SUPPLEMENTAL DIGITAL CONTENT 2

CONTENTS

PICO QUESTIONS

In patients with sepsis or septic shock, should we use crystalloid with supplemental albumin for initial resuscitation versus crystalloids alone?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Crystalloids and supplemental Albumin	Crystalloids alone	Mortality Renal replacement therapy
In patients with sepsis or septic shock, should we be using HES versus crystalloids for acute resuscitation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	HES	Crystalloids	Mortality Renal replacement therapy
In patients with severe sepsis or septic shock, should we be using gelatin versus crystalloid for acute resuscitation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Gelatins	Crystalloids	Mortality Renal replacement therapy
In patients with sepsis or septic shock, should we use using balanced crystalloid solutions versus normal saline?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis or septic shock	Balanced crystalloid Solutions	Crystalloids	Mortality Renal Replacement Therapy
In patients with sepsis or septic shock, should we recommend using repeated fluid challenge based on hemodynamic variables?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock, that are suspected to be hypovolemic	Repeated fluid challenge as long guided by hemodynamic improvement in dynamic or static variables	Not continue fluid challenges or use alternative criteria	Mortality
In patients with sepsis or septic shock, should we use early goal directed therapy protocol for resuscitation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	EGDT protocol	Other protocols or physician guided therapy	Mortality
In patients with sepsis or septic shock with elevated serum lactate, should we incorporate resuscitation goals aiming to normalize lactate levels?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock and elevated lactate level	Resuscitation targeting normalization of lactate levels	Resuscitation targeting other goals Not including lactate	Mortality
In patients with septic shock requiring vasopressors, should we target mean arterial pressure (MAP) of 65 mmHg vs. higher MAP?			

Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock requiring vasopressors	MAP of 65 mmHg	MAP above 65 mmHg	Mortality
In patients with septic shock requiring vasopressors, should we use norepinephrine versus other agents?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock requiring vasopressors	Norepinephrine	Other vasopressors	Mortality
In patients with septic shock not responding to single vasopressors, should we add epinephrine?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock not responding to single vasopressor	Addition of epinephrine	Other vasopressors	Mortality Arrhythmia
In patients with septic shock requiring vasopressors, should we use norepinephrine alone versus combination with vasopressin?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock requiring vasopressin	Norepinephrine alone	Norepinephrine and Vasopressin	Mortality Renal replacement therapy Arrhythmia Limb ischemia
In patients with septic shock requiring vasopressors, should we use of vasopressin versus other agents?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with septic shock requiring vasopressors	Vasopressin	Other agents	Mortality Renal replacement therapy Arrhythmia Limb ischemia
In patients with septic shock requiring vasopressors, should we use dopamine versus other agents?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock requiring vasopressors	Dopamine	Other agents	Mortality Arrhythmia
In patients with septic shock and persistent hypoperfusion, should we use alternative inotropic agents to increase cardiac output?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock with evidence of persistent hypoperfusion and cardiac dysfunction	levosimendan	Dobutamine	Mortality
In patients with sepsis or septic shock, should we use dynamic parameters (versus static parameters) to predict fluid responsiveness?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Dynamic parameters	Static parameters	Improvement in hemodynamics
Should hospitals use formal resourced performance improvement program for sepsis including sepsis screening for acutely ill, high risk patients?			

Population	Intervention	Comparator	Outcome(s)
Adult acutely ill patients with sepsis	Hospital-based performance programs	No program	Mortality Costs
In patients with sepsis, should we use broad empiric antimicrobial coverage?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis	Antimicrobials with activity against all likely pathogens (broad empiric coverage)	Narrow coverage	Mortality
In patients with septic shock, should we administer empirically appropriate antimicrobials (within one hour of recognition)?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock	Administer empirically appropriate within 1 hour	Administration after 1 hour of recognition	Mortality
In patients with sepsis, should we administer empirically appropriate antimicrobials (within one hour of recognition)?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis	Administer empirically appropriate antimicrobials within 1 hour	Administration after 1 hour of recognition	Mortality
In critically ill septic patients, should we implement pharmacokinetic dosing optimization for each antimicrobial?			
Population	Intervention	Comparator	Outcome(s)

Critically ill adult septic patients	Pharmacokinetic dosing optimization	Standard dosing	Mortality Clinical cure Microbiologic cure
In patients with sepsis and neutropenia, should we use empiric combination antimicrobial therapy versus mono-therapy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis and neutropenia	Combination empiric antimicrobial therapy	Single empiric antimicrobial therapy	Mortality
In patients with sepsis at high risk for multi-drug resistant pathogens, should we use empiric combination antibiotic therapy (versus mono-therapy) until sensitivities are determined?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis caused by difficult-to-treat, multidrug-resistant pathogens, such as *Acinetobacter and Pseudomonas* spp.	Combination antibiotic therapy	monotherapy	Mortality
In patients with septic shock, should we use empiric double-coverage antibiotic agents until hemodynamic stabilization and pathogen identification?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock	Combination empiric antibiotic therapy with a beta-lactam and an aminoglycoside or fluoroquinolone	Empiric monotherapy	Mortality

In patients with sepsis who are receiving antimicrobials, should we assess for de-escalation of therapy daily?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis who are on antimicrobials	Assess antimicrobials daily for de-escalation	Continue antimicrobial course without daily assessment	Mortality Drug resistance Adverse events
In patients with uncomplicated infections causing sepsis or septic shock, should we recommend a duration of therapy of 7-10 days versus longer course?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Antimicrobial therapy for 7-10 days	Therapy for >10 days	Mortality
In patients with sepsis or septic shock who are receiving empiric combination of antimicrobials should we assess for de-escalation of therapy daily?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock who are on empiric combination of antimicrobials (excluding patients with endocarditis)	De-escalation in 3 to 5 days to the most appropriate single antimicrobial agent as soon as the susceptibility profile is known and/or clinical stability is achieved.	Continue antimicrobial course without daily assessment	Mortality Drug resistance Adverse events
In patients with sepsis, should we use procalcitonin levels to support de-escalation of antimicrobial therapy?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with a diagnosis of sepsis	Use procalcitonin levels or similar biomarkers to assist in empiric antimicrobial discontinuation	Not use biomarkers to assist in empiric antimicrobial discontinuation	Mortality Drug resistance Adverse events
In patients with sepsis or septic shock, should we attempt early (within 12 hours) source control?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock, and remediable source of infection is identified	Source control intervention within first 12 hours	Intervention beyond 12 hours	Mortality
In patients with severe inflammatory state of non-infectious origin should we use systemic prophylactic antimicrobials?			
Population	Intervention	Comparator	Outcome(s)
Adult critically ill patients with severe inflammatory state of non-infectious cause	Prophylactic antimicrobials	No prophylaxis	Mortality
In patients with septic shock, should we use intravenous corticosteroids (versus not)?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with septic shock	Intravenous corticosteroids	Placebo or no intervention	Mortality
In patients with sepsis, should we use plasma filtration therapy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis	Blood purification	No Blood purification	Mortality Vasopressor use

			Organ dysfunction
In patients with sepsis, should we use a hemoperfusion therapy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis	plasma filtration therapy	No plasma filtration therapy	Mortality Vasopressor use Organ dysfunction
In patients with sepsis, should we use a restrictive transfusion strategy versus liberal transfusion?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis	Restrictive blood transfusion threshold (< 7-8 g/dL hemoglobin)	Liberal blood transfusion threshold (9-10 g/dL)	Mortality Amount of blood transfused Myocardial ischemia
In patients with sepsis and anemia, should we use erythropoietin to treat anemia?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis and anemia	erythropoietin	No erythropoietin	Mortality VTE
In non-bleeding patients with sepsis and coagulation abnormalities, should we use prophylactic FFP?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis and laboratory coagulation abnormalities (prolonged PT, PTT), non-bleeding	Fresh frozen plasma	No FFP	Mortality Major bleeding
In non-bleeding patients with sepsis and thrombocytopenia, should we use prophylactic platelet transfusion based on specific platelet levels?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis and thrombocytopenia, non-bleeding	Platelet transfusion for specific threshold (platelet counts </= 10,000/mm3, </= 20,000/mm3 if bleeding risk, or </= 50,000/mm3 active bleeding, surgery or invasive procedures)	Different platelet transfusion threshold	Mortality Major bleeding
In adult patients with sepsis or septic shock, should we use intravenous immunoglobulins (versus not)?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Intravenous immunoglobulins	Placebo or no intervention	Mortality
In adult patients with sepsis or septic shock, should we antithrombin (versus not)?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis or septic shock	Antithrombin	Placebo or no intervention	Mortality Major bleeding
Should we use stress ulcer prophylaxis in critically ill septic patients?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock and risk factors for stress ulcer	PPIs or H2RA	Placebo or No prophylaxis	Clinically important bleeding Pneumonia C. difficile infection Mortality ICU length of stay
Should we use PPIs (versus H2RA) for stress ulcer prophylaxis in critically ill septic patients?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock and risk factors for stress ulcer	PPIs	H2RA	Clinically important bleeding Pneumonia C. difficile infection Mortality ICU length of stay
Should we use pharmacologic VTE prophylaxis (UFH or LMWH) in critically ill patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)

Adult, critically ill patients with sepsis or septic shock	Pharmacologic prophylaxis (UFH or LMWH)	Placebo or No Prophylaxis	Mortality DVT PE Major Bleeding
Should we use LMWH (versus UFH) for VTE prophylaxis in critically ill patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	prophylactic LMWH	prophylactic UFH	Mortality DVT PE Major Bleeding
Should we use mechanical VTE prophylaxis in critically ill patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Mechanical prophylaxis (intermittent compression devices)	No prophylaxis	Mortality DVT PE
Should we use a combination of pharmacologic and mechanical prophylaxis vs. either alone in critically ill patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult, critically ill patients with severe sepsis or septic shock	Pharmacologic prophylaxis (UFH or LMWH) and mechanical prophylaxis	Pharmacologic or mechanical prophylaxis alone	Mortality DVT PE Major Bleeding

Should we use early TPN versus early full enteral feeding in critically ill patients with sepsis or septic shock who can be fed enterally?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock without contraindications for enteral feeding	Early TPN +/- trophic enteral feeding (started ≤48 hrs) in the first 7 days	Early full enteral feeding alone (started ≤48 hrs and to goal ≤72 hrs)	Mortality Infections ICU length of stay
Should we use early TPN versus no or early trophic enteral feeding in critically ill patients with sepsis or septic shock who have contraindications for early full enteral feeding?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock with contraindications for early full enteral feeding	Early TPN +/- trophic enteral feeding in the first 7 days	No or early trophic enteral feeding alone, or enteral feeding according to usual/standard care	Mortality Infections ICU length of stay
Should we use early full enteral feeding versus no initial enteral feeding (except IV glucose/dextrose) in critically ill patients with sepsis or septic shock without contraindications to enteral feeding?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock without contraindications for enteral feeding	Early full enteral feeding	Fasting or intravenous glucose/dextrose with delayed enteral feeding started >48 hours	Mortality Infections ICU length of stay
Should we use early full enteral feeding versus early trophic enteral feeding in patients with sepsis or septic shock without contraindications to enteral feeding?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis or septic shock without contraindications for enteral feeding	Early trophic feeding (trophic ≤70% of standard goal)	Early full enteral feeding	Mortality Infections ICU length of stay
Should we use early trophic enteral feeding versus no early enteral feeding (except IV glucose/dextrose) in patients with sepsis or septic shock without contraindications to enteral feeding?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock without contraindications for enteral feeding	Early trophic feeding	Fasting or IV glucose/dextrose with delayed enteral feeding started >48 hrs	Mortality Infections ICU length of stay
Should we use omega-3 supplementation in patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Enteral or parenteral feeding with omega-3 as an immunomodulating supplement	Enteral or parenteral feeding alone	Mortality Infections ICU length of stay
Should we measure gastric residuals when enterally feeding critically ill patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock receiving enteral feeding	Measuring gastric residuals and withholding feeding when residuals exceed a given threshold	No measurement of gastric residuals	Mortality Aspiration pneumonia ICU length of stay
Should we use enteral feeding via a gastric tube versus a post-pyloric tube in patients with sepsis or septic shock?			

Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock receiving enteral feeding	Enteral feeding with a gastric tube	Enteral feeding with a post pyloric feeding tube	Mortality Aspiration or aspiration pneumonia ICU length of stay
Should we use of prokinetic agents for enterally fed patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock who can be enterally fed	Use of pro-kinetic agents (metoclopramide, domperidone, erythromycin)	Placebo; or intervention	Mortality Aspiration or aspiration pneumonia ICU length of stay Successful post pyloric tube placement
Should we use selenium therapy in patients with severe sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Selenium in therapeutic doses	Placebo or No selenium	Mortality Pneumonia ICU length of stay DMV
Should we recommend glutamine therapy in critically ill patients with severe sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis or septic shock	Glutamine in therapeutic doses	Placebo or No glutamine	Mortality ICU LoS DMV
Should we use* arginine *therapy in patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Arginine in therapeutic doses	Placebo or No arginine	Mortality ICU LoS DMV
Should we use carnitine therapy patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Carnitine in therapeutic doses	Placebo or No carnitine	Mortality ICU LoS DMV
Should we use intensive insulin therapy in patients with sepsis or septic shock?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Intensive insulin therapy	Conventional insulin therapy	Mortality Hypoglycemia
Should we use arterial blood glucose level (versus to point of care resting) in critically ill patients with severe sepsis or septic shock on insulin infusion?			

Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock	Arterial glucose level measurement	Point of care testing	Accuracy of glucose level
In patients with sepsis, should we recommend discussion of goals of cares and prognosis with family?			
Population	Intervention	Comparator	Outcome(s)
Adult, critically ill patients with sepsis or septic shock	Goals of care and prognosis discussed with patients and families	No discussion	Communication and understanding Family satisfaction Stress Anxiety Depression Facilitated decision-making ICU LOS for moribund patients
In patients with sepsis, should we recommend incorporating palliative and end-of-life care?			
Population	Intervention	Comparator	Outcome(s)
Adult, critically ill patients with sepsis or septic shock	Palliative and end-of-life planning incorporated into treatment in ICU	Limited use of palliative or end-of-life care in ICU	Percent of patients receiving a palliative care consult Percent of patients receiving end-of-life care in the ICU

			Withdrawal of life support/DNR rates Family hospital anxiety and depression score Family satisfaction Family member quality of dying score Nurse quality of dying score Health care provider satisfaction score ICU LOS for moribund patients
Should we recommend addressing goals of care early (within 72 hours) during ICU stay?			
Population	Intervention	Comparator	Outcome(s)
Adult, critically ill patients with sepsis or septic shock	Goals of care addressed within 72 h of admission, as early as feasible	Address goals of care after 72 h	Family care conference held within 72 h of ICU admission Communication and understanding Family satisfaction Facilitated decision-making

			Staff moral distress, staff burnout ICU LOS
In patients with sepsis induced ARDS, should we use low tidal volume ventilation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis induced ARDS	Target Vt of 6 mL/kg PBW	Target Vt of 12 mL/kg PBW	Mortality Duration of mechanical ventilation
In patients with sepsis induced ARDS who are mechanically ventilated, should we use plateau pressures less than 30 cm H2O?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis induced ARDS	Upper limit of plateau pressure: 30 cmH2O	Plateau pressure > 30 cmH2O	Mortality Barotrauma
In patients with sepsis induced ARDS who are mechanically ventilated, should we use high PEEP strategy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced moderate to severe ARDS	“Higher” PEEP	“Lower” PEEP	Mortality
In patients with sepsis induced ARDS, should we use recruitment maneuvers?			
Population	Intervention	Comparator	Outcome(s)

Adult patients with sepsis-induced ARDS and refractory hypoxemia	Recruitment maneuvers	No recruitment maneuvers	Mortality Oxygenation
In patients with sepsis induced severe ARDS, should we use prone ventilation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced severe ARDS	Prone ventilation	No proning	Mortality Oxygenation Complications
In patients with sepsis who are mechanically ventilated, should we elevate the head of the bed?			
Population	Intervention	Comparator	Outcome(s)
Mechanically ventilated adult patients with sepsis	Head of bed between 30 and 45 degrees	No head of bed elevation	Mortality Pneumonia
In patients with sepsis induced ARDS, should we use non-invasive ventilation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS	Noninvasive ventilation (NIV)	Invasive mechanical ventilation	Mortality

In patients with sepsis who are mechanically ventilated and ready for weaning, should we use weaning protocol versus physician guided weaning?			
Population	Intervention	Comparator	Outcome(s)
Mechanically ventilated adult patients with sepsis who are can tolerate weaning from mechanical ventilation	Weaning protocol	No protocol	Mortality Successful extubation Duration of mechanical ventilation
In patients with sepsis who are mechanically ventilated and ready for weaning, should we use spontaneous breathing trials (SBT)?			
Population	Intervention	Comparator	Outcome(s)
Mechanically ventilated adult patients with sepsis who are can tolerate weaning from mechanical ventilation	Regular SBT	No SBT	Mortality Successful extubation Duration of mechanical ventilation
In patients with sepsis induced ARDS, should we use pulmonary artery catheter (PAC)?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS	Use of PAC	No PAC	Mortality Duration of mechanical ventilation

In patients with sepsis induced ARDS, should we use conservative fluid strategy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS, and no signs of tissue hypoperfusion	"Conservative" fluid strategy	"Liberal" fluid strategy	Mortality Duration of mechanical ventilation ICU length of stay
In patients with sepsis induced ARDS, should we use inhaled Beta agonists?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS and no bronchospasm	Use of inhaled Beta agonists	No Beta agonists or placebo	Mortality Duration of mechanical ventilation
In patients with sepsis induced ARDS, should we use ECMO treatment?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS	ECMO/expert therapy	Usual Care	Mortality Duration of mechanical ventilation
In patients with sepsis induced ARDS, should we use High Frequency Oscillation (HFO) versus conventional ventilation?			

Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced ARDS	HFO ventilation	Conventional Mechanical Ventilation	Mortality Duration of mechanical ventilation
In patients with sepsis induced respiratory failure without ARDS, should we use low tidal volume ventilation?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis-induced respiratory failure	Low tidal volume ventilation	Conventional Mechanical Ventilation	Mortality Duration of mechanical ventilation Development of ARDS
In mechanically ventilated patients with sepsis, should we use sedation targets?			
Population	Intervention	Comparator	Outcome(s)
Adult mechanically ventilated patients with sepsis	Sedation targets “specific endpoints”	No targets used to guide sedation	Mortality Duration of mechanical ventilation ICU length of stay
In patients with severe ARDS who are mechanically ventilated, should we use neuromuscular blocking agents?			

Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis induced ARDS	Neuromuscular blocking agent	Placebo	Mortality Ventilator-free days ICU-acquired weakness Barotrauma
In patients with sepsis and indication for hemodialysis, should we use CRRT versus intermittent hemodialysis?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis and acute kidney injury requiring dialysis	CRRT	IHD	Mortality
In patients with sepsis and AKI with no indication for hemodialysis, should we use renal replacement therapy versus not?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis and acute kidney injury without indication for hemodialysis	Renal replacement therapy (early initiation of renal replacement therapy)	No dialysis	Mortality
In patients with sepsis or septic shock and hypoperfusion-induced lactic acidosis, should we use sodium bicarbonate therapy?			
Population	Intervention	Comparator	Outcome(s)
Adult patients with sepsis or septic shock and hypoperfusion-induced lactic acidosis	Intravenous sodium bicarbonate	Placebo or no intervention	Mortality

HES: Hydroxyethyl starches; EGDT: Early goal directed therapy; MAP: Mean arterial pressure; PT: prothrombin time; PTT: Partial thromboplastin time; FFP: Fresh frozen plasma; PPI: Proton pump inhibitor; H2RA: Histamine 2 receptor antagonist; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; TPN: Total parenteral nutrition; ICU: Intensive care unit; DMV: Duration of mechanical

ventilation; LOS: length of stay; DNR: Do not resuscitate; Vt: Tidal volume; PBW: Per body weight; PEEP: Peak end expiratory pressure; SBT: Spontaneous breathing trial; PAC: Pulmonary arterial catheter; ECMO: Extra-corporeal membrane oxygenation; HFO: High frequency oscillation; CRRT: Continuous renal replacement therapy

HEMODYNAMICS

Table 1. Crystalloid with supplemental Albumin compared to Crystalloids alone for resuscitating patients with sepsis or septic shock

Author(s): Alhazzani W, Osborne T, Antonelli M
Question: Crystalloid with supplemental Albumin compared to Crystalloids alone for resuscitating patients with sepsis or septic shock
Setting: ICU
Bibliography: Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-21. doi:10.1056/NEJMoa1305727.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Crystalloid with supplemental Albumin**	**Crystalloids alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
28 days Mortality in all patients												
1	randomized trials	not serious	not serious	serious [1]	not serious [2]	none	285/895 (31.8%)	288/900 (32.0%)	**RR 1.00** (0.87 to 1.14)	**0 fewer per 1,000** (from 42 fewer to 45 more)	⊕⊕⊕◯ MODERATE	CRITICAL
90 days Mortality (all patients)												
1	randomized trials	not serious	not serious	serious [1]	not serious	none	365/888 (41.1%)	389/893 (43.6%)	**RR 0.94** (0.85 to 1.05)	**26 fewer per 1,000** (from 22 more to 65 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
90 days Mortality (subgroup with septic shock)												

1	randomized trials	not serious [3]	not serious	serious [1]	serious [4]	none	243/557 (43.6%)	281/564 (49.8%)	**RR 0.87** (0.77 to 0.99)	**65 fewer per 1,000** (from 5 fewer to 115 fewer)	⨁⨁◯◯ LOW	CRITICAL
Renal Replacement Therapy												
1	randomized trials	not serious	not serious	serious [1]	serious [5]	none	222/903 (24.6%)	194/907 (21.4%)	**RR 1.15** (0.97 to 1.36)	**32 more per 1,000** (from 6 fewer to 77 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

1. We downgraded the quality of evidence for indirectness by one level, the administration of albumin in the intervention group was after the first 6 hours, as early goal directed therapy was implemented for all patients, therefore, we considered this as indirectness in the intervention
2. Although the confidence interval includes 13% relative risk reduction, and 14% relative risk increase in mortality, we decided not to downgrade for imprecision because the CI was narrow and point estimate was 1
3. Although this was a post hoc subgroup analysis, we decided not to downgrade the quality of evidence for risk of bias because randomization was stratified by presence of shock
4. We downgraded for imprecision by one level, the upper limit of the CI was 0.99 which include negligible benefit
5. We downgraded the quality of evidence by one level for imprecision, the CI contains significant benefit and harm

Table 2. HES compared to Crystalloids in patients with severe sepsis or septic shock

Author(s): Perner A, Alhazzani W
Date: December 2 2015
Question: HES compared to Crystalloids in patients with severe sepsis or septic shock
Setting: Intensive Care Unit (ICU)
Bibliography: Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013 Feb 15;346:f839.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HES**[1]	**Crystalloids**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: Long-term follow-up, >28 days)												
4	randomized trials	not serious	not serious	not serious	not serious [2]	none	533/1591 (33.5%)	478/1565 (30.5%)	**RR 1.11** (1.01 to 1.22)	**34 more per 1000** (from 3 more to 67 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Renal Replacement Therapy												
5	randomized trials [3]	not serious	not serious	not serious	not serious	none	136/650 (20.9%)	101/661 (15.3%)	**RR 1.36** (1.08 to 1.72)	**55 more per 1000** (from 12 more to 110 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Serious Adverse Events												

4	randomized trials	not serious	not serious	not serious	not serious [1]	none	100/533 (18.8%)	76/536 (14.2%)	**RR 1.30** (1.03 to 1.67)	**43 more per 1000** (from 4 more to 95 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

MD: mean difference; RR: relative risk; HES – Hydroxyethyl starch; CI: confidence interval

1. HES 130/0.38-0.45
2. Although the lower limit of confidence interval was close to 1, we did not downgrade for imprecision because the signal for harm is consistent with other outcomes and even small increase in harm is considered significant
3. In one study (Dolecek 2009) albumin 20% was used as a comparison, but there were no RRT events

Table 3. Gelatin compared to Crystalloids in patients with sepsis or septic shock

Author(s): Rochwerg B, Alhazzani W
Question: Gelatin compared to Crystalloids in patients with sepsis or septic shock
Setting: Intensive Care Unit (ICU)
Bibliography: Moeller C, Fleischmann C, Thomas-Rueddel D, Vlasakov V, Rochwerg B, Theurer P, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75-83.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**gelatin**	**other fluid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: Longest available)												
6	randomized trials	not serious [1]	not serious	serious [2]	serious [3]	none	95/556 (17.1%)	97/595 (16.3%)	**RR 1.10** (0.85 to 1.43)	**16 more per 1000** (from 24 fewer to 70 more)	⨁⨁◯◯ LOW	CRITICAL
Acute Kidney Injury (assessed with: Urea > 30mmol/L, need for RRT, Cr increase by 2.0 mg/dL or Cr > 1.5 mg/dL)												
3	randomized trials	serious [4]	not serious	very serious [5]	very serious [6]	none	14/108 (13.0%)	10/104 (9.6%)	**RR 1.35** (0.58 to 3.14)	**34 more per 1000** (from 40 fewer to 206 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI**:** Confidence interval; RR: Risk ratio

1. Lack of blinding in two of included trials although not lowered for mortality outcome.
2. We downgraded the quality of evidence by one level for imprecision. One trial (Upadhyay) was in children with sepsis. Another (Parker) was in critically ill postoperative patients. The intervention and comparator fluid regimes varied across included studies.
3. We downgraded the quality of evidence by one level for imprecision. Confidence intervals fail to exclude harm or benefit.
4. We downgraded the quality of evidence by one level for risk of bias due to lack of blinding in 2 out of 3 included studies.

5. We downgraded the quality of evidence by two levels for indirectness in population and intervention. One trial (Soares) was in post cardiac surgery patients, another (Upadhyay) was in children with sepsis. Trials used varying fluid regimes and comparators. The definition of AKI varied per trial. AKI is a surrogate outcome for dialysis need and death.
6. We downgraded the quality of evidence by one level for imprecision due to wide confidence intervals do not exclude benefit or harm. Very small number of events make overall results very uncertain.

Table 4. Balanced crystalloids compared to Normal saline in patients with sepsis or septic shock

Author(s): Alhazzani W, Perner A
Date: December 2 2015
Question: Balanced crystalloids compared to Normal saline in in patients with sepsis or septic shock
Setting: ICU
Bibliography: Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347-55. doi:10.7326/M14-0178.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Balanced crystalloids**	**Normal saline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
N/A	randomized trials [1]	not serious	not serious	Very serious [2]	serious [3]	none	N/A	25.0%	**RR 0.78** (0.58 to 1.05)	**55 fewer per 1000** (from 13 more to 105 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Renal Replacement Therapy												
N/A	randomized trials [1]	not serious	not serious [4]	Very serious [2]	serious [5]	none	N/A	23.0% [6]	**RR 0.85** (0.56 to 1.30)	**35 fewer per 1000** (from 69 more to 101 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								51.0% [6]		**77 fewer per 1000** (from 153 more to 224 fewer)		

MD – mean difference, RR – relative risk

1. There are no head to head RCTs on this question, we used the estimates from network meta-analysis (indirect comparison)
2. We downgraded by two levels for indirectness, we used data from indirect comparison only, no direct comparison studies are available
3. We downgraded the quality of evidence by one level for imprecision, the CI includes significant benefit and small harm.
4. We could not assess inconsistency as all the evidence is derived from indirect comparisons
5. We downgraded the quality of evidence by one level for imprecision, the CI contained both significant benefit and harm
6. Data from Rangel-Frausto et al.

Table 5. EGDT compared to other protocols or usual care in the acute management of patients with sepsis or septic shock

Author(s): Alhazzani W
Date: December 4, 2015
Question: EGDT compared to other protocols or Usual care in the acute management of patients with sepsis or septic shock
Setting: ICU
Bibliography: Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41(9):1549-60. doi:10.1007/s00134-015-3822-1.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EGDT**	**Other protocols or Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
90 days mortality												
3	randomized trials	not serious	not serious	not serious	not serious	none	460/1820 (25.3%)	598/2243 (26.7%)	**OR 0.99** (0.86 to 1.15)	**2 fewer per 1000** (from 28 fewer to 28 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								40.0%		**2 fewer per 1000** (from 34 more to 36 fewer)		
ICU length of Stay												
3	randomized trials	not serious	not serious	not serious	not serious	none	1825	2051	-	MD **0.02 days fewer** (0.47 fewer to	⨁⨁⨁⨁ HIGH	IMPORTANT

										0.43 more)		
Need for RRT												
3	randomized trials	not serious	not serious	not serious	not serious	none	206/1795 (11.5%)	244/2208 (11.1%)	**OR 0.99** (0.81 to 1.22)	**1 fewer per 1000** (from 19 fewer to 21 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Need for ICU admission												
3	randomized trials	not serious	not serious	not serious	not serious	none	1827/2006 (91.1%)	2052/2472 (83.0%)	**OR 2.19** (1.82 to 2.65)	**84 more per 1000** (from 69 more to 98 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

MD – mean difference, RR – relative risk

Table 6. Targeted Higher MP (>65 mmHg) compared to Lower MAP (65 mmHg) in Patients with sepsis or septic shock

Author(s): Alhazzani W, Annane D
Date: December 1 2015
Question: Targeted Higher MP (>65 mmHg) compared to Lower MAP (65 mmHg) in Patients with sepsis or septic shock
Setting: ICU
Bibliography: Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. The New England journal of medicine. Apr 24 2014;370(17):1583-1593.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**targeted Higher MP (>65 mmHg)**	**Lower MAP (65 mmHg)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality at 28 days												
1	randomized trials	not serious	not serious	not serious	serious [1]	none	142/388 (36.6%)	132/388 (34.0%)	**HR 1.07** (0.84 to 1.38)	**19 more per 1000** (from 45 fewer to 96 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality at 90 days												
1	randomized trials	not serious	not serious	not serious	serious [2]	none	170/388 (43.8%)	164/388 (42.3%)	**HR 1.04** (0.83 to 1.30)	**13 more per 1000** (from 57 fewer to 88 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events												
1	randomized trials	not serious	not serious	not serious	serious [2]	none	74/388 (19.1%)	69/388 (17.8%)	**RR 1.07** (0.80 to 1.44)	**12 more per 1000** (from 36 fewer to 78 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk, HR– hazard ratio

1. We downgraded the quality of evidence by one level for imprecision, the CI contained significant benefit and harm
2. We downgraded the quality of evidence by one level for imprecision, the CI contained significant benefit and harm
3. We downgraded the quality of evidence for risk of bias, this is a subgroup analysis from a single study, although authors used stratified randomization and a priori hypothesis we decided to downgrade for risk of bias

Table 7. Norepinephrine compared to other vasopressors in patients with septic shock

Author(s): Alhazzani W
Date: April 5, 2016
Question: NE compared to other vasopressors in patients with septic shock
Setting: ICU
Bibliography: Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015;10(8):e0129305.
Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H. Vasopressors for hypotensive shock. The Cochrane Library. 2016 Feb 15.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NE**	**other vasopressors**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality – NE vs. Other vasopressors												
19	randomized trials	not serious	not serious	not serious	not serious	none	716/1431 (50.0%)	762/1486 (51.3%)	**RR 0.97** (0.91 to 1.04)	**15 fewer per 1000** (from 21 more to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality - NE vs. PE												
2	randomized trials	serious [1]	not serious	not serious	very serious [2]	none [3]	24/43 (55.8%)	26/43 (60.5%)	**RR 0.92** (0.64 to 1.32)	**48 fewer per 1000** (from 193 more to 218 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality - NE vs. Epinephrine												
4	randomized trials [4]	not serious	not serious	not serious	very serious [5]	none [3]	95/277 (34.3%)	94/263 (35.7%)	**RR 0.96** (0.77 to 1.21)	**14 fewer per 1,000** (from 75 more to	⊕⊕◯◯ LOW	CRITICAL

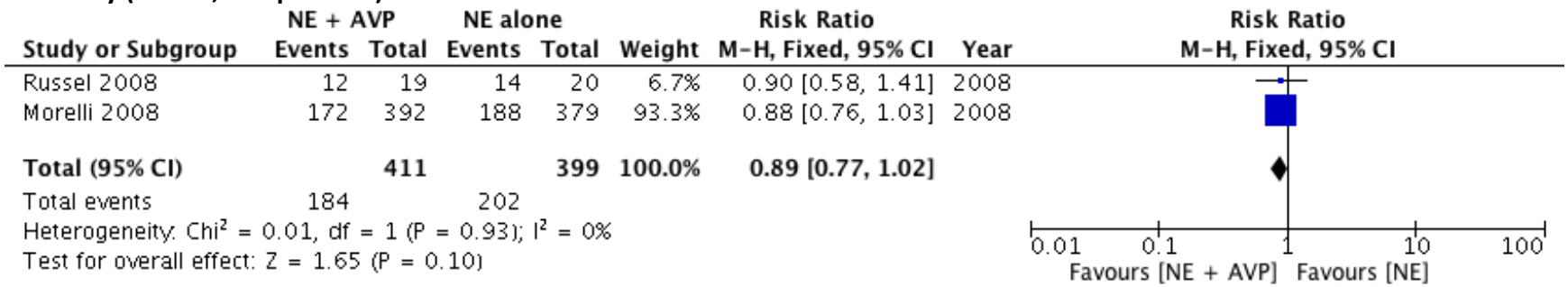
										82 fewer)		
Mortality - NE vs. AVP												
3	randomized trials	not serious	not serious	not serious	serious [6]	none [3]	196/397 (49.4%)	182/415 (43.9%)	**RR 1.12** (0.98 to 1.29)	**53 more per 1000** (from 9 fewer to 127 more) **53 more per 1000** (from 9 fewer to 127 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio, **PE**: phenylephrine, **NE**: Norepinephrine, **AVP**: vasopressin

1. We downgraded the quality of evidence by one level for risk of bias, the two studies were judged to be at high and unclear risk of bias.
2. We downgraded the quality of evidence for imprecision by two levels, the CI was very wide
3. We could not reliably assess for publication bias due to small number of included studies
4. Data from Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015;10(8):e0129305.
5. We downgraded the quality of evidence for imprecision by two levels, the CI is wide and small number of events
6. We downgraded the quality of evidence by one level for imprecision, the confidence interval contains significant benefit and harm

Figure 1. Norepinephrine and vasopressin compared to Norepinephrine alone in patients with septic shock

Mortality (2 RCTs, 810 patients)



NE: norepinephrine, **AVP**: Vasopressin, **M-H**: Mantel-Haenszel

Table 8. Norepinephrine compared with arginine vasopressin compared to Norepinephrine alone in patients with septic shock

Author(s): Alhazzani W, Alshamis F
Date: April 6, 2016
Question: NE with AVP compared to NE alone in patients with septic shock
Setting: ICU
Bibliography: Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D, VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008, 358:877-887.; Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Bachetoni A, D'Alessandro M, Van Aken H, Pietropaoli P, Westphal M: Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 2009, 13: R130-R143.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NE with AVP**	**NE alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	randomized trials	not serious	not serious	not serious	serious [1]	none [2]	184/411 (44.8%)	202/399 (50.6%)	**RR 0.89** (0.77 to 1.02)	**56 fewer per 1000** (from 10 more to 116 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
								40.0% [3]		**44 fewer per 1000** (from 8 more to 92 fewer)		

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for imprecision, the CI crossed the line of no difference
2. We could not reliably assess for publication bias due to small number of studies, we conducted a comprehensive literature search therefore we considered the possibility of publication bias to be very small
3. Data from Sepsis-3

Table 9. Vasopressin compared to other vasopressors in patients with septic shock

Author(s): Alshamsi F, Alhazzani W, Singer M
Date: October 7 2016
Question: Vasopressin compared to other pressors in patients with septic shock
Setting: ICU
Bibliography: Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PloS one. 2015 Aug 3;10(8):e0129305.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vasopressin**	**other pressors**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
9	randomized trials	not serious	not serious	not serious [1]	serious [2]	none [3]	273/674 (40.5%)	293/650 (45.1%)	**RR 0.89** (0.79 to 1.00)	**50 fewer per 1,000** (from 0 fewer to 95 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								40.0% [4]		**44 fewer per 1,000** (from 0 fewer to 84 fewer)		

CI: Confidence interval; **RR:** Risk ratio

1. Although there was some indirectness at the intervention level, majority of trials used a combination of AVP or terlipressin with norepinephrine in the intervention arm, however, a sensitivity analysis excluding these studies did not significantly affect the quality of evidence or direction of treatment effect, therefore, we did not downgrade for indirectness

2. The CI interval included significant benefit and crossed the unity line, therefore, we downgraded the quality of evidence for imprecision by one level
3. We could not reliably assess for publication bias due to small number of included studies
4. Data on septic shock mortality from Sepsis-3

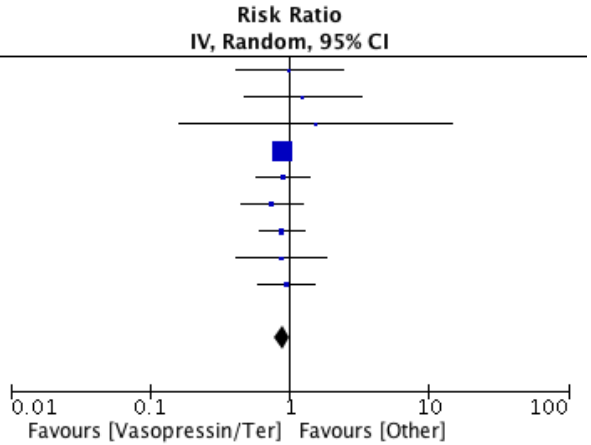
Figure 2. Vasopressin compared to other vasopressors in patients with septic shock

Mortality Outcome (9 RCTs 1234 patients)

Study or Subgroup	Vasopressin/Terlipressin Events	Total	Other vasopressors Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Diinser 2003	7	24	7	24	1.9%	1.00 [0.41, 2.42]	2003
Albanese 2005	5	10	4	10	1.5%	1.25 [0.47, 3.33]	2005
Lauzier 2006	2	13	1	10	0.3%	1.54 [0.16, 14.66]	2006
Russel 2008	172	392	188	379	63.8%	0.88 [0.76, 1.03]	2008
Morelli 2008	12	19	14	20	7.3%	0.90 [0.58, 1.41]	2008
Morelli 2009	15	30	10	15	5.7%	0.75 [0.45, 1.24]	2009
Han 2012	27	66	34	73	10.1%	0.88 [0.60, 1.28]	2012
Hua 2013	7	16	8	16	2.7%	0.88 [0.42, 1.84]	2013
Gordon 2016	26	104	27	103	6.8%	0.95 [0.60, 1.52]	2016
Total (95% CI)		**674**		**650**	**100.0%**	**0.89 [0.79, 1.00]**	
Total events	273		293				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.30$, df = 8 (P = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 1.91 (P = 0.06)



IV: Inverse variance

Table 10. Dopamine versus Norepinephrine for the Treatment of Septic Shock

Author(s): Alhazzani W
Bibliography: Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One 2015;10:e0129305.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NE**	**Dopamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
11	randomized trials	not serious	not serious	not serious	not serious	none	376/832 (45.2%)	450/886 (50.8%)	**RR 0.89** (0.81 to 0.98)	**56 fewer per 1000** (from 10 fewer to 97 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
								40.0% [1]		**44 fewer per 1000** (from 8 fewer to 76 fewer)		
Arrhythmias												
4	randomized trials	not serious	not serious	not serious	not serious	none	120/669 (17.9%)	272/721 (37.7%)	**RR 0.48** (0.40 to 0.58)	**196 fewer per 1000** (from 158 fewer to 226 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio, NE: Norepinephrine

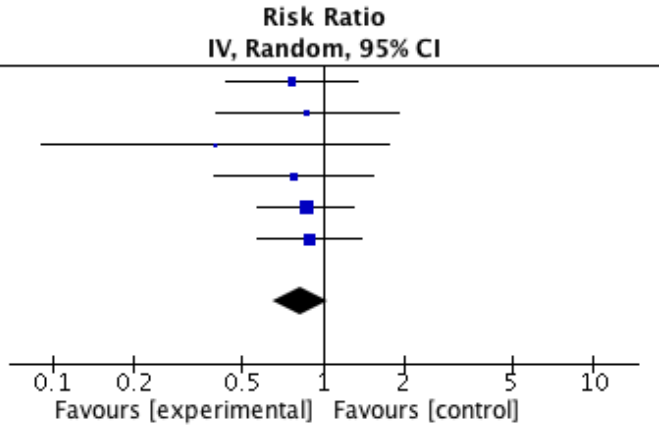
1. Mortality in septic shock assumed to be 40% in the control arm data from Sepsis-3.

Figure 3. Levosimendean versus dobutamine in patients with septic shock and hypoperfusion: Mortality Outcome

Study or Subgroup	Levosimendan Events	Total	Dobutamine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Alhashemi 2009	10	21	13	21	17.3%	0.77 [0.44, 1.35]
Fang 2014	7	18	8	18	9.0%	0.88 [0.40, 1.90]
Memis 2012	2	15	5	15	2.5%	0.40 [0.09, 1.75]
Morelli 2005	7	15	9	15	11.7%	0.78 [0.39, 1.54]
Morellli 2010	13	20	15	20	32.4%	0.87 [0.58, 1.30]
Vaitsis 2009	14	23	13	19	27.1%	0.89 [0.57, 1.39]
Total (95% CI)		**112**		**108**	**100.0%**	**0.83 [0.66, 1.05]**
Total events	53		63			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.20$, df = 5 (P = 0.94); $I^2 = 0\%$

Test for overall effect: Z = 1.58 (P = 0.11)



IV: inverse variance

Table 11. Levosimendan versus dobutamine in patients with septic shock and persistent hypoperfusion

Author(s): Alhazzani W, Machado F
Bibliography: Fang M Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014; 26(10):692-6, Memis D J Crit Care 2012; 27(3):18e1-6, Morelli A Intensive Care Med 2005; 31(5):638-44, Morelli A Crit Care 2010; 14(6):R232, Alhashemi JA J Crit Care 2009; 24(3):e14-5, Vaitsis J Crit Care 2009;13 (Suplem 1):165.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levosimendan**	**dobutamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
6	randomized trials	serious [1]	not serious [2]	not serious	serious [3]	none	53/112 (47.3%)	63/108 (58.3%)	**RR 0.83** (0.66 to 1.05)	**99 fewer per 1000** (from 29 more to 198 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded for risk of bias by one level, the randomization process and allocation concealment was unclear for most trials. small sample size, blindness and allocation concealment not adequately described
2. The $I^2 = 0\%$, no significant statistical heterogeneity identified
3. We downgraded the quality of evidence for imprecision by one level, the CI contained significant benefit and small harm

Table 12. Pulse pressure variation in predicting fluid responsiveness in patients with sepsis or septic shock

Sensitivity	0.72 (95% CI: 0.61 to 0.81)
Specificity	0.91 (95% CI: 0.83 to 0.95)

Prevalence	40%[5]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 40%	
True positives (patients with Fluid responsiveness)	5 studies 219 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	serious [2]	none	288 (244 to 324)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having Fluid responsiveness)								112 (76 to 156)	
True negatives (patients without Fluid responsiveness)	5 studies 219 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [3]	not serious	serious [4]	none	546 (498 to 570)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having Fluid responsiveness)								54 (30 to 102)	

1. We downgraded the quality of evidence for risk of bias by one level, most studies were at high risk of bias with QUADAS Tool
2. We downgraded the quality for imprecision by one level, 112 per 1000 tested patients will have a false negative results, the CI of pooled sensitivity was wide
3. Although the reference test was not a static measure in included studies, we did not downgrade the quality of evidence because we can indirectly compare with other static measures
4. We downgraded the quality of evidence by one level for imprecision, small number of patients and the CI of the pooled specificity included values below the desired threshold
5. Prevalence of fluid responsiveness is estimated to be 40%, data from Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? JAMA. 2016;316(12):1298-309.

Table 13. Central venous pressure in predicting fluid responsiveness in patients with sepsis or septic shock

Sensitivity	0.62 (95% CI: 0.54 to 0.69)
Specificity	0.76 (95% CI: 0.60 to 0.87)

Prevalence	40%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 40%	
True positives (patients with fluid responsiveness)	7 studies 356 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	serious [2]	none	248 (216 to 276)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having fluid responsiveness)								152 (124 to 184)	
True negatives (patients without fluid responsiveness)	7 studies 356 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	serious [3]	none [4]	456 (360 to 522)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having fluid responsiveness)								144 (78 to 240)	

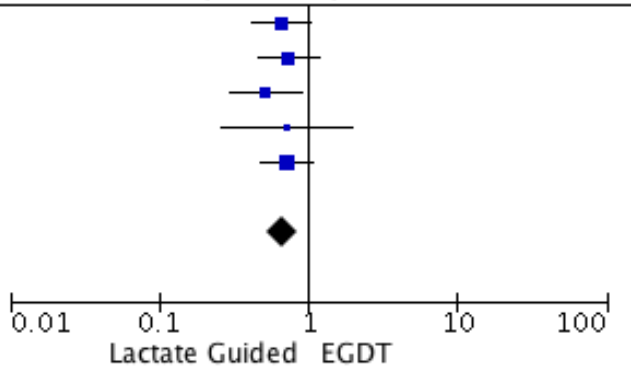
1. We downgraded the quality of evidence for risk of bias by one level, the risk of bias was high in most studies as judged by review authors
2. We downgraded the quality of evidence for imprecision by one level, the CI around false negatives is wide, and the total number of participant is small
3. We downgraded the quality of evidence for imprecision by one level, the CI around specificity is wide
4. No report on publication bias was provided in the manuscript, we couldn't assess this category
5. The prevalence of fluid responsiveness is assumed to be 40%, data from Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? JAMA. 2016;316(12):1298-309.

Figure 4. Targeted Lactate Clearance in the Management of Patients with Sepsis and Septic Shock: Mortality

Study or Subgroup	Lactate Guided Events	Total	Standard Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	34	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 3.51 (P = 0.0004)



CI: confidence interval; IV: inverse variance

Table 14. Targeted Lactate Clearance in the Management of Patients with Sepsis and Septic Shock

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**resuscitation targeting lactate clearance**	**other strategies**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital Mortality												
5	randomized trials	serious [1]	not serious	not serious	serious [2]	none	84/336 (25.0%)	111/311 (35.7%)	**RR 0.67** (0.53 to 0.84)	**118 fewer per 1,000** (from 57 fewer to 168 fewer)	⨁⨁◯◯ LOW	CRITICAL
								40.0% [3]		**132 fewer per 1,000** (from 64 fewer to 188 fewer)		
ICU LoS												
3	randomized trials	not serious	serious [4]	not serious	serious [5]	none	194	196	-	MD 1.51 days lower (3.65 lower to 0.62 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. All studies were judged to be at high risk of bias due to lack of clarity of the intervention, therefore, we downgraded the quality of evidence by one level for risk of bias
2. We downgraded the quality of evidence by one level for imprecision, the CI contained small benefit that was lower than the decision threshold
3. We assumed a mortality rate for patients with septic shock to be 40%
4. We downgraded for inconsistency by one level, I^2= 64%
5. We downgraded the quality of evidence for imprecision by one level, the CI contained significant benefit and harm

INFECTION

Table 15. Performance improvement programs compared to routine care for sepsis

Author(s): Mark Nunnally
Date: 29 July 2016
Question: Performance improvement programs compared to routine care for sepsis
Setting: inpatients
Bibliography: Damiani E et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. Plos One 10(5): e0125827. 2015

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Performance improvement programs**	**routine care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall mortality												
43	observational studies	not serious	serious [1]	not serious	not serious	none	N/A	N/A	**OR 0.66** (0.61 to 0.72)	**N/A**	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; N/A: Not applicable

1. We downgraded the quality of evidence by one level for significant inconsistency, I^2= 89%

Table 16. Appropriate initial antibiotics compared to inappropriate initial antibiotics for sepsis

Author(s): Mark E. Nunnally
Date: 2 March 2016
Question: Appropriate initial antibiotics compared to inappropriate initial antibiotics for sepsis.
Setting: hospital-aquired or healthcare-associated gram-negative bacterial infections
Bibliography: Raman G, Avendano E, Berger S, Menon V. Appropriate initial antibiotic therapy in hospitalized patients with gam-negative infections: systemic review and meta-analysis. BMC Infect Dis 2015;15:395

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Broad empiric initial antibiotics**	**Narrow, incomplete initial antibiotics**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adjusted mortality, inappropriate, all follow-up (2493 patients)												
16	observational studies [1]	not serious	serious [2]	not serious	not serious	strong association[3]	N/A	N/A	OR 3.30 (2.42 to 4.49)	3 fewer per 1000 (from 2 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adjusted mortality, appropriate, all follow-up (1409 patients)												
6	observational studies [4]	not serious	serious [5]	not serious	not serious	strong association[6]	N/A	N/A	OR 0.43 (0.23 to 0.83)	0 fewer per 1000 (from 0 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Unadjusted mortality, 30 days (5809 patients)												
39	observational studies [7]	not serious	serious [8]	not serious	not serious	strong association			OR 0.38 (0.30 to 0.47)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio

1. Studies included a total of 2493 patients
2. We downgraded the quality of evidence by one level for significant inconsistency, the I^2 = 54%
3. We upgraded the quality of evidence by one level for strong treatment effect OR > 3
4. Studies included a total of 1409 patients
5. We downgraded the quality of evidence by one level for significant inconsistency, the I^2= 74.7%
6. We upgraded the quality of evidence by one level for strong treatment effect OR <0.5
7. Studies included a total of 5809 patients

8. We downgraded the quality of evidence by one level for significant inconsistency, the I^2=65%

Table 17. Appropriate antimicrobials compared to inappropriate antimicrobials for sepsis

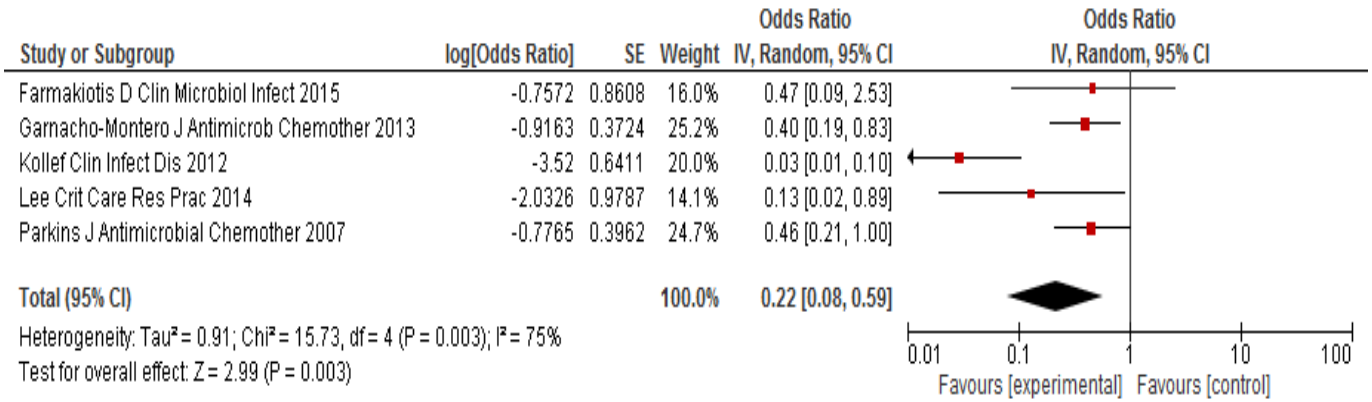
Author(s): Mark E. Nunnally
Date: 26 January 2016
Question: Appropriate antimicrobials compared to inappropriate antimicrobials for sepsis
Setting: Severe in-hospital infections
Bibliography: Marquet K. Critical Care (2015) 19:63

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Broad empiric antimicrobials	Narrow incomplete initial antimicrobials	Relative (95% CI)	Absolute (95% CI)		
30-day mortality, severe infections (Marquet)												
10	observational studies	not serious [1]	not serious [2]	not serious	not serious	none	322/1167 (27.6%)	518/1324 (39.1%)	**RR 0.71** (0.62 to 0.82)	**113 fewer per 1000** (from 70 fewer to 149 fewer)	⨁⨁◯◯ LOW	CRITICAL
In-hospital mortality, serious infections (Marquet)												
11	observational studies	not serious [1]	serious [3]	not serious	not serious	none	2981/7512 (39.7%)	1801/3011 (59.8%)	**RR 0.67** (0.56 to 0.80)	**197 fewer per 1000** (from 120 fewer to 263 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No indication of ROB assessment in meta-analysis. Observational studies, however.
2. I^2= 20.8%, we did not downgrade for inconsistency
3. We downgraded the quality of evidence for inconsistency by one level, the I^2 =86.6%

Figure 5. Empiric antifungal coverage in high risk patients with sepsis: mortality outcome



SE: Standard error, **IV:** Inverse variance

Table 18. Empiric antifungal compared to culture-directed for sepsis

Author(s): Mark E. Nunnally
Date: 21 December 2015
Question: Empiric antifungal compared to culture-directed for sepsis
Setting: ICU
Bibliography: 1. Parkins MD J Antimicrobial Chemother 2007 2. Garnacho-Montero M J Antimicrob Chemother 2013 3. Kollef M Clin Infect Dis 2012 4. Lee W Crit Care Res Prac 2014 5. Farmakiotis D Clin Microbiol Infect 2015

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Empiric antifungal	culture-directed	Relative (95% CI)	Absolute (95% CI)		
Overall mortality												
5	observational studies	not serious	serious [1]	not serious	not serious	none	N/A	N/A	**OR 0.22** (0.08 to 0.59)	N/A	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

1. We downgraded the quality of evidence by one level for significant inconsistency, the I^2=75%.

Table 19. Early administration (within 1 hour) of empirically appropriate antimicrobials compared to delay beyond 1 hour for sepsis

Author(s): Mark E. Nunnally
Date: 2 March 2016
Question: Early administration (within 1 hour) of empirically appropriate antimicrobials compared to delay beyond 1 hour for sepsis
Setting: Intensive care unit, emergency department
Bibliography: 1. Kumar A., et al. Critical Care medicine (2006) 34:1589 2. Ferrer R., et al. Critical Care Medicine (2014)

Quality assessment							**Impact**	**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality at hospital discharge (Kumar logistic regression model (follow up: discharge))									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Adjusted Odds Ratio 1.119 [1.103, 1.136] per hour delay in initiation of effective antimicrobial therapy after onset of hypotension.	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality, adjusted, based on time receiving antibiotics after time of presentation with severe sepsis criteria (Ferrer)									
1	observational studies	not serious	not serious	not serious	not serious	none	Stratified by hour of receiving antibiotics, an increase in OR at each hour: 0-1: 1.00, 1-2: 1.07 [0.97, 1.18], 2-3: 1.14 [1.02, 1.26], 3-4: 1.19 [1.04, 1.35], 4-5: 1.24 [1.06, 1.45], 5-6: 1.47 [1.22, 1.76], >6: 1.52 [1.36, 1.70] [1]	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

1. Adjusted analysis predicated on a much sicker cohort receiving antibiotics in the first hour. Unadjusted mortality declined from first hour (32.0%) to second (28.1%), and then steadily increased. Adjusted OR with significant CI starting at hour 2-3 (1.14 [1.02, 1.26])

Table 20. Early administration (within 1 hour) of empirically appropriate antimicrobials compared to delay beyond 1 hour for sepsis

Author(s): Mark E. Nunnally
Date: 29 July 2016
Question: Early administration (within 1 hour) of empirically appropriate antimicrobials compared to delay beyond 1 hour for sepsis
Setting: Intensive care unit, emergency department
Bibliography: 1. Kumar A., et al. Critical Care medicine (2006) 34:1589 2. Ferrer R., et al. Critical Care Medicine (2014)

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality at hospital discharge (Kumar logistic regression model (follow up: discharge)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Adjusted Odds Ratio 1.119 [1.103, 1.136] per hour delay in initiation of effective antimicrobial therapy after onset of hypotension.	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality, adjusted, based on time receiving antibiotics after time of presentation with severe sepsis criteria (Ferrer)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Stratified by hour of receiving antibiotics, an increase in OR at each hour: 0-1: 1.00, 1-2: 1.07 [0.97, 1.18], 2-3: 1.14 [1.02, 1.26], 3-4: 1.19 [1.04, 1.35], 4-5: 1.24 [1.06, 1.45], 5-6: 1.47 [1.22, 1.76], >6: 1.52 [1.36, 1.70] [1]	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

1. Adjusted analysis predicated on a much sicker cohort receiving antibiotics in the first hour. Unadjusted mortality declined from first hour (32.0%) to second (28.1%), and then steadily increased. Adjusted OR with significant CI starting at hour 2-3 (1.14 [1.02, 1.26])

Table 21. Monotherapy with a broad-spectrum beta lactam compared to combination therapy for sepsis

Author(s): Mark E. Nunnally
Date: 2 March 2016
Question: Monotherapy with a broad spectrum beta lactam compared to combination therapy for sepsis (serious infections?)
Setting: hospitalized patients
Bibliography: 1. Paul et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev 2014;1:CD003344 2. Paul et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. Cochrane Database Syst Rev 2013;(6)

Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**monotherapy with a broad spectrum beta lactam**	**combination therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality, same beta-lactam in both groups. (follow up: mean 30 days). Paul meta-analysis for septic patients												
13	randomized trials	not serious [1]	not serious	not serious	serious [2]	publication bias strongly suspected [3]	76/716 (10.6%)	80/715 (11.2%)	**RR 0.97** (0.73 to 1.30)	**3 fewer per 1000** (from 30 fewer to 34 more)	⨁⨁◯◯ LOW	CRITICAL
All-cause mortality, different beta-lactam in both groups (follow up: mean 30 days). Paul meta-analysis for septic patients												
31	randomized trials	serious [4]	not serious	not serious	not serious	publication bias strongly suspected [3]	197/2175 (9.1%)	222/1971 (11.3%)	**RR 0.85** (0.71 to 1.01)	**17 fewer per 1000** (from 1 more to 33 fewer)	⨁⨁◯◯ LOW	CRITICAL
All-cause mortality, febrile neutropenic cancer patients. Paul meta-analysis for neutropenic patients												

44	randomized trials	not serious [1]	not serious	serious [5]	not serious	none	266/3674 (7.2%)	291/3512 (8.3%)	**RR 0.87** (0.75 to 1.02)	**11 fewer per 1000** (from 2 more to 21 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
All-cause mortality, febrile neutropenic cancer patients, same beta-lactam in both groups. Paul meta-analysis for neutropenic patients												
11	randomized trials	not serious [1]	not serious	serious [5]	not serious	none	49/825 (5.9%)	70/893 (7.8%)	**RR 0.74** (0.53 to 1.06)	**20 fewer per 1000** (from 5 more to 37 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
All-cause mortality, febrile neutropenic cancer patients, different beta-lactam in both groups. Paul meta-analysis for neutropenic patients												
33	randomized trials	not serious [1]	not serious	serious [5]	not serious	none	217/2849 (7.6%)	221/2619 (8.4%)	**RR 0.91** (0.77 to 1.09)	**8 fewer per 1000** (from 8 more to 19 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Although no blinding in most studies, no downgrade as we were assessing mortality.
2. We downgraded the quality of evidence by one level for imprecision, the 95% CI range from 27% improved survival to 30% higher risk of death with monotherapy.
3. Funnel plot asymmetrical pointing out missing studies (unpublished or published but not reporting on mortality) favoring combination therapy.
4. We downgraded the quality of evidence by one level for risk of bias, advantage of monotherapy accentuated in studies with unclear allocation concealment and per-protocol analysis.
5. We downgraded the quality of evidence for indirectness of population by one level. Patients febrile, not necessarily septic.

Table 22. Empiric combination antibiotic therapy compared to monotherapy for critically ill patients at high risk for infection with multi-resistant pathogens, such as Pseudomonas and Acinetobacter

Author(s): Mark E. Nunnally
Date: 2 March 2016
Question: Empiric combination antibiotic therapy compared to monotherapy for critically ill patients at high risk for infection with multi-resistant pathogens, such as Pseudomonas and Acinetobacter
Setting: Intensive care unit
Bibliography: 1. Vardakas et al. International Journal of Antimicrobial Agents (2013) 41(4):301-10

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**empiric combination antibiotic therapy**	**monotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (Vardakas, empiric coverage)												
6	observational studies	not serious	not serious	serious [1]	serious [2]	none	88/290 (30.3%)	64/239 (26.8%)	**RR 1.02** (0.78 to 1.34)	**5 more per 1,000** (from 59 fewer to 91 more)	⨁◯◯◯ VERY LOW	CRITICAL
								33.0%		**7 more per 1,000** (from 73 fewer to 112 more)		
All-cause mortality (Vardakas, empiric coverage - Non-RCTs)												

5	observational studies	not serious	not serious	serious [1]	serious [2]	none	84/273 (30.8%)	63/232 (27.2%)	**RR 1.01** (0.77 to 1.33)	**3 more per 1,000** (from 62 fewer to 90 more)	⨁◯◯◯ VERY LOW	CRITICAL
								34.4%		**3 more per 1,000** (from 79 fewer to 114 more)		
All-cause mortality (Vardakas, empiric coverage - RCTs)												
1	randomized trials	serious [3]	not serious	serious [1]	serious [2]	none	4/17 (23.5%)	1/7 (14.3%)	**RR 1.65** (0.22 to 12.25)	**93 more per 1,000** (from 111 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
								14.3%		**93 more per 1,000** (from 111 fewer to 1,000 more)		
All-cause mortality (Combined- I BELIEVE with HU)												
14	observational studies	not serious	serious [4]	serious [1]	serious [2]	none	256/850 (30.1%)	323/755 (42.8%)		**21 fewer per 1,000**		CRITICAL

									RR 0.95 (0.72 to 1.24)	(from 103 more to 120 fewer)	⨁◯◯◯ VERY LOW	
								30.1%		**15 fewer per 1,000** (from 72 more to 84 fewer)		
Clinical cure, empirical combination therapy (Vardakas)												
12	observational studies	not serious	not serious	not serious	not serious	none	142/219 (64.8%)	168/285 (58.9%)	**RR 1.23** (1.05 to 1.43)	**136 more per 1,000** (from 29 more to 253 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for indirectness of population, the population included bacteremia without severe illness
2. We downgraded the quality of evidence for imprecision by one level, the 95% CI includes substantial harm
3. We downgraded the quality of evidence by one level for risk of bias, open-label design and meta-analysis authors suggest monotherapy patients more likely to receive additional antibiotics.
4. We downgraded the quality of evidence by one level for inconsistency, the I^2=55%

Table 23. Double-coverage antibiotic agents compared to monotherapy for septic shock

Author(s): Mark E. Nunnally
Date: 29 July 2016
Question: Double-coverage antibiotic agents compared to monotherapy for septic shock
Setting: intensive care
Bibliography: 1. Nie W et al. J Antimicrob Chemother 2014;69:1441-6 2. Garin N et al. JAMA Intern Med 2014;174(12):1894-1901 3. Díaz-Martin et al. Critical Care (2012) 16:R223 4. Delannoy et al. European Journal of Clinical Microbiology & Infectious Diseases (2012) 31:2293 5. Kumar et al. Critical Care Medicine (2010) 38(8):1651 6. Kumar et al. Critical Care Medicine (2010) 38(9):1773

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**double-coverage antibiotic agents**	**monotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (Nie meta-analysis)												
16	observational studies	not serious	not serious	not serious [1]	not serious	none [2]	N/A	N/A	**OR 0.67** (0.61 to 0.73)	N/A	⨁⨁◯◯ LOW	CRITICAL
Clinical stability at day 7 (Garin RCT)												
1	randomized trials	not serious [3]	not serious	serious [4]	serious [5]	none	120/291 (41.2%)	97/289 (33.6%)	**RR 1.64** (1.32 to 2.05)	**215 more per 1,000** (from 107 more to 352 more)	⨁⨁◯◯ LOW	IMPORTANT
								33.0%		**211 more per 1,000** (from 106 more to		

										347 more)		
ICU mortality, meta regression, stratified by rate of mortality/clinical failure in datasets (Kumar)												
28	observational studies	not serious	not serious	not serious	not serious	none	Although datasets with lower mortality/clinical failure rates demonstrated a nonsignificant increased mortality with combination therapy, this increased as that rate increased, such that at a mortality/clinical failure rate of >25%, the OR for dual therapy= 0.54 [0.45,0.66].				⨁⨁◯◯ LOW	CRITICAL
ICU mortality, consolidated dataset of combined shock and critically ill patients (Kumar)												
12	observational studies	not serious	not serious	not serious	not serious	strong association	N/A	N/A	**OR 0.51** (0.36 to 0.72)	N/A	⨁⨁⨁◯ MODERATE	CRITICAL
Survival by meta-regression, dual therapy, per 10% increase in monotherapy group mortality (Kumar).												
62	observational studies	not serious	not serious	not serious	not serious	strong association	The probability of combination therapy having a beneficial effect increases for every 10% increase in monotherapy group mortality in the datasets. OR 1.318 [1.190-1.460].				⨁⨁⨁◯ MODERATE	CRITICAL
Mortality, propensity-matched analysis (Kumar) (follow up: 28 days)												
1	observational studies	not serious	not serious	not serious [6]	not serious	none	355/1223 (29.0%)	444/1223 (36.3%)	**HR 0.77** (0.67 to 0.88)	**70 fewer per 1,000** (from 35 fewer to 102 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio; **HR:** Hazard Ratio

1. Although the analysis included less ill-subjects, the subgroup with severe CAP (OR 0.66 [0.58,0.76]).
2. Although funnel plot and Egger's test showed asymmetry, the fail-safe number was large (436).
3. Open-label study, but objective outcome judged by blinded investigators.
4. Trial included 41 % Pneumonia Severity Index IV (5 point scale) patients. Remainder less severe.
5. Non-inferiority trial showed 95% CI for risk difference: -0.8% to 16%.
6. Septic shock patients, antimicrobial therapy determined to be appropriate by in vitro testing.

Table 24. Seven days of appropriate antimicrobials compared to greater than seven days of antimicrobials for pyelonephritis and urinary tract infection with sepsis

Author(s): Mark E. Nunnally
Date: 25 January 2016
Question: 7 days of appropriate antimicrobials compared to > 7 days of antimicrobials for pyelonephritis and urinary tract infection with sepsis
Setting: community infections
Bibliography: Eliakim-Raz N et al. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection- 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. Journal of antimicrobial chemotherapy 2013;68:2183-91

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**7 days of appropriate antimicrobials**	**> 7 days of antimicrobials**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical failure at end of therapy (lack of resolution of fever, symptoms, or modification of antibiotic treatment)												
5	randomized trials	not serious [1]	serious [2]	not serious [3]	serious [4]	none	37/549 (6.7%)	59/527 (11.2%)	**RR 0.63** (0.33 to 1.18)	**41 fewer per 1000** (from 20 more to 75 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Clinical failure at end of follow-up (lack of resolution of fever, symptoms, or modification of antibiotic treatment) (follow up: range 22 to 63 days)												
7	randomized trials	not serious	not serious	not serious [3]	serious [5]	none	54/706 (7.6%)	66/692 (9.5%)	**RR 0.79** (0.56 to 1.12)	**20 fewer per 1000** (from 11 more to 42 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Although not all aspects clear, most trials were rigorous 4/5 double-blinded.
2. I^2 =41%, sensitivity analysis suggested heterogeneity from one trial comparing short treatment with fluoroquinolones with long treatment with trimethoprim/sulfamethoxazole, benefitting short therapy.
3. Some may dispute whether urosepsis is direct to all sepsis.
4. We downgraded the quality of evidence for imprecision, the 95% CI includes possible harm, but largely covers benefit. 96 total events.
5. We downgraded the quality of evidence for imprecision, the 95% CI includes possible harm, but largely covers benefit. 110 total events.

Table 25. 7 or 8 days antibiotics compared to 10 or 15 days antibiotics for ventilator-associated pneumonia

Author(s): Mark E. Nunnally
Date: 25 January 2016
Question: 7 or 8 days antibiotics compared to 10 or 15 days antibiotics for ventilator-associated pneumonia
Setting: Intensive care units
Bibliography: Dimopoulos G et al. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia. A systematic review and meta-analysis. Chest 2013;144(6):1759-1767

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**7 or 8 days antibiotics**	**10 or 15 days antibiotics**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 21 to 28 days)												
4	randomized trials	not serious [1]	not serious	serious [2]	serious [3]	none	78/442 (17.6%)	68/441 (15.4%)	**OR 1.20** (0.84 to 1.72)	**25 more per 1000** (from 21 fewer to 85 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality, patients with non-fermentative gram-negative bacteria (follow up: 28 days)												
2	randomized trials	not serious	serious [4]	serious [2]	serious [3]	none	27/111 (24.3%)	23/101 (22.8%)	**OR 1.33** (0.33 to 5.26)	**54 more per 1000** (from 139 fewer to 380 more)	⊕◯◯◯ VERY LOW	CRITICAL
Antibiotic-free days (follow up: 28 days)												
2	randomized trials	not serious	serious [5]	serious [2]	not serious	none			-	MD **3.4 days more** (1.43 more to 5.37 more)	⊕⊕◯◯ LOW	IMPORTANT

Relapses (follow up: range 21 to 28 days)												
3	randomized trials	not serious	not serious	serious [2]	serious [6]	none	40/329 (12.2%)	26/327 (8.0%)	**OR 1.67** (0.99 to 2.83)	**47 more per 1000** (from 1 fewer to 117 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

1. Bias assessed by Jadad scores: 3,3,3,4 out of 5.
2. We downgraded the quality of evidence for indirectness of population by one level, the severity of patient illness likely lower than for PICO. Predicted mortality < 35% in all trials.
3. We downgraded the quality of evidence for imprecision by one level, the 95% CI includes harm and benefit.
4. We downgraded the quality of evidence for inconsistency by one level, the I^2 =72%
5. We downgraded the quality of evidence for inconsistency by one level, the I^2 =79%
6. We downgraded the quality of evidence for imprecision by one level, 66 total events.

Table 26. 4 days of antibiotics after source control compared to therapy for 2 days after resolution of symptoms for intra-abdominal infection

Author(s): Mark E. Nunnally, MD
Date: 25 January 2016
Question: 4 days of antibiotics after source control compared to therapy for 2 days after resolution of symptoms for intra-abdominal infection
Setting: hospitalized patients
Bibliography: Sawyer RG, et al. Trial of short-course antimicrobial therapy for intra-abdominal infection.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**4 days of antibiotics after source control**	**therapy for 2 days after resolution of symptoms**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death (follow up: 30 days)												
1	randomized trials	not serious	not serious	serious [1]	very serious [2]	none	3/257 (1.2%)	2/260 (0.8%)	**RR 1.52** (0.26 to 9.01)	**4 more per 1000** (from 6 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Surgical site infection (follow up: 30 days)												
1	randomized trials	not serious	not serious	serious [1]	serious [3]	none	17/257 (6.6%)	23/260 (8.8%)	**RR 0.75** (0.41 to 1.37)	**22 fewer per 1000** (from 33 more to 52 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Antibiotic free days (follow up: 30 days)												
1	randomized trials	not serious	not serious	serious [1]	not serious	none	25	21	-	MD **4 days higher** (3.23 higher to 4.77 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Mortality in patients with APACHE II > 15 (follow up: 30 days)												
1	randomized trials	not serious	not serious	serious [4]	serious [5]	none			not estimable		⨁⨁◯◯ LOW	CRITICAL
Mortality in patients with APACHE II > 20 (follow up: 30 days)												
1	randomized trials	not serious	not serious	not serious	serious [5]	none			not estimable		⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. Patients not severely ill in many cases. Control mortality 0.8%.
2. 5 total events
3. 95% confidence interval includes important harm and benefit. 40 total events.
4. APACHE II predicted postoperative mortality 12% may not reflect PICO
5. Total events:

Table 27. Short course antibiotics (typically 7 or 8 days) compared to longer course (typically 10-15 days) for hospital-acquired pneumonia

Author(s): Mark E. Nunnally
Date: 31 March 2016
Question: Short course antibiotics (typically 7 or 8 days) compared to longer course (typically 10-15 days) for hospital-acquired pneumonia
Setting: Hospitalized patients
Bibliography: Pugh R, et al. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. The Cochrane Library 2015, Issue 8

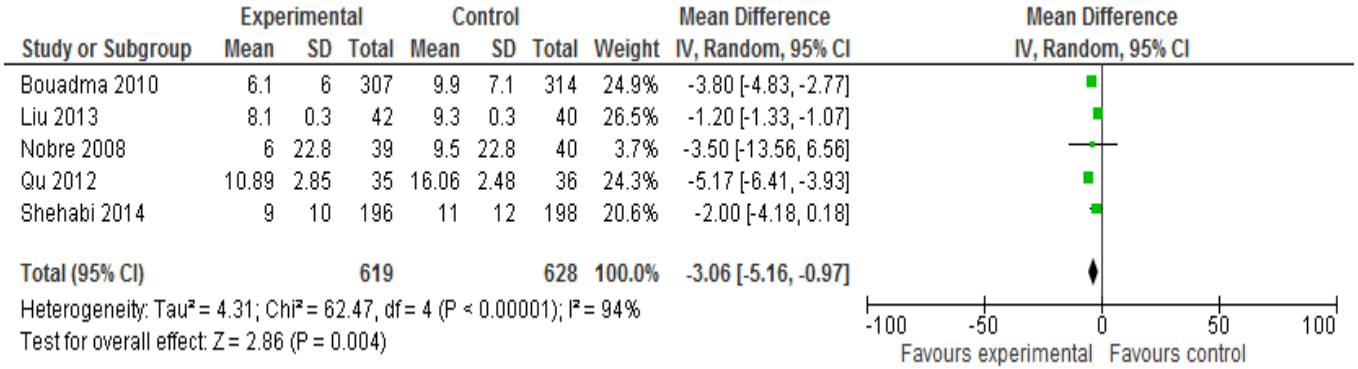
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**short course antibiotics (typically 7 or 8 days)**	**longer course (typically 10-15 days)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 28 days)												
3	randomized trials	not serious	not serious	serious [1]	serious [2]	none	59/290 (20.3%)	54/308 (17.5%)	**OR 1.18** (0.77 to 1.80)	**25 more per 1000** (from 35 fewer to 101 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality, non-fermenting gram-negative bacilli (follow up: 28 days)												
2	randomized trials	serious [3]	not serious	not serious	serious [4]	none	23/96 (24.0%)	22/83 (26.5%)	**OR 0.95** (0.39 to 2.27)	**10 fewer per 1000** (from 142 fewer to 185 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality, MRSA (follow up: 28)												

1	randomized trials	not serious	not serious	not serious	very serious [5]	none	6/21 (28.6%)	5/21 (23.8%)	**OR** 1.28 (0.32 to 5.09)	48 more per 1000 (from 147 fewer to 376 more)	⨁⨁◯◯ LOW	CRITICAL
Recurrence of pneumonia (follow up: 28 days)												
4	randomized trials	not serious	serious [6]	serious [1]	serious [7]	none	84/367 (22.9%)	66/366 (18.0%)	**OR 1.41** (0.94 to 2.12)	**56 more per 1000** (from 9 fewer to 138 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Recurrence of pneumonia, non-fermenting gram-negative bacilli (follow up: 28 days)												
2	randomized trials	not serious	not serious	not serious	serious [8]	none	38/91 (41.8%)	21/85 (24.7%)	**OR 2.18** (1.14 to 4.16)	**170 more per 1000** (from 25 more to 330 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Recurrence of pneumonia, MRSA (follow up: 28 days)												
2	randomized trials	not serious	not serious	not serious	very serious [9]	none	8/22 (36.4%)	10/27 (37.0%)	**OR 1.56** (0.12 to 19.61)	**108 more per 1000** (from 304 fewer to 550 more)	⨁⨁◯◯ LOW	IMPORTANT
Antibiotic-free days (follow up: 28 days)												
2	randomized trials	serious [10]	not serious	serious [1]	serious [11]	none	211	220	-	MD **4.02 days more** (2.26 more to 5.78 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

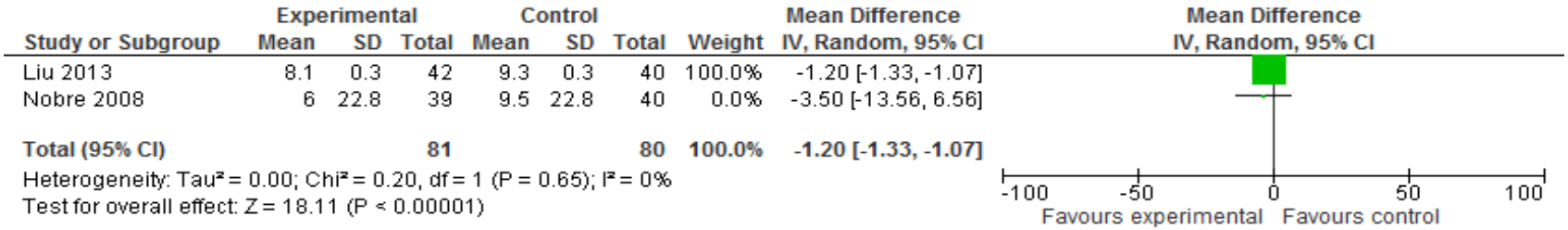
1. Hospital-acquired pneumonia population may not reflect PICO. 18% control mortality
2. 113 total events
3. Cochrane authors cited Kollef et al as having multiple interventions, protocol violations and early stopping
4. 95% confidence interval includes substantial harm and benefit. 45 total events
5. 95% confidence interval includes substantial harm and benefit. 11 total events
6. Differences in mechanical ventilation duration and infecting bacteria between studies
7. 150 total events
8. 95% confidence interval includes substantial harm and benefit. 59 total events
9. 95% confidence interval includes substantial harm and benefit. 18 total events
10. Cochrane authors presumed differences in administration of antibiotics between studies
11. Total of 431 patients. Cochrane authors elected to downgrade for imprecision

Figure 6. Procalcitonin versus usual care in determining the duration of antibiotic therapy in patients with infection



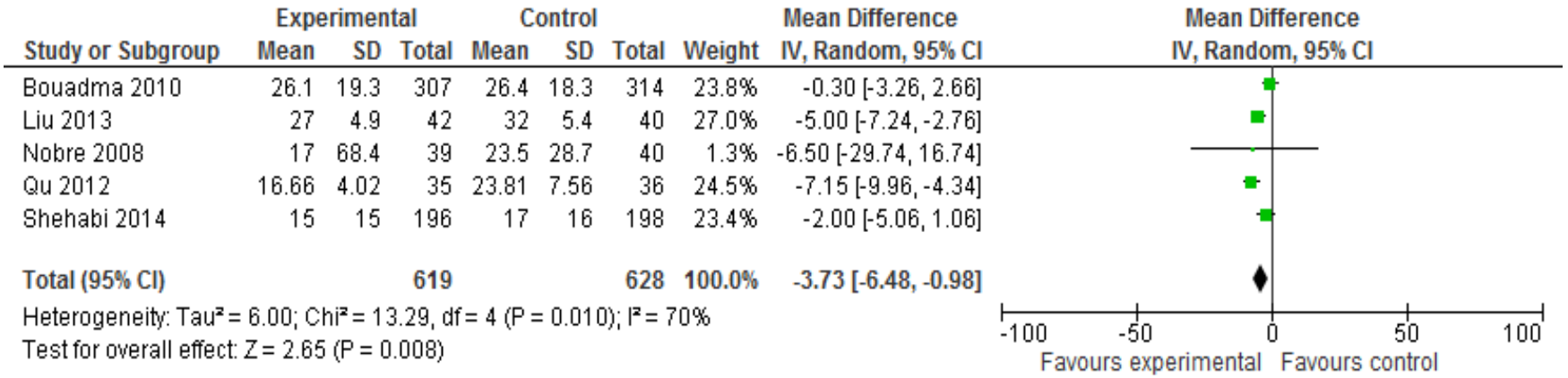
Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Figure 7. Procalcitonin versus usual care in determining the duration of antibiotic therapy in patients with sepsis



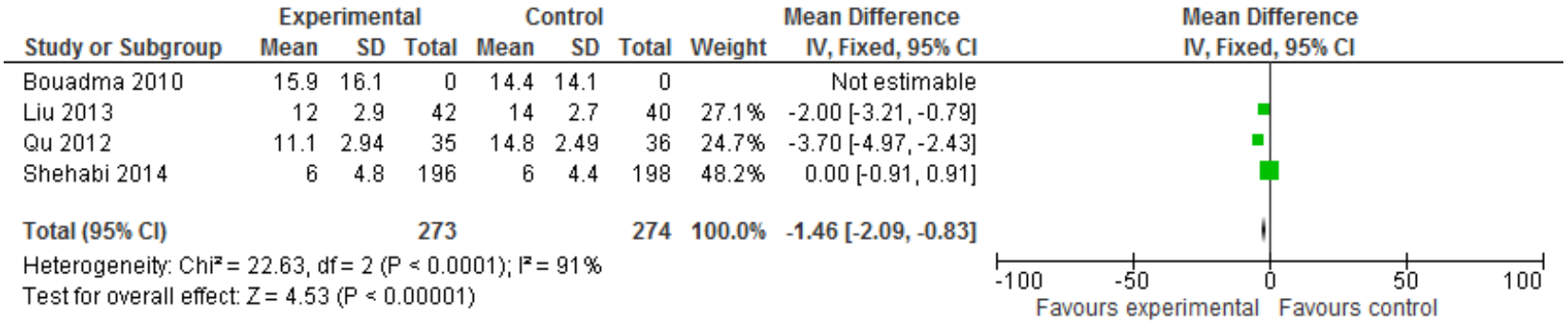
Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Figure 8. Procalcitonin versus usual care: hospital length of stay



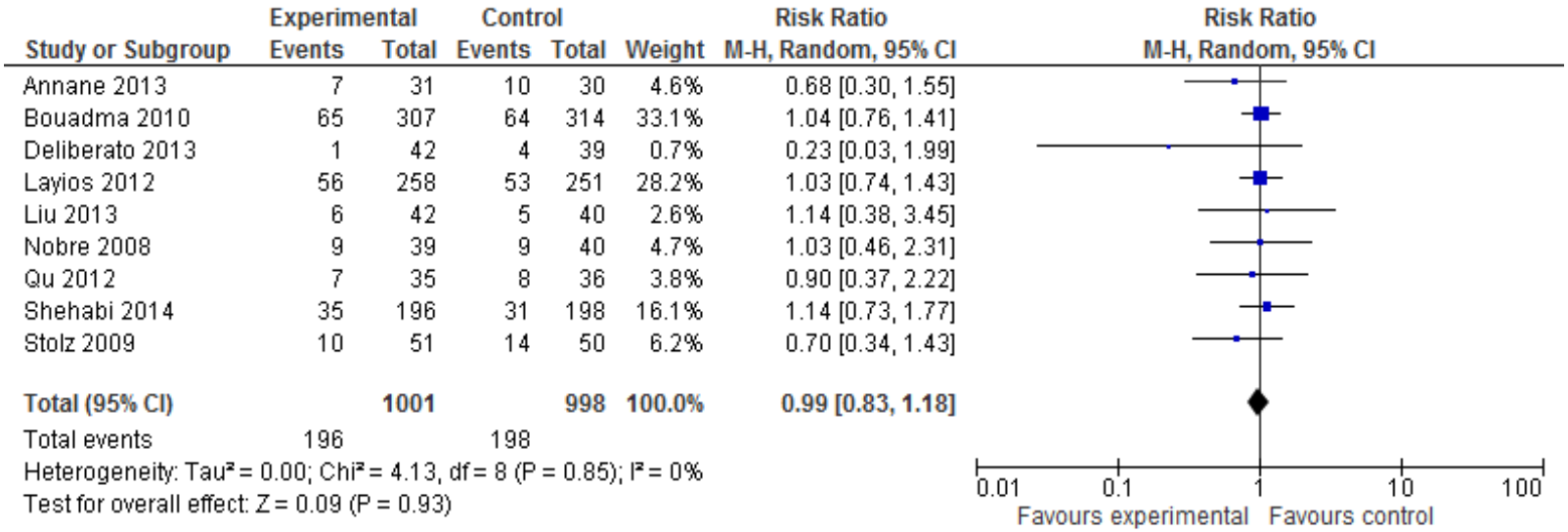
Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Figure 9. Procalcitonin versus usual care: ICU length of stay



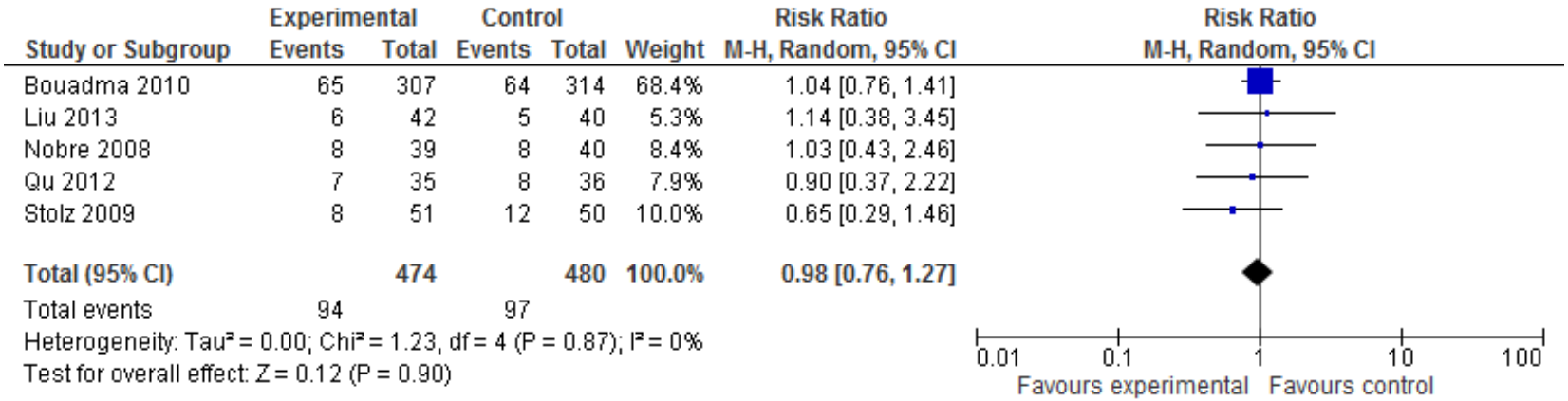
Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Figure 10. Procalcitonin versus usual care: Mortality outcome (longest follow-up)



Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Figure 11. Procalcitonin versus usual care: Mortality outcome (at 28 days)



Experimental: procalcitonin; **Control**: no biomarkers; **IV**: inverse variance

Table 28. Procalcitonin-guided de-escalation compared to routine care for guiding antimicrobial dosing in uncertain sepsis

Setting: Intensive Care Unit

Author(s): Mark E. Nunnally
Date: 3 March 2016
Question: Procalcitonin-guided de-escalation compared to routine care for guiding antimicrobial dosing in uncertain sepsis
Setting: Intensive Care Unit
Bibliography: 1. Westwood, et al. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis. Health Technol Assess 2015; 19(96):1-236 2. Shehabi Y, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014 Nov 15;190(10):1102-10

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Procalcitonin-guided de-escalation**	**routine care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Duration of antibiotic therapy												
5	randomized trials	serious [1]	serious [2]	not serious	not serious	none	619	628	-	MD **3.06 fewer days** (5.16 fewer to 0.97 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Duration of antibiotic therapy in only people with suspected or confirmed sepsis.												
2	randomized trials	serious [3]	not serious	not serious	not serious	none	81	80	-	MD **1.2 fewer days** (1.33 fewer to	⊕⊕⊕◯ MODERATE	IMPORTANT

										1.07 fewer)		
Duration of hospital stay (days)												
5 [4]	randomized trials	serious [1]	serious [5]	not serious	not serious	none	619	628	-	MD **3.73 fewer days** (6.48 lower to 0.98 lower)	⨁⨁◯◯ LOW	IMPORTANT
Duration of ICU stay (days)												
4	randomized trials	serious [6]	serious [7]	not serious	not serious	none	273	274	-	MD **1.46 fewer days** (2.09 fewer to 0.83 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Total mortality (longest follow-up)												
9	randomized trials	serious [8]	not serious	not serious	not serious [9]	none	196/1001 (19.6%)	198/998 (19.8%)	**RR 0.99** (0.83 to 1.18)	**2 fewer per 1,000** (from 34 fewer to 36 more)	⨁⨁⨁◯ MODERATE	CRITICAL
All-cause mortality (28 days)												
5	randomized trials	serious [10]	not serious	not serious	serious [11]	none	94/474 (19.8%)	97/480 (20.2%)	**RR 0.98** (0.76 to 1.27)	**4 fewer per 1,000** (from 49 fewer to	⨁⨁◯◯ LOW	CRITICAL

										55 more)		

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. Uncertain blinding in 4 trials. Incomplete outcomes assessment in 1 (Nobre).
2. I-squared 94%.
3. Uncertain blinding. Incomplete outcome data (Nombre).
4. For one RCT (Shehabi), we assume even distribution between groups, as data not available.
5. I-squared 70%.
6. Uncertain blinding in 3 trials. Incomplete outcomes assessment in 1 (Nobre).
7. I-squared 91%.
8. Uncertain blinding in all but 1 trial (Annane). Incomplete outcome data for 2 (Deliberato, Nobre).
9. Decision not to downgrade, given uncertain significance of confidence intervals for harm/benefit. (0.83, 1.18)
10. Uncertain blinding in all 5 trials. 1 trial (Nobre) assessed to have incomplete outcome data.
11. Confidence interval embraces important harm and benefit.

Figure 12. Impact of early source control on mortality.

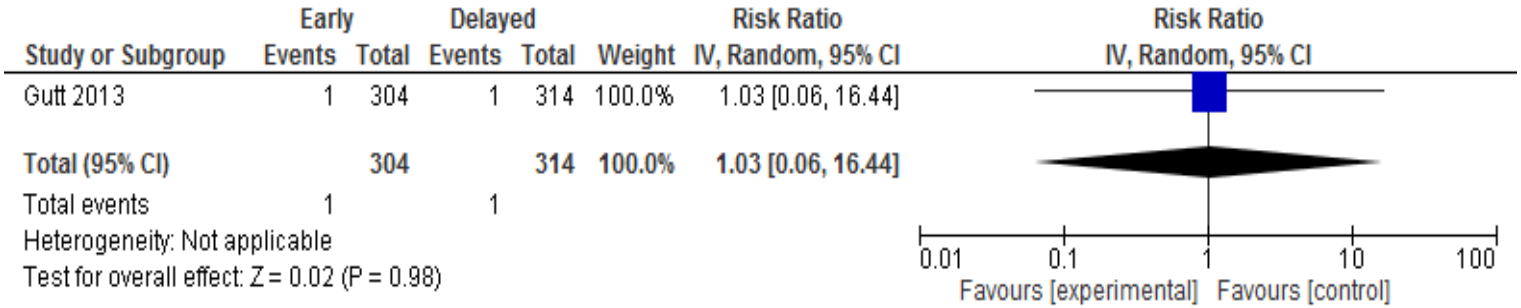


Figure 13. Impact of early source control on complications.

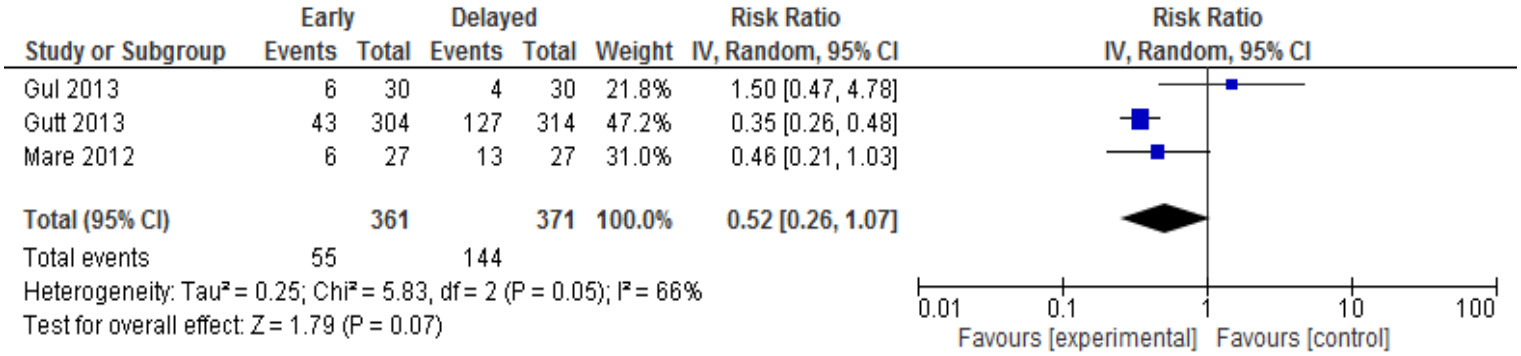


Figure 14. Impact of early source control on hospital length of stay

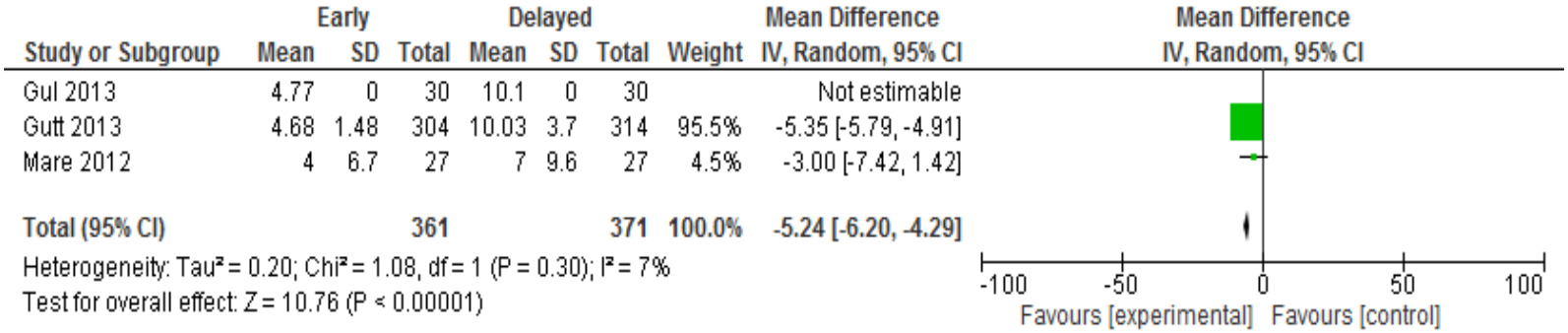


Table 29. Early compared to late cholecystectomy for cholecystitis

Author(s): Mark E. Nunnally
Date: 7 August 2016
Question: Early compared to late cholecystectomy for cholecystitis
Setting: Hospitalized patients
Bibliography: 1. Gutt CN et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). Ann Surg 2013;258(3):385-93 2. Gul R et al. Comparison of early and delayed laparoscopic cholecystectomy for acute cholecystitis: Experience from a single center. North American Journal of Medical Sciences 2013;5(7):414-8 3. Mare LD et al. Delayed versus early laparoscopic cholecystectomy for acute cholecystitis: A prospective randomized study. HPB 2012;14:130 (abstract)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early**	**late cholecystectomy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	1/304 (0.3%)	1/314 (0.3%)	**RR 1.03** (0.06 to 16.44)	**0 fewer per 1,000** (from 3 fewer to 49 more)	⨁⨁◯◯ LOW	CRITICAL
Patients with complications												
3	randomized trials	not serious	serious [2]	serious [3]	not serious	none	55/361 (15.2%)	144/371 (38.8%)	**RR 0.52** (0.26 to 1.07)	**186 fewer per 1,000** (from 27 more to 287 fewer)	⨁⨁◯◯ LOW	IMPORTANT

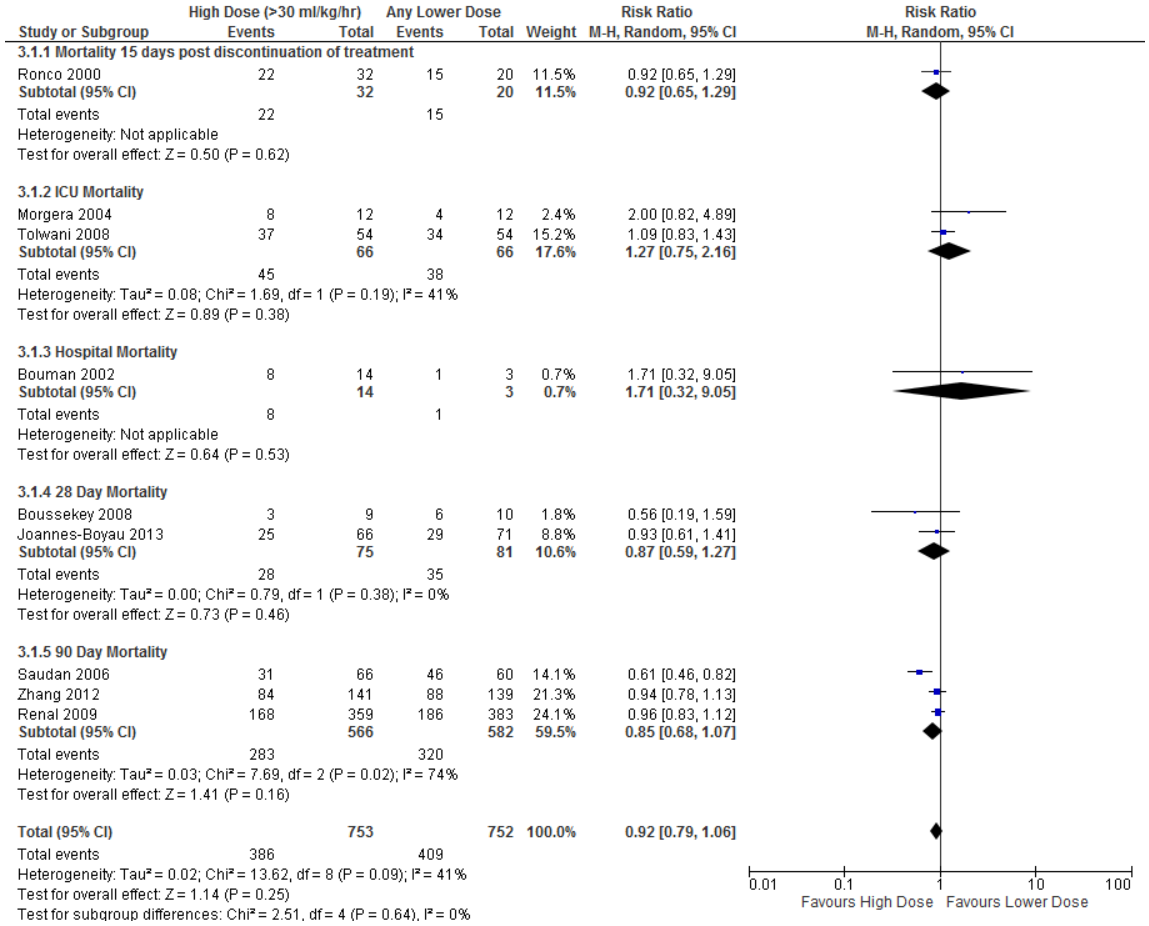
Hospital length of stay												
3	randomized trials	not serious	not serious	serious [3]	not serious	none	361	371	-	MD **5.24 lower** (6.2 lower to 4.29 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. We downgraded the quality of evidence by two levels for imprecision, there only two events.
2. We downgraded the quality of evidence for inconsistency by one level, the I^2 =66%.
3. We downgraded the quality of evidence for indirectness of the population, the patient population not likely as severe as PICO population.

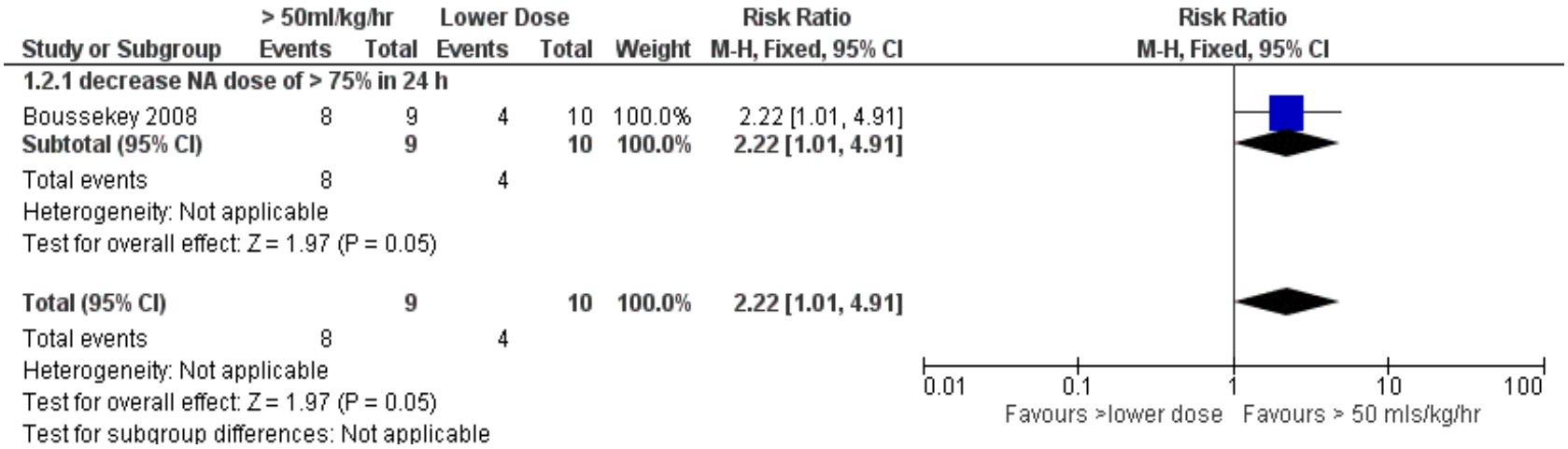
ADJUNCTIVE THERAPY

Figure 15. High dose CRRT versus lower dose: Mortality Outcome



M-H: Mantel-Haenszel; **CRRT:** Continuous renal replacement therapy

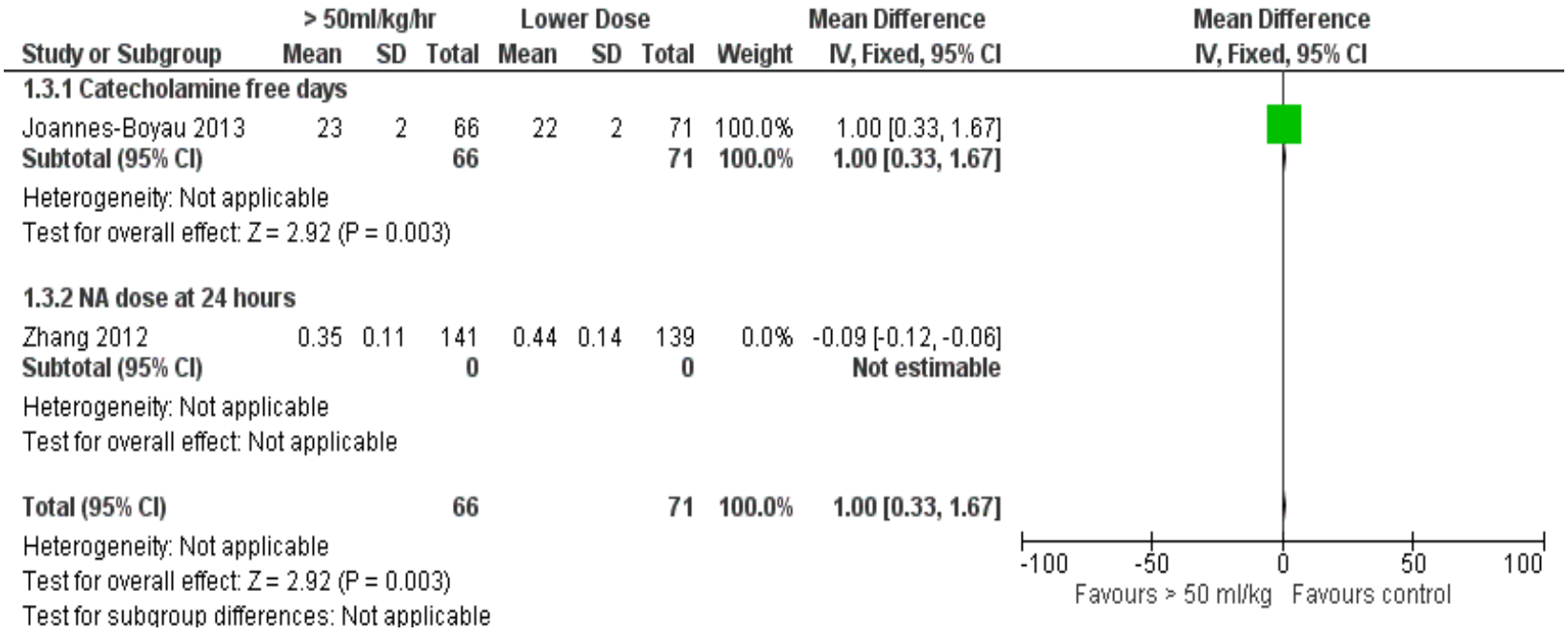
Figure 16. High dose CRRT verus lower dose: Reduction in Norepinephrine dose *



M-H: Mantel-Haenszel; **CRRT:** Continuous renal replacement therapy

* Decrease in Norepinephrine dose of > 75% in 24 hours

Figure 17. High dose CRRT verus lower dose : Catecholamine free days outcome



IV: Inverse variance; **CRRT:** Continuous renal replacement therapy

Figure 18. High dose CRRT versus lower dose: Renal recovery Outcome

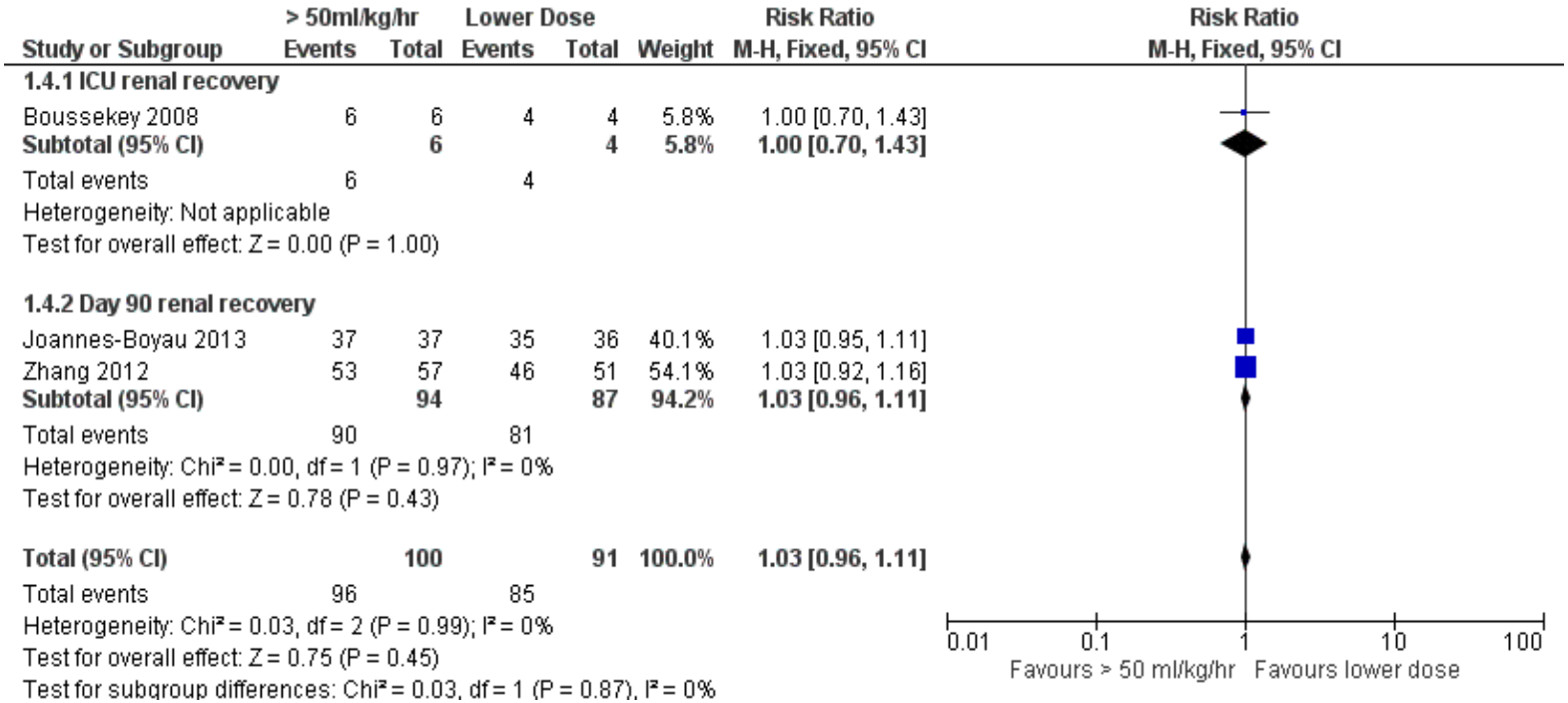


Table 30. High dose (>30 ml/kg/hr) CRRT compared to lower dose CRRT in critically ill patients with sepsis and acute kidney injury

Author(s): Craig French, Mark E. Nunnally
Date: 18 July 2016
Question: Any high dose (>30 ml/kg/hr) CRRT compared to Any lower dose CRRT in critically ill patients with sepsis and acute kidney injury affect outcome?
Setting: Intensive care unit

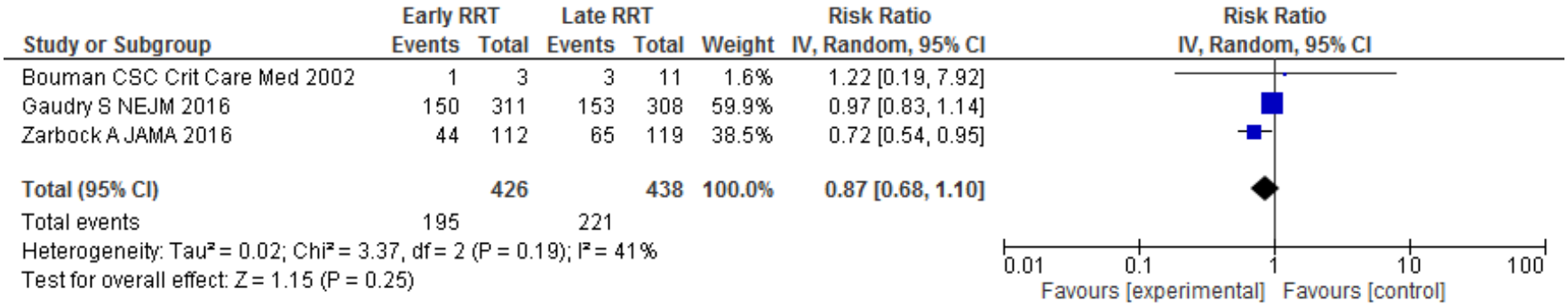
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Any high dose (>30 ml/kg/hr) CRRT**	**Any lower dose CRRT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
9	randomized trials	serious [1]	not serious	not serious	serious [2]	none	386/753 (51.3%)	409/752 (54.4%)	**RR 0.92** (0.79 to 1.06)	**44 fewer per 1,000** (from 33 more to 114 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality - Mortality 15 days post discontinuation of treatment												
1	randomized trials	serious [1]	not serious	not serious	serious [2]	none	22/32 (68.8%)	15/20 (75.0%)	**RR 0.92** (0.65 to 1.29)	**60 fewer per 1,000** (from 218 more to 262 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality - ICU Mortality												

2	randomized trials	serious [3]	serious [4]	not serious	serious [2]	none	45/66 (68.2%)	38/66 (57.6%)	**RR 1.26** (0.76 to 2.11)	**150 more per 1,000** (from 138 fewer to 639 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - Hospital Mortality												
1	randomized trials	serious [5]	not serious	not serious	very serious [6]	none	8/14 (57.1%)	1/3 (33.3%)	**RR 1.71** (0.32 to 9.05)	**237 more per 1,000** (from 227 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality - 28 Day Mortality												
2	randomized trials	not serious	not serious	not serious	serious [2]	none	28/75 (37.3%)	35/81 (43.2%)	**RR 0.87** (0.59 to 1.27)	**56 fewer per 1,000** (from 117 more to 177 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality - 90 Day Mortality												
3	randomized trials	not serious	serious [7]	not serious	serious [2]	none	283/566 (50.0%)	320/582 (55.0%)	**RR 0.85** (0.68 to 1.07)	**82 fewer per 1,000** (from 38 more to 176 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **ICU**: Intensive care unit

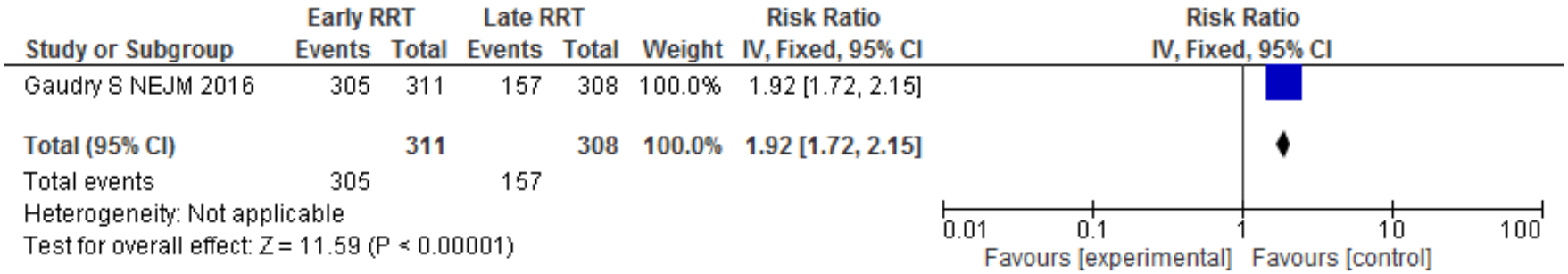
1. We downgraded the quality of evidence for risk of bias by one level, there was no blinding of caregivers, uncertain blinding of outcome assessment. At least 5 contributing studies were post hoc assessments.
2. We downgraded the quality of evidence by one level for imprecision, the 95 % CI embrace harm and benefit.
3. Imbalances in baseline data, primary and secondary outcomes not defined for 1 study (Morgera 2004).
4. I^2 =41%. Visual inspection of Forest plot suggests significant heterogeneity.
5. Post hoc analysis of unpublished data. Significant imbalances between groups.
6. Wide CI embracing harm and benefit. 9 total events.
7. I^2 =74%. visual inspection of Forest plot suggests significant heterogeneity.

Figure 19. Early RRT versus Late RRT: Mortality Outcome



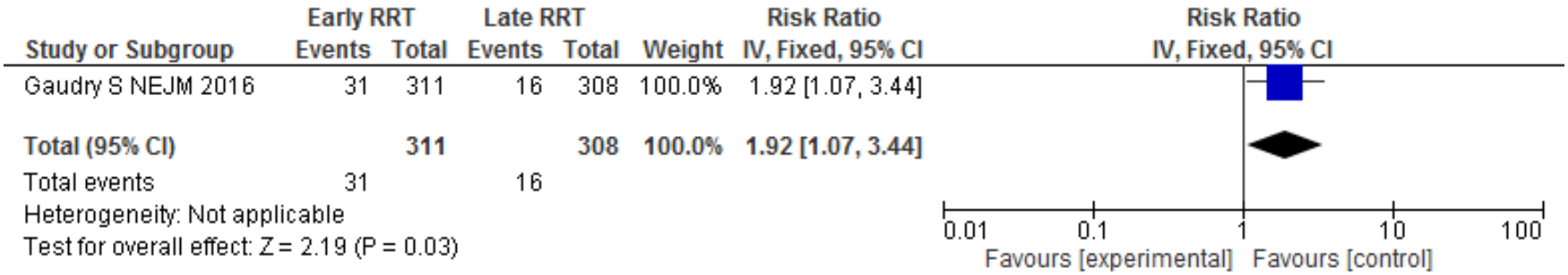
RRT: Renal replacement therapy; **IV:** Inverse variance

Figure 20. Early RRT versus Late RRT: Initiation of RRT



RRT: Renal replacement therapy; **IV:** Inverse variance

Figure 21. Early RRT versus Late RRT: CLABSI Outcome



CLABSI: Central line associated blood stream infection**; RRT:** Renal replacement therapy; **IV:** Inverse variance

Table 31. Early RRT compared to late RRT for acute kidney injury and sepsis

Author(s): Mark E. Nunnally, Craig French
Date: 18 July 2016
Question: Early RRT compared to late RRT for acute kidney injury and sepsis
Setting: Intensive care unit
Bibliography: 1. Bouman CSC, et al. Crit Care med 2002;30(10) 2. Gaudry S, et al. New Engl J Med 2016;375(2) 3. Zarbock A., et al. JAMA 2016;315(20)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early RRT**	**late RRT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality, longest follow-up												
3	randomized trials	not serious	not serious [1]	serious [2]	serious [3]	none	195/426 (45.8%)	221/438 (50.5%)	**RR 0.87** (0.68 to 1.10)	**66 fewer per 1,000** (from 50 more to 161 fewer)	⊕⊕◯◯ LOW	CRITICAL
Percentage receiving RRT												
1	randomized trials	not serious	not serious	serious [4]	serious [3]	none	305/311 (98.1%)	157/308 (51.0%)	**RR 1.92** (1.72 to 2.15)	**469 more per 1,000** (from 367 more to 586 more)	⊕⊕◯◯ LOW	IMPORTANT
Catheter-related bloodstream infection												
1	randomized trials	not serious	not serious	serious [4]	serious [5]	none	31/311 (10.0%)	16/308 (5.2%)	**RR 1.92** (1.07 to 3.44)	**48 more per 1,000** (from 4 more to	⊕⊕◯◯ LOW	IMPORTANT

										127 more)		

CI: Confidence interval; **RR:** Risk ratio

1. I^2 =41%. Visual inspection of forest plot suggests significant heterogeneity.
2. We downgraded the quality of evidence for indirectness of population, 70% septic patients in Gaudry et al., uncertain in Zarbock et al.
3. We downgraded the quality of evidence for imprecision, wide CI embrace harm and benefit.
4. We downgraded the quality of evidence for indirectness of population, 70% septic patients in study (Gaudry).
5. We downgraded the quality of evidence for imprecision, small number of events (47 total events).

Figure 22. Effect of Intermittent vs. Continuous RRT on Mortality

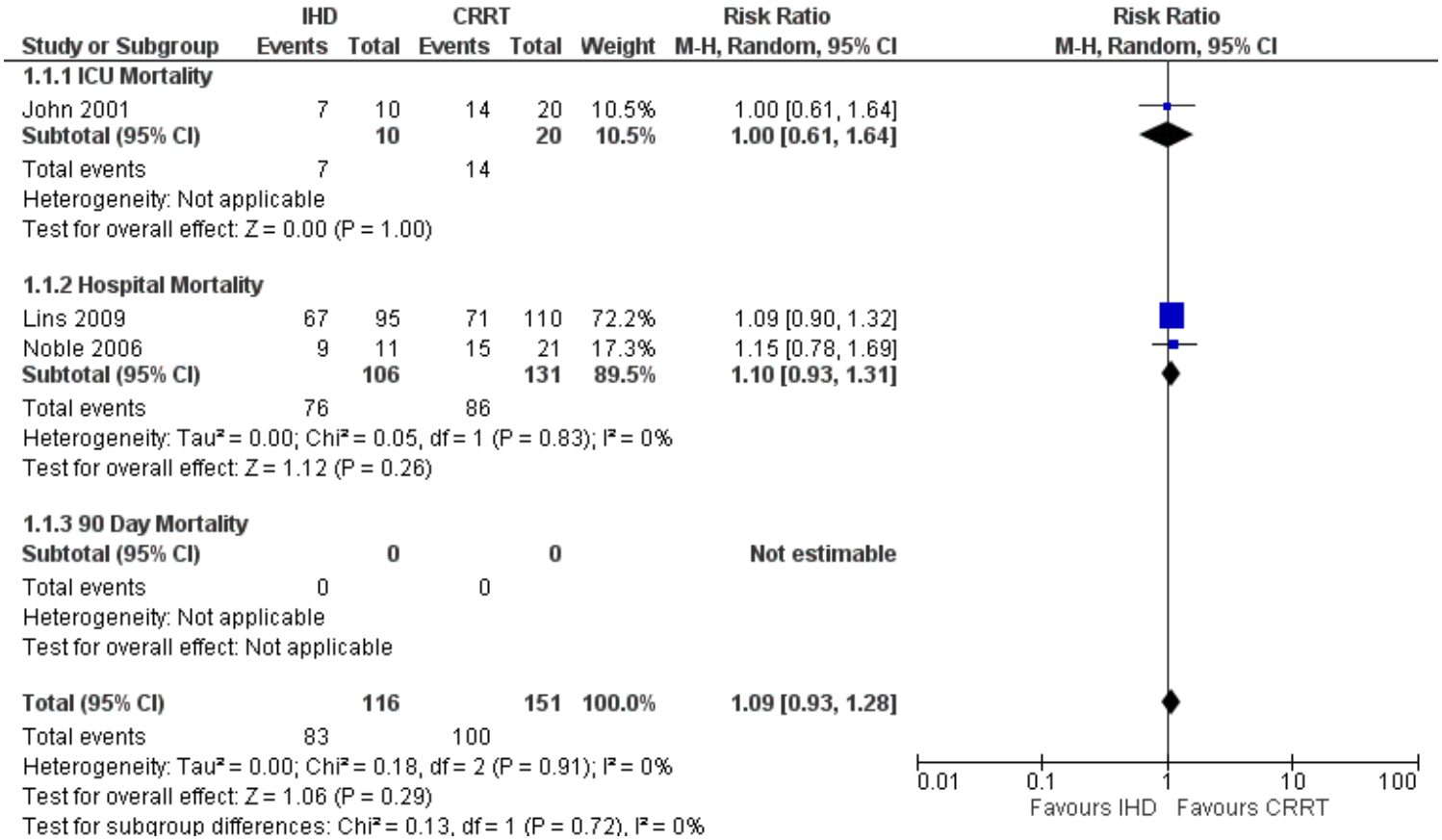


Table 32. Intermittent RRT compared to continuous RRT for sepsis and renal failure

Author(s): Craig French, Mark E. Nunnally
Date: June 2015
Question: Intermittent RRT compared to continuous RRT for sepsis and renal failure
Setting: ICU
Bibliography: John 2001, Lins 2009, Noble 2006

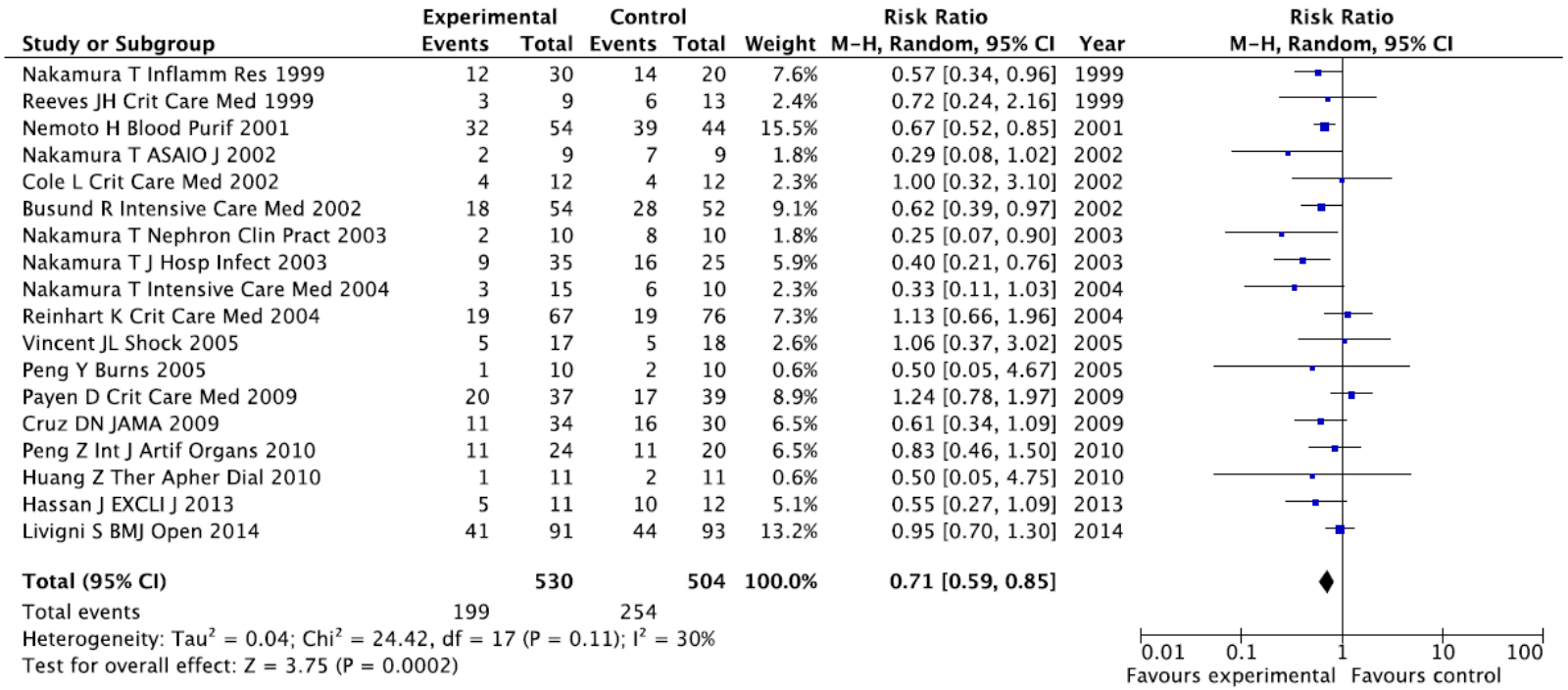
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intermittent RRT**	**continuous RRT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total Mortality												
3	randomized trials	serious [1]	not serious	not serious	serious [2]	none	83/116 (71.6%)	100/151 (66.2%)	**RR 1.09** (0.93 to 1.28)	**60 more per 1,000** (from 46 fewer to 185 more)	⊕⊕◯◯ LOW	CRITICAL
ICU Mortality												
1	randomized trials	not serious	not serious	not serious	serious [3]	none	7/10 (70.0%)	14/20 (70.0%)	**RR 1.00** (0.61 to 1.64)	**0 fewer per 1,000** (from 273 fewer to 448 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital Mortality												
2	randomized trials	serious [1]	not serious	not serious	serious [4]	none	76/106 (71.7%)	86/131 (65.6%)	**RR 1.10** (0.93 to 1.31)	**66 more per 1,000** (from 46 fewer to	⊕⊕◯◯ LOW	CRITICAL

										204 more)		

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for risk of bias, one study (Noble 2006) only partially randomized, conducted over 15 years
2. We downgraded the quality of evidence by one level for imprecision, the 95 % CI embraces 1, and total number of events was not large enough (183 total events).
3. We downgraded the quality of evidence by one level for imprecision, the 95% CI embraces 1, 21 total events
4. We downgraded the quality of evidence by one level for imprecision, the 95% CI embraces 1, 162 total events.

Figure 23. Blood purification therapy in patients with sepsis: Mortality Outcome



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nakamura T Inflamm Res 1999	12	30	14	20	7.6%	0.57 [0.34, 0.96]	1999
Reeves JH Crit Care Med 1999	3	9	6	13	2.4%	0.72 [0.24, 2.16]	1999
Nemoto H Blood Purif 2001	32	54	39	44	15.5%	0.67 [0.52, 0.85]	2001
Nakamura T ASAIO J 2002	2	9	7	9	1.8%	0.29 [0.08, 1.02]	2002
Cole L Crit Care Med 2002	4	12	4	12	2.3%	1.00 [0.32, 3.10]	2002
Busund R Intensive Care Med 2002	18	54	28	52	9.1%	0.62 [0.39, 0.97]	2002
Nakamura T Nephron Clin Pract 2003	2	10	8	10	1.8%	0.25 [0.07, 0.90]	2003
Nakamura T J Hosp Infect 2003	9	35	16	25	5.9%	0.40 [0.21, 0.76]	2003
Nakamura T Intensive Care Med 2004	3	15	6	10	2.3%	0.33 [0.11, 1.03]	2004
Reinhart K Crit Care Med 2004	19	67	19	76	7.3%	1.13 [0.66, 1.96]	2004
Vincent JL Shock 2005	5	17	5	18	2.6%	1.06 [0.37, 3.02]	2005
Peng Y Burns 2005	1	10	2	10	0.6%	0.50 [0.05, 4.67]	2005
Payen D Crit Care Med 2009	20	37	17	39	8.9%	1.24 [0.78, 1.97]	2009
Cruz DN JAMA 2009	11	34	16	30	6.5%	0.61 [0.34, 1.09]	2009
Peng Z Int J Artif Organs 2010	11	24	11	20	6.5%	0.83 [0.46, 1.50]	2010
Huang Z Ther Apher Dial 2010	1	11	2	11	0.6%	0.50 [0.05, 4.75]	2010
Hassan J EXCLI J 2013	5	11	10	12	5.1%	0.55 [0.27, 1.09]	2013
Livigni S BMJ Open 2014	41	91	44	93	13.2%	0.95 [0.70, 1.30]	2014
Total (95% CI)		**530**		**504**	**100.0%**	**0.71 [0.59, 0.85]**	
Total events	199		254				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 24.42$, df = 17 (P = 0.11); $I^2 = 30\%$

Test for overall effect: Z = 3.75 (P = 0.0002)

Experimental: Blood purification**; M-H**: Mantel-Haenszel

Table 33. Blood purification compared to placebo for sepsis

Author(s): Paolo Navalesi, Mark E. Nunnally
Date: 18 July 2016
Question: Blood purification compared to placebo for sepsis
Setting: Intensive care unit

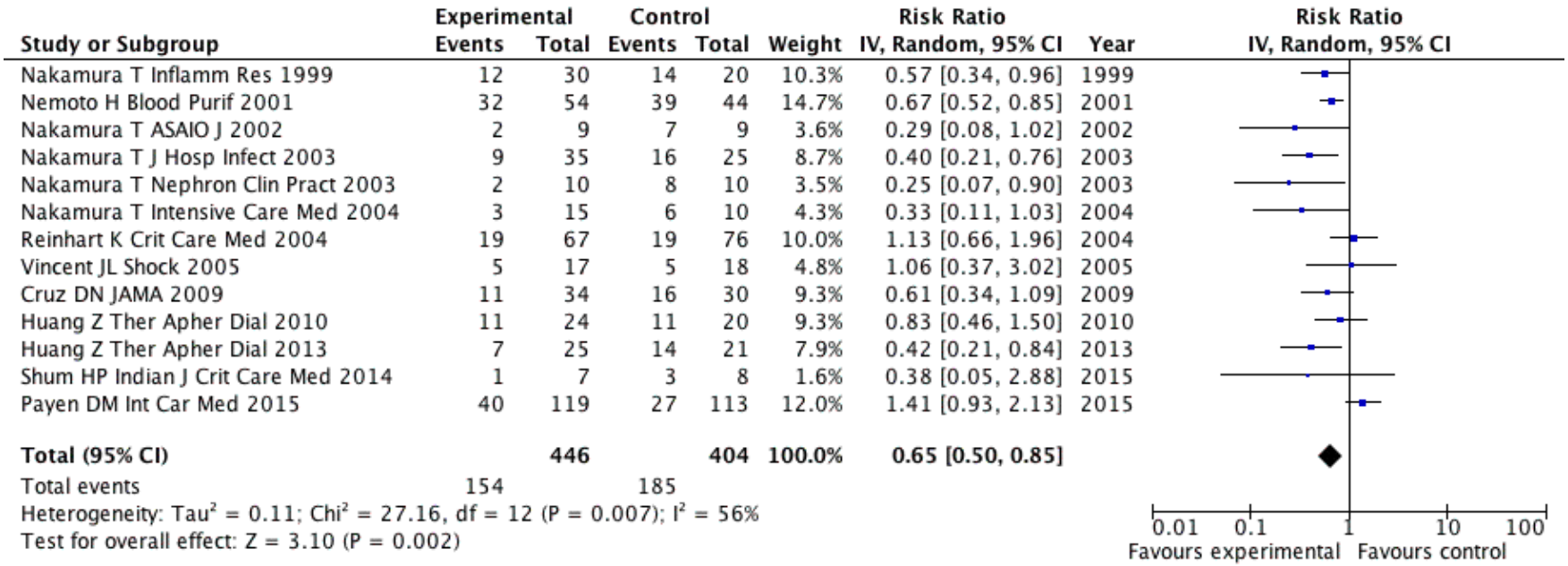
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Blood purification**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
18	randomized trials	not serious	serious [1]	very serious [2]	not serious	none	199/530 (37.5%)	254/504 (50.4%)	**RR 0.71** (0.59 to 0.85)	**146 fewer per 1,000** (from 76 fewer to 207 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
28-30 day mortality												
9	randomized trials	not serious	not serious [3]	very serious [2]	not serious	none	122/309 (39.5%)	147/302 (48.7%)	**RR 0.77** (0.63 to 0.95)	**112 fewer per 1,000** (from 24 fewer to 180 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospital mortality												

7	randomized trials	not serious	serious [4]	very serious [5]	not serious [6]	none	91/236 (38.6%)	116/210 (55.2%)	**RR 0.65** (0.48 to 0.88)	**193 fewer per 1,000** (from 66 fewer to 287 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence for inconsistency by one level, the I^2 =30%
2. We downgraded the quality of evidence by one level for indirectness of population, the analysis included small studies, mostly from Japan.
3. I^2 =24% therefore we did not downgrade for inconsistency
4. We downgraded the quality of evidence by one level for inconsistency, the I^2 =43%
5. We downgraded the quality of evidence by one level for indirectness of population, the analysis included small studies, mostly from Japan.
6. We did not downgrade for imprecision as we have 207 events

Figure 24. Hemoperfusion therapy in patients with sepsis: Mortality Outcome



Experminetal: Hemoperfusion; **IV:** Inverse variance

Table 34. Hemoperfusion compared to usual care for sepsis

Author(s): Paolo Navalesi, Mark E. Nunnally
Date: 18 July 2016
Question: Hemoperfusion compared to placebo for sepsis
Setting: Intensive care unit

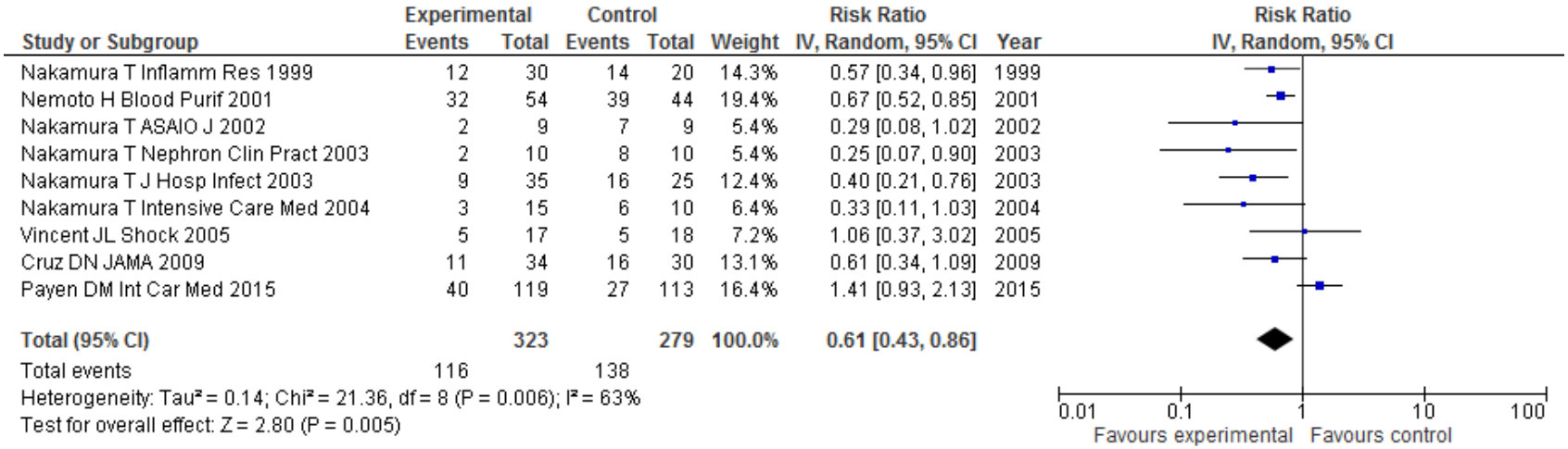
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hemoperfusion**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
13	randomized trials	not serious	serious [1]	very serious [2]	not serious	none	154/446 (34.5%)	185/404 (45.8%)	**RR 0.65** (0.50 to 0.85)	**160 fewer per 1,000** (from 69 fewer to 229 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
28 day mortality												
8	randomized trials	not serious	serious [3]	very serious [2]	serious [4]	none	119/347 (34.3%)	127/330 (38.5%)	**RR 0.82** (0.62 to 1.08)	**69 fewer per 1,000** (from 31 more to 146 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital mortality												
5	randomized trials	not serious	not serious	very serious [2]	not serious	none	46/133 (34.6%)	68/105 (64.8%)	**RR 0.55** (0.42 to 0.73)	**291 fewer per 1,000** (from 175	⨁⨁◯◯ LOW	CRITICAL

										fewer to 376 fewer)		

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. We downgrade the quality of evidence for inconsistency by one level, the I^2 =56%
2. We downgraded the quality of evidence by two levels for indirectness of population, the analysis included small studies, mostly from Japan.
3. We downgraded the quality of evidence by one level for inconsistency, the I^2 =45%
4. We downgraded the quality of evidence by one level for imprecision, the 95% CI embraces 1

Figure 25. Hemoperfusion with Polymyxin B in patients with sepsis: Mortality Outcome



Expermintal: Hemoperfusion with Polymyxin B; **IV:** Inverse variance

Table 35. Hemoperfusion with Polymxin B compared to usual care for sepsis

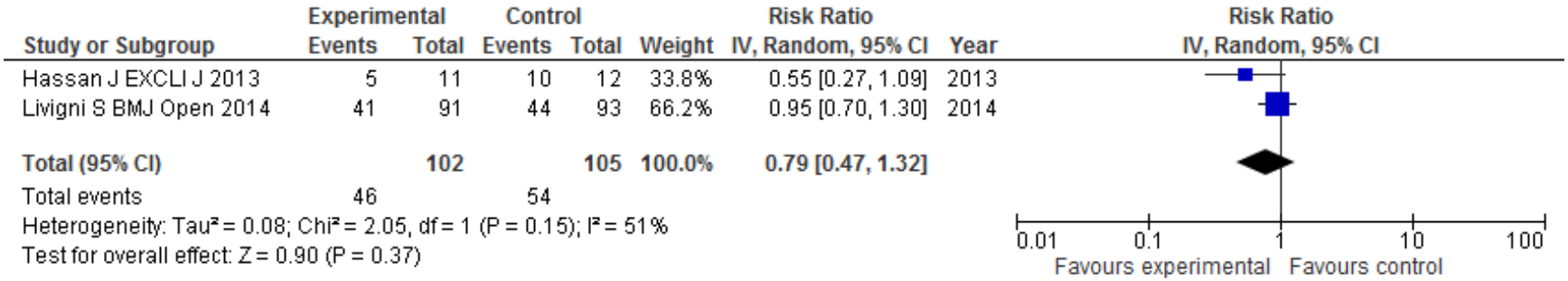
Author(s): Paolo Navalesi, Mark E. Nunnally
Date: 18 July 2016
Question: Hemoperfusion with Polymxin B compared to placebo for sepsis
Setting: ICU

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hemoperfusion with Polymxin B**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total Mortality												
9	randomized trials	not serious	serious [1]	very serious [2]	not serious	none	116/323 (35.9%)	138/279 (49.5%)	**RR 0.61** (0.43 to 0.86)	**193 fewer per 1,000** (from 69 fewer to 282 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

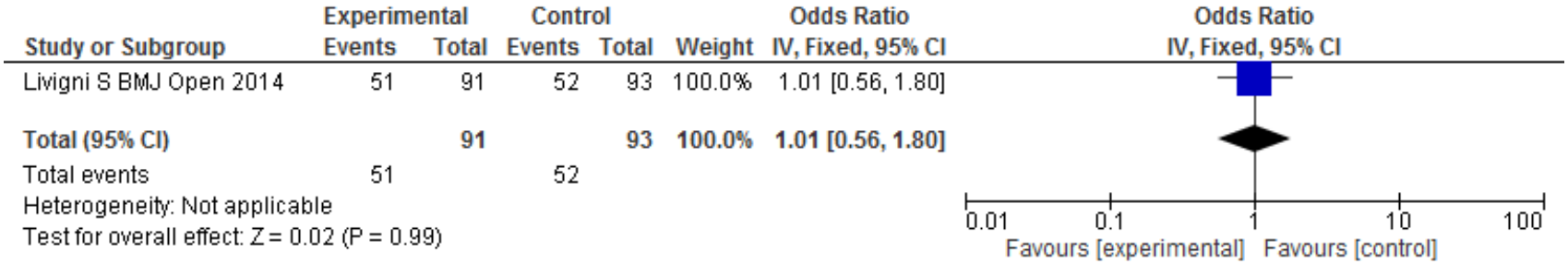
1. We downgraded the quality of evidence by one level for inconsistency, the I^2 =63%
2. We downgraded the quality of evidence by two levels for indirectness of population, the analysis included small studies, mostly from Japan.

Figure 26. Coupled plasma filtration and adsorption in patients with sepsis: Mortality Outcome (at discharge or 30 days)



Expermintal: coupled plasma filtration and adsorption; **IV:** inverse variance

Figure 27. Coupled plasma filtration and adsorption in patients with sepsis: New organ dysfunction Outcome



Expermintal: coupled plasma filtration and adsorption; **IV:** inverse variance

Table 36. Coupled plasma filtration adsorption compared to usual care for sepsis

Author(s): Paolo Navalesi, Mark E. Nunnally
Date: 18 July 2016
Question: Coupled plasma filtration adsorption compared to placebo for sepsis
Setting: Intensive care unit

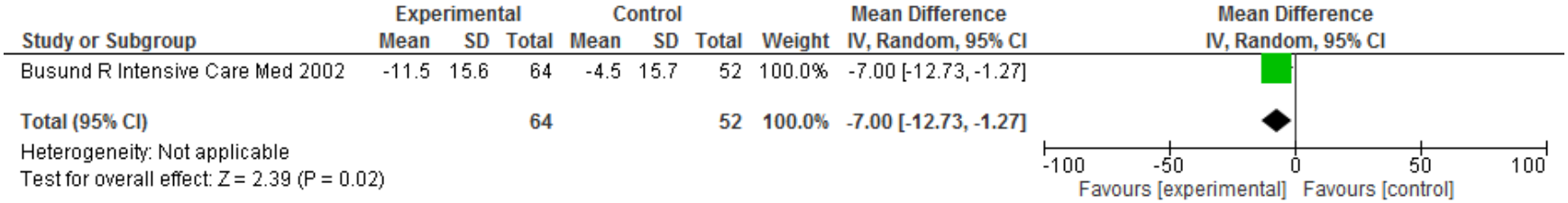
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Coupled plasma filtration adsorption**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality- discharge or 30 days												
2	randomized trials	not serious [1]	serious [2]	not serious	very serious [3]	none	46/102 (45.1%)	54/105 (51.4%)	**RR 0.79** (0.47 to 1.32)	**108 fewer per 1,000** (from 165 more to 273 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
New Organ Dysfunction												
1	randomized trials	not serious [4]	not serious	not serious	very serious [5]	none	51/91 (56.0%)	52/93 (55.9%)	**OR 1.01** (0.56 to 1.80)	**2 more per 1,000** (from 136 more to 144 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

1. Both studies unclear risk of bias. No downgrade because the outcome is less prone to bias.

2. We downgraded the quality of evidence by one level for inconsistency, the I^2 =51%
3. We downgraded the quality of evidence by two levels for imprecision, the 95% CI embraces 1 and the number of events is small (100 total events)
4. Although risk of bias unclear, we elected not to downgrade for risk of bias as we downgraded for other categories
5. We downgraded the quality of evidence by two levels for imprecision, the 95% CI embraces 1 and the number of events is small (103 total events)

Figure 28. Plasmapheresis In patients with sepsis: Change in APACHE III score



Experimental: Plasmapheresis**; IV:** Inverse variance

Table 37. Plasmapheresis compared to usual care for sepsis

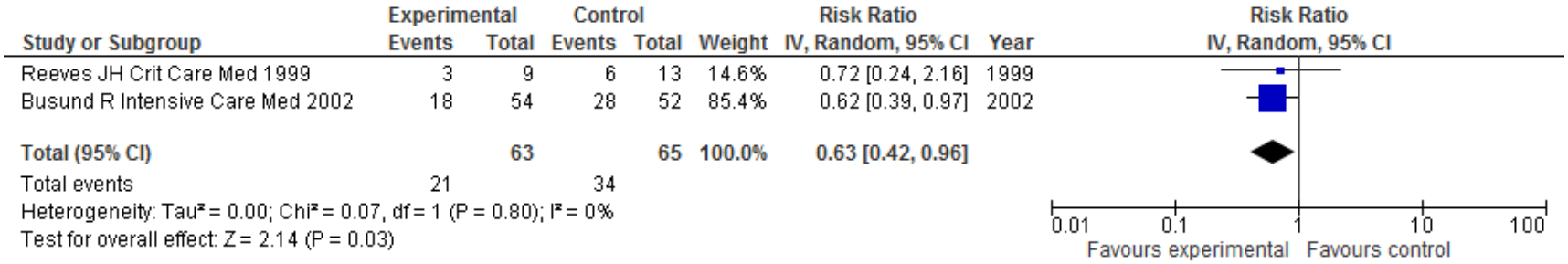
Author(s): Paolo Navalesi, Mark E. Nunnally
Date: 18 July 2016
Question: Plasmapheresis compared to placebo for sepsis
Setting: Intensive care unit
Bibliography:

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasmapheresis**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Change in APACHE III from day 1 to day 2												
1	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	64	52	-	MD 7 lower (12.73 lower to 1.27 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

1. Selective reporting plausible. Only change in APACHE reported
2. We downgraded the quality of evidence by two levels for imprecision, the sample size is small (116 patients), and the 95% CI embraces effect of questionable significance.

Figure 29. Plasma exchange in patients with sepsis: Mortality Outcome



Experimental: Plasma exchange; **IV:** Inverse variance

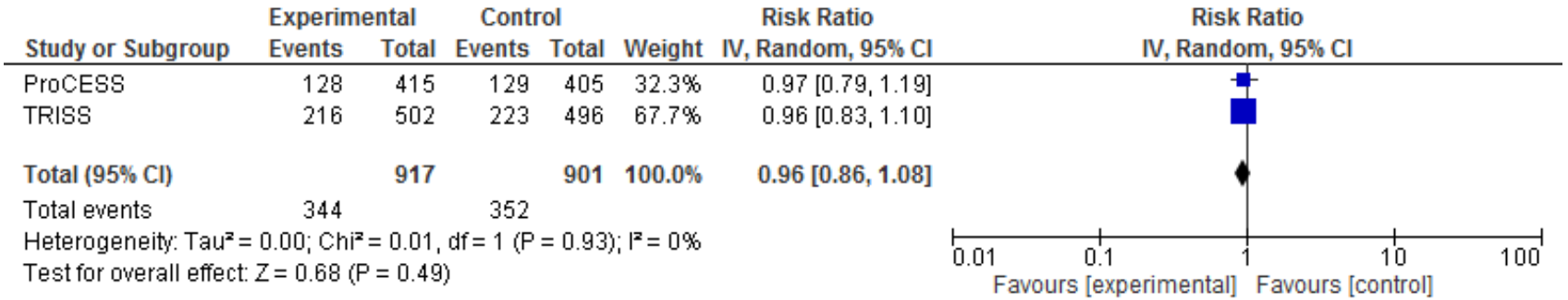
Table 38. Plasma exchange compared to usual care for sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasma Exchange**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total mortality												
2	randomized trials	not serious	not serious	not serious	very serious [1]	none	21/63 (33.3%)	34/65 (52.3%)	**RR 0.63** (0.42 to 0.96)	**194 fewer per 1,000** (from 21 fewer to 303 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

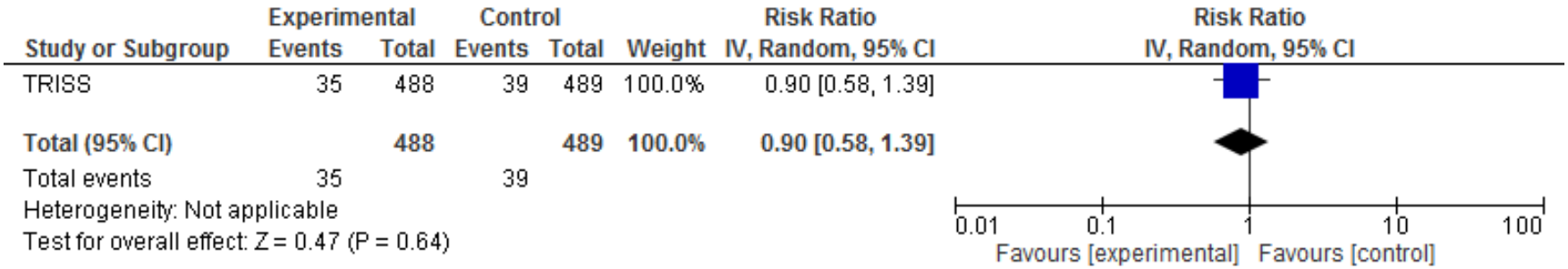
1. We downgraded the quality of evidence by two levels for imprecision, small number of events (55 total events)

Figure 30. Restrictive transfusion strategy versus liberal transfusion in patients with sepsis: 90-day Mortality Outcome



Experimental: Restrictive transfusion strategy; **Control:** Liberal transfusion strategy; **IV:** inverse variance

Figure 31. Restrictive transfusion strategy versus liberal transfusion in patients with sepsis: New ischaemic events



Experimental: Restrictive transfusion strategy; **Control:** Liberal transfusion strategy; **IV:** inverse variance

Table 39. Restrictive transfusion strategy (target or trigger 7-7.5 g/dL) compared to permissive strategy (10 g/dL) for sepsis

Setting: Intensive care unit
Author(s): Janice Zimmerman, Mark E. Nunnally
Question: Restrictive transfusion strategy (target or trigger 7-7.5 g/dL) compared to permissive strategy (10 g/dL) for sepsis
Setting: Intensive care unit
Bibliography: 1. ProCESS Invetigators. A randomized trial of protocol-based care for early septic shock. New Eng J Med 2014;370:1683-93 2. Holst LJ, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. New Eng J Med 2014;371(15):1381-91

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**restrictive transfusion strategy (target or trigger 7-7.5 g/dL)**	**permissive strategy (10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
90 d Mortality (TRISS only) (follow up: 90 days)												
1	randomized trials	not serious	not serious	not serious	not serious	none	216/502 (43.0%)	223/496 (45.0%)	**RR 0.94** (0.78 to 1.09)	**27 fewer per 1000** (from 40 more to 99 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality (at 90 days)												
2	randomized trials [1]	not serious	not serious	not serious	not serious	none	344/917 (37.5%)	352/901 (39.1%)	**RR 0.96** (0.86 to 1.08)	**16 fewer per 1000** (from 31 more to 55 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Ischemic events											
1	randomized trials	not serious	not serious	not serious	not serious	none	35/488 (7.2%)	39/489 (8.0%)	**RR 0.90** (0.58 to 1.39)	**8 fewer per 1000** (from 31 more to 33 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. ProCESS randomized by resuscitation protocol, which included different transfusion goals. This, however, was part of a more complex intervention. Hemoglobin goal 7.5 versus 10 g/dL.

Table 40. Erythropoietin-receptor agonists compared to placebo for sepsis

Author(s): Mark E. Nunnally
Date: 18 July 2016
Question: Erythropoietin-receptor agonists compared to placebo for sepsis
Setting: intensive care units
Bibliography: Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. Canadian Medical Association Journal. 2007 Sep 25;177(7):725-34.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**erythropoietin-receptopr agonists**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 21-140 days)												
9	randomized trials	not serious [1]	not serious	serious [2]	not serious	none	238/1695 (14.0%)	255/1619 (15.8%)	**OR 0.86** (0.71 to 1.05)	**19 fewer per 1,000** (from 7 more to 40 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

1. Only 3 studies judged to be at low risk of bias, however, we did not downgrade for risk of bias.
2. We downgraded the quality of evidence by one level for indirectness of population, the population not representative of acutely septic patients. The 3 Corwin studies, which contribute the largest number of patients to the meta-analysis, did not enroll patients until they had been in the ICU for at least 48 h. The Silver study is indirect in that they enrolled patients in the first 7 days after transfer to a long-term acute care facility.

Table 41. Antithrombin III compared to placebo for sepsis

Author(s): Mark E. Nunnally
Date: 18 July 2016
Question: Antithrombin III compared to placebo for sepsis
Setting: Intensive care unit
Bibliography: Afshari A et al. The Cochrane Library, 2008, Issue 3

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antithrombin III**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality, overall												
20	randomized trials	serious [1]	not serious	not serious	not serious	none	667/1708 (39.1%)	699/1750 (39.9%)	**RR 0.96** (0.89 to 1.03)	**16 fewer per 1,000** (from 12 more to 44 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality, trials with low risk of bias												
8	randomized trials	not serious	not serious	not serious	not serious	none	536/1157 (46.3%)	561/1157 (48.5%)	**RR 0.95** (0.88 to 1.03)	**24 fewer per 1,000** (from 15 more to 58 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Bleeding events												

9	randomized trials	not serious	not serious	not serious	not serious	none	312/1447 (21.6%)	199/1482 (13.4%)	**RR 1.52** (1.30 to 1.78)	**70 more per 1,000** (from 40 more to 105 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for risk of bias, substantial loss to follow up in 6 trials. Not reported for 2.

Table 42. Recombinant thrombomodulin compared to no thrombomuodulin, placebo or heparin for sepsis

Author(s): Mark E. Nunnally
Date: 18 July 2016
Question: Recombinant thrombomodulin compared to no thrombomuodulin, placebo or heparin for sepsis
Setting: Intensive care unit
Bibliography: Yamakawa K et al, Int Soc Thrombosis and Haemostasis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**recombinant thrombomodulin**	**no thrombomuodulin, placebo or heparin**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-Cause mortality, 28-30 days (follow up: mean 28-30 days)												
3	randomized trials	not serious	not serious	not serious	serious [1]	none	77/421 (18.3%)	94/417 (22.5%)	**RR 0.81** (0.62 to 1.06)	**43 fewer per 1,000** (from 14 more to 86 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence for imprecision by one level, the 95% CI include both small harm and significant benefit.

Table 43. Heparin compared to placebo or usual care for sepsis

Author(s): Mark E. Nunnally
Date: 17 February 2016
Question: Heparin compared to placebo or usual care for sepsis
Setting: intensive care unit
Bibliography: Zarychanski R, et al. Crit Care Med, 2015

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**heparin**	**placebo or usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: Not recorded to 28 days)												
6	randomized trials	serious [1]	not serious	not serious	serious [2]	none	315/1244 (25.3%)	355/1233 (28.8%)	**RR 0.88** (0.77 to 1.00)	**35 fewer per 1,000** (from 0 fewer to 66 fewer)	⨁⨁◯◯ LOW	CRITICAL
Major hemorrhage												
3	randomized trials	serious [1]	not serious	not serious	serious [3]	none	42/1200 (3.5%)	52/1192 (4.4%)	**RR 0.79** (0.53 to 1.17)	**9 fewer per 1,000** (from 7 more to 21 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for risk of bias, unclear risk of bias in all but 1 trial
2. We downgraded the quality of evidence by one level for imprecision, the 95% CI includes no effect
3. We downgraded the quality of evidence by one level for imprecision, the 95% CI embraces harm and benefit.

Table 44. Steroids compared to placebo for Sepsis

Question: Steroids v control compared to placebo for Sepsis
Setting: Intensive care unit

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroids v control**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
28-Day all-cause mortality												
27	randomized trials	not serious	serious [1]	not serious	serious [2]	none [3]	474/1618 (29.3%)	495/1558 (31.8%)	**RR 0.87** (0.76 to 1.00)	**41 fewer per 1,000** (from 0 fewer to 76 fewer)	⨁⨁◯◯ LOW	CRITICAL
Shock reversal at d 7												
13	randomized trials	not serious	serious [4]	not serious	not serious	none	532/806 (66.0%)	395/755 (52.3%)	**RR 1.31** (1.14 to 1.50)	**162 more per 1,000** (from 73 more to 262 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. We downgraded the quality of evidence for inconsistency by one level, the I^2 =42%
2. We downgraded the quality of evidence for imprecision by one level, the 95% CI embraces 1

3. Funnel plot asymmetry noted, however, we did not downgrade for publication bias because we downgraded for other categories
4. We downgraded the quality of evidence for inconsistency by one level, the I^2 =57%

MECHANICAL VENTILATION

Table 45. Low tidal versus high tidal volume ventilation in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**low tidal volume ventilation (6ml/kg)**	**high tidal volume ventilation (12ml/kg)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: longest available)												
6	randomized trials	not serious [1]	not serious	not serious [2]	not serious	none	233/655 (35.6%)	274/642 (42.7%)	**RR 0.83** (0.72 to 0.95)	**73 fewer per 1000** (from 21 fewer to 120 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Duration of mechanical ventilation												
3	randomized trials	serious [3]	not serious	not serious [2]	serious [4]	none	144	144	-	MD **0.83 days lower** (1.92 lower to 0.27 higher)	⨁⨁◯◯ LOW	IMPORTANT

MD – mean difference, RR – relative risk

1. Intervention was not blinded in any of the trials however we did not downgrade the quality of evidence for the outcome of mortality.
2. The intervention and comparator did vary slightly from study to study and some used intervention of 8ml/kg rather than 6 or comparator of 10ml/kg rather than 12ml/kg. However, the signal seems robust and decision was made not to lower.
3. We downgraded the quality of evidence for risk of bias by one level, unblinded intervention for a subjective outcome that could be affected.
4. We downgraded the quality of evidence for imprecision by one level, wide confidence intervals do not exclude harm.

Table 46. Targeting plateau pressures in mechanically ventilated patients with sepsis

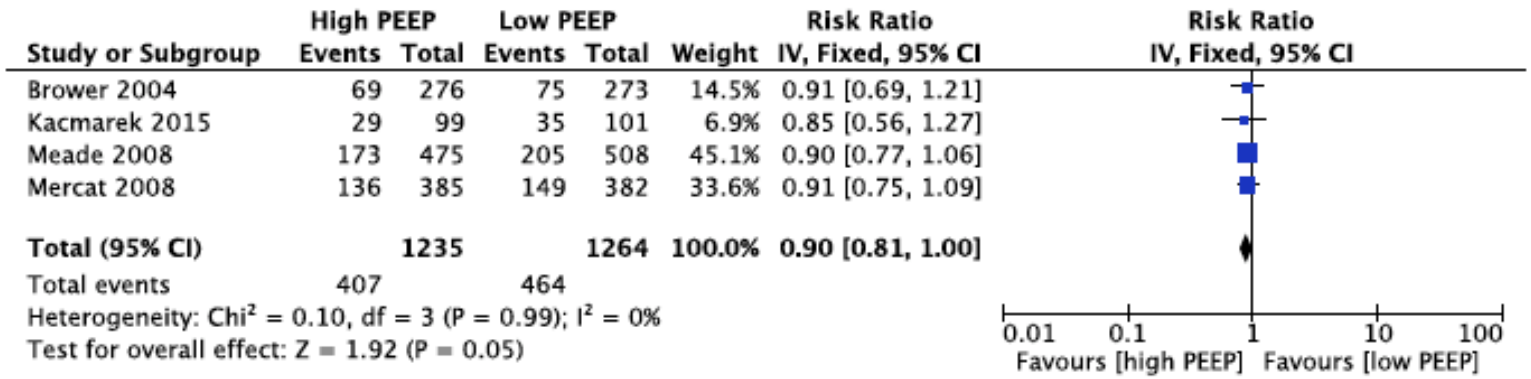
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upper limit of plateau pressure: 30 cmH2O**	**Plateau pressure > 30 cmH2O**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: in hospital)												
3	randomized trials	not serious	not serious	not serious	serious [1]	none	201/528 (38.1%)	245/561 (43.7%)	**RR 0.83** (0.67 to 1.02)	**74 fewer per 1000** (from 9 more to 144 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Barotrauma												
2	randomized trials	not serious	not serious	not serious	serious [2]	none	59/512 (11.5%)	51/550 (9.3%)	**RR 1.24** (0.87 to 1.77)	**22 more per 1000** (from 12 fewer to 71 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by one level for imprecision, the CI does not exclude harm.
2. We downgraded the quality of evidence by one level for imprecision, the Wide confidence intervals don't exclude harm or benefit.

Reference for Evidence Synthesis: Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD008807. DOI: 10.1002/14651858.CD008807.pub2.

Figure 32. High PEEP versus Low PEEP in mechanically ventilated patients: In-hospital Mortality



PEEP: Peak end expiratory pressure; **IV**: inverse variance

Table 47. High PEEP versus Low PEEP in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High PEEP**	**low PEEP**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: hospital stay)												
4	randomized trials	not serious	not serious	not serious	serious [1]	none	407/1235 (33.0%)	464/1264 (36.7%)	**RR 0.90** (0.81 to 1.00)	**37 fewer per 1000** (from 0 fewer to 70 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Barotrauma												
6	randomized trials	not serious	not serious	not serious	serious [2]	none	116/1245 (9.3%)	113/1247 (9.1%)	**RR 0.97** (0.66 to 1.42)	**3 fewer per 1000** (from 31 fewer to 38 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. CI crosses 1 and does not exclude no effect.
2. Wide confidence intervals do not exclude benefit or harm.

Reference for Evidence Synthesis: Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009098. DOI: 10.1002/14651858.CD009098.pub2.

Table 48. Recruitment maneuvers in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**recruitment maneuvers**	**no recruitment maneuvers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: in-hospital)												
10	randomized trials	serious [1]	not serious	not serious	not serious	none	281/780 (36.0%)	331/793 (41.7%)	**RR 0.84** (0.74 to 0.95)	**67 fewer per 1000** (from 21 fewer to 109 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Oxygenation (assessed with: Severe hypoxemia requiring rescue therapy)												
5	randomized trials	serious [2]	not serious	not serious	serious [3]	none	49/549 (8.9%)	73/567 (12.9%)	**RR 0.76** (0.41 to 1.40)	**31 fewer per 1000** (from 51 more to 76 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Statistically significant treatment benefit was lost when excluded the high risk of bias RCTs in sensitivity analysis.
2. High risk of bias in included studies.
3. Wide confidence intervals don't exclude harm.

Reference for Evidence Synthesis: Suzumura, E.A., Figueiró, M., Normilio-Silva, K. et al. Intensive Care Med (2014) 40: 1227. doi:10.1007/s00134-014-3413-6

Table 49. Prone ventilation compared to supine ventilation in patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prone ventilation**	**no prone ventilation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: 30-180 day mortality)												
8	randomized trials	not serious [1]	not serious	not serious	serious [2]	none	377/912 (41.3%)	409/846 (48.3%)	**RR 0.85** (0.71 to 1.01)	**73 fewer per 1000** (from 5 more to 140 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Oxygenation (assessed with: mean change in PF ratio)												
4	randomized trials	serious [3]	not serious	not serious	not serious	none	424	403	-	MD **24.03 higher** (13.35 higher to 34.71 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pressure Sores												
3	randomized trials	serious [3]	not serious	not serious	serious [4]	none	76/184 (41.3%)	54/182 (29.7%)	**RR 1.37** (1.05 to 1.79)	**110 more per 1000** (from 15 more to 234 more)	⊕⊕◯◯ LOW	IMPORTANT
Tracheal Tube Displacement												
8	randomized trials	serious [3]	not serious	not serious	serious [5]	none	117/1031 (11.3%)	103/990 (10.4%)	**RR 1.09** (0.85 to 1.39)	**9 more per 1000** (from 16 fewer to 41 more)	⊕⊕◯◯ LOW	IMPORTANT
Cardiac Arrythmia												
3	randomized trials	serious [3]	not serious	not serious	serious [6]	none	51/334 (15.3%)	76/308 (24.7%)	**RR 0.64** (0.47 to 0.87)	**89 fewer per 1000** (from 32 fewer to 131 fewer)	⊕⊕◯◯ LOW	IMPORTANT

MD – mean difference, RR – relative risk

1. Blinding not possible for this intervention. Did not lower for objective outcome of mortality.
2. Confidence intervals do not exclude lack of benefit. If no benefit then would affect clinical decision as resources/time required to perform prone ventilation.
3. Lack of blinding for a subjective outcome may have influenced outcome.
4. Despite confidence intervals that suggest harm, the number of events was small and therefore less confident overall with precision.
5. Wide confidence intervals do not exclude harm or benefit.
6. Despite confidence intervals that suggest benefit, the number of events was small leading to less certain estimates of precision.

Reference for Evidence Synthesis: Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD008095. DOI: 10.1002/14651858.CD008095.pub2.

Table 50. Head of bed elevation compared to no elevation in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HOB elevation between 30 and 45 degrees**	**no head of bed elevation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: days)												
3	randomized trials	not serious	not serious	serious [1]	serious [2]	none	45/168 (26.8%)	50/169 (29.6%)	**RR 0.90** (0.64 to 1.27)	**30 fewer per 1000** (from 80 more to 107 fewer)	⨁⨁◯◯ LOW	CRITICAL
VAP (assessed with: various scoring systems)												
3	randomized trials	serious [3]	serious [4]	serious [1,5]	very serious [6]	none	19/168 (11.3%)	24/169 (14.2%)	**RR 0.67** (0.23 to 2.01)	**47 fewer per 1000** (from 109 fewer to 143 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **VAP**: Ventilator associated pneumonia; **HOB**: Head of bed

1. One trial (Drakulovic, n=86) compared 45 degrees vs 0, one trial (Keeley, n=30) compared 45 degrees vs 25, one trial (van Niewenhoven, n=221) compared 45 degrees to 10.
2. Wide confidence intervals do not exclude harm.
3. Lack of blinding and a subjective outcome.
4. High Isquared value (66%).
5. Various definitions of VAP used in individual studies.
6. Wide confidence intervals and small number of events.

Reference for Evidence Synthesis: Niël-Weise et al. Critical Care 2011, 15:R111

Table 51. The use of weaning protocol compared to no protocol in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**weaning protocol**	**no protocol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: ICU Mortality)												
7	randomized trials	not serious	not serious	not serious	serious [1]	none	249/1119 (22.3%)	247/1115 (22.2%)	**OR 0.93** (0.58 to 1.48)	**12 fewer per 1000** (from 75 more to 80 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Successful Extubation (assessed with: Reintubation rate)												
11	randomized trials	not serious	not serious	not serious	serious [2]	none	70/747 (9.4%)	88/740 (11.9%)	**OR 0.74** (0.44 to 1.23)	**28 fewer per 1000** (from 23 more to 63 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of Mechanical Ventilation (assessed with: days)												
14	randomized trials	not serious [3]	serious [4]	not serious	not serious	none	1107	1098	-	MD **0.3 days fewer** (0.46 fewer to 0.14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

1. Wide confidence intervals do not exclude harm or benefit.
2. Wide confidence intervals do not exclude harm with weaning protocol.
3. Sensitivity analysis excluding high risk of bias studies showed no difference.
4. We downgraded the quality of evidence by one level for inconsistency, I^2 =70%.

Reference for Evidence Synthesis: Blackwood B, Burns KEA, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD006904. DOI: 10.1002/14651858.CD006904.pub3.

Table 52. The use of SBTs compared to no SBTs in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SBTs**	**no SBTs**	**Relative (95% CI)**	**Absolute (95% CI)**		
Duration of Mechanical Ventilation (assessed with: days)												
8	randomized trials	not serious	not serious	not serious	not serious [1]	none	600	588	-	MD **0.18 days fewer** (0.36 fewer to 0)	⊕⊕⊕⊕ HIGH	CRITICAL
Weaning Duration (assessed with: log hours)												
2	randomized trials	not serious	not serious	not serious	not serious	none	167	169	-	MD **3.23 log hours fewer** (3.57 fewer to 2.89 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SBT**: Spontaneous breathing trial

1. Confidence intervals do not rule out no effect of SBT however even if no effect would probably still perform SBT because of the positive impact on other critical outcomes.

Reference for Evidence Synthesis: Blackwood B, Burns KEA, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD006904. DOI: 10.1002/14651858.CD006904.pub3.

Table 53. The use of PAC compared to no PAC in mechanically ventilated patients with sepsis

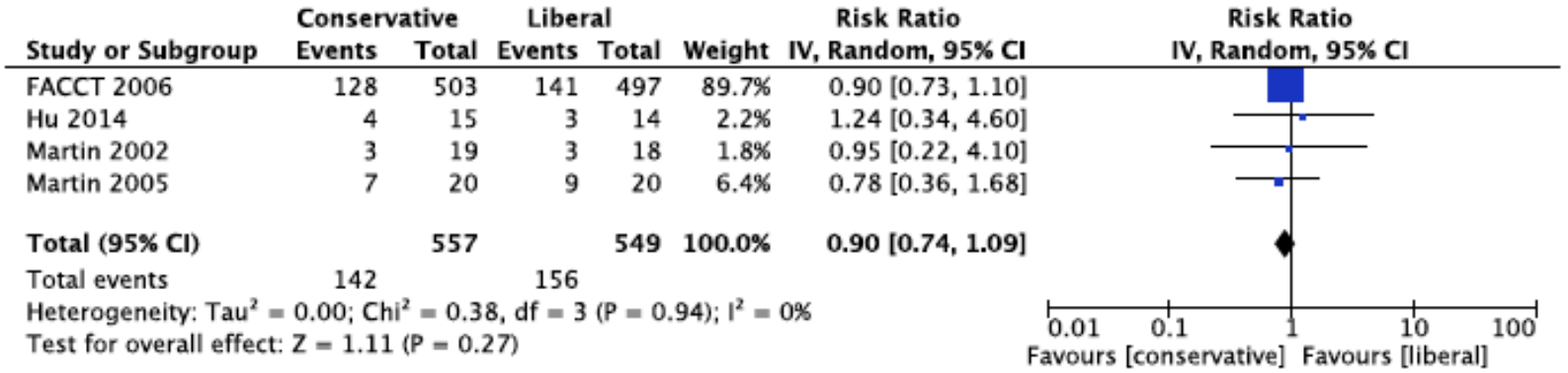
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PACs**	**no PACs**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: varying duration)												
5 [1]	randomized trials	not serious	not serious	not serious	not serious	none	741/1466 (50.5%)	728/1457 (50.0%)	**RR 1.02** (0.96 to 1.09)	**10 more per 1000** (from 20 fewer to 45 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ICU length of stay (assessed with: days)												
4 [1]	randomized trials	not serious	not serious	not serious	not serious	none	1370	1353	-	MD **0.15 days higher** (0.74 lower to 1.03 higher)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **PAC**: Pulmonary artery catheter

1. Only included general ICU patient subgroup from Cochrane review (not perioperative patients).

Reference for Evidence Synthesis: Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W, Young D, Harvey S, Rowan K. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD003408. DOI: 10.1002/14651858.CD003408.pub3.

Figure 33. Conservative versus liberal fluid strategy in mechanically ventilated patients



IV: Inverse variance

Table 54. Conservative versus liberal fluid strategy in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**conservative fluid strategy**	**liberal fluid strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
4	randomized trials	not serious [1]	not serious	not serious	serious [2]	none	142/557 (25.5%)	156/549 (28.4%)	**RR 0.90** (0.74 to 1.09)	**28 fewer per 1000** (from 26 more to 74 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Ventilator Free Days												
1	randomized trials	serious [3]	not serious	not serious	not serious	none	503	497	-	MD **2.5 days higher** (2.28 higher to 2.73 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU Free Days												
1	randomized trials	serious [3]	not serious	not serious	not serious	none	503	497	-	MD **2.2 days higher** (2.15 higher to 2.25 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. Unblinded intervention in largest study (FACCT) however objective outcome so did not lower for risk of bias.
2. Wide confidence intervals due to not exclude harm.
3. Unblinded intervention for subjective outcome could lead to bias.

Ventilator free days & ICU free days only reported in the FACCT trial.

Table 55. Inhaled Beta-agonists compared to placebo in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**inhaled B-agonists**	**no inhaled B-agonists**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital Mortality (assessed with: days)												
2	randomized trials	not serious	not serious	not serious	serious [1]	none	97/313 (31.0%)	76/293 (25.9%)	**RR 1.22** (0.95 to 1.56)	**57 more per 1000** (from 13 fewer to 145 more)	⊕⊕⊕◯ MODERATE	CRITICAL
MV Duration (assessed with: Ventilator free days)												
3	randomized trials	not serious	not serious	not serious	not serious	none	334	312	-	MD **2.19 days fewer** (3.68 fewer to 0.71 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

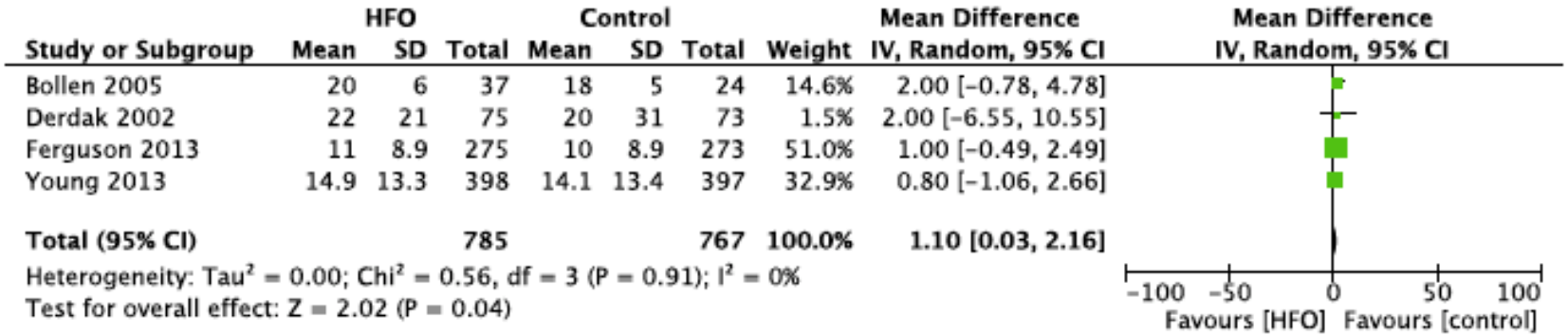
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. Wide confidence intervals do not exclude benefit.

Reference for Evidence Synthesis: Singh B, Tiwari AK, Singh K, Singh SK, Ahmed A, Erwin PJ, Franco PM. B2 Agonist for the Treatment of Acute Lung Injury: A Systematic Review and Meta-analysis. Respir Care 2014;59(2):288 –296.

We recommend against the use of beta-2 agonists for the treatment of patients with sepsis induced ARDS without bronchospasm (1B).

Figure 34. High Frequency Oscillation (HFO) versus no HFO in mechanically ventilated patients with ARDS: Duration of mechanical ventilation Outcome



HFO: High frequency Oscillation; **IV**: Inverse variance; **ARDS**: Acute respiratory distress syndrome

Table 56. High Frequency Oscillation (HFO) versus conventional ventilation in mechanically ventilated patients with ARDS and sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HFO**	**conventional mechanical ventilation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
5	randomized trials	not serious [1]	serious [2]	not serious	not serious	none	375/800 (46.9%)	340/780 (43.6%)	**RR 1.04** (0.83 to 1.31)	**17 more per 1000** (from 74 fewer to 135 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of mechanical Ventilation (assessed with: days)												
4	randomized trials	serious [3]	not serious	not serious	not serious	none	785	767	-	MD **1.1 days higher** (0.03 higher to 2.16 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **ARDS**: Acute respiratory distress syndrome; HFO: High frequency oscillation

1. 2 of 5 trials (Bollen 2005 and Ferguson 2013) were stopped early however sensitivity analysis excluding these 2 trials showed no significant effect on overall point estimate or confidence intervals.
2. We downgraded the quality of evidence by one level for inconsistency, I^2 >60%.
3. 2 trials stopped early. Sensitivity analysis loses significance when these trials are excluded.

Reference for Evidence Synthesis: Sud S, Sud M, Friedrich JO,Wunsch H, Meade MO, Ferguson ND, Adhikari NKJ. High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No. CD004085. DOI: 10.1002/14651858.CD004085.pub4.

Figure 35. Low versus high tidal volumes in mechanically ventilated patients: Mortality Outcome

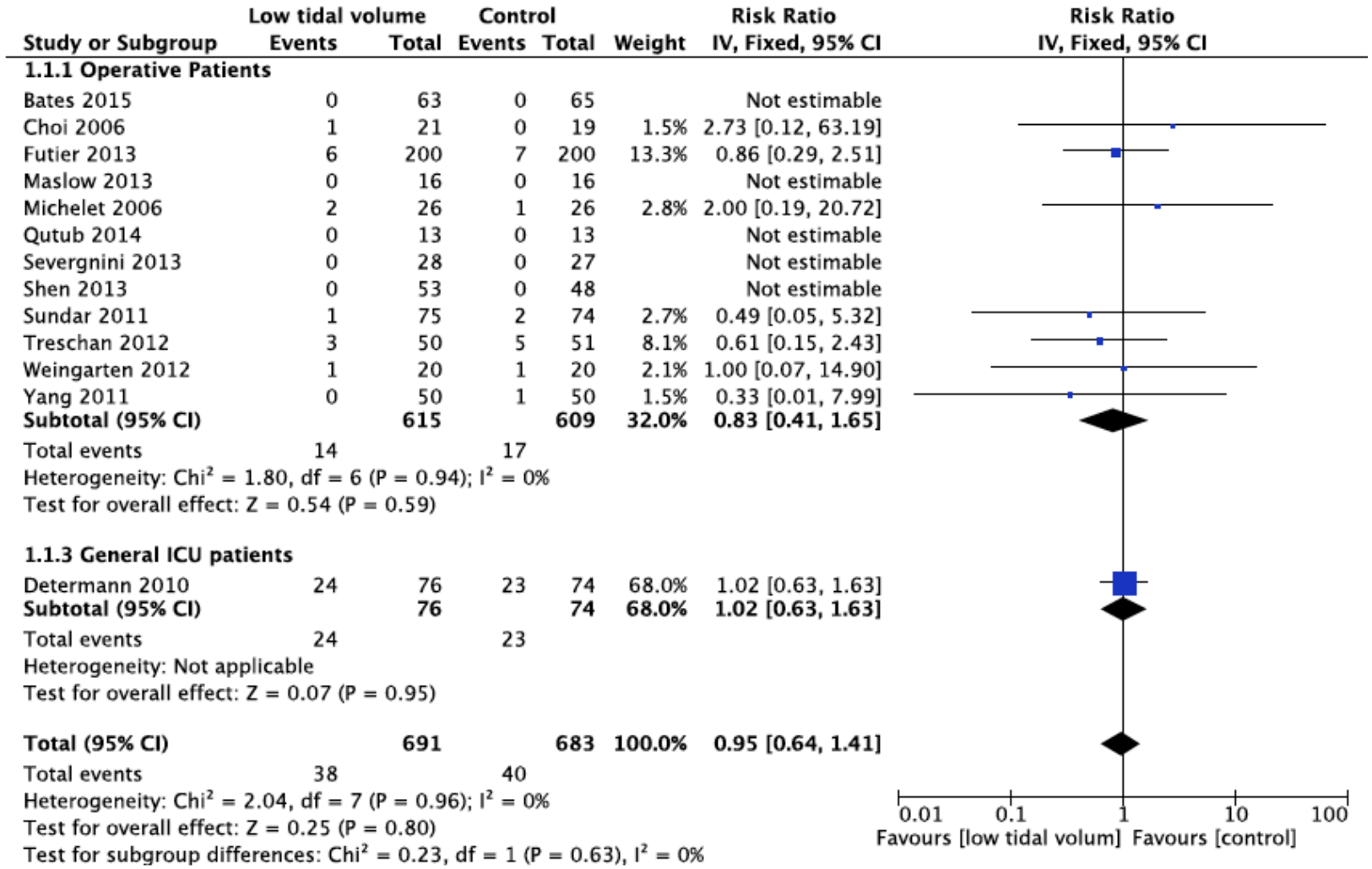
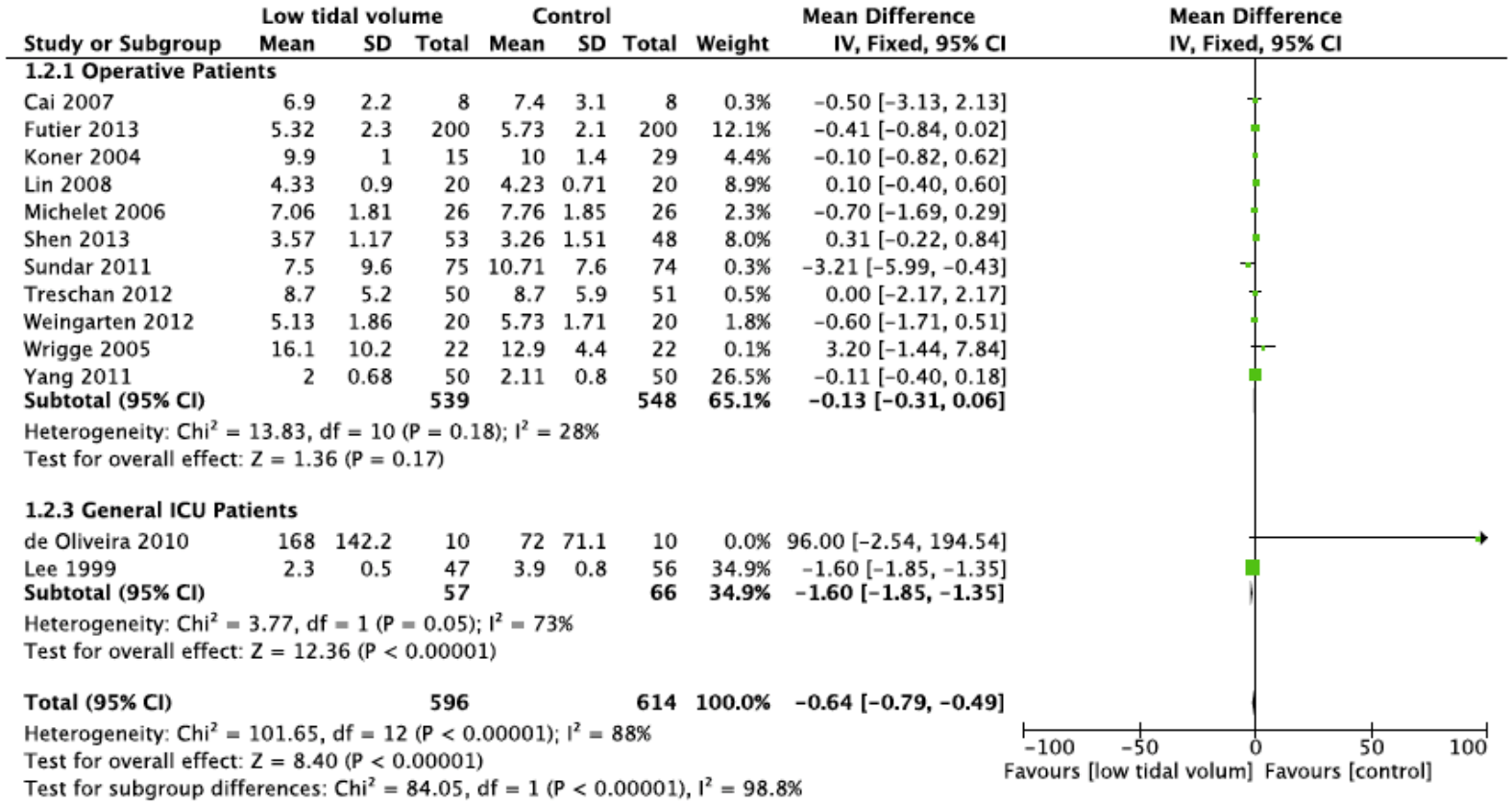
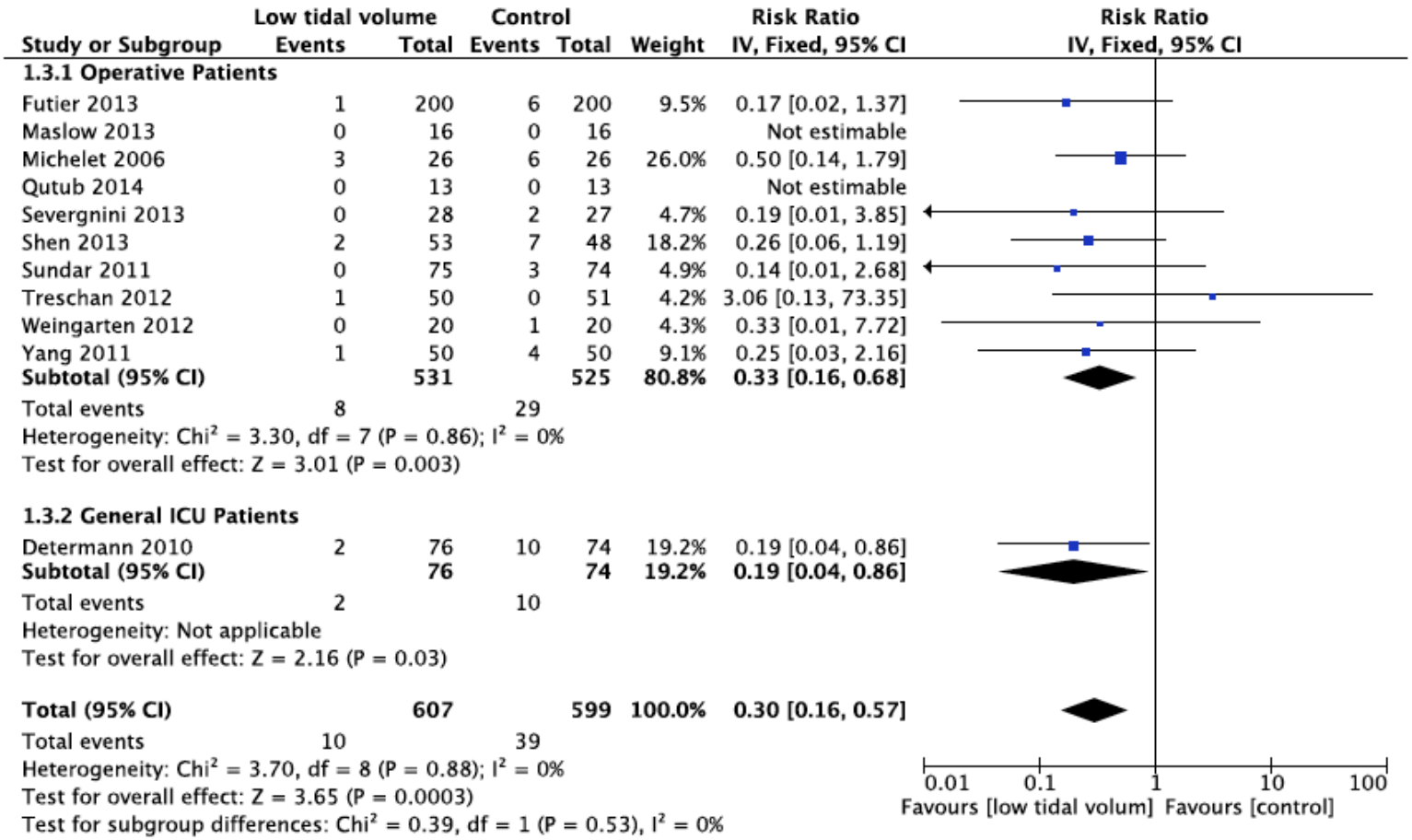


Figure 36. Low versus high tidal volumes in mechanically ventilated patients: Duration of mechanical ventilation Outcome



IV: Inverse variance

Figure 37. Low versus high tidal volumes in mechanically ventilated patients: Development of ARDS Outcome



ARDS: acute respiratory distress syndrome; **IV**: Inverse variance

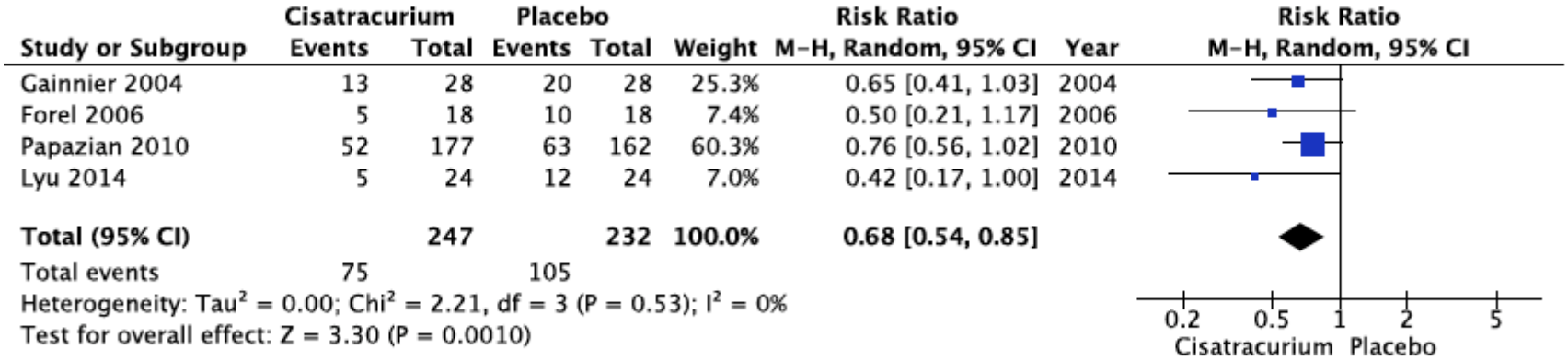
Table 57. Low versus high tidal volumes in mechanically ventilated patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low tidal volume ventilation**	**high tidal volume ventilation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: Longest available)												
13	randomized trials	not serious [1]	not serious	serious [2]	serious [3]	none	38/691 (5.5%)	40/683 (5.9%)	**RR 0.95** (0.64 to 1.41)	**3 fewer per 1000** (from 21 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
Duration of Mechanical Ventilation (assessed with: days)												
13	randomized trials	serious [4]	serious [5]	serious [2]	not serious	none	596	614	-	MD **0.64 days lower** (0.79 lower to 0.49 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Development of ARDS (assessed with: PF ratio)												
11	randomized trials	serious [4]	not serious	serious [2]	serious [6]	none	10/607 (1.6%)	39/599 (6.5%)	**RR 0.30** (0.16 to 0.57)	**46 fewer per 1000** (from 28 fewer to 55 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk

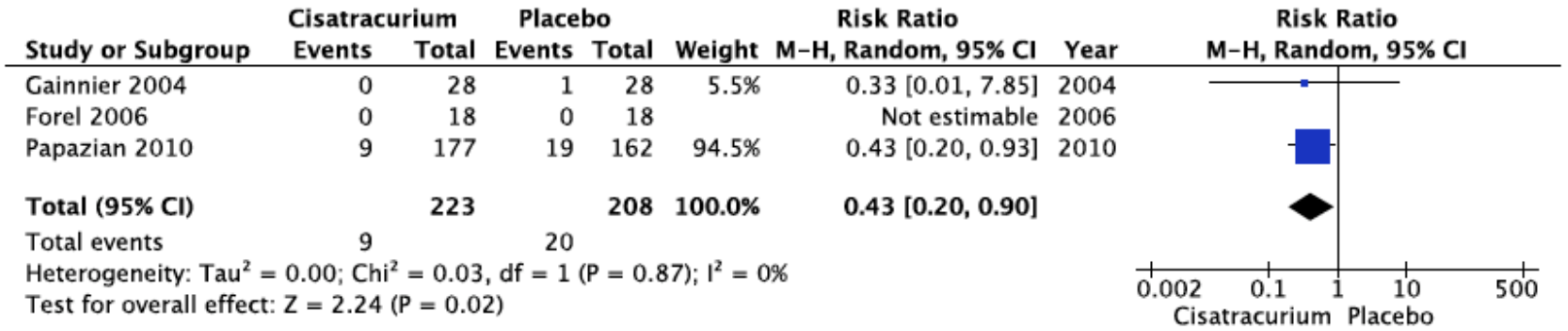
1. Intervention was not blinded in most studies however not lowered for ROB for objective outcome of mortality.
2. Studies were performed in a wide variety of patients. Only one study (68%) of the total weight was done in ICU patients. All other studies were done in the postoperative setting although some of these were in CV Surgery and ended up as ICU patients. Importantly the point estimate did not vary much between the operative and ICU subgroups.
3. Wide confidence intervals that do not exclude significant harm or benefit.
4. Intervention was not blinded in most studies.
5. High degree of statistical heterogeneity with I^2 >75%.
6. Despite tight confidence intervals that exclude harm, event numbers are small leading to imprecision

Figure 38. Neuromuscular blocking agents compared to placebo in mechanically ventilated patients with ARDS: Mortality Outcome



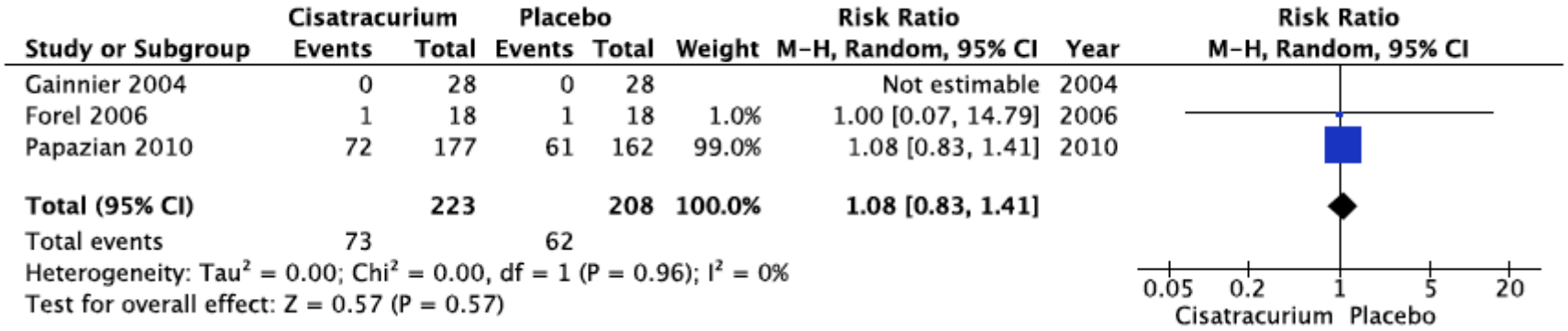
M-H: Mantel-Haenszel

Figure 39. Neuromuscular blocking agents compared to placebo in mechanically ventilated patients with ARDS: Barotrauma Outcome



M-H: Mantel-Haenszel

Figure 40. Neuromuscular blocking agents compared to placebo in mechanically ventilated patients with ARDS: ICU acquired weakness Outcome

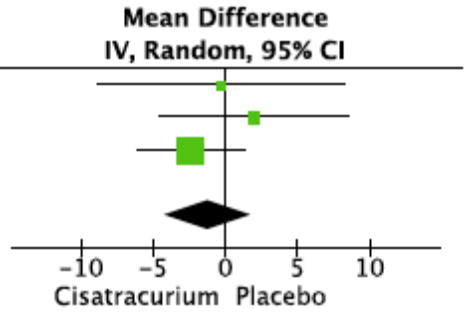


M-H: Mantel-Haenszel; **ICU**: Intensive care unit

Figure 41. Neuromuscular blocking agents compared to placebo in mechanically ventilated patients with ARDS: Duration of mechanical ventilation Outcome

Study or Subgroup	Cisatracurium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gainnier 2004	20.9	15	28	21.2	17.4	28	12.6%	-0.30 [-8.81, 8.21]	2004
Forel 2006	20	11.6	18	18	8.3	18	21.0%	2.00 [-4.59, 8.59]	2006
Papazian 2010	15.9	15.4	177	18.3	19	162	66.4%	-2.40 [-6.10, 1.30]	2010
Total (95% CI)			**223**			**208**	**100.0%**	**-1.21 [-4.23, 1.81]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, df = 2 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 0.79 (P = 0.43)



IV: Inverse variance

Table 58. Neuromuscular blocking agents compared to usual care/placebo in patients with ARDS and sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NMBA administration**	**not administering NMBA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 90 days)												
4	randomized trials	serious [1]	not serious [2]	not serious [3]	not serious	none	75/247 (34.1%)	105/232 (47.1%)	**RR 0.68** (0.54 to 0.85)	**132 fewer per 1000** (from 42 fewer to 198 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Barotrauma (assessed with: New pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele)												
3	randomized trials	serious [4]	not serious	not serious [3]	not serious	none	9/223 (4.0%)	20/208 (9.6%)	**RR 0.43** (0.20 to 0.90)	**55 fewer per 1000** (from 10 fewer to 77 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
ICU acquired Weakness (assessed with: Medical Research Council (MRC) scale)												
3	randomized trials	very serious [5]	not serious	not serious [3]	serious [6]	none	73/223 (32.7%)	62/208 (29.8%)	**RR 1.08** (0.83 to 1.41)	**24 more per 1000** (from 51 fewer to 122 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Duration of Mechanical Ventilation												
3	randomized trials	serious [4]	not serious	not serious [3]	serious [6]	none	223	208	-	MD **1.21 fewer** (4.23 fewer to 1.81 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **NMBA**: Neuromuscular blocking agents

1. Lack of blinding in most included trials and no assessment of publication bias given the small number of trials included.
2. I^2 = 0% and results were robust in sensitivity analysis.
3. Although included studies looked at all patients with ARDS we have no reason to believe they will behave differently than those with sepsis-induced ARDS. Subgroup analysis was done for sepsis-induced ARDS for mortality outcome and there was no difference between those with sepsis ARDS and all-comers with ARDS.
4. incomplete blinding in included trials
5. rated down 2 levels for incomplete blinding & ascertainment bias (limited assessment in 2 of the included trials)
6. wide confidence intervals which do not include no effect

METABOLIC SECTION

Table 59. Stress ulcer prophylaxis compared to no prophylaxis in critically ill patients

Author(s): Alhazzani W

Date: September 27 2015
Question: Stress ulcer prophylaxis compared to no prophylaxis in critically ill patients
Setting: ICU
Bibliography: Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. Intensive care medicine 2014, 40:11-22.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**stress ulcer prophylaxis**	**no prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinically important bleeding												
22	randomized trials	serious [1]	not serious [2]	not serious	serious [3]	none	67/1001 (6.7%)	161/970 (16.6%)	**RR 0.44** (0.28 to 0.68)	93 fewer per 1000 (from 53 fewer to 120 fewer)	⊕⊕◯◯ LOW [1 2 3]	CRITICAL
Mortality												
17	randomized trials	not serious	not serious	not serious	serious [4]	none	155/806 (19.2%)	164/798 (20.6%)	**RR 1.00** (0.84 to 1.20)	0 fewer per 1000 (from 33 fewer to 41 more)	⊕⊕⊕◯ MODERATE [4]	CRITICAL
Pneumonia												
7	randomized trials	serious [1]	not serious	not serious	serious [5]	none	64/510 (12.5%)	56/498 (11.2%)	**RR 1.23** (0.86 to 1.78)	26 more per 1000 (from 16 fewer to 88 more)	⊕⊕◯◯ LOW [1 5]	CRITICAL

MD – mean difference, RR – relative risk

1. We downgraded by one level for risk of bias, majority of studies were unblinded.
2. Although I^2 = 48%, we considered this as mild heterogeneity and we did not downgrade the quality of evidence
3. We downgraded by one level, due to small number of events (number of events 228)
4. We downgraded by one level, the confidence interval contained significant benefit and harm (95% CI 0.84, 1.20)
5. We downgraded by one level, the confidence interval contained significant benefit and harm (95 % CI 0.86–1.78)

Table 60. Evidence Profile for proton pump inhibitors versus histamine-2 receptor antagonists.

Author(s): Alhazzani W
Date: November 27 2015
Question: Proton pump inhibitors compared to histamine-2-antagonists for stress ulcer prophylaxis
Setting: ICU
Bibliography: Alshamsi et al 2016 (not published); MaClaren 2014

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**proton pump inhibitors**	**histamine-2-antagonists**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinically important Bleeding												
14	randomized trials	serious [1]	not serious	not serious	not serious [2]	none	13/986 (1.3%)	39/693 (5.6%)	**RR 0.39** (0.21 to 0.71)	15 fewer per 1000 (from 7 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE [1 2]	CRITICAL
Mortality												
11	randomized trials	not serious [3]	not serious	not serious	serious [4]	none	151/874 (17.3%)	120/614 (19.5%)	**RR 1.05** (0.87 to 1.27)	10 more per 1000 (from 25 fewer to 53 more)	⨁⨁⨁◯ MODERATE [3 4]	CRITICAL
Nosocomial pneumonia												
12	randomized trials	serious [1]	not serious [5]	not serious	serious [4]	none	108/812 (13.3%)	79/659 (12.0%)	**RR 1.17** (0.88 to 1.56)	20 more per 1000 (from 14 fewer to 67 more)	⨁⨁◯◯ LOW [1 4 5]	CRITICAL
Clostridium difficile												
1	Observational studies	Not serious	Not serious	Not serious	Serious [6]	none	300/8799 (3.4%)	227/8799 (2.6%)	**OR 1.28** (1.02 to 1.61)	7 more per 1000 (from 1 more to 15 more)	⨁◯◯◯ VERY LOW	CRITICAL
ICU length of stay												

7	randomized trials	serious [7]	not serious	not serious	serious [8]	none	371	373	-	MD **0.58 days fewer** (2.03 fewer to 0.86 more)	⨁⨁◯◯ LOW [7,8]	CRITICAL

MD – mean difference, RR – relative risk

1. We downgraded by one level, for risk of bias, most studies were un-blinded.
2. Although the total number of events was small, we did not downgrade for imprecision.
3. We did not downgrade for risk of bias because mortality is an objective outcome that is less likely to be affected by lack of blinding in clinical trials.
4. We downgraded by one level for imprecision, the confidence interval contains significant benefit and harm.
5. Significant inconsistency was not present (I^2=4%)
6. We downgraded by one level for imprecision, the confidence interval contains small and large harm.
7. We downgraded by one level for risk of bias
8. We downgraded by one level for imprecision, the confidence interval contained significant benefit and harm (95% CI 0.88, 1.53).

Table 61. Pharmacologic anticoagulation compared to No anticoagulation for VTE prevention

Question: Pharmacologic anticoagulation compared to No anticoagulation for VTE prevention
Setting: ICU
Bibliography: Alhazzani W et al. Crit Care Med 2013; 41:2088-2098

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pharmacologic anticoagulation**	**No anticoagulation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any DVT												
4	randomized trials	not serious [1]	serious [2]	not serious [3]	not serious	none [4]	114/1521 (7.5%)	219/1493 (14.7%)	**RR 0.53** (0.32 to 0.86)	**69 fewer per 1000** (from 21 fewer to 100 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Symptomatic DVT												
1	randomized trials	not serious	not serious	not serious	very serious [5]	none	49/976 (5.0%)	56/959 (5.8%)	**RR 0.86** (0.59 to 1.25)	**8 fewer per 1000** (from 15 more to 24 fewer)	⊕⊕◯◯ LOW	CRITICAL
								5.0%		**7 fewer per 1000** (from 13 more to 21 fewer)		
Pulmonary Embolism												
3	randomized trials	not serious	not serious	not serious [3]	serious [6]	none [4]	15/1461 (1.0%)	28/1434 (2.0%)	**RR 0.53** (0.28 to 0.98)	**9 fewer per 1000** (from 0 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Major Bleeding												

2	randomized trials	serious [7]	serious [8]	not serious	very serious [9]	none [4]	44/1084 (4.1%)	53/1072 (4.9%)	**RR 0.81** (0.55 to 1.21)	**9 fewer per 1000** (from 10 more to 22 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality												
2	randomized trials	not serious	not serious	not serious	serious [10]	none [4]	283/1080 (26.2%)	313/1068 (29.3%)	**RR 0.89** (0.78 to 1.02)	**32 fewer per 1000** (from 6 more to 64 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								25.0%		**27 fewer per 1000** (from 5 more to 55 fewer)		

CI: Confidence interval; **RR:** Risk ratio

1. Two trials were at low risk of bias [Shorr et al., Cade et al.], one trial was at high risk of bias due to incomplete outcome assessment [Fraisse et al.], after excluding this trial there was a residual benefit from the intervention for this outcome
2. We downgraded by one level for inconsistency, unexplained heterogeneity was present I^2= 77%
3. Although studies included mixed ICU population, we did not consider this as a significant indirectness, therefore, we did not downgrade for indirectness
4. We could not reliably assess for publication bias due to small number
5. The CI interval is wide, it includes significant benefit and harm, therefore, we downgraded by two levels for serious imprecision
6. We downgraded by one level for imprecision, the number of event is small and the confidence interval included non-significant benefit
7. We downgraded by one level for risk of bias
8. We downgraded by one level for serious inconsistency, I^2= 50%
9. We downgraded by two levels for serious imprecision, the CI contained significant benefit and harm
10. We downgraded by one level for imprecision, the CI contained significant benefit and small harm

Table 62. LMWH compared to UFH for VTE prevention

Author(s): Alhazzani W, Townsend S, Mazuski J
Question: LMWH compared to UFH for VTE prevention
Setting: in patients with sepsis in the ICU
Bibliography: Alhazzani et al. Crit Care Med 2013; 41:2088-2098

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**UFH**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any DVT												
3	randomized trials	not serious	not serious	not serious [1]	serious [2]	none [3]	187/2588 (7.2%)	209/2600 (8.0%)	**RR 0.90** (0.74 to 1.08)	**8 fewer per 1000** (from 6 more to 21 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Symptomatic DVT												
2	randomized trials	not serious	not serious	not serious [1]	serious [4]	none [3]	51/2351 (2.2%)	60/2371 (2.5%)	**RR 0.87** (0.60 to 1.25)	**3 fewer per 1000** (from 6 more to 10 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Pulmonary embolism												
2	randomized trials	not serious	serious [5]	not serious	serious [6]	none [3]	28/2351 (1.2%)	45/2371 (1.9%)	**RR 0.62** (0.39 to 1.00)	**7 fewer per 1000** (from 0 fewer to 12 fewer)	⊕⊕◯◯ LOW	CRITICAL
Symptomatic pulmonary embolism												
1	randomized trials	not serious	not serious	not serious	serious [7]	none	22/1873 (1.2%)	38/1873 (2.0%)	**RR 0.58** (0.34 to 0.97)	**9 fewer per 1000** (from 1 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Major bleeding												
3	randomized trials	not serious	not serious	not serious	serious [8]	none [3]	107/2110 (5.1%)	110/2102 (5.2%)	**RR 0.97** (0.75 to 1.26)	**2 fewer per 1000** (from 13 fewer to 14 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality												
3	randomized trials	not serious	not serious [9]	not serious [1]	serious [10]	none [3]	424/2587 (16.4%)	110/2102 (5.2%)	**RR 0.93** (0.82 to 1.04)	**4 fewer per 1000** (from 2 more to 9 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Heparin induced thrombocytopenia												
1	randomized trials	not serious	not serious	not serious	serious [11]	none	5/1873 (0.3%)	12/1873 (0.6%)	**RR 0.42** (0.15 to 1.18)	**4 fewer per 1000** (from 1 more to 5 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Although studies included mixed critically ill population, we did not consider this as a significant indirectness, therefore, we did not downgrade for indirectness
2. We downgraded by one level for imprecision, the CI included significant benefit and minimal harm
3. Although we could not reliably assess for publication bias, we did not downgrade for the quality f evidence
4. We downgraded by one level for imprecision, the CI included a significant benefit and harm
5. We downgraded by one level for inconsistency, the I^2= 53%
6. We downgraded by one level for imprecision, the number of event is small
7. We downgraded by one level for imprecision, the number of events is small
8. We downgraded by one level for imprecision, the CI included both significant benefit and harm
9. I^2= 31%
10. We downgraded by one level for imprecision, the CI contained significant benefit and minimal harm
11. We downgraded by one level for imprecision, the CI included significant benefit and small harm

Table 63. Intermittent pneumatic compression (IPC) compared to No prophylaxis for VTE prevention in patients with sepsis

Author(s): Alhazzani W
Question: IPC compared to No prophylaxis for VTE prevention in patients with sepsis
Setting: Intensive Care Unit
Bibliography: Zhang C, Zeng W, Zhou H, Zheng BX, Cheng JC, Li XY et al. [The efficacy of intermittent pneumatic compression in the prevention of venous thromboembolism in medical critically ill patients]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2011;23(9):563-5. ; Arabi YM, Khedr M, Dara SI, Dhar GS, Bhat SA, Tamim HM et al. Use of intermittent pneumatic compression and not graduated compression stockings is associated with lower incident VTE in critically ill patients: a multiple propensity scores adjusted analysis. Chest. 2013;144(1):152-9. doi:10.1378/chest.12-2028.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPC**	**No prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
Deep Vein Thrombosis												
1	randomized trials	serious [1]	not serious	not serious [2]	serious [3]	none	3/79 (3.8%)	16/83 (19.3%)	**RR 0.20** (0.06 to 0.65)	**154 fewer per 1000** (from 67 fewer to 181 fewer)	⨁⨁◯◯ LOW	CRITICAL
								5.0%		**40 fewer per 1000** (from 17 fewer to 47 fewer)		
Pulmonary Embolism												
1	randomized trials	serious [1]	not serious	not serious [2]	very serious [4]	none	0/79 (0.0%)	8/83 (9.6%)	**RR 0.06** (0.00 to 1.05)	**91 fewer per 1000** (from -- to 5 more)	⨁◯◯◯ VERY LOW	CRITICAL
								2.0%		**19 fewer per 1000** (from -- to 1 more)		

Venous Thromboembolism (observational data)												
1	observational studies	not serious	not serious	not serious	serious [5]	strong association [6]	11/229 (4.8%)	28/389 (7.2%)	**HR 0.45** (0.22 to 0.95)	**39 fewer per 1000** (from 3 fewer to 56 fewer)	⨁⨁◯◯ LOW	CRITICAL
								5.0%		**27 fewer per 1000** (from 2 fewer to 39 fewer)		

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **IPC**: intermittent pneumatic compression

1. We downgraded the quality of evidence by one level for risk of bias, the risk of bias assessment was not possible
2. Although this study included critically ill patients, we did not consider this significant indirectness
3. We downgraded the quality of evidence for imprecision, the CI was wide contained large and small benefit
4. We downgraded the quality of evidence for imprecision by two levels, the CI was very wide
5. We downgraded the quality of evidence by one level for imprecision, the CI is wide and number of events is small
6. We upgraded the quality of evidence by one level for large treatment effect, the HR < 0.5

Table 64. Graduate compression stockings compared to no prophylaxis for VTE prevention in patients with sepsis or septic shock

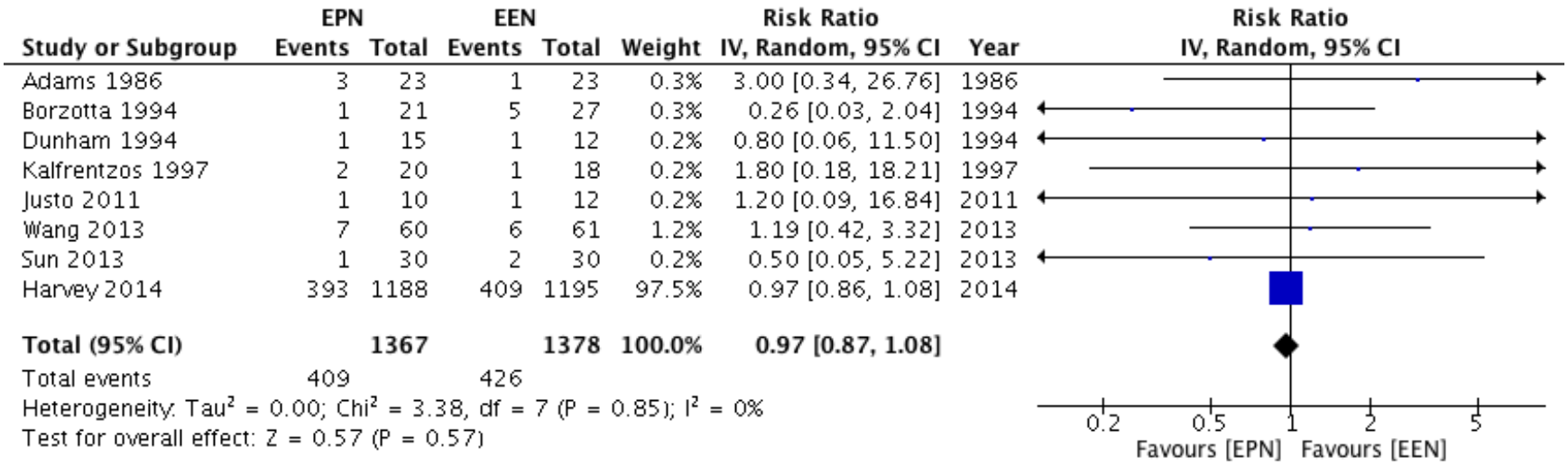
Author(s): Alhazzani W
Question: GCS compared to no prophylaxis for VTE prevention in patients with sepsis or septic shock
Setting: Intensive Care Unit
Bibliography: Arabi YM, Khedr M, Dara SI, Dhar GS, Bhat SA, Tamim HM et al. Use of intermittent pneumatic compression and not graduated compression stockings is associated with lower incident VTE in critically ill patients: a multiple propensity scores adjusted analysis. Chest. 2013;144(1):152-9. doi:10.1378/chest.12-2028.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GCS**	**no prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
Venous Thromboembolism												
1	observational studies	not serious	not serious	not serious	serious [1]	none	18/180 (10.0%)	28/389 (7.2%)	**HR 1.04** (0.59 to 2.04)	**3 more per 1000** (from 29 fewer to 69 more)	⨁◯◯◯ VERY LOW	CRITICAL
								5.0%		**2 more per 1000** (from 20 fewer to 49 more)		

CI: Confidence interval; **HR:** Hazard Ratio

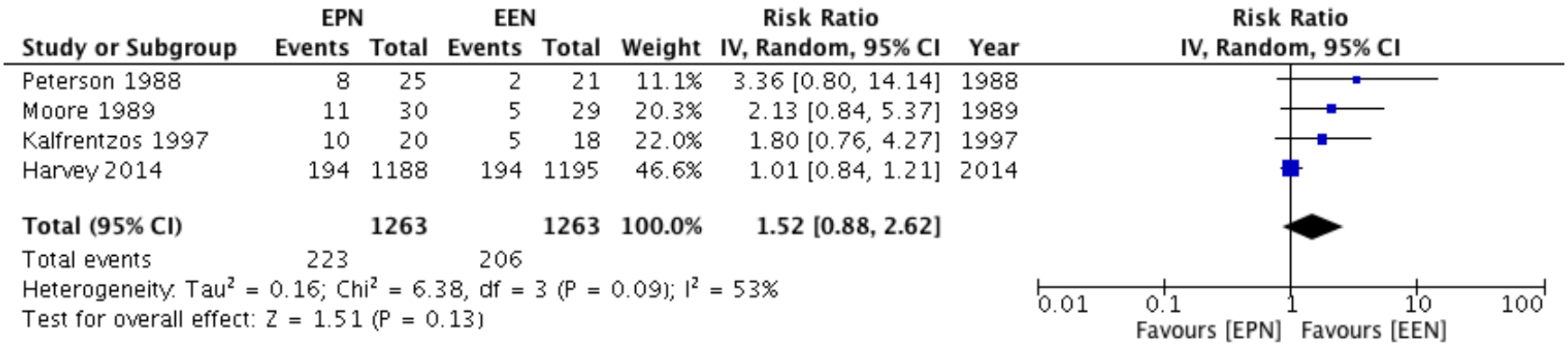
1. We downgraded the quality of evidence for imprecision by one level, the CI interval contained significant benefit and harm

Figure 42. Early parenteral nutrition versus early enteral nutrition in critically ill patients who can be enterally fed: Mortality Outcome



EPN: Early parenteral nutrition; **EEN:** Early enteral nutrition; **IV:** inverse variance

Figure 43. Early parenteral nutrition versus early enteral nutrition in critically ill patients who can be enterally fed: Infections Outcome



EPN: Early parenteral nutrition; **EEN:** Early enteral nutrition; **IV:** inverse variance

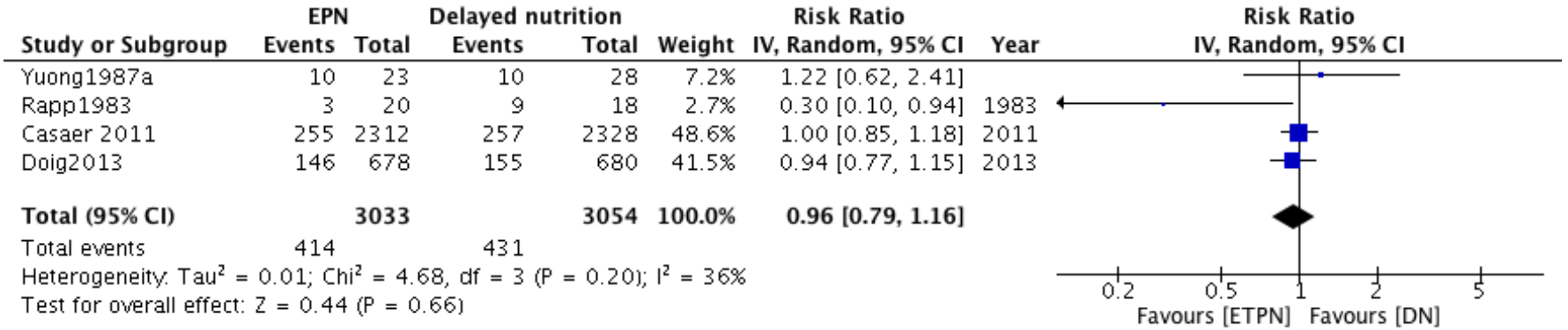
Table 65. Early parenteral nutrition compared early enteral nutrition in patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EPN**	**EEN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
8	randomized trials	not serious	not serious	not serious	serious [1]	none [2]	409/1367 (29.9%)	426/1378 (30.9%)	**RR 0.97** (0.87 to 1.08)	**9 fewer per 1000** (from 25 more to 40 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								40.0%		**12 fewer per 1000** (from 32 more to 52 fewer)		
Infections												
4	randomized trials	not serious [3]	serious [4]	not serious	serious [5]	none [2]	223/1263 (17.7%)	206/1263 (16.3%)	**RR 1.52** (0.88 to 2.26)	**85 more per 1000** (from 20 fewer to 206 more)	⨁⨁◯◯ LOW	CRITICAL
Infections (Low Risk of Bias Subgroup)												
1	randomized trials	not serious	not serious	not serious	serious [6]	none	194/1188 (16.3%)	194/1195 (16.2%)	**RR 1.01** (0.84 to 1.21)	**2 more per 1000** (from 26 fewer to 34 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU Length of stay												
1	randomized trials	serious [7]	not serious [8]	not serious	very serious [9]	none	25	21	-	MD **0.9 more** (0.38 more to 1.42 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **EPN**: early parental nutrition; **EEN**: early enteral nutrition

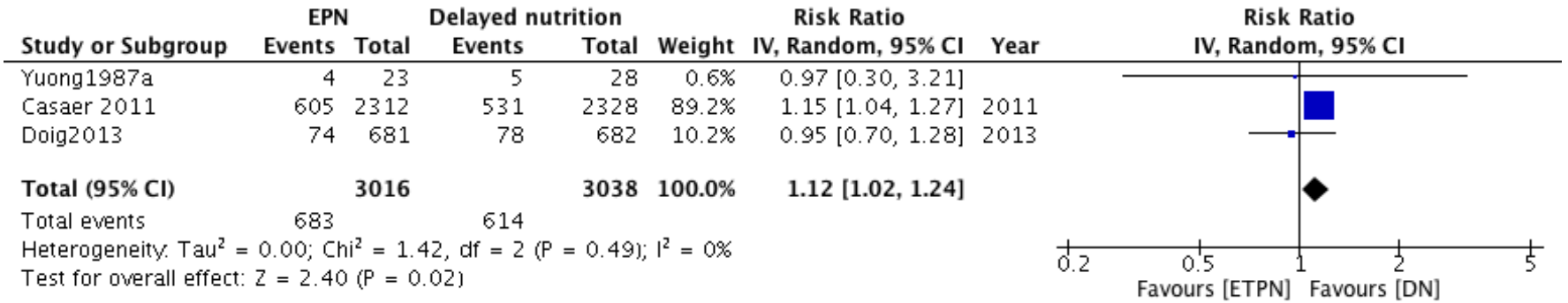
1. We downgraded the quality of evidence for imprecision by one level, the CI included significant benefit and harm
2. We did not downgrade the quality of evidence for publication bias, although the number of included studies is less than 10 which did not allow us to use statistical tests to assess for publication bias
3. We did not downgrade for risk of bias, although it is difficult to blind caregivers and patients, most studies blinded outcome assessors, therefore, the risk of ascertainment bias is low
4. We downgraded the quality of evidence for inconsistency, the I^2= 54%
5. We downgraded the quality of evidence for imprecision by two levels, the number of event was small based on the optimal information size estimation
6. We downgraded the quality of evidence for imprecision by one level, the CI included both significant benefit and harm
7. We downgraded the quality of evidence by one level for risk of bias, the study was unblinded and therefore considered at high risk of bias for this outcome
8. Only one RCT included, therefore, this category is not applicable
9. We downgraded the quality of evidence by two levels for imprecision, the CI is very wide and the sample size is small

Figure 44. Early parenteral nutrition versus delayed initiation of nutrition in critically ill patients: Mortality Outcome



EPN: Early parenteral nutrition**; IV:** Inverse variance

Figure 45. Early parenteral nutrition versus delayed initiation of nutrition in critically ill patients: Infections Outcome



EPN: Early parenteral nutrition**; IV:** Inverse variance

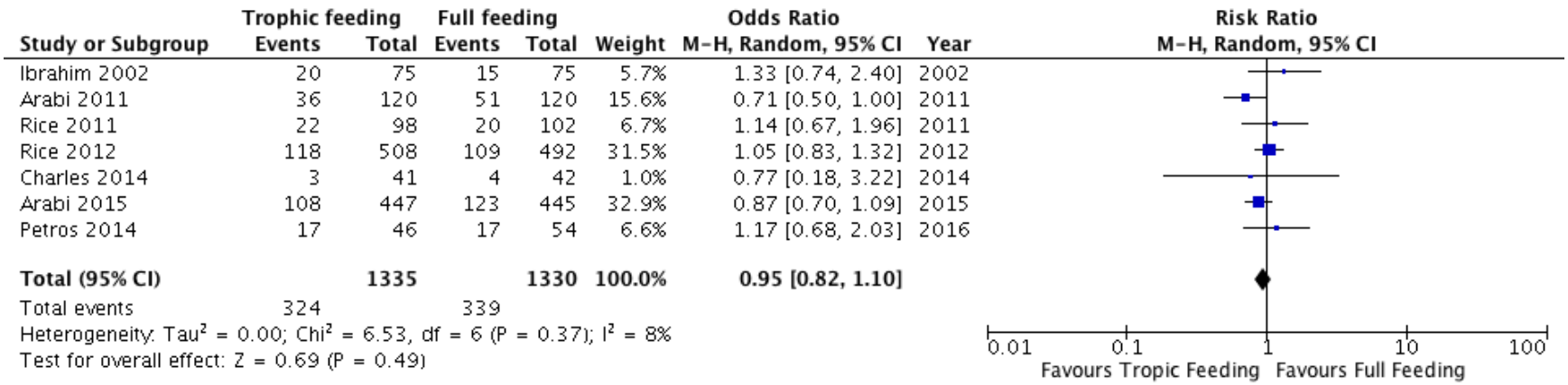
Table 66. Early parenteral nutrition versus delayed initiation of nutrition in critically ill patients with sepsis

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EPN**	**delayed nutrition**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
4	randomized trials	not serious	not serious [1]	not serious	serious [2]	none	414/3033 (13.6%)	431/3054 (14.1%)	**RR 0.96** (0.79 to 1.16)	**6 fewer per 1000** (from 23 more to 30 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								40.0% [3]		**16 fewer per 1000** (from 64 more to 84 fewer)		
Infections												
3	randomized trials	not serious	not serious	serious	not serious [4]	none	683/3016 (22.6%)	614/3038 (20.2%)	**RR 1.12** (1.02 to 1.24)	**24 more per 1000** (from 4 more to 49 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

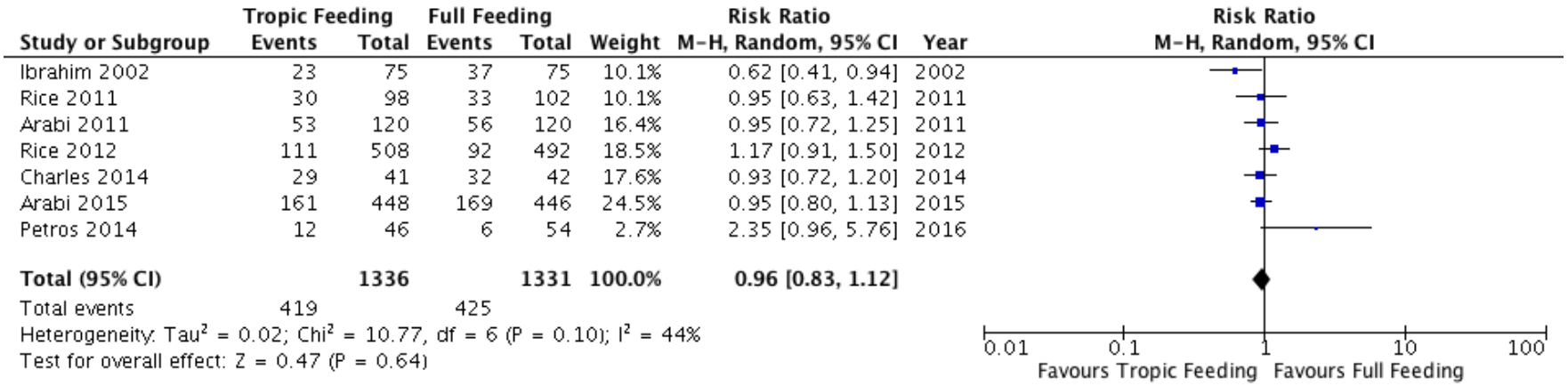
1. Although the I^2 = 36%, we did not consider this as significant heterogeneity, we did not downgrade the quality of evidence
2. We downgraded the quality of evidence for imprecision, the CI interval included significant benefit and harm
3. We assumed a mortality rate of 40% in septic shock patients, data from Sepsis-3
4. Although the lower end of the CI contained small benefit, we did not downgrade for imprecision as the total number of events was large (1,297 events)

Figure 46. Trophic feeding versus full feeding in critically ill patients: Mortality Outcome



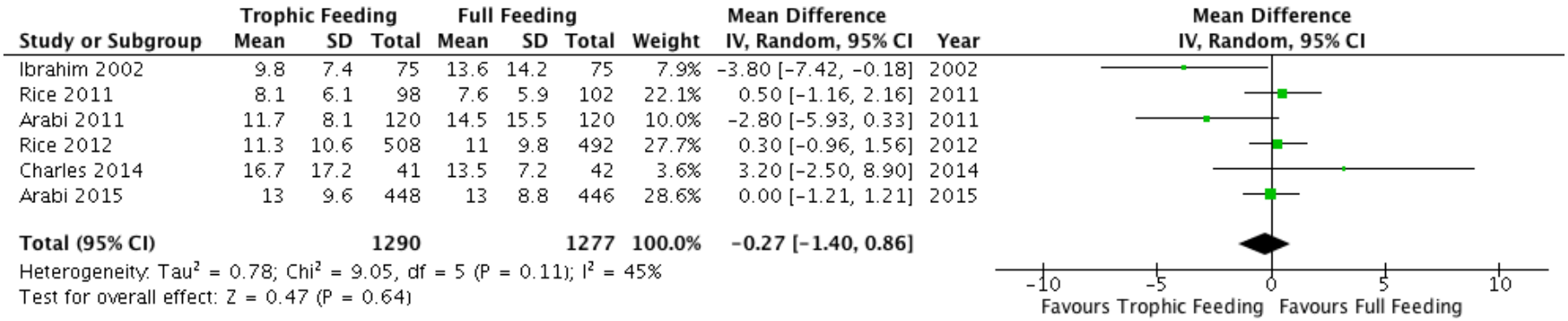
M-H: Mantel-Haenszel

Figure 47. Trophic feeding versus full feeding in critically ill patients: Infections Outcome



M-H: Mantel-Haenszel

Figure 48. Trophic feeding versus full feeding in critically ill patients: ICU LoS Outcome



IV: Inverse variance

Table 67. Trophic feeds compared to Full EEN in septic patients

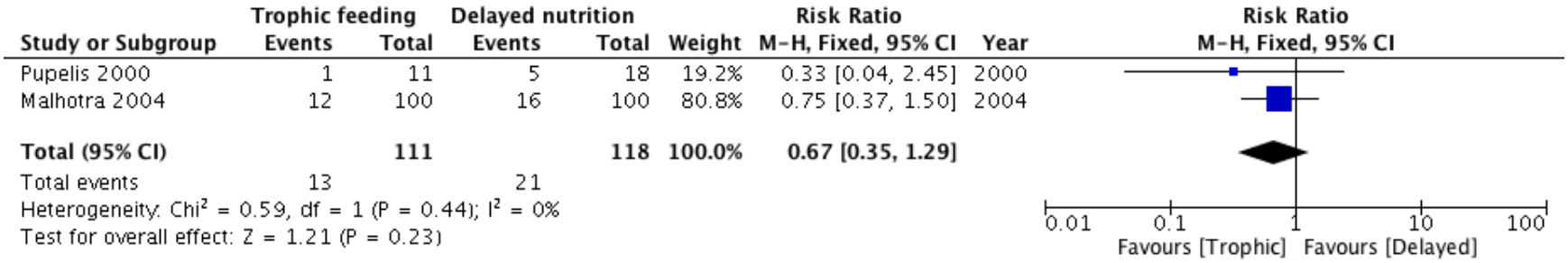
Author(s): Eric Duan, Lauralyn Mcintyre, Waleed Alhazzani
Date: February 17, 2016
Question: Trophic feeds compared to Full EEN in Septic patients
Setting: ICU

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Trophic feeds**	**Full EEN**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital mortality												
7	randomized trials	not serious	not serious	not serious	not serious	none	324/1335 (24.3%)	339/1330 (25.5%)	**OR 0.95** (0.82 to 1.11)	**13 fewer per 1000** (from 28 more to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospital Acquired Infection												
7	randomized trials	not serious	serious [1]	not serious	not serious	none	419/1336 (31.4%)	425/1331 (31.9%)	**RR 0.96** (0.83 to 1.12)	**13 fewer per 1000** (from 38 more to 54 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
ICU length of stay												
6	randomized trials	not serious	not serious	not serious	serious [2]	none	1290	1277	-	MD **0.27 fewer days** (1.4 fewer to 0.86 more)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio; **MD:** Mean difference; **EEN**: Early enteral nutrition

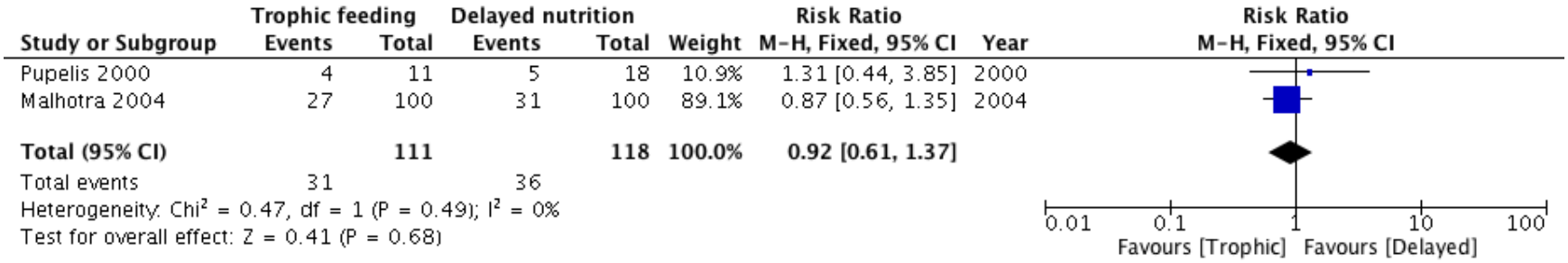
1. We downgraded the quality of evidence for inconsistency, the I^2=40% and Chi ^{2}=0.1
2. We downgraded the quality of evidence for imprecision, the CI contained significant benefit and harm

Figure 49. Trophic feeds compared to Full EEN in Septic patients: impact on mortality



M-H: Mantel-Haenszel

Figure 50. Trophic feeds compared to Full EEN in Septic patients: impact on infections



M-H: Mantel-Haenszel

Table 68. Trophic feeding compared to Delayed nutrition in patients with sepsis or septic shock

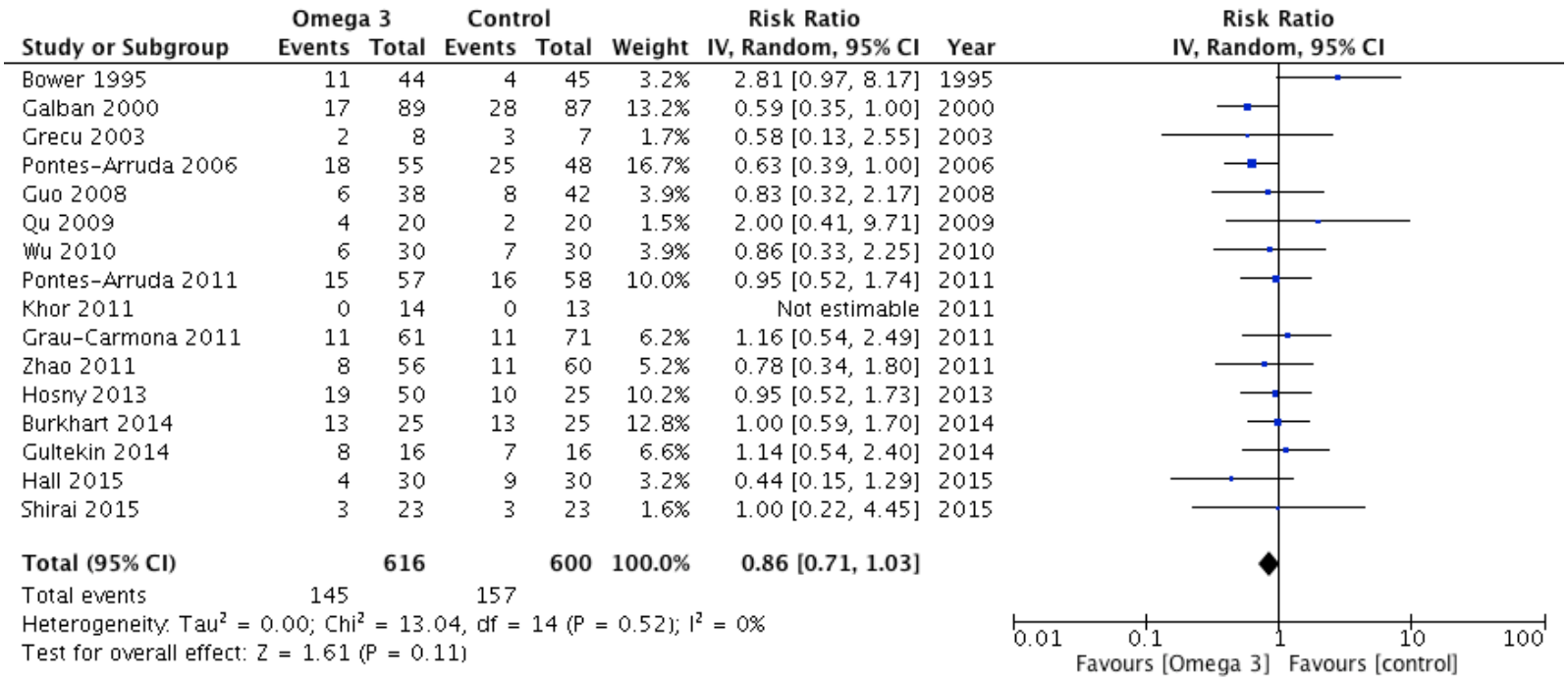
Author(s): Alhazzani W, Lauralyn M
Date: April 8, 2016
Question: Trophic feeding compared to Delayed nutrition in patients with sepsis or septic shock
Setting: ICU
Bibliography: Malhotra 2004; Pupelis 2000

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Trophic feeding**	**Delayed nutrition**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	randomized trials	not serious	not serious	not serious	very serious [1]	none [2]	13/111 (11.7%)	21/118 (17.8%)	**RR 0.67** (0.35 to 1.29)	**59 fewer per 1000** (from 52 more to 116 fewer)	⨁⨁◯◯ LOW	CRITICAL
Infection (Wound infection)												
2	randomized trials	serious [3]	not serious	serious [4]	serious [5]	none [2]	31/111 (27.9%)	36/118 (30.5%)	**RR 0.92** (0.61 to 1.37)	**24 fewer per 1000** (from 113 more to 119 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence by two levels for imprecision, the CI included extreme benefit and harm
2. Although we could not reliably assess for publication bias due to small number of eligible studies, we decided not to downgrade the quality of evidence, we conducted a comprehensive search and its unlikely that small studies are not identified
3. We downgraded the quality of evidence for risk of bias, both studies were judged to be at high risk of bias for this outcome
4. We downgraded the quality of evidence for indirectness, the outcome of interest is any infection, while the included outcome is wound infection
5. We downgraded the quality evidence for imprecision, the CI contained significant benefit and harm

Figure 51. Omega-3 in critically ill patients with sepsis: Mortality Outcome



IV: Inverse variance

Figure 52. Omega-3 in critically ill patients with sepsis: ICU length of stay Outcome

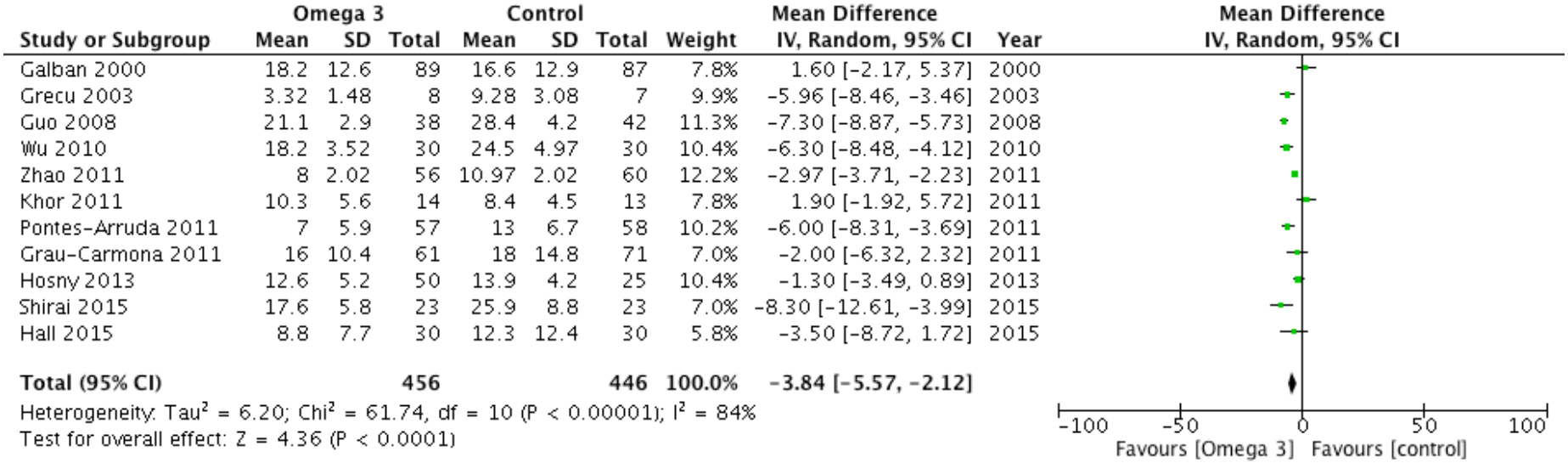


Table 69. Omega-3 versus placebo in patients with sepsis

Quality assessment						№ of patients		Effect		Quality
№ of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega-3 supplementation**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mortality										
16	not serious	not serious	serious [1]	serious [2]	none	145/616 (23.5%)	157/600 (26.2%)	RR 0.86 (0.71 to 1.03)	37 fewer per 1,000 (from 8 more to 76 fewer)	⨁⨁◯◯ LOW
ICU length of stay										
11	serious [3]	serious [4]	serious [1]	not serious	none	456	446	-	MD 3.84 days fewer (5.57 fewer to 2.12 fewer)	⨁◯◯◯ VERY LOW
Duration of mechanical ventilation										
6	serious [3]	serious [5]	serious [1]	not serious	none	241	231	-	MD 2.33 days fewer (4.44 fewer to 0.22 fewer)	⨁◯◯◯ VERY LOW

1. We rated down the quality of evidence by one level for multiple sources of indirectness. Population: mechanical ventilation and sepsis severity varied as inclusion criteria across studies. Intervention: content of enteral/parenteral formulations differed across studies (9 used omega-3 alone while 7 used formulae with additional supplements such as omega-6, antioxidants, mRNA, arginine, and selenium). Outcome: different mortality definitions (28-day, 60-day, in-hospital, ICU).
2. We rated down the quality of evidence by one level for imprecision. The CI included both significant benefit and harm.
3. We rated down the quality of evidence by one level for risk of bias. Several studies showed high risk of attrition bias and performance bias.
4. We rated down the quality of evidence by one level for significant unexplained heterogeneity ($P < 0.00001$, $I^2 = 84\%$).
5. We rated down the quality of evidence by one level for significant unexplained heterogeneity ($P = 0.010$, $I^2 = 67\%$).

Table 70. Not measuring gastric residual volume (GRV) compared to measuring GRV in enterally fed septic patients

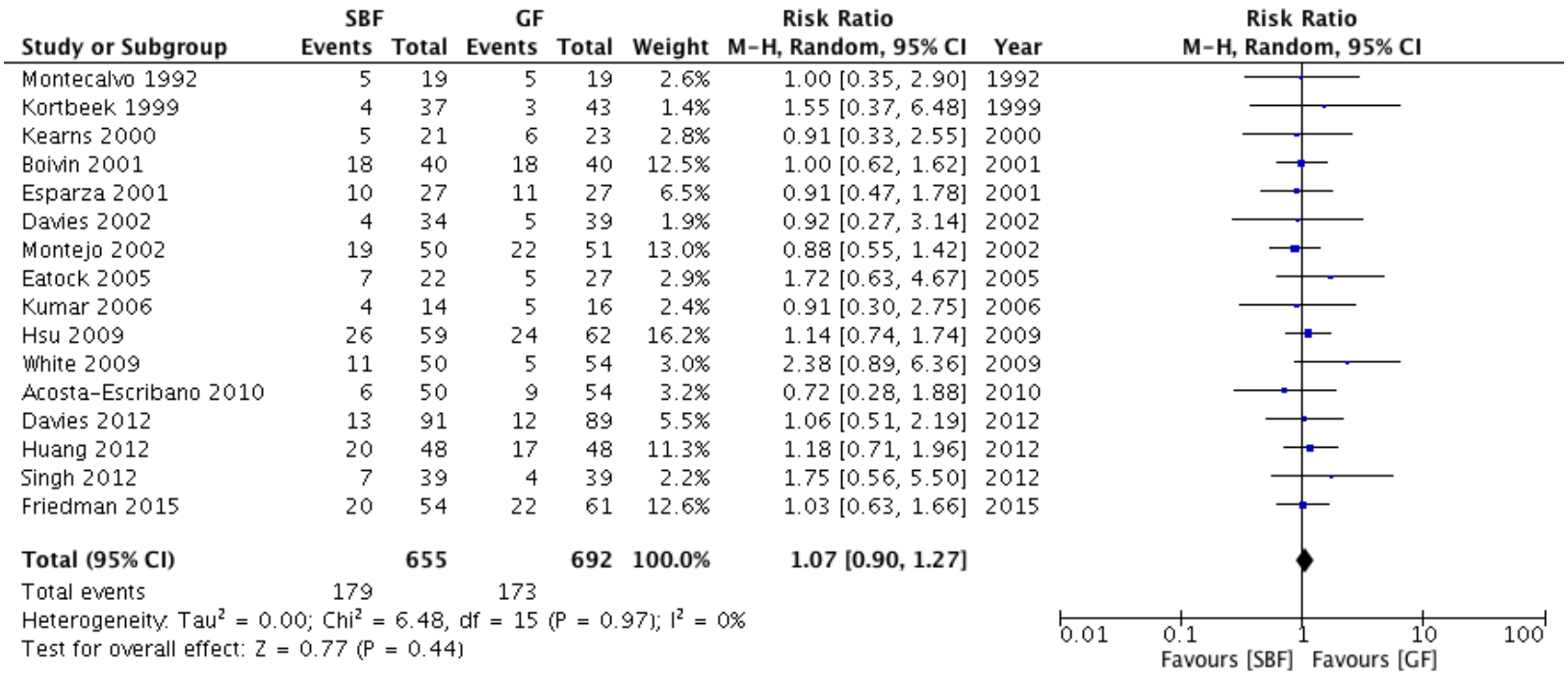
Author(s): Alhazzani W, McIntyre L
Date: January 8, 2016
Question: Not measuring GRV compared to measuring GRV in enterally fed septic patients
Setting: ICU
Bibliography: Reignier, J., Mercier, E., Le Gouge, A., Boulain, T., Desachy, A., Bellec, F., ... & Lascarrou, J. B. (2013). Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA, 309(3), 249-256.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**not measuring GRV**	**measuring GRV**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 90 days)												
1	randomized trials	not serious	not serious	not serious [1]	serious [2]	none	82/227 (36.1%)	76/222 (34.2%)	**RR 1.06** (0.82 to 1.36)	**21 more per 1000** (from 62 fewer to 123 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Ventilator associated pneumonia												
1	randomized trials	not serious	not serious	not serious	very serious [3]	none	38/227 (16.7%)	35/222 (15.8%)	**RR 1.06** (0.70 to 1.62)	**9 more per 1000** (from 47 fewer to 98 more)	⊕⊕◯◯ LOW	CRITICAL
Vomiting												
1	randomized trials	not serious	not serious	not serious	serious [4]	none	90/227 (39.6%)	60/222 (27.0%)	**RR 1.47** (1.12 to 1.92)	**127 more per 1000** (from 32 more to 249 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
interruption of enteral feeding												
1	randomized trials	not serious	not serious	not serious	not serious	none	90/227 (39.6%)	141/222 (63.5%)	**RR 0.62** (0.52 to 0.75)	**241 fewer per 1000** (from 159 fewer to 305 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **GRV**: Gastric residual volume

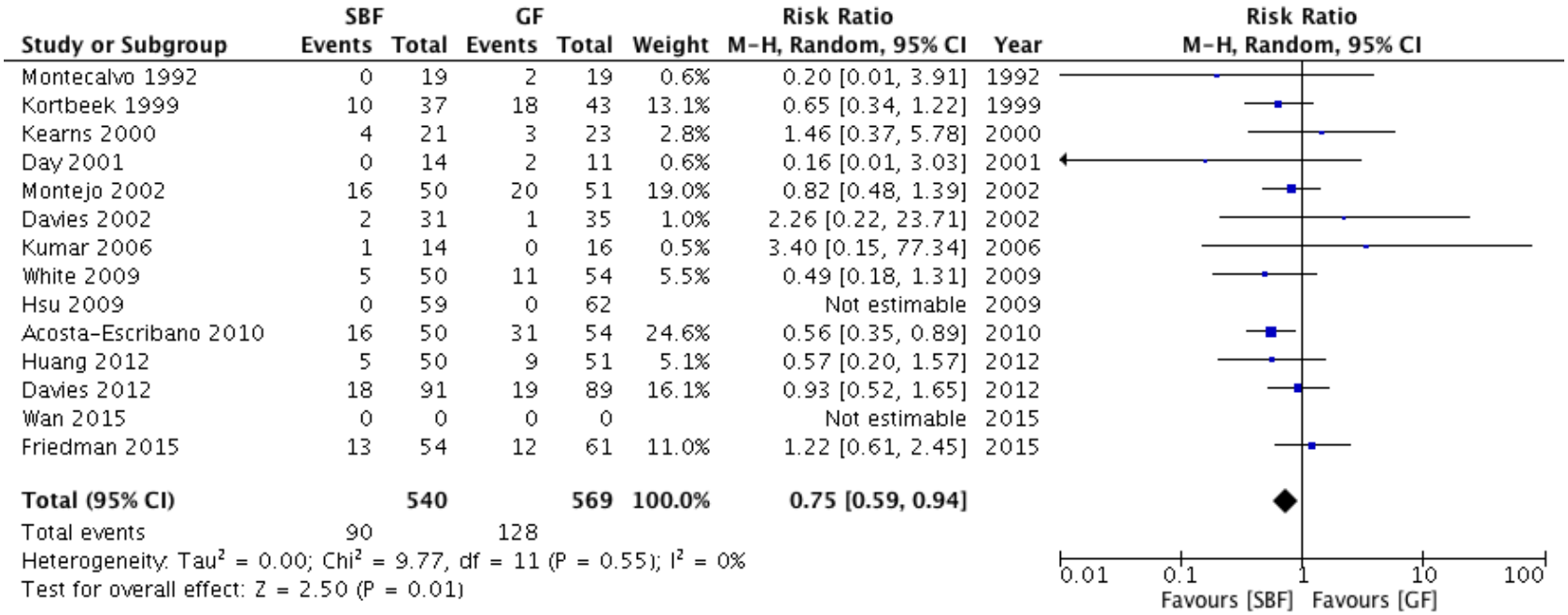
1. This study included critically ill patient population (12%) were septic patients, we did not consider this as a significant indirectness.
2. We downgraded the quality of evidence for imprecision, the CI included significant benefit and harm
3. We downgraded the quality of evidence for imprecision, the CI included significant benefit and harm
4. We downgraded the quality of evidence for imprecision, the CI included small benefit that was lower than the clinical decision threshold

Figure 53. Small bowel feeding versus gastric feeding in critically ill patients: Mortality Outcome



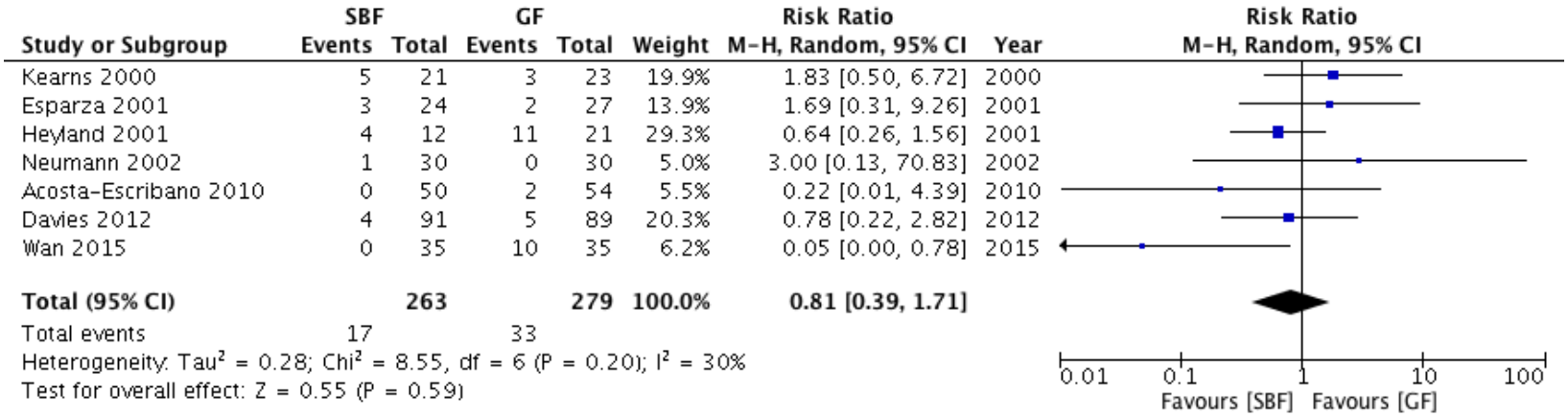
M-H: Mantel-Haenszel; **SBF**: Small bowel feeding; **GF**: Gastric feeding

Figure 54. Small bowel feeding versus gastric feeding in critically ill patients: pneumonia Outcome



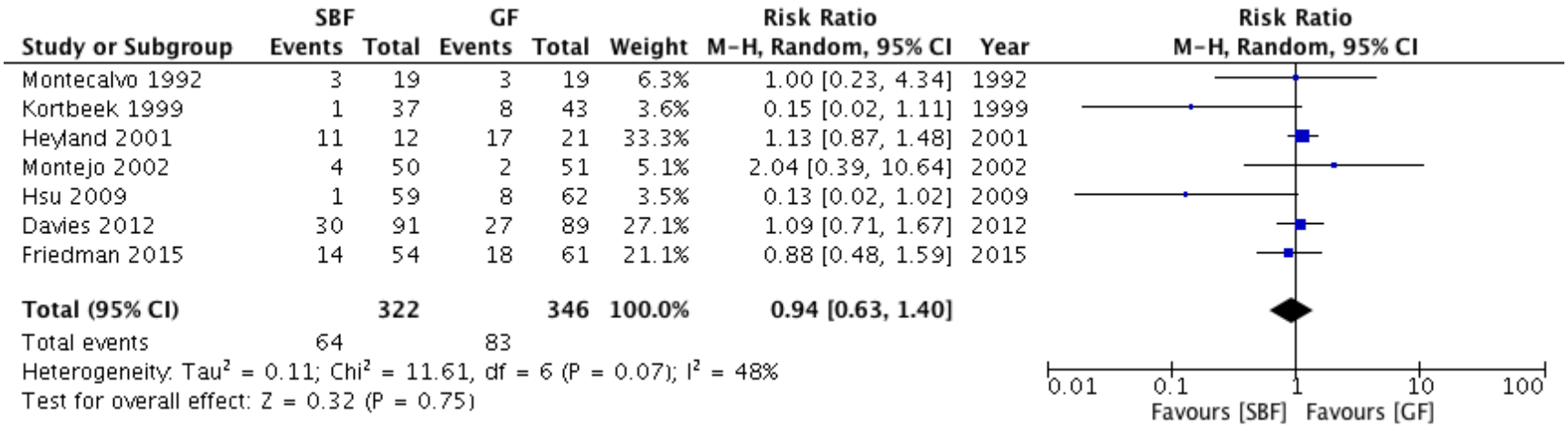
M-H: Mantel-Haenszel; **SBF**: Small bowel feeding; **GF**: Gastric feeding

Figure 55. Small bowel feeding versus gastric feeding in critically ill patients: Aspiration Outcome



M-H: Mantel-Haenszel; **SBF**: Small bowel feeding; **GF**: Gastric feeding

Figure 56. Small bowel feeding versus gastric feeding in critically ill patients: Vomiting Outcome



M-H: Mantel-Haenszel; **SBF**: Small bowel feeding; **GF**: Gastric feeding

Table 71. Post pyloric feeding compared to Gastric feeding in patients with sepsis

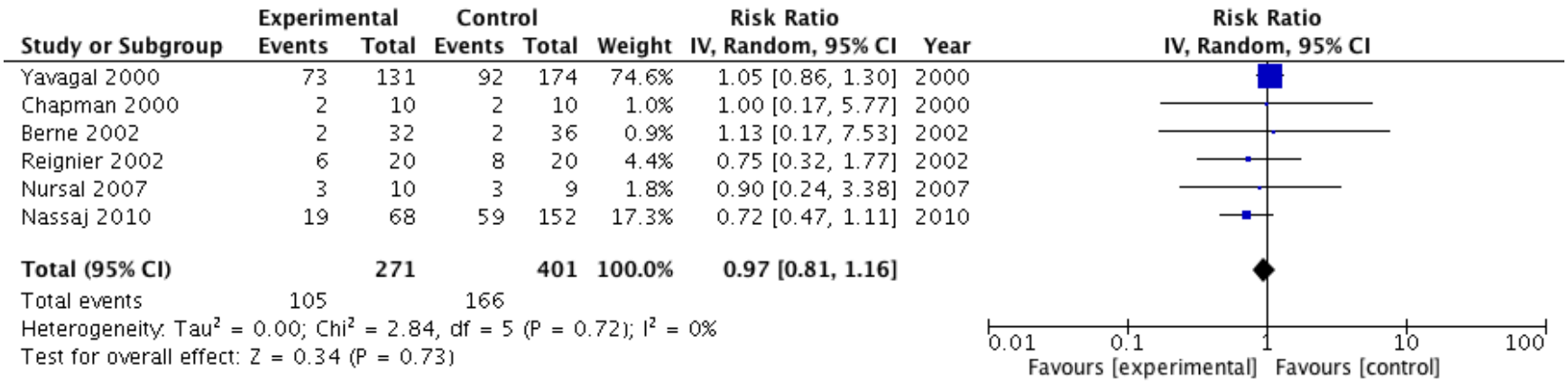
Author(s): Alhazzani W, Mcintyre L, Angus D
Date: November 30 2015
Question: Post pyloric feeding compared to Gastric feeding in patients with sepsis
Setting: Intensive Care Unit
Bibliography: Alhazzani W, Almasoud A, Jaeschke R, Lo BW, Sindi A, Altayyar S et al. Small bowel feeding and risk of pneumonia in adult critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care. 2013;17(4):R127. doi:10.1186/cc12806.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post pyloric feeding**	**Gastric feeding**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pneumonia												
14	randomized trials	serious [1]	not serious	not serious	serious [2]	none	90/540 (16.7%)	128/569 (22.5%)	**RR 0.75** (0.59 to 0.94)	**25 fewer per 1000** (from 6 fewer to 41 fewer) [3]	⊕⊕◯◯ LOW	CRITICAL
Mortality												
16	randomized trials	not serious	not serious	not serious	serious [4]	none	179/655 (27.3%)	173/692 (25.0%)	**RR 1.07** (0.90 to 1.27)	**18 more per 1000** (from 25 fewer to 68 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Aspiration												
7	randomized trials	serious [5]	not serious	not serious	serious [6]	none	17/263 (6.5%)	33/279 (11.8%)	**RR 0.81** (0.39 to 1.71)	**22 fewer per 1000** (from 72 fewer to 84 more)	⊕⊕◯◯ LOW	CRITICAL
Vomiting												
7	randomized trials	serious [5]	not serious [7]	not serious	serious [8]	none	64/322 (19.9%)	83/346 (24.0%)	**RR 0.94** (0.63 to 1.40)	**14 fewer per 1000** (from 89 fewer to 96 more)	⊕⊕◯◯ LOW	CRITICAL

MD – mean difference, RR – relative risk

1. We downgraded the quality of evidence by one level for risk of bias, most RCTs were unblended and pneumonia definition varied between studies
2. We downgraded the quality of evidence by one level for imprecision, the CI included small benefit
3. We used a control group event rate of 10%
4. We downgraded the quality of evidence by one level for imprecision, the CI contained both significant benefit and harm
5. We downgraded the quality of evidence by one level for risk of bias, this is because of poor outcome definition and risk of ascertainment bias
6. We downgraded the quality of evidence by one level for imprecision, the CI contained significant benefit and harm
7. Although the I^2=48%, we did not downgrade for inconsistency, because we considered this as minimal heterogeneity
8. We downgraded the quality of evidence by one level for imprecision, the CI contained significant benefit and harm

Figure 57. Prokinetic agents in critically ill patients: Mortality Outcome



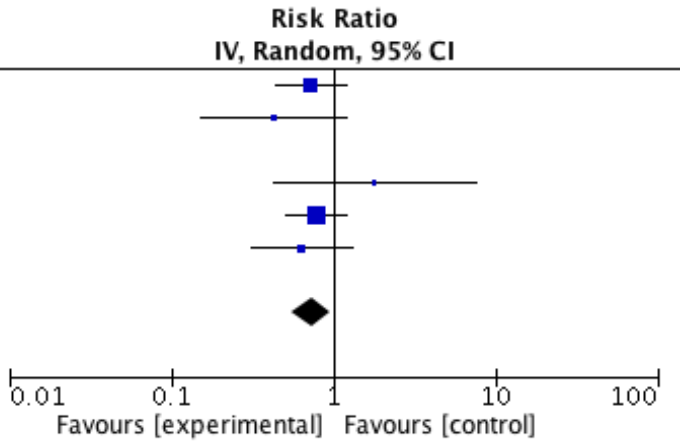
Experimental: Prokinetic agents; **IV**: Inverse variance

Figure 58. Prokinetic agents in critically ill patients: Feeding intolerance Outcome

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Berne 2002	13	32	20	36	30.1%	0.73 [0.44, 1.22]
Chapman 2000	3	10	7	10	7.4%	0.43 [0.15, 1.20]
Jooste 1999	0	0	0	0		Not estimable
Nursal 2007	4	10	2	9	3.8%	1.80 [0.43, 7.59]
Pinilla 2001	20	44	21	36	43.4%	0.78 [0.51, 1.19]
Reignier 2002	7	20	11	20	15.3%	0.64 [0.31, 1.30]
Total (95% CI)		**116**		**111**	**100.0%**	**0.73 [0.55, 0.97]**
Total events	47		61			

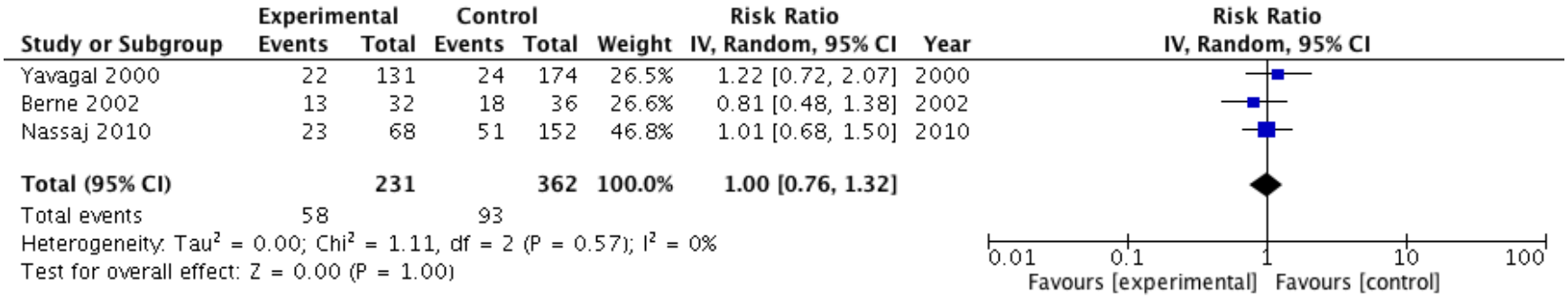
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.77$, df = 4 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.18 (P = 0.03)



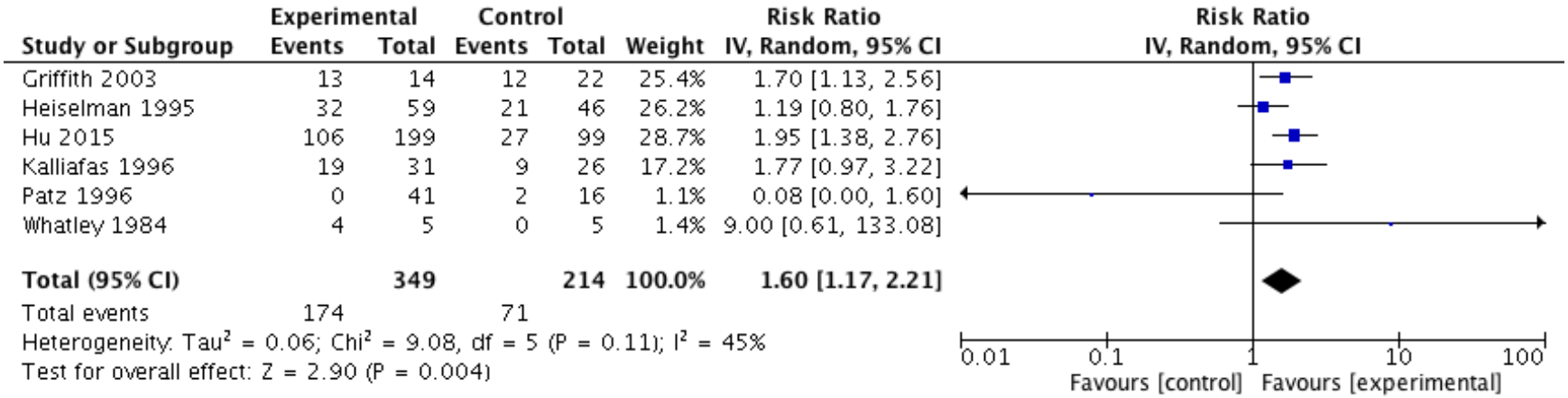
Experimental: Prokinetic agents; **IV**: Inverse variance

Figure 59. Prokinetic agents in critically ill patients: Pneumonia Outcome



Experimental: Prokinetic agents; **IV**: Inverse variance

Figure 60. Prokinetic agents in critically ill patients: Successful SB feeding tube placement Outcome



Experimental: Prokinetic agents; **IV**: Inverse variance

Table 72. Prokinetic agents compared to placebo in septic patients who are enterally fed

Author(s): Kim Lewis, Zuhoor Alqahtani, Waleed Alahazzani
Date: April 13, 2016
Question: Prokinetic agents compared to placebo in septic patients who are enterally fed
Setting: ICU
Bibliography: Lewis K, Alqahtani Z, Mcintyre L, Almenawer S, Alshamsi F, Rhodes A, Evans L, Angus DC, Alhazzani W. The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. Critical Care. 2016 Aug 15;20(1):259.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prokinetic agents**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pneumonia												
3	randomized trials	serious [1]	not serious	not serious [2]	serious [3]	none [4]	58/231 (25.1%)	93/362 (25.7%)	**RR 1.00** (0.76 to 1.32)	**0 fewer per 1000** (from 62 fewer to 82 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
6	randomized trials	not serious	not serious	not serious [2]	serious [5]	none [4]	105/271 (38.7%)	166/401 (41.4%)	**RR 0.97** (0.81 to 1.16)	**12 fewer per 1000** (from 66 more to 79 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								25.0%		**8 fewer per 1000** (from 40 more to 47 fewer)		
High Gastric Residual Volumes												

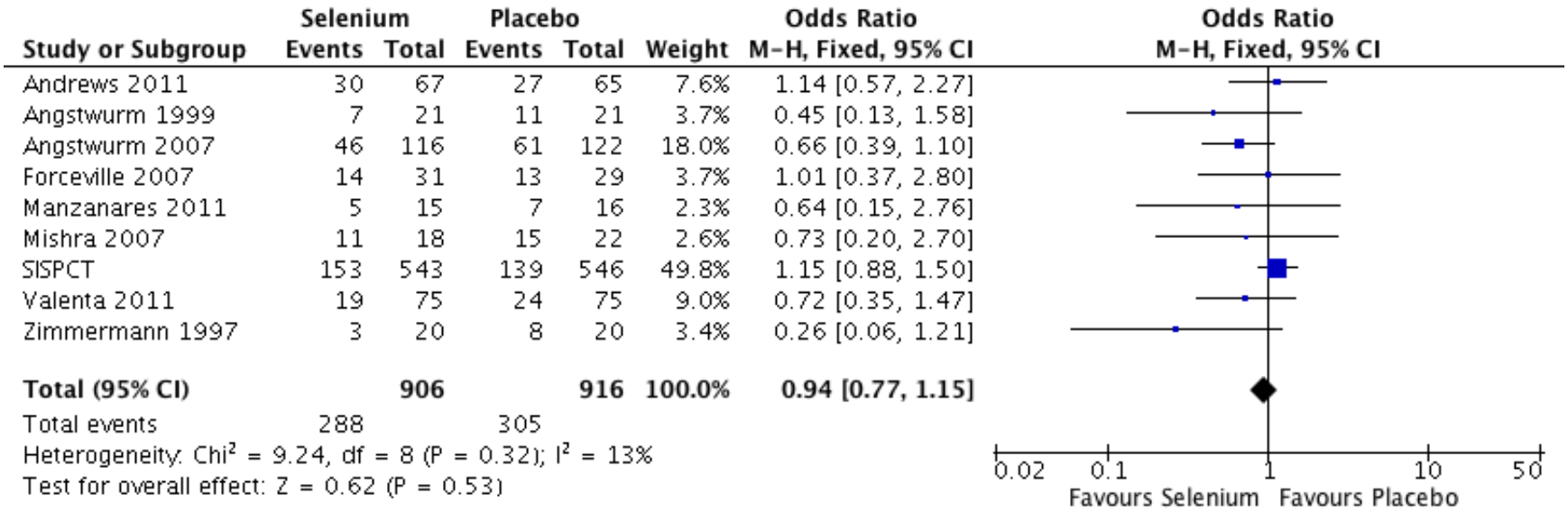
5	randomized trials	not serious	not serious	not serious	serious [6]	none [4]	44/116 (37.9%)	62/111 (55.9%) 30.0%	**RR 0.69** (0.52 to 0.91)	**173 fewer per 1000** (from 50 fewer to 268 fewer) **93 fewer per 1000** (from 27 fewer to 144 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Feeding Intolerance												
6	randomized trials	not serious	not serious	not serious	serious [7]	none [4]	47/116 (40.5%)	61/111 (55.0%)	**RR 0.73** (0.55 to 0.97)	**148 fewer per 1000** (from 16 fewer to 247 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Success of Post-Pyloric Feeding Tube Placement												
6	randomized trials	serious [8]	not serious [9]	not serious	not serious	none [4]	174/349 (49.9%)	71/214 (33.2%) 30.9%	**RR 1.60** (1.17 to 2.21)	**199 more per 1000** (from 56 more to 401 more) **186 more per 1000** (from 53 more to 374 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
ICU Length of Stay												
2	randomized trials	not serious	not serious	not serious	very serious [10]	none [4]	42	45	-	MD **1.24 more** (5.21 fewer to 7.68 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. We downgraded the quality of evidence by one level for risk of bias, the included were not properly blinded
2. Although the studies included any critically ill patient, we did not downgrade for indirectness
3. We downgraded for imprecision by one level, the CI included both significant benefit and harm
4. We did not downgrade for publication bias, although we could not assess this category reliably due to small number of eligible studies
5. We downgraded the quality of evidence by one level for imprecision, the CI contained significant harm
6. We downgraded the quality of evidence by one level for imprecision, the CI contained small benefit that did not meet the clinical decision threshold

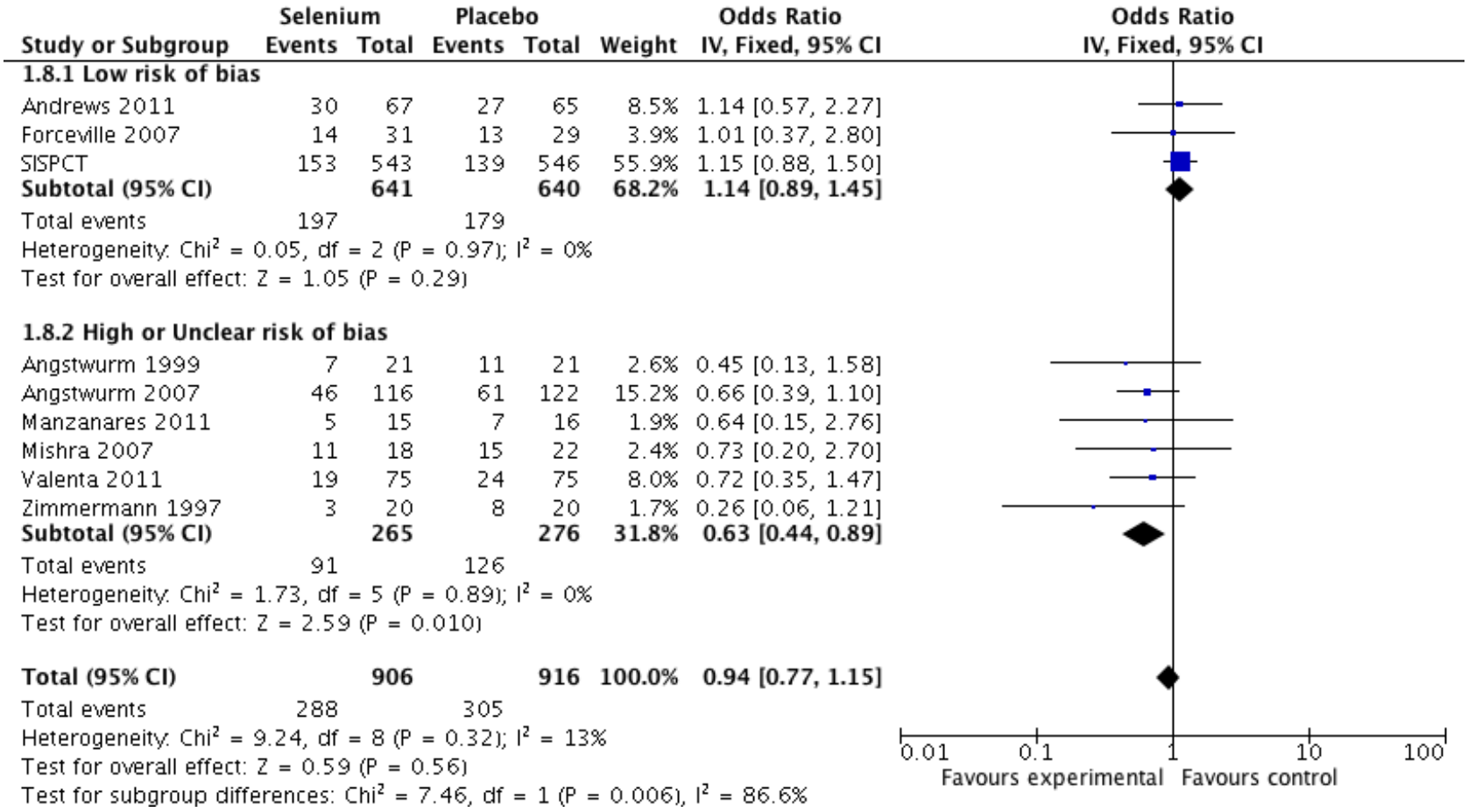
7. We downgraded the quality of evidence by one level for imprecision, the CI contained small benefit that did not meet the clinical decision threshold
8. We downgraded the quality of evidence by one level for risk of bias, blinding of outcome assessors and healthcare workers was not appropriate in majority of studies
9. I^2=45% and Chi^2 = 0.11, we did not downgrade for inconsistency
10. We downgraded the quality of evidence by two levels for imprecision, the CI is very wide containing extreme benefit and harm

Figure 61. Selenium compared to placebo in septic patients: Mortality Outcome



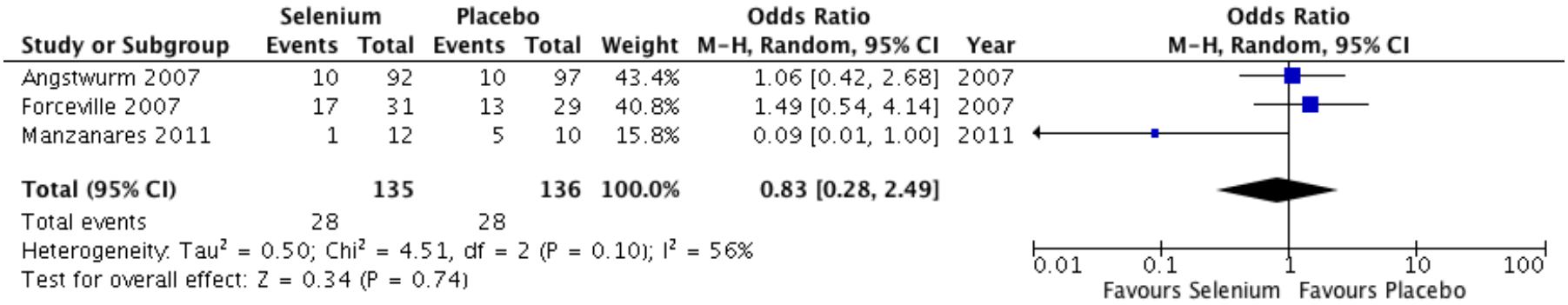
M-H: Mantel-Haenszel

Figure 62. Selenium compared to placebo in septic patients: Mortality Outcome Split by risk of bias of underlying studies.



IV: Inverse variance

Figure 63. Selenium compared to placebo in septic patients: Pneumonia Outcome



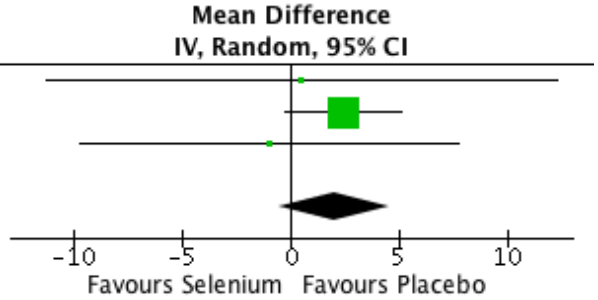
M-H: Mantel-Haenszel

Figure 64. Selenium compared to placebo in septic patients: ICU length of stay Outcome

Study or Subgroup	Selenium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mishra 2007	21.3	16.2	18	20.8	21.8	22	4.6%	0.50 [-11.29, 12.29]	2007
Angstwurm 2007	15.1	10	92	12.7	9	97	87.1%	2.40 [-0.32, 5.12]	2007
Manzanares 2011	15	12	12	16	9	10	8.3%	-1.00 [-9.79, 7.79]	2011
Total (95% CI)			**122**			**129**	**100.0%**	**2.03 [-0.51, 4.56]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.59$, df = 2 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 1.57 (P = 0.12)



IV: Inverse variance

Table 73. Selenium supplement compared to no selenium in sepsis or septic shock

Author(s): Jones A, Alhazzani W
Date: April 13, 2016
Question: Selenium supplement compared to no selenium in sepsis or septic shock
Setting: ICU
Bibliography: Alhazzani W, Jacobi J, Sindi A, Hartog C, Reinhart K, Kokkoris S, Gerlach H, Andrews P, Drabek T, Manzanares W, Cook DJ. The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomized controlled trials. Critical care medicine. 2013 Jun 1;41(6):1555-64.; Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, Moerer O, Weyland A, Marx G, Gründling M, Kluge S. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA internal medicine. 2016 Sep 1;176(9):1266.
(unpublished)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Selenium supplement**	**no selenium**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (hospital or if not reported ICU/28 days mortality)												
10	randomized trials	serious [1]	not serious	not serious	serious [2]	none	288/906 (31.8%)	305/916 (33.3%) [3]	**OR 0.94** (0.77 to 1.15)	**14 fewer per 1000** (from 32 more to 55 fewer)	⨁⨁◯◯ LOW	CRITICAL
								20.0%		**10 fewer per 1000** (from 23 more to 39 fewer)		
Mortality (Low RoB Trials)												
3	randomized trials	not serious	not serious	not serious	serious [4]	none	197/641 (30.7%)	179/640 (28.0%)	**OR 1.14** (0.89 to 1.45)	**27 more per 1000** (from 23 fewer to 81 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Nosocomial Pneumonia												

3	randomized trials	serious [5]	not serious [6]	not serious	very serious [7]	none	28/135 (20.7%)	28/136 (20.6%)	**OR 0.83** (0.28 to 2.49)	**29 fewer per 1000** (from 138 fewer to 186 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								10.0%		**16 fewer per 1000** (from 70 fewer to 117 more)		
ICU length of stay												
3	randomized trials	serious [5]	not serious	not serious	serious [8]	none	668	681	-	MD **0.12 days lower** (1.42 lower to 1.17 higher)	⨁⨁◯◯ LOW	IMPORTANT

MD – mean difference, RR – relative risk

1. We downgraded the quality of evidence by one level for risk of bias, three studies were at high risk of bias, mainly due to lack of blinding (detection and performance biases) and incomplete outcome data (attrition bias), and four studies were classified as unclear risk of bias.
2. We downgraded the quality of evidence by one level for imprecision, the results were sensitive to the metric used to summarize the results, if RR is used the UL of CI reaches 1, therefore we decided to lower the quality of evidence
3. estimates of mortality from sepsis is approximately 20% (Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308-16.)
4. We downgraded the quality of evidence for imprecision by one level, the CI contained small benefit but significant harm (45% relative risk increase in mortality)
5. We downgraded the quality if evidence for risk of bias by one level.
6. Although I^2 = 50% we did not downgrade for imprecision, because we downgraded for other categories
7. We downgraded the quality of evidence by two levels for imprecision, the CI was very wide including substantial benefit and harm
8. We downgraded the quality of evidence for imprecision by one level

Table 74. Glutamine compared to No Glutamine in sepsis or septic shock

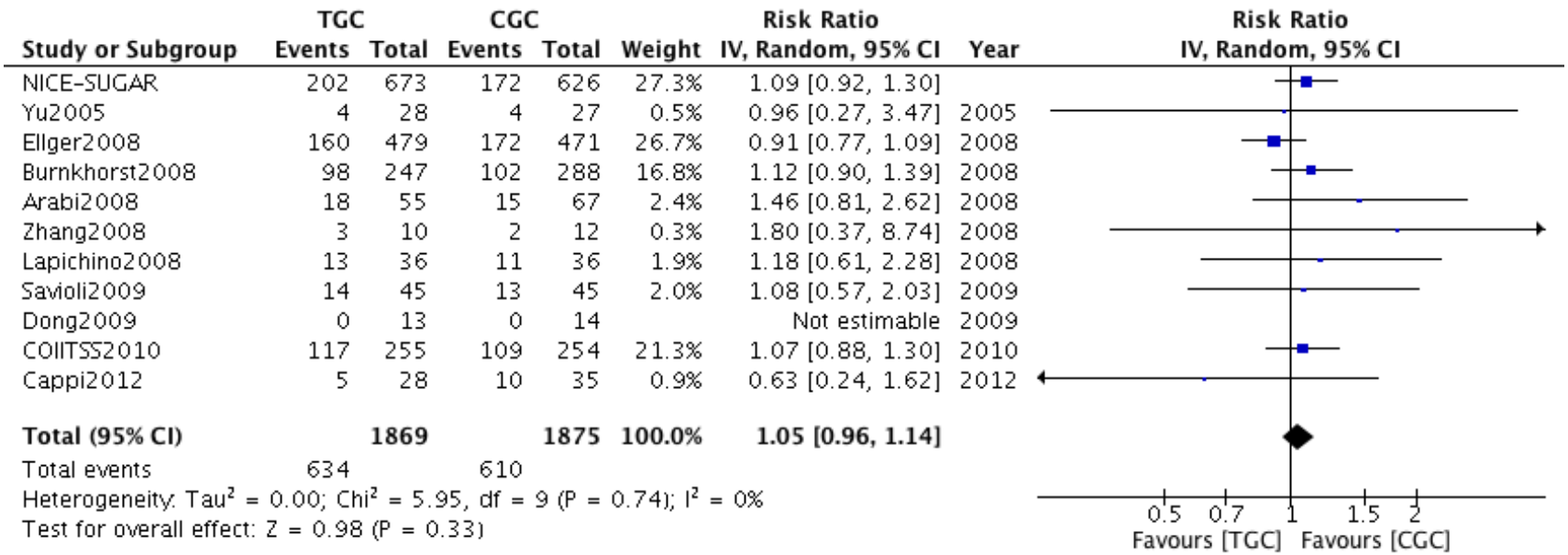
Author(s): Jones A, Alhazzani W
Date: December 3 2015
Question: Glutamine compared to No Glutamine in sepsis or septic shock
Setting: ICU
Bibliography: Tao KM, Li XQ, Yang LQ, Yu WF, Lu ZJ, Sun YM, Wu FX. Glutamine supplementation for critically ill adults. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD010050. DOI: 10.1002/14651858.CD010050.pub2

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glutamine**	**No Glutamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (long term) (follow up: 6 months)												
11	randomized trials	not serious	not serious [1]	serious [2]	not serious	none	373/1140 (32.7%)	373/1137 (32.8%)	**RR 1.00** (0.89 to 1.12)	**0 fewer per 1000** (from 36 fewer to 39 more)	⊕⊕⊕◯ MODERATE	CRITICAL

MD – mean difference, RR – relative risk

1. I^2=30%, we did not downgrade for inconsistency
2. We downgraded the quality of evidence for indirectness by one level, all RCTs looked at critically ill population and were not focused on septic population

Figure 65. Tight glucose control versus conventional control in patients with sepsis: Mortality Outcome



TGC: Tight glucose control; **CGC**: Conventional glucose control; **IV**: Inverse variance

Table 75. Tight glucose control (TGC) compared to Conventional glucose control (CGC) in patients with sepsis or septic shock

Author(s): Alhazzani W, Sprung C, Nishida O
Date: January 8, 2016
Question: Tight glucose control (TGC) compared to Conventional glucose control (CGC) in patients with sepsis or septic shock
Setting: Intensive Care Unit (ICU)
Bibliography: Song F, Zhong LJ, Han L, Xie GH, Xiao C, Zhao B et al. Intensive insulin therapy for septic patients: a meta-analysis of randomized controlled trials. Biomed Res Int. 2014;2014:698265. doi:10.1155/2014/698265.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tight glucose control (TGC)**	**Conventional glucose control (CGC)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
11	randomized trials [1]	not serious [2]	not serious	not serious	not serious	none	634/1869 (33.9%)	610/1875 (32.5%)	**RR 1.05** (0.96 to 1.14)	**16 more per 1000** (from 13 fewer to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								25.0%		**13 more per 1000** (from 10 fewer to 35 more)		
Hypoglycemia												
7	randomized trials	not serious	serious [3]	not serious	not serious	strong association [4]	196/1093 (17.9%)	55/1120 (4.9%)	**RR 2.93** (1.69 to 5.06)	**95 more per 1000** (from 34 more to 199 more)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. We excluded one trial that was published as an abstract (Jin et al) in which pertinent information was not available
2. Although all RCTs were unblinded, the impact on mortality outcome is unlikely to be important, therefore, we did not lower the quality of evidence for risk of bias
3. We lowered the quality of evidence by one level for heterogeneity, the I 2= 61%, this was not explained by subgroup analyses for risk of bias or blood glucose level target
4. The RR > 2, therefore, we upgraded the quality of evidence by one level

Table 76. Arterial glucose level compared to capillary glucose level for glucose monitoring in patients with sepsis or septic shock on insulin infusion

Author(s): Alhazzani W, Nishida O
Date: April 17, 2016
Question: Arterial glucose level compared to capillary glucose level for glucose monitoring in patients with sepsis or septic shock on insulin infusion
Setting: ICU
Bibliography: Inoue S, Egi M, Kotani J, Morita K. Accuracy of blood glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review. Crit Care. 2013 Mar 18;17:R48. doi: 10.1186/cc12567.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**arterial glucose level**	**capillary glucose level**	**Relative (95% CI)**	**Absolute (95% CI)**		
accuracy of glucose measurement (assessed with: proportion of wrong glucose readings)												
6	observational studies	serious [1]	not serious [2]	not serious	not serious	strong association [3,4]	79/2647 (3.0%)	204/2501 (8.2%)	**RR 0.36** (0.25 to 0.52)	**52 fewer per 1,000** (from 39 fewer to 61 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. We downgraded the quality of evidence for risk of bias, as the studies were diagnostic accuracy but did not measure accuracy outcomes appropriately
2. $I^2 = 29\%$
3. We upgraded the quality of evidence by one level for large effect RR<0.5
4. Dose-response gradient is not applicable, therefore, not assessed