglobulin) OR immune globulin) OR gamma globulin, Filters: meta-analysis or systematic review or practice guideline or RCT, English or Japanese, Human, 5 years
2. (((((("severe sepsis") OR "septic shock")) AND (((pediatric) OR child*) OR infant))) AND (((immunoglobulin) OR immune globulin) OR gamma globulin)
3. (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR "severe sepsis"[All Fields] OR "septic shock"[All Fields]) AND (("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR child*) OR ("infant"[MeSH Terms] OR "infant"[All Fields]) OR neonatal[All Fields])) AND (immune[All Fields] OR ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "immunoglobulin"[All Fields]) OR ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields]) OR ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR ("immune"[All Fields] AND "globulin"[All Fields]) OR "immune globulin"[All Fields]) OR (immuno[All Fields] AND ("globulins"[MeSH Terms] OR "globulins"[All Fields])) OR ("gamma-globulins"[MeSH Terms] OR "gamma-globulins"[All Fields] OR ("gamma"[All Fields] AND "globulin"[All Fields]) OR "gamma globulin"[All Fields]) OR "gamma globulin"[All Fields] OR ("gamma-globulins"[MeSH Terms] OR "gamma-globulins"[All Fields] OR ("gamma"[All Fields] AND "globulins"[All Fields]) OR "gamma globulins"[All Fields]) OR "gamma globulins"[All Fields]) AND ((meta-analysis[ptyp] OR systematic[sb] OR randomized controlled trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang])

CQ19-13

PICO

Patients (P): Pediatric septic patients
Intervention (I): Intensive insulin therapy
Control (C): Conventional blood glucose management
Outcomes (O): Mortality, incidence of hypoglycemia, incidence of secondary infection

Search terms

1. (((((("severe sepsis") OR "septic shock")) AND (((pediatric) OR child*) OR infant))) OR (((((("critically ill") OR "critical care") OR "intensive care")) AND (((pediatric) OR child*) OR infant)) ("intensive insulin therapy") OR "tight glycemic control" Filters: meta-analysis or systematic review or practice guideline or RCT, English or Japanese, Human, 5years
2. ("intensive insulin therapy" OR "tight glycemic control" OR "glucose control") AND (pediatric OR child OR infant)
3. (severe sepsis OR septic shock OR critically ill OR critical care OR intensive care) AND (pediatric OR child OR infant) AND (tight glycemic control OR intensive insulin therapy) AND (meta-analysis[pt] OR randomized controlled trial[pt] OR guideline[pt] OR systematic[sb]) AND humans[mh] AND (english[la] OR japanese[la]) AND has abstract[tw]

Body of the evidence

							The numbers of persons at risk (outcome rate)											
Outcome	Design /number	RoB	Inconsistency	Imprecision	Indirectness	Others	Control group			Intervention group			Type	Value	95%CI	Strength	Importance	Comment
							Denominator	Numerator	(%)	Denominator	Numerator	(%)						
Mortality	RCT/4	-1	0	-1	-1	0	1646	73	4.4	1579	50	3.2	OR	0.792	0.547-1.146	B	9	1)
Hypoglycemia	RCT/4	-1	0	-1	-1	0	1653	32	1.9	1582	167	10.6	OR	6.14	2.735-13.784	B	8	2)
Secondary infection	RCT/4	-1	-2	-1	-1	0	1653	227	13.7	1582	168	10.6	OR	0.763	0.591-0.985	D	7	3)

1) In Jeschke (2010) RCT, number of patients who died within 30 days was unclear.
2) Definition of hypoglycemia in Macrae (2014) RCT was different from other studies.
3) Definitions of secondary infection among 4 RCTs were differences.

CQ19-14

PICO

Patients (P): Pediatric septic shock patients
Intervention (I): Management using ACCM-PALS algorism
Control (C): Management not using ACCM-PALS algorism
Outcomes (O): Mortality, length of hospital stay

Search terms

1. “sepsis” OR“ shock, septic” AND “American College of Critical Care Medicine guidelines” Filters activated: meta-analysis or systematic review or practice guideline or RCT, Human, 5years, Child: birth-18 years

CQ19-15

PICO

Patients (P): Pediatric septic shock patients
Intervention (I): Intraosseus access (+)
Control (C): Intraosseus access (-)
Outcomes (O): Time until establishing of access, successful rate

Search terms

1. “sepsis” OR“ shock, septic” AND“ infusions, intraosseous” Filters activated: meta-analysis or systematic review or practice guideline or RCT or clinical trial, Human, 5years, Child: birth-18 years

Revision lists

The first edition was published at 5th October 2017