<Supplemental Tables and Figures>

SUPPLEMENTAL TABLE 1: PICO QUESTIONS FOR SURVIVING SEPSIS CAMPAIGN INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEPTIC SHOCK AND SEPSIS-ASSOCIATED ORGAN DYSFUNCTION IN CHILDREN

1) RECOGNITION AND MANAGEMENT OF SEPSIS AND SEPTIC SHOCK

1 Should acute care settings implement systematic screening for timely recognition of children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with suspected infection in acute care settings	Systematic screening program	Usual care	Mortality Hospital LOS Transfer to the ICU
2 Should lactic acid be used to stratify children at low-versus versus high-risk of sepsis with organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with suspected infection in acute care settings	Measurement of lactate	Usual care	Mortality ICU LOS Hospital LOS
3 Should acute care settings implement a protocol/guideline for management of children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Patients in the acute care setting with concern for severe sepsis or septic shock	Protocol/guideline	Usual care/No protocol	Mortality ICU LOS Organ failure free days Hospital LOS Transfer to the ICU

4 In children with sepsis-associated organ dysfunction, should blood cultures be obtained routinely before initiating antimicrobial therapy?			
Population	Intervention	Comparator	Outcome(s)
Children in the acute care setting with concern for sepsis-associated organ dysfunction	Blood culture prior to antimicrobials	No culture	Prolonged exposure to broad spectrum agents? Delayed time to appropriate therapy? Mortality LOS
5 In children with suspected sepsis-associated organ dysfunction, should we use broad-spectrum empiric antimicrobial coverage as first-line therapy until sensitivities are determined?			
Population	Intervention	Comparator	Outcome(s)
Children with suspected sepsis-associated organ dysfunction	Empiric broad-spectrum antimicrobial therapy (i.e., 1 or more antibiotics that intend to broaden the range of pathogens covered)	Single antimicrobial therapy	Mortality ICU LOS Hospital LOS Source control
6 In children with suspected sepsis-associated organ dysfunction, should we administer empiric parenteral antimicrobials within one hour of recognition? (includes IV, IO, parenteral administration)			
Population	Intervention	Comparator	Outcome(s)
Children with suspected sepsis-associated organ dysfunction	Administer empirically intravenous antimicrobials within 1 hour	Administration delayed beyond 1 hour	Mortality Duration of vasoactives MODS or NPMODS LOS PICU

			LOS hospital
7 In children with sepsis-associated organ dysfunction, should we implement pharmacokinetic dose optimization for each antimicrobial? (i.e., should we be adjusting doses based on our knowledge of drug indicators?)			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Pharmacokinetic dosing optimization	Standard dosing	Mortality Time to resolution of infection
8/9 In children with sepsis-associated organ dysfunction, should we use empiric combination antibiotic therapy (versus mono-therapy) until sensitivities are determined?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction Those who are immunocompromised (e.g., neutropenic) and/or at high risk for multi-drug resistant pathogens	Empiric combination antibiotic therapy (i.e., 2 or more antibiotics that cover the same pathogens)	Empiric antimicrobial therapy	Mortality ICU LOS Hospital LOS Source control
10 In children with uncomplicated infections causing organ dysfunction, should we recommend a duration of therapy of 7-10 days?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Antimicrobial therapy for 7-10 days	Therapy for >10 days	Mortality LOS

11 In children with sepsis-associated organ dysfunction who are receiving empiric combination of antimicrobials should we recommend daily assessment (eg, clinical, laboratory assessment) for de-escalation of therapy?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction who are on empiric combination of antimicrobials	De-escalation within 3 to 5 days of starting antimicrobial therapy 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 LOS
12 In children with an anatomic (e.g., loculated, drainable) source of infection with sepsis-associated organ dysfunction, should we attempt source control as soon as possible?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction, and remediable source of infection is identified	Source control intervention within first 12 hours	Intervention beyond 12 hours	Mortality MODS/NPMODS Ventilator days (or vent-free days) Vasoactive days (or vaso-free days)
13 In children with an indwelling central line as the most likely source of sepsis-associated organ dysfunction, should we remove the central line as soon as possible?			
Population	Intervention	Comparator	Outcome(s)

Children with sepsis-associated organ dysfunction with an indwelling central line as the suspected or confirmed source of infection	Line removal within the first 1-2 days	Line removal only if persistent bacteremia	Mortality NPMODS Ventilator days (or vent-free days) Vasoactive days (or vaso-free days)

2) HEMODYNAMICS AND RESUSCITATION

14 In children with sepsis-associated organ dysfunction, should we begin resuscitation with balanced crystalloid solutions versus normal saline?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Balanced crystalloid solutions	Normal saline	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Acute kidney injury Renal replacement therapy NPMODS Cumulative fluid balance

15 In children with sepsis-associated organ dysfunction, should we use human albumin solution for initial resuscitation versus crystalloids alone?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Human albumin solution (any strength)	Crystalloid	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Acute kidney injury Renal replacement therapy NPMODS Cumulative fluid balance

16 In children with sepsis-associated organ dysfunction, should we be using synthetic colloids versus crystalloids for acute resuscitation?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Synthetic colloids	Crystalloids or albumin	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Acute kidney injury Renal replacement therapy Coagulopathy NPMODS Cumulative fluid balance

17 In children with sepsis-associated organ dysfunction, should we use restrictive fluid boluses or fluid boluses as currently recommended for initial resuscitation?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Restrictive fluid resuscitation with either smaller fluid boluses and/or early initiation of vasoactives if shock persists	20 ml/kg bolus up to three times (60 ml/kg) over first hour	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS Cumulative fluid balance Long-term neurological outcome

18 In children with sepsis-associated cardiovascular dysfunction (septic shock), should we use advanced hemodynamic parameters along with bedside clinical signs to guide resuscitation?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated cardiovascular dysfunction (septic shock)	Resuscitation guided by improvement in advanced hemodynamic variables, including pulse pressure variation, $ScvO_2$, cardiac output, etc, in addition to bedside clinical signs	Therapy guided by bedside clinical signs (heart rate, BP, CRT, CVP) alone	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS Cumulative fluid balance Long-term neurological outcome
19 In children with sepsis-associated organ dysfunction, should we include measurement of lactate along with clinical signs to guide resuscitation?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Lactate and bedside clinical sign guided resuscitation	Bedside clinical signs guided resuscitation alone	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) NPMODS Long-term neurological outcome

20 In children with sepsis-associated cardiovascular dysfunction (septic shock), should we recommend categorization of patients as "warm" versus "cold" shock?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated cardiovascular dysfunction (septic shock)	Clinical differential of "warm" versus "cold" shock	No differentiation of "warm" vs "cold" shock	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS Long-term neurological outcome
21 In children with sepsis-associated cardiovascular dysfunction (septic shock) requiring vasoactives, should the initial blood pressure target be the 5th percentile or 50th percentile MAP for age**?**			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock requiring vasoactives	MAP of > 5th percentile for age mmHg	MAP of > 50th percentile for age mmHg	Mortality Ventilator days (or vent-free days) Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS ECMO Long-term neurological outcome
22 In children with sepsis-associated cardiovascular dysfunction (septic shock) requiring vasoactive therapy, should we recommend epinephrine as first-line therapy?			
Population	Intervention	Comparator	Outcome(s)

Children with septic shock refractory to fluids and requiring vasoactives	Epinephrine	Dopamine	Mortality Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS ECMO Arrhythmia Long-term neurological outcome
23 In children with sepsis-associated cardiovascular dysfunction (septic shock) requiring vasoactive therapy, should we recommend norepinephrine as first-line therapy?			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock refractory to fluids and requiring vasoactives	Norepinephrine	Dopamine	Mortality Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS ECMO Arrhythmia Long-term neurological outcome
24 In children with sepsis-associated cardiovascular dysfunction (septic shock) and myocardial dysfunction despite other vasoactive agents, should we recommend adding an inodilator?			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock with evidence of persistent hypoperfusion and cardiac dysfunction despite vasoactives	Milrinone, dobutamine, or levosimendan	No inodilator	Mortality Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS

			ECMO Long-term neurological outcome
25 In children with sepsis-associated cardiovascular dysfunction (septic shock) requiring vasoactives but refractory to catecholaminergic drugs, should we recommend vasopressin or terlipressin?			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock with evidence of shock refractory to catecholaminergic drugs	Vasopressin or terlipressin	Titrating catecholaminergic drugs alone (no vasopressin)	Mortality Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS ECMO Ischemic events (limb, gut, myocardium) Long-term neurological outcome
26 In children with sepsis-associated cardiovascular dysfunction (septic shock) who require a vasoactive agent, should we recommend initiation of those through peripheral venous access?			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock requiring vasoactives	Peripheral venous access	Central venous access	Mortality Vasoactive infusion days (or vaso-free days) Renal replacement therapy NPMODS ECMO Limb ischemia

			Complications of central line insertion, eg, pneumothorax, hemothorax, arterial puncture, CLABSI Skin necrosis

3) VENTILATION

27 In children with septic shock, when should we intubate patients with fluid-refractory, catecholamine-resistant shock?			
Population	Intervention	Comparator	Outcome(s)
Children with hypoperfusion despite fluid resuscitation and vasoactive support	Early intubation for refractory shock	Usual care with delayed/no intubation for refractory shock without respiratory failure	Mortality Ventilator days Vasoactive days NPMODS Hemodynamic complication at time of intubation
28 In children with sepsis-associated organ dysfunction, should we recommend intubation with etomidate to facilitate intubation?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction who require intubation	Etomidate	Other sedative/anesthetic/analgesic	Mortality Ventilator days Vasoactive days NPMODS Adrenal insufficiency
29 In children with sepsis-induced PARDS, should we use non-invasive respiratory support?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced PARDS	Noninvasive respiratory support (HFNC, CPAP, BIPAP)	Invasive mechanical ventilation	Mortality LOS Ventilator days
30 In children with sepsis-induced moderate-severe PARDS who are mechanically ventilated, should we use high PEEP strategy?			

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced moderate to severe PARDS	"Higher" PEEP	"Lower" PEEP	Mortality Ventilator days
31 In children with sepsis-induced PARDS and refractory hypoxemia, should we use recruitment maneuvers?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced PARDS and refractory hypoxemia	Recruitment maneuvers	No recruitment maneuvers	Mortality Ventilator days Oxygenation
32 In children with sepsis-induced severe PARDS, should we use prone ventilation?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced severe PARDS	Prone ventilation	No proning	Mortality Oxygenation Ventilator days Accidental extubation
33 In children with sepsis-induced PARDS with refractory hypoxemia or pulmonary hypertension, should we use inhaled nitric oxide?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced PARDS and refractory hypoxemia or pulmonary hypertension	iNO	Usual care	Mortality Oxygenation Ventilator days LOS
34 In children with sepsis-induced PARDS, should we use high frequency oscillation (HFO) versus conventional ventilation?			

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced PARDS	HFOV	Conventional mechanical ventilation	Mortality Duration of mechanical ventilation
35 In children with sepsis-induced severe PARDS who are mechanically ventilated, should we use neuromuscular blocking agents?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced severe PARDS who are mechanically ventilated	Neuromuscular blocking agent	Usual care	Mortality Ventilator days ICU-acquired weakness Barotrauma (or air-leak)
36 In children with sepsis-induced lung failure and refractory hypoxemia and/or hypercarbia, <u>if and when</u> should we recommend ECMO?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-induced lung failure and refractory hypoxemia and/or hypercarbia	ECMO	No ECMO	Mortality Survival without neurologic injury

4) ADJUNCTIVE THERAPIES

37 In children with sepsis-associated organ dysfunction including TAMOF, should we use plasma exchange therapy?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction including TAMOF	Plasma exchange	No plasma exchange	Mortality Vasoactive days NPMODS
38 In children with sepsis-associated organ dysfunction, should we use a restrictive transfusion strategy versus liberal transfusion?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Restrictive blood transfusion threshold (7-8 g/dL hemoglobin)	Liberal blood transfusion threshold (9-10 g/dL)	Mortality Amount of blood transfused NPMODS LOS
39 In non-bleeding children with sepsis-associated organ dysfunction and coagulation abnormalities, should we use prophylactic FFP?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction and laboratory coagulation abnormalities (prolonged PT, PTT) who are not bleeding	Prophylactic plasma transfusion	No transfusion	Mortality Major bleeding Ventilator-free days
40 In non-bleeding children with sepsis-associated organ dysfunction and thrombocytopenia, should we use prophylactic platelet transfusion based on specific platelet levels?			

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction and thrombocytopenia who are not 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)	No specific platelet transfusion threshold	Mortality Major bleeding Ventilator-free days
41 Should we use stress ulcer prophylaxis in critically ill children with sepsis-associated organ dysfunction			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction and risk factors for stress ulcer	PPIs or H2RA	Placebo or No prophylaxis	Clinically important bleeding Pneumonia C. difficile infection Mortality LOS NEC incidence
42 Should we use DVT prophylaxis (mechanical or pharmacologic) in critically ill children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	DVT prophylaxis	No DVT Prophylaxis	Mortality VTE Major bleeding CLABSI incidence
43 In children with sepsis-associated organ dysfunction, should we recommend renal replacement therapy to prevent or treat fluid overload?			
Population	Intervention	Comparator	Outcome(s)

Children with sepsis-associated organ dysfunction and risk for or evidence of fluid overload	Renal replacement therapy	Diuretics or usual care	Mortality Ventilator days NPMODS Vasoactive days
44 In children with sepsis-associated organ dysfunction treated with continuous renal replacement therapy, should we recommend high-volume hemofiltration?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction treated with CRRT	HVHF (>50 ml/kg/hr)	Standard volume hemofiltration (<35 mL/kg/hr)	Mortality Ventilator days NPMODS Vasoactive days Duration of RRT
45 In children with refractory septic shock, <u>if and when</u> should we recommend veno-arterial ECMO?			
Population	Intervention	Comparator	Outcome(s)
Children with septic shock with hypoperfusion despite fluid and vasoactives	ECMO	No ECMO	Mortality Survival with neurologic injury
46 In children with sepsis-associated organ dysfunction with selected infections, should we recommend IVIG?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction with selected infections, such as toxic shock syndrome	IVIG	Usual care	Mortality Source control Antibiotic days Ventilator days Vasoactive days LOS

5) ENDOCRINE AND METABOLIC THERAPIES

47 In children with sepsis-associated cardiovascular dysfunction (septic shock), should we use adjunctive hydrocortisone?

Population	Intervention	Comparator	Outcome(s)
Children with septic shock with hypoperfusion or hypotension despite fluid and vasoactive-inotropic support	Hydrocortisone	No hydrocortisone	Mortality Hospital-acquired infections MODS (PELOD, NPMODS or similar) Vasoactive- free days (or similar) Ventilator-free days ECMO Hyperglycemia treated with insulin Renal replacement therapy

48 In children with sepsis-associated cardiovascular dysfunction (septic shock) with vasoactive-inotropic medications, is enteral feeding contraindicated?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction treated with vasoactive medications	Enteral feeding	No enteral feeding	Mortality ICU LOS Intestinal ischemia (including NEC) GI bleeding Hospital-acquired infections

49 Should we use enteral nutrition (EN) alone or add parenteral nutrition (PN) as a supplement to meet nutritional goals in children with sepsis-associated organ dysfunction during their first week in the ICU?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction without contraindications for enteral feeding	EN + supplemental PN in the first 7 days	EN alone in the first 7 days	Mortality Hospital-acquired infections ICU LOS Hyperglycemia treated with insulin

50 Should we use early PN versus no PN with trophic EN in children with sepsis-associated organ dysfunction who have contraindications for full enteral feeding?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction with contraindications for full enteral feeding	Early PN +/- trophic enteral feeding in the first 7 days	No or early trophic enteral feeding alone, or enteral feeding according to usual/standard care	Mortality Hospital-acquired infections ICU LOS

51 Should we use early hypocaloric/trophic enteral feeding followed by slow increase to full goals versus early full enteral feeding in children with sepsis-associated organ dysfunction without contraindications to enteral feeding?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction without contraindications for enteral feeding	Early hypocaloric/trophic enteral feeding	Early full enteral feeding (within 48 hours)	Mortality Hospital-acquired infections ICU LOS

52 For *children with sepsis-associated organ dysfunction* with contraindications to enteral feeding and not on parenteral nutrition, should we use high or low glucose-infusion rates?

Population	Intervention	Comparator	Outcome(s)

Children with sepsis-associated organ dysfunction with contraindications for enteral feeding and not on parental nutrition	High glucose-infusion rate (>5 mg/kg/min)	Low glucose-infusion rate (≤5 mg/kg/min)	Mortality Hypoglycemia ICU LOS
53 Should we use supplementation with specialized lipid emulsions in children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Enteral feeding with specialized lipid emulsions (fish oils, MCT oils, omega-3 fatty acids, or proprietary combinations) as an immunomodulating supplement	Standard enteral feeding alone	Mortality Hospital-acquired infections ICU LOS
54 Should we measure gastric residuals when enterally feeding children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction receiving enteral feeding	Measuring gastric residuals and withholding feeding when residuals exceed a given threshold	No measurement of gastric residuals	Mortality Aspiration pneumonia ICU LOS Time to full nutrition
55 Should we use enteral feeding via a post-pyloric or gastric tube children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction receiving enteral feeding	Enteral feeding via a post-pyloric tube	Enteral feeding with a gastric tube	Mortality Aspiration or aspiration pneumonia ICU LOS

			Time to full enteral caloric support KCal/day
56 Should we use prokinetic agents to assist in enteral feeding of children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction who can be enterally fed	Use of pro-kinetic agents (metoclopramide, domperidone, erythromycin, cisapride)	Usual care	Time to full enteral caloric support Aspiration pneumonia KCal/day ICU LOS Successful post-pyloric tube placement Mortality
57 Should we use selenium therapy for children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Selenium in therapeutic doses	No selenium	Mortality Ventilator-free days ICU LOS MODS (PELOD, NPMODS, or similar)
58 Should we recommend glutamine therapy in critically ill children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Glutamine in therapeutic doses	No glutamine	Mortality Ventilator-free days ICU LOS

			MODS (PELOD, NPMODS, or similar)
59 Should we use* arginine *therapy in children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Arginine in therapeutic doses	No arginine	Mortality Ventilator-free days ICU LOS MODS (PELOD, NPMODS, or similar)
60 Should we use intensive insulin therapy in children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Intensive insulin therapy	Conventional insulin therapy	Mortality Hypoglycemia Neurodevelopmental outcomes MODS (PELOD, NPMODS, or similar)
61 Should we use zinc therapy in children with sepsis-associated organ dysfunction?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Zinc in therapeutic doses	No zinc	Mortality ICU LOS MODS (PELOD, NPMODS, or similar)
62 In children with sepsis-associated organ dysfunction, should we target normal blood calcium levels?			

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Supplemental calcium to target ionized calcium >1.20 mmol/L	Supplemental calcium to treat symptomatic hypocalcemia	Mortality Vasoactive use/free days ICU LOS Hospital LOS Ventilator-free days Hospital-acquired infection RBC transfusions Anemia

63 In children with sepsis-associated organ dysfunction, should we treat the sick euthyroid state?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction in a sick euthyroid state	Treat with thyroxine (T3 or T4)	No levothyroxine	Mortality Vasoactive days ICU LOS

64 Should we treat fever in critically ill in children with sepsis-associated organ dysfunction?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Restrictive approach to fever, including maintaining normothermia or mild hypothermia	Permissive approach to fever	Mortality ICU LOS Source control

65 Should we use ascorbic acid (vitamin C) therapy in children with sepsis-associated organ dysfunction?

Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Ascorbic acid in therapeutic doses	No ascorbic acid	Mortality Vasoactive-inotropic infusion days (or vasoactive-inotropic-free days) ICU LOS Hospital-acquired/secondary infections NPMODS/organ dysfunction
66 Should we used thiamine therapy in children with sepsis-associated organ dysfunction? Verger			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction	Thiamine in therapeutic doses	No thiamine	Mortality ICU LOS NPMODS/organ dysfunction
67 Should we treat vitamin D deficiency acutely in children with sepsis-associated organ dysfunction who are 25(OH)D deficient?			
Population	Intervention	Comparator	Outcome(s)
Children with sepsis-associated organ dysfunction with 25(OH)D levels <20 ng/mL.	Vitamin D3 in therapeutic doses	No acute vitamin D3 repletion	Mortality Vasoactive-inotropic infusion days (or vasoactive-inotropic-free days) ICU LOS Secondary infections NPMODS Motor strength Osteopenia

Supplemental Table 2. Evidence Profile for Recommendation 5-6

Quality Assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antibiotics be administered with 1 hour**	**after 1 hour**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	observational studies	not serious	not serious	not serious	serious [a]	none	91/822 (11.1%)	64/487 (13.1%)	**OR 0.77** (0.55 to 1.08)	**27 fewer per 1,000** (from 9 more to 55 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								10.0%		**21 fewer per 1,000** (from 7 more to 42 fewer)		
Mortality (hospital)												
1	observational studies	not serious [b]	not serious	not serious	serious [c]	none	89/798 (11.2%)	50/381 (13.1%)	**HR 0.78** (0.55 to 1.12)	**27 fewer per 1,000** (from 15 more to 57 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								10.0%		**21 fewer per 1,000** (from 11 more to 44 fewer)		
Vasoactive days - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
MODS - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
PICU length of stay - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

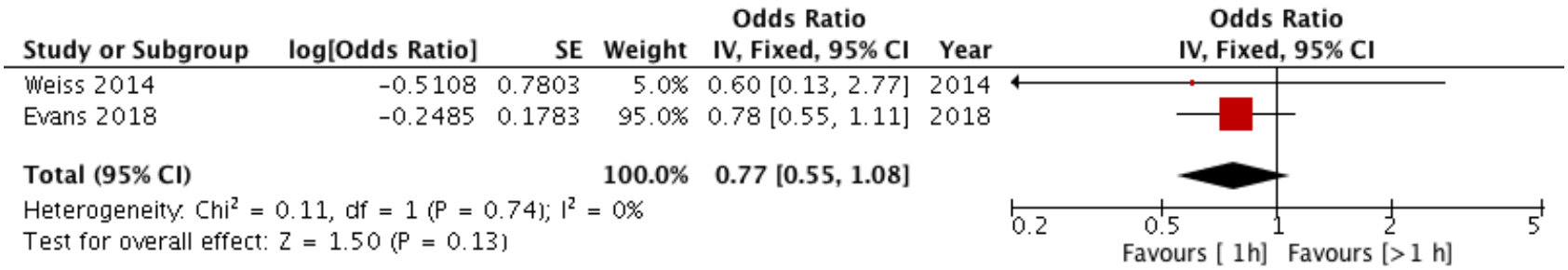
CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations
a. We downgraded the quality of evidence for imprecision by one level for serious imprecision, the CI included both large benefit and small harm

b. Although there was statistically significant imbalance in baseline characteristics between two study population, we did not downgrade for risk of bias because authors used adjusted regression analysis to report the results.

c. We downgraded the quality of evidence by one level for imprecision, the 95% CI included large benefit and moderate harm

Supplemental Figure 1. Mortality: adjusted ORs from observational studies on 1 hour antibiotics



Supplemental Table 3. Evidence Profile for Recommendation 16

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**early central line removal**	**delayed removal**	**Relative (95% CI)**	**Absolute (95% CI)**		
Infection resolution												
1	observational studies	not serious	not serious	not serious	serious [a]	strong association		57.0%	**OR 3.45** (1.75 to 6.67)	**251 more per 1,000** (from 129 more to 328 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality												
1	observational studies						observational studies addressing this issue for children with fungemia and Enterobacteriaceae bacteremia suggested that the catheter retention is associated with an increased risk of death on any given day after candidemia or bacteremia onset.				-	CRITICAL
Vasoactive days - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
NPMODS - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Ventilator days - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

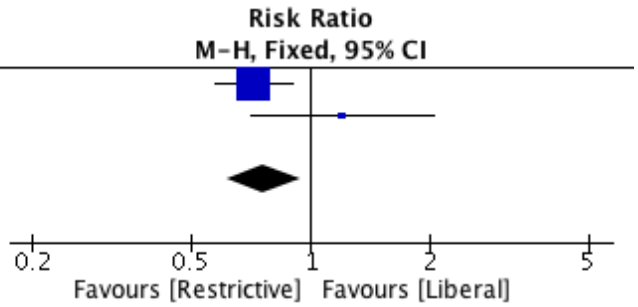
a. We downgraded the quality of evidence for imprecision

b. We upgraded the quality of evidence by one level for strong association; the OR 3.45

Supplemental Figure 2a. Mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Maitland 2011	91	1044	254	2097	91.4%	0.72 [0.57, 0.90]	2011
Sankar 2017	18	45	17	51	8.6%	1.20 [0.71, 2.03]	2017
Total (95% CI)		**1089**		**2148**	**100.0%**	**0.76 [0.62, 0.94]**	
Total events	109		271				

Heterogeneity: $Chi^2 = 3.09$, df = 1 (P = 0.08); $I^2 = 68\%$
Test for overall effect: Z = 2.55 (P = 0.01)



Supplemental Figure 2b. Mortality (excluding albumin arm)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maitland 2011	91	1044	126	1047	88.8%	0.72 [0.56, 0.94]
Sankar 2017	18	45	17	51	11.2%	1.20 [0.71, 2.03]
Total (95% CI)		**1089**		**1098**	**100.0%**	**0.78 [0.62, 0.98]**
Total events	109		143			

Heterogeneity: $Chi^2 = 2.89$, df = 1 (P = 0.09); $I^2 = 65\%$
Test for overall effect: Z = 2.13 (P = 0.03)

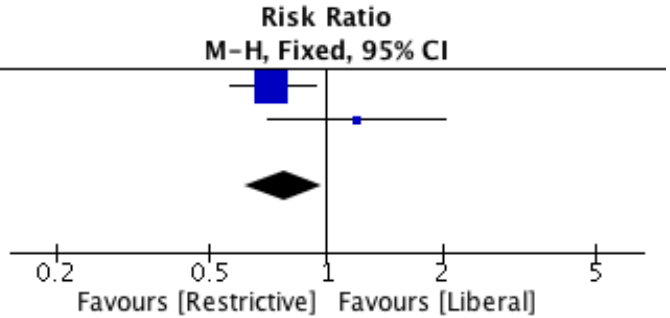
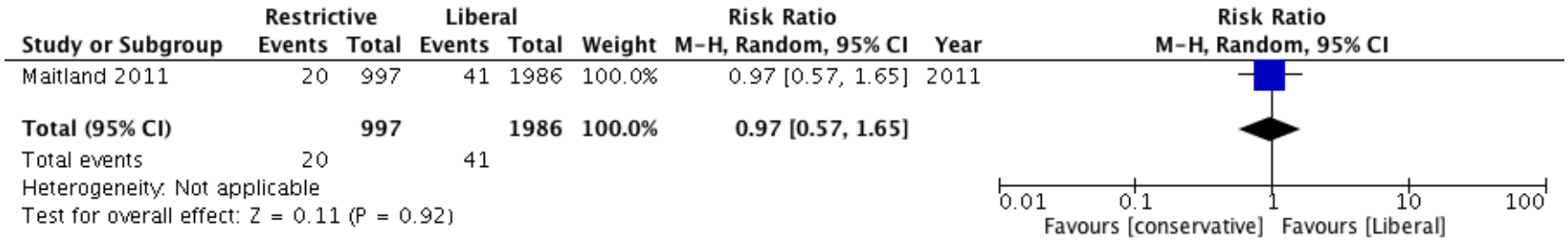


Figure 2c. Neurological sequelae



Supplemental Table 4. Evidence Profile for Recommendations 17 - 19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**restricted fluid boluses**	**current practice**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality - Low resource setting												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	91/1044 (8.7%)	254/2097 (12.1%)	**RR 0.72** (0.57 to 0.90)	**34 fewer per 1,000** (from 52 fewer to 12 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality - High resource setting												
3	randomised trials	not serious	not serious	not serious	very serious [b]	none	31/158 (19.6%)	30/158 (19.0%)	**RR 1.10** (0.72 to 1.69)	**19 more per 1,000** (from 53 fewer to 131 more)	⊕⊕◯◯ LOW	CRITICAL
Poor Neurologic outcomes												
1	randomised trials	not serious	not serious	serious	serious [c]	none	20/997 (2.0%)	41/1986 (2.1%)	**RR 0.97** (0.57 to 1.65)	**1 fewer per 1,000** (from 9 fewer to 13 more)	⊕⊕◯◯ LOW	CRITICAL
Duration of Mechanical Ventilation (assessed with: in hours)												
1	randomised trials	serious [d]	not serious	not serious	serious [c]	none			-	MD **12.03 hours more** (28.9 fewer to 52.9 more)	⊕⊕◯◯ LOW	CRITICAL

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

Explanations

a. We downgraded the quality of evidence by one level for indirectness, majority of patients had dengue fever rather than bacterial sepsis

b. We downgraded the quality of evidence by two levels for very serious indirectness, the CI included both large benefit and harm

c. We downgraded the quality of evidence for imprecision, the CI included both benefit and harm

d. unblinded study

Supplemental Table 5. Evidence Profile for Recommendation 21

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Balanced Crystalloids**	**Normal Saline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	observational studies	not serious	not serious	not serious	serious [a]	none	125/1000 (12.5%)	954/6000 (15.9%)	**OR 0.76** (0.62 to 0.93)	**33 fewer per 1,000** (from 9 fewer to 54 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								10.0%		**22 fewer per 1,000** (from 6 fewer to 36 fewer)		
Acute kidney injury												
1	observational studies	not serious	not serious	not serious	serious [b]	none	160/1000 (16.0%)	1153/6000 (19.2%)	**OR 0.82** (0.68 to 0.98)	**32 fewer per 1,000** (from 3 fewer to 57 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Supplemental Table 6. Evidence profile on HES vs Crystalloids, Recommendation 22

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HES**	**Crystalloids**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (assessed with: Long-term follow-up, >28 days)												
4	randomised trials	not serious	not serious	serious [a]	not serious	none	533/1591 (33.5%)	478/1565 (30.5%)	**RR 1.11** (1.01 to 1.22)	**34 more per 1,000** (from 3 more to 67 more)	⊕⊕⊕◯ MODERATE	CRITICAL
								25.0%		**28 more per 1,000** (from 3 more to 55 more)		
Renal Replacement Therapy												
5	randomised trials	not serious	not serious	serious [a]	not serious	none	136/650 (20.9%)	101/661 (15.3%)	**RR 1.36** (1.08 to 1.72)	**55 more per 1,000** (from 12 more to 110 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious Adverse Events												
4	randomised trials	not serious	not serious	serious [a]	not serious	none	100/533 (18.8%)	76/536 (14.2%)	**RR 1.30** (1.03 to 1.67)	**43 more per 1,000** (from 4 more to 95 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

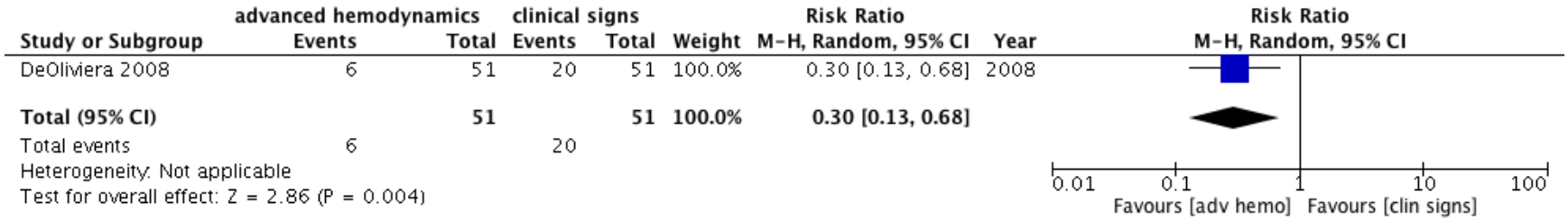
a we downgraded the quality of evidence by one level for serious indirectness, the data are from adult literature

Supplemental Table 7. Evidence profile Gelatin vs Normal saline, Recommendation 23

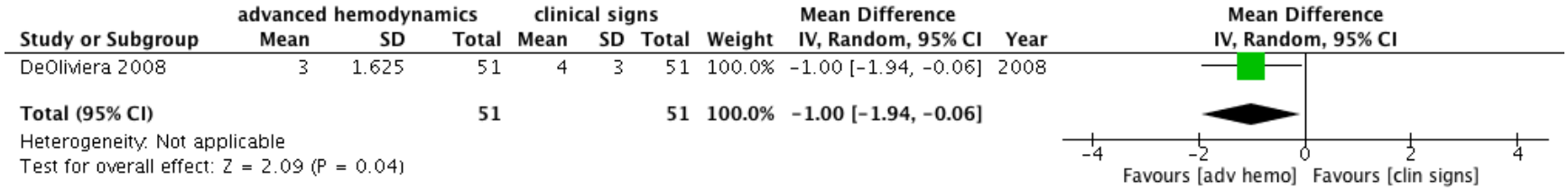
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gelatin**	**Normal Saline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	9/29 (31.0%)	9/31 (29.0%)	**RR 1.07** (0.49 to 2.32)	**20 more per 1,000** (from 148 fewer to 383 more)	⊕⊕◯◯ LOW	CRITICAL
Vasoactive days (assessed with: Days)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	21	19	-	MD **0.02 days higher** (0.85 lower to 0.89 higher)	⊕⊕◯◯ LOW	CRITICAL
Acute Kidney Injury												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/29 (3.4%)	3/31 (9.7%)	**RR 0.36** (0.04 to 3.23)	**62 fewer per 1,000** (from 93 fewer to 216 more)	⊕⊕◯◯ LOW	CRITICAL

[a] we downgraded the quality of evidence by two levels for very serious imprecision, the CI included both substantial benefit and harm

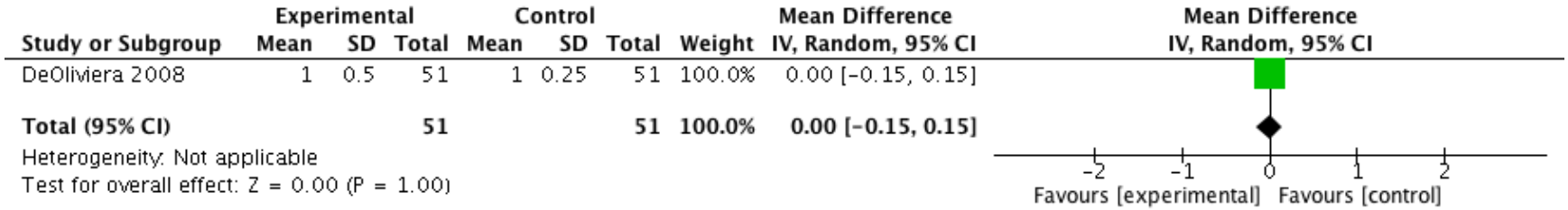
Supplemental Figure 3a. Mortality (28 d – hospital)



Supplemental Figure 3b. Duration of Mechanical Ventilation



Supplemental Figure 3c. Organ dysfunction (number of organ dysfunction at 24 h)



Supplemental Table 8. Evidence Profile for Recommendation 26

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**advanced hemodynamic variables**	**bedside clinical variables**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	6/51 (11.8%)	10.0% [b]	**RR 0.30** (0.13 to 0.68)	**70 fewer per 1,000** (from 32 fewer to 87 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of mechanical ventilation												
1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	51	51	-	MD **1 days fewer** (1.94 fewer to 0.06 fewer)	⨁⨁◯◯ LOW	CRITICAL
Number of organ dysfunction												
1	randomised trials	not serious	not serious	not serious	very serious [d]	none	51	51	-	MD **0 organs** (0.15 fewer to 0.15 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean differenceExplanationsa. We downgraded the quality of evidence by one level for serious imprecision, the CI included both substantial and small benefit

b. We estimate that mortality rate of children with sepsis in developed countries is 10%

c. We downgraded the quality of evidence by one level for risk of bias, the we estimated mean and SD from small sample size data, can't rule out skewed results

d. We downgraded the quality of evidence by one level for serious imprecision, the CI included both benefit and harm

Supplemental Table 9. Evidence Profile for Recommendation 27

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lactate levels measurement**	**other parameters**	**Relative (95% CI)**	**Absolute (95% CI)**		
Organ dysfunction (assessed with: PELOD Score)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	Lactate normalization: adjusted RR 0.47, 95% CI 0.29-0.78 Lactate clearance: adjusted RR 0.75, 95% CI 0.38-1.50				⨁◯◯◯ VERY LOW	CRITICAL
Mortality: Indirect Evidence												
6	randomised trials	serious [b]	not serious	serious [c]	not serious	none	117/516 (22.7%)	161/491 (32.8%)	**RR 0.66** (0.55 to 0.81)	**111 fewer per 1,000** (from 62 fewer to 148 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

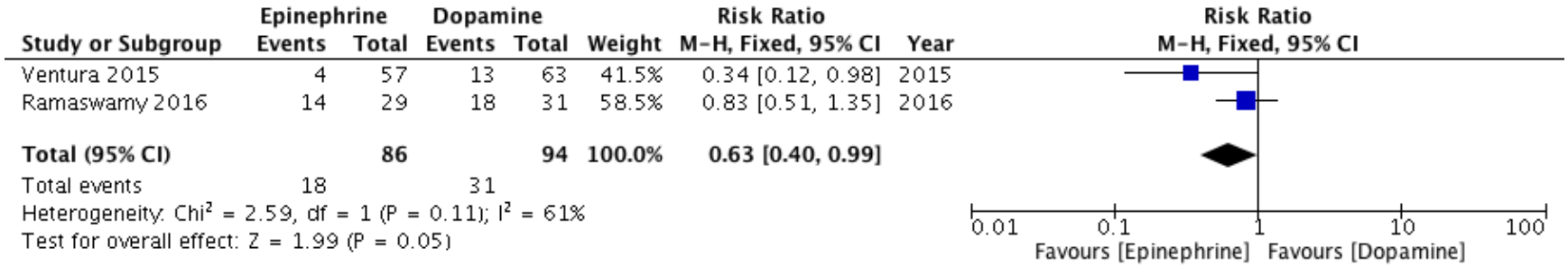
Explanations

a. We downgraded the quality of evidence by one level for risk of bias, although authors adjusted for several variables, there was significant baseline imbalance between groups

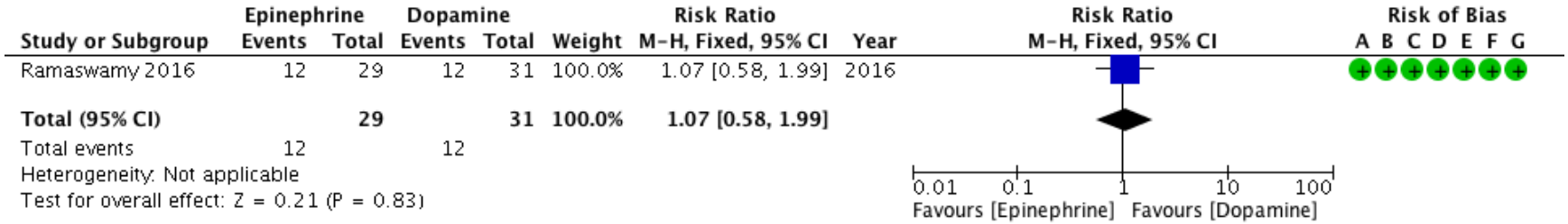
b. We downgraded the quality of evidence by one level for risk of bias, several studies were at unclear risk of bias

c. We downgraded the quality of evidence by one level for indirectness of the population (adults with sepsis)

Supplemental Figure 4a. 28-day mortality.



Supplemental Figure 4b. Renal Replacement Therapy.



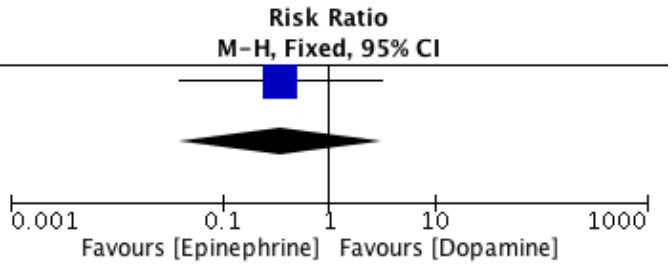
Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Supplemental Figure 4c. Arrhythmias.

Study or Subgroup	Epinephrine Events	Epinephrine Total	Dopamine Events	Dopamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Ramaswamy 2016	1	29	3	31	100.0%	0.36 [0.04, 3.23]	2016
Total (95% CI)		**29**		**31**	**100.0%**	**0.36 [0.04, 3.23]**	
Total events	1		3				

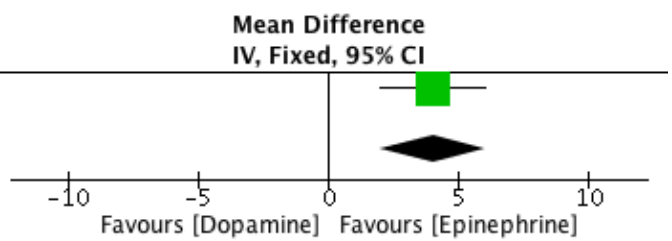
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)



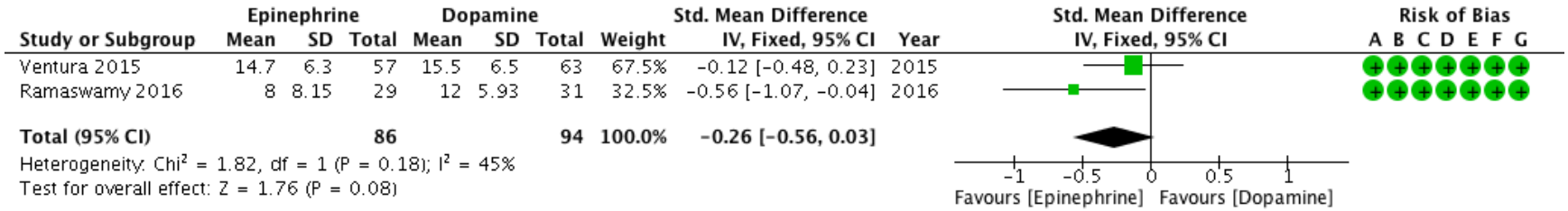
Supplemental Figure 4d. Organ dysfunction free days among survivors at 28 days.

Study or Subgroup	Epinephrine Mean	Epinephrine SD	Epinephrine Total	Dopamine Mean	Dopamine SD	Dopamine Total	Weight	Mean Difference IV, Fixed, 95% CI
Ramaswamy 2016	24	2.22	15	20	4.07	22	100.0%	4.00 [1.96, 6.04]
Total (95% CI)			**15**			**22**	**100.0%**	**4.00 [1.96, 6.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.85 (P = 0.0001)



Supplemental Figure 4e. Organ dysfunction scores.



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Supplemental Table 10. Evidence profile for epinephrine vs dopamine, Recommendation 28

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epinephrine**	**Dopamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
28 days Mortality												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none [c]	18/86 (20.9%)	10.0%	**RR 0.63** (0.40 to 0.99)	**37 fewer per 1,000** (from 60 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
								25.0%		**93 fewer per 1,000** (from 150 fewer to 3 fewer)		
Need for RRT												
1	randomised trials	not serious	not serious	not serious	serious [b]	none [c]	12/29 (41.4%)	12/31 (38.7%)	**RR 1.07** (0.58 to 1.99)	**27 more per 1,000** (from 163 fewer to 383 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Arrhythmia												
1	randomised trials	not serious	not serious	not serious	very serious [d]	none [c]	1/29 (3.4%)	3/31 (9.7%)	**RR 0.36** (0.04 to 3.23)	**62 fewer per 1,000** (from 93 fewer to 216 more)	⨁⨁◯◯ LOW	CRITICAL
Organ free failure days among survivors at day 28												

1	randomised trials	not serious	not serious	not serious	serious [e]	none [c]	15	22	-	MD **4 days more** (1.96 more to 6.04 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Organ dysfunction scores												
2	randomised trials	serious [f]	not serious [g]	not serious	serious [h]	none [c]	86	94	-	SMD **0.26 SD lower** (0.56 lower to 0.03 higher)	⊕⊕◯◯ LOW	IMPORTANT

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

Explanations

a. We downgraded the quality of evidence by one level for serious inconsistency, the I^2=85%

b. We downgraded the quality of evidence by one level for serious imprecision, the CI included both substantial benefit and harm

c. We were not able to assess publication bias due to small number of studies

d. We downgraded the quality of evidence by two levels for vey serious imprecision, the CI was extremely wide including both implausible benefit and harm

e. We downgraded the quality of evidence by one level for imprecision, the sample size was small and the CI included very large and moderate benefit

f. We downgraded the quality of evidence by one level for risk of bias, we estimated mean and SD by mathematical transformation that could have resulted in less accurate data

g. We did not downgrade the quality of evidence for inconsistency, although I^2=45% it seemed that variability in magnitude of effect was clinically of small difference

h. We downgraded the quality of evidence by one level for serious imprecision, the CI crossed the line of unity

Supplemental Table 11a. Evidence Profile for Recommendation 29

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Norepinephrine**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	2/20 (10.0%)	4/20 (20.0%)	**RR 0.50** (0.10 to 2.43)	**100 fewer per 1,000** (from 180 fewer to 286 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. We downgraded the quality of evidence by one level for indirectness, the control arm was normal saline rather than dopamine

b. We downgraded the quality of evidence by two levels for very serious imprecision, the CI included extremely large benefit and harm

Supplemental Table 11b. Indirect Evidence (Adults) for Recommendation 29

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.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NE**	**other pressors**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
19	randomised trials	not serious	not serious	serious	not serious	none	716/1431 (50.0%)	762/1486 (51.3%)	**RR 0.97** (0.91 to 1.04)	**15 fewer per 1,000** (from 21 more to 46 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality - NE vs. Epinephrine												
4	randomised trials [b]	not serious	not serious	not serious	very serious [c]	none [a]	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 82 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality - NE vs. Dopamine												
11	randomised trials	not serious	not serious	serious	not serious	none	446/837 (53.3%)	508/873 (58.2%)	**RR 0.93** (0.86 to 1.00)	**41 fewer per 1,000** (from 0 fewer to 81 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Arrhythmias												
4	randomised trials	not serious	not serious	serious	not serious	none	120/669 (17.9%)	272/721 (37.7%)	**RR 0.48** (0.40 to 0.58)	**196 fewer per 1,000** (from 158 fewer to 226 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. We could not reliably assess for publication bias due to small number of included studies

b. 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.

c. We downgraded the quality of evidence for imprecision by two levels, the CI is wide and small number of events

Supplemental Table 12. Evidence Profile for Recommendation 32

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vasopressin**	**no vasopressin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
3	randomised trials	not serious	serious [a]	not serious	serious [b]	none	30/77 (39.0%)	25/75 (33.3%)	**RR 1.14** (0.80 to 1.62)	**47 more per 1,000** (from 67 fewer to 207 more)	⊕⊕◯◯ LOW	CRITICAL
Ischemic events												
2	randomised trials	not serious	not serious	not serious	very serious [c]	none	5/42 (11.9%)	3/40 (7.5%)	**RR 1.56** (0.41 to 5.91)	**42 more per 1,000** (from 44 fewer to 368 more)	⊕⊕◯◯ LOW	CRITICAL
Vasoactive Free Days												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	median 25.2d in AVP (IQR0.0-28.3), median 27.5d in control (IQR23.1-28.9)				⊕⊕◯◯ LOW	CRITICAL
Renal replacement therapy (Indirect evidence)												
6	randomised trials	not serious	not serious	serious [d]	serious [e]	none	97/412 (23.5%)	125/393 (31.8%)	**RR 0.74** (0.51 to 1.08)	**83 fewer per 1,000** (from 25 more to 156 fewer)	⊕⊕◯◯ LOW	CRITICAL

								10.0%		**26 fewer per 1,000** (from 8 more to 49 fewer)		
NPMODS - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Need for ECMO - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. We downgraded the quality of evidence for inconsistency, I^2>60% for 2 RCTs (unable to do subgroup analysis)

b. We downgraded the quality of evidence by one level for serious imprecision, the number of events was small

c. We downgraded the quality of evidence by two levels for very serious imprecision, the CI extremely wide

d. We downgraded the quality of evidence by one level for serious indirectness of population

e. We downgraded the quality of evidence by one level for serious imprecision, the CI crossed the line of no effect

Supplemental Table 13. Evidence profile for Etomidate for Intubation, Recommendation 35

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Etomidate**	**other sedatives**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
2	observational studies	serious [a]	not serious	serious [b]	not serious	none [c]			**OR 4.51** (1.82 to 11.16)	**5 fewer per 1,000** (from 2 fewer to 11 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (indirect: adults)												
6 [d]	randomised trials	serious [e]	not serious	serious [f]	not serious	none	127/390 (32.6%)	94/382 (24.6%)	**OR 1.17** (0.86 to 1.60)	**30 more per 1,000** (from 27 fewer to 97 more)	⊕⊕◯◯ LOW	CRITICAL
Adrenal insufficiency												
2	observational studies						De Brinker 2008 showed that Cortisol to 11-deoxycortisol ratio was 3.2 times lower in exposure group- on ICU admission. De Brinker 2005 study showed that Cortisol to ACTH ratio decreased by 83% with etomidate exposure, For cortisol to 11-deoxycortisol ratio on ICU admission, intubation with etomidate was the only significant predictor (explaining 78% variability).				-	CRITICAL
Adrenal insufficiency (indirect: adults)												
4 [d]	randomised trials	not serious	not serious	serious [b]	not serious	none	129/295 (43.7%)	63/286 (22.0%)	**RR 1.89** (1.47 to 2.44)	**196 more per 1,000** (from 104 more to 317 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Surrogate for NPMODS (SOFA score in adults)												

1 [d]	randomised trials	not serious	not serious	serious [b]	serious [g]	none	234	235	-	MD **0.7 units more** (0.01 more to 1.39 more)	⊕⊕◯◯ LOW	CRITICAL
Duration of vasopressor support												
1 [d]	randomised trials	not serious	not serious	serious [b]	serious [h]	none	234	235	-	MD **1 day more** (0.53 fewer to 2.53 more)	⊕⊕◯◯ LOW	CRITICAL
Duration of mechanical ventilation - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Vasoactive days - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. We downgraded the quality of evidence by one level for serious risk of bias, the estimates of these observational studies were not adjusted for confounders

b. We downgraded the quality of evidence by one level for serious indirectness of the population, studies included non-septic children and adults

c. Although the treatment effect was large, we did not upgrade the quality of evidence because the effect is likely inflated secondary to lack of adjustments for confounders

d. Bruder EA, Ball IM, Ridi S, Pickett W, Hohl C. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD010225. DOI: 10.1002/14651858.CD010225.pub2.

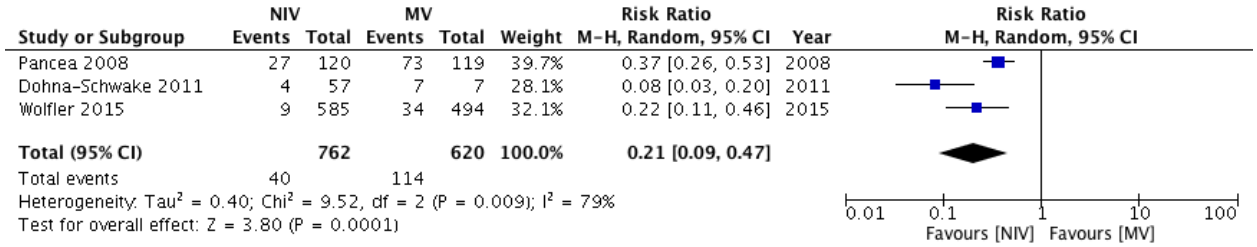
e. We downgraded the quality of evidence for risk of bias by one level, attrition bias was suspected for most studies

f. We downgraded the quality of evidence by one level for serious indirectness of population, the population included critically ill adults not septic children

g. We downgraded the quality of evidence by one level for serious imprecision, the CI included large and trivial harm

h. We downgraded the quality of evidence by one level for serious imprecision, the CI included both shorter and longer time on vasopressors

Supplemental Figure 5. Recommendation 36



Supplemental Table 14. Evidence profile High PEEP vs Lower PEEP, Recommendation 37

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												
1	observational studies	serious [a]	not serious [b]	not serious [c]	not serious	strong association [d]	111/745 (14.9%)	80/302 (26.5%)	**OR 0.50** (0.31 to 0.81) [e]	**112 fewer per 1,000** (from 39 fewer to 164 fewer)	⨁⨁◯◯ LOW	CRITICAL
Ventilator Free Days (follow up: 28 days)												
1	observational studies	serious [a]	not serious	not serious	serious [f]	none	745	302	-	MD **1.8 days more** (0.24 fewer to 3.84 more)	⨁◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. We downgraded the quality of evidence by one level for risk of bias, although authors used adjusted analysis to report the results; there was a significant baseline difference between the two groups and given the retrospective nature of the study, we decided to be conservative and downgrade for risk of bias

b. Only a single study, therefore, not applicable

c. The definition of high or low PEEP was based on predicted required PEEP based on ARDSNet study

d. We upgraded the quality of evidence for large treatment effect, the odds ratio was 0.5

e. We reversed the odds ratio reported in the study, because the intervention in our PICO question is high PEEP, which was the control in the observational study

f. We downgraded the quality of evidence by one level for imprecision, the CI include the both benefit and harm

Supplemental Table 15. Evidence Profile for Recruitment Maneuvers, Recommendation 38

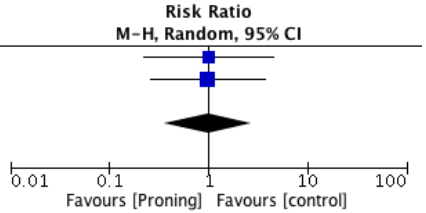
Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality - not reported									
-	-	-	-	-	-	-	effect on mortality is unknown	-	CRITICAL
Ventilator days - not reported									
-	-	-	-	-	-	-	Effect unknown	-	CRITICAL
Oxygenation (assessed with: improvement in P/F ratio or PaO2)									
2	observational studies	not serious	not serious	not serious	not serious	none	In Duff et al. 32 patients with hypoxia underwent recruitment maneuver (RM) using 30–40 cmH2O for 15–20 s. There was sustained significant decrease in FiO2 by 6.1% lasting up to 6 h post-RM. In Boriosi et al. 21 children with ALI or ARDS underwent RM, PaO2/FIO2 ratio) increased 53% immediately after the recruitment maneuver. The median PaO2/FIO2 ratio increased from 111 (IQR 73–266) pre RM to 170 (IQR 102–341) immediately post RM ($p < .01$)	⊕⊕◯◯ LOW	CRITICAL
Adverse Events									
4	observational studies	not serious	not serious	serious [a]	not serious	none	No serious adverse events were reported in two studies. In Halbertsma et al. there were 2/7 patients with hemodynamic deterioration (no detailed explanation but one needed to receive fluid bolus). In Wolf et al. one patient had to stop the RM due to hypercarbia (meeting stopping criteria)	⊕◯◯◯ VERY LOW	CRITICAL

Supplemental Figure 6a-b. <u>Direct evidence in children for proning,</u> Recommendation 39

a. Mortality

Study or Subgroup	Prone ventilation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kornecki 2001	2	5	2	5	43.4%	1.00 [0.22, 4.56]	2001
Curley 2005	4	51	4	50	56.6%	0.98 [0.26, 3.71]	2005
Total (95% CI)		**56**		**55**	**100.0%**	**0.99 [0.36, 2.69]**	
Total events	6		6				

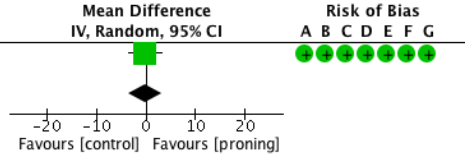
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.02 (P = 0.98)



b. Ventilator free days

Study or Subgroup	Prone ventilation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Curley 2005	15.6	8.6	51	15.8	8.5	50	100.0%	-0.20 [-3.53, 3.13]	2005
Total (95% CI)			**51**			**50**	**100.0%**	**-0.20 [-3.53, 3.13]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)



<u>Risk of bias legend</u>
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Supplemental Table 16a. Evidence Profile for Proning, Recommendation 39

Direct evidence in children:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone ventilation	no proning	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	RCTs	not serious	not serious	not serious [a]	very serious [b]	none [c]	6/56 (10.7%)	6/55 (10.9%)	RR 0.99 (0.36 to 2.69)	1 fewer per 1,000 (from 70 fewer to 184 more)	⊕⊕◯◯ LOW	CRITICAL
Ventilator free days												
1	RCTs	not serious	not serious	not serious	very serious [b]	none [c]	51	50	-	MD 0.2 days fewer (3.53 fewer to 3.13 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
	RCT and Cohort study	not serious	not serious	not serious	not serious	none	1 RCT and observational study did not report any serious adverse events (including accidental extubation)				⊕⊕⊕⊕ HIGH	CRITICAL
Oxygenation (assessed with: improvement in oxygenation index)												
	RCTs	not serious	not serious	not serious	serious [d]	none [c]	Improvement in OI with proning: 7.9 +/- 5.3 Units (34 +/- 17%) ; P= 0.002				⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Although these trials were not exclusive for septic patients with ARDS, we did not consider this as serious indirectness requiring downgrading of quality of evidence, we hypothesize that the treatment effect will be similar in septic population

b. We downgraded the quality of evidence for very serious imprecision, the CI included both large benefit and harm

c. We couldn't assess for publication bias

d. We downgraded the quality of evidence by one level for serious imprecision, the total number of patients was small

Supplemental Table 16b. Indirect evidence in adults:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone ventilation	no proning	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	RCTs	not serious	not serious	not serious [a]	very serious [b]	none [c]	6/56 (10.7%)	6/55 (10.9%)	RR 0.99 (0.36 to 2.69)	1 fewer per 1,000 (from 70 fewer to 184 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality (indirect adult evidence)												
8	RCTs	not serious	not serious	serious [d]	serious [e]	none	345/1099 (31.4%)	372/1042 (35.7%)	RR 0.84 (0.68 to 1.04)	57 fewer per 1,000 (from 14 more to 114 fewer)	⊕⊕◯◯ LOW	CRITICAL
Ventilator free days												
1	RCTs	not serious	not serious	not serious	very serious [b]	none [c]	51	50	-	MD 0.2 days fewer (3.53 fewer to 3.13 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
	RCT and Cohort study	not serious	not serious	not serious	not serious	none	1 RCT and observational study did not report any serious adverse events (including accidental extubation)				⊕⊕⊕⊕ HIGH	CRITICAL
Unplanned extubation (indirect adult evidence)												

8	RCTs	not serious	not serious	serious [d]	serious [f]	none	119/1093 (10.9%)	99/1036 (9.6%)	RR 1.12 (0.86 to 1.45)	11 more per 1,000 (from 13 fewer to 43 more)	⊕⊕◯◯ LOW	CRITICAL
Oxygenation (assessed with: improvement in oxygenation index)												
1	RCTs	not serious	not serious	not serious	serious [g]	none [c]	Improvement in OI with proning 7.9 +/- 5.3 U (34 +/- 17%; P= 0.002)				⊕⊕⊕◯ MODERATE	CRITICAL
Oxygenation (indirect adult evidence) (follow up: mean 4 days)												
5	RCTs	not serious	not serious	serious [d]	not serious	none	609	609	-	MD 23.45 units higher (12.37 higher to 34.53 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Although these trials were not exclusive for septic patients with ARDS, we did not consider this as serious indirectness requiring downgrading of quality of evidence, we hypothesize that the treatment effect will be similar in septic population

b. We downgraded the quality of evidence for very serious imprecision, the CI included both large benefit and harm

c. We couldn't assess for publication bias

d. We downgraded the quality of evidence by one level for series indirectness of population, all studies included (adult) patients with moderate to severe ARDS

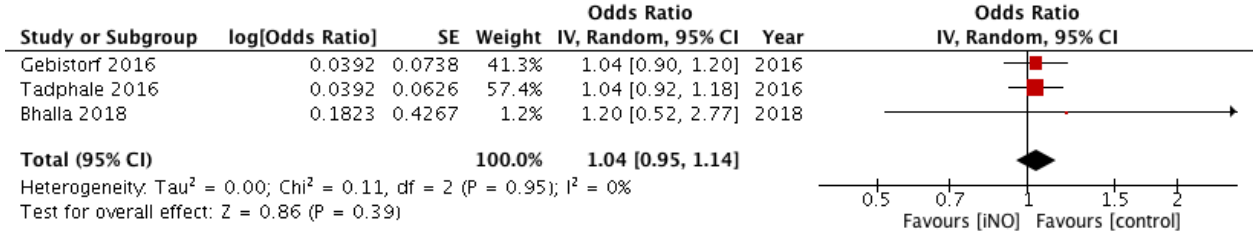
e. We downgraded the quality of evidence for serious imprecision, the CI crossed the line of unity

f. We downgraded the quality of evidence by one level for serious imprecision, the CI included both small benefit and harm

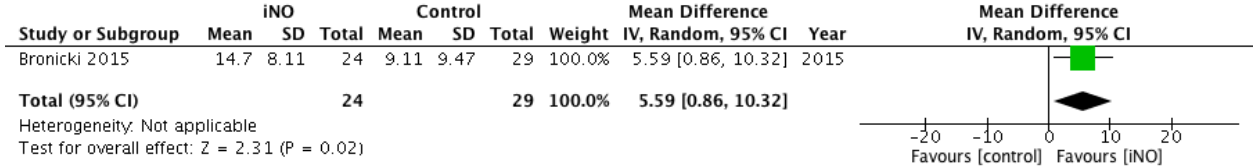
g. We downgraded the quality of evidence by one level for serious imprecision, the total number of patients was small

Supplemental Figure 7a-d. Recommendation 41

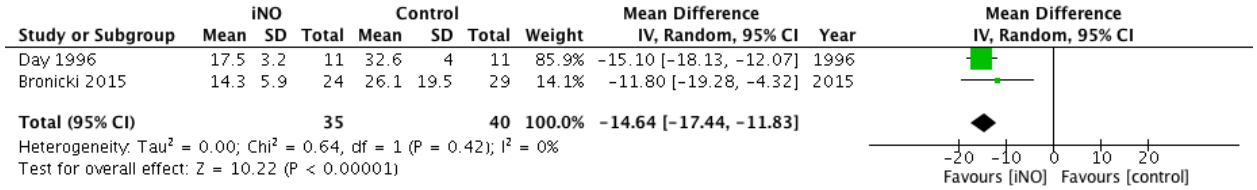
a. **Mortality (observational studies)**



b. **Ventilator free days**



c. **Oxygenation Index (Early)**

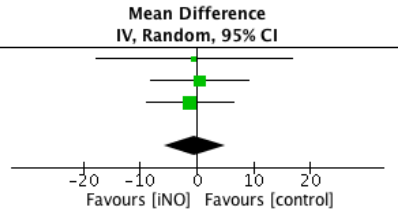


d. Oxygenation Index at 24 hours

Study or Subgroup	iNO Mean	iNO SD	iNO Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Day 1996	33.2	23.4	11	33.7	16.4	10	10.0%	-0.50 [-17.66, 16.66]	1996
Dobyns 1999	24.8	21.5	49	24.3	22	50	40.0%	0.50 [-8.07, 9.07]	1999
Bronicki 2015	16.1	10.3	24	17.3	16.8	26	50.0%	-1.20 [-8.86, 6.46]	2015
Total (95% CI)			**84**			**86**	**100.0%**	**-0.45 [-5.87, 4.97]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 0.16 (P = 0.87)



Supplemental Table 17. Evidence Profile for Recommendations 40-41

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	inhaled Nitric Oxide (iNO)	No inhaled iNO	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none [c]	25/89 (28.1%)	34/96 (35.4%)	RR 0.78 (0.51 to 1.18)	78 fewer per 1,000 (from 174 fewer to 64 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality (observayional studies)												
3	observational studies	serious [d]	not serious	not serious	not serious	none		50.0%	OR 1.04 (0.95 to 1.14)	10 more per 1,000 (from 13 fewer to 33 more)	⨁◯◯◯ VERY LOW	CRITICAL
Oxygenation Index (early)												
2	randomised trials	not serious	not serious	not serious	serious [e]	none	35	40	-	MD 14.64 lower (17.44 lower to 11.83 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Oxygenation Index at 24 hours												
3	randomised trials	not serious	not serious	not serious	serious [e]	none	84	86	-	MD 0.45 lower (5.87 lower to 4.97 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
VFD												
1 [f]	randomised trials	not serious	not serious	not serious	serious [e]	none	24	29	-	MD 5.59 higher (0.86 higher to 10.32 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Explanations

a. Cochrane Database Syst Rev. 2016 Jun 27;(6):CD002787

b. We downgraded the quality of evidence by one level for serious imprecision, CI was wide

c. We couldn't assess for publication bias due to small number of studies

d. Although all studies were at unclear risk of bias, we did not observe any positive results, the chances of biased estimates is very low.

e. We downgraded the quality of evidence for imprecision by one level, the ample size was small and the CI was imprecise

f. J Pediatr 2015;166:365-9

Supplemental Table 18. Evidence Profile for Neuromuscular Blocking Agents, Recommendation 43

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**neuromuscular blocking agents**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1 [a]	observational studies	serious [b]	not serious	not serious	serious [c]	none	3/34 (8.8%)	50/283 (17.7%)	**RR 0.50** (0.16 to 1.51)	**88 fewer per 1,000** (from 148 fewer to 90 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (indirect evidence adults)												
3	randomised trials	not serious	not serious	serious [d]	serious [e]	none	76/223 (34.1%)	98/208 (47.1%)	**RR 0.72** (0.58 to 0.91)	**132 fewer per 1,000** (from 198 fewer to 42 fewer)	⊕⊕◯◯ LOW	CRITICAL
Duration of mechanical ventilation (assessed with: days)												
1 [a]	observational studies	serious [b]	not serious	serious [f]	not serious	strong association	34	283	-	MD **8.5 days more** (4.91 more to 12.09 more) [g]	⊕◯◯◯ VERY LOW	CRITICAL
Duration of mechanical ventilation (indirect evidence: adults) (assessed with: Days)												
3	randomised trials	not serious	not serious	serious [d]	serious [h]	none	223	208	-	MD **1.21 days fewer** (4.23 fewer to 1.81 more)	⊕⊕◯◯ LOW	CRITICAL

Barotrauma - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Barotrauma (indirect evidence: adults)												
3	randomised trials	not serious	not serious	serious [d]	serious [e]	none	9/223 (4.0%)	20/208 (9.6%)	**RR 0.43** (0.20 to 0.90)	**55 fewer per 1,000** (from 77 fewer to 10 fewer)	⊕⊕◯◯ LOW	CRITICAL
ICU acquired weakness												
1	observational studies	serious [b]	not serious	not serious	not serious	none	0/34 (0.0%)	0/283 (0.0%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
ICU acquired weakness (indirect evidence: adults)												
3	randomised trials	serious [i]	not serious	serious [d]	serious [c]	none	73/223 (32.7%)	62/208 (29.8%)	**RR 1.08** (0.83 to 1.41)	**24 more per 1,000** (from 51 fewer to 122 more)	⊕◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. Pediatrics International (2010) 52, 438–443

b. We downgraded the quality of evidence for risk of bias by one level, the study design was retrospective and the analysis did not adjust for important confounders

c. We downgraded the quality of evidence by one level for imprecision, the CI crossed the unity line including both large benefit and small harm

d. We downgraded the quality of evidence by one level for serious indirectness, the population included in these RCTs are adults >18 years old.

e. We downgraded the quality of evidence by one level for imprecision, the number of events was small

f. We downgraded the quality of evidence by one level for serious indirectness of the outcomes, the mean difference was estimated from median and IQR in original article, which lowers our confidence in the results

g. The values are estimates based on the median and IQR provided by De Silva 2010

h. We downgraded the quality of evidence by one level for serious imprecision, the CI included both large benefit and harm

i. We downgraded the quality of evidence by one level for risk of bias, the studies were not blinded properly which could have introduced detection bias

Supplemental Table 19: Evidence Profile for Hydrocortisone, Recommendations 44-45

Summary of findings:

Hydrocortisone compared to No Hydrocortisone for Children with Sepsis/Septic Shock

Patient or population: Children with Sepsis/Septic Shock
Setting:
Intervention: Hydrocortisone
Comparison: No Hydrocortisone

Outcomes	sk with No Hydrocortisone	Risk with Hydrocortisone			
Mortality (sepsis and non sepsis RCTs)	185 per 1,000	**232 per 1,000** (170 to 309)	**OR 1.33** (0.90 to 1.97)	116 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Hospital acquired infections (sepsis RCTs) (HAI)	133 per 1,000	**175 per 1,000** (59 to 418)	**OR 1.38** (0.41 to 4.66)	87 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]
MODS	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-
Vasoactive Days (sepsis subcohort)	The mean vasoactive Days (sepsis subcohort) was **0** days	The mean vasoactive Days (sepsis subcohort) in the intervention group was 1.11 days higher (0.01 lower to 2.23 higher)	-	94 (1 observational study)	⨁◯◯◯ VERY LOW [d,e]
Ventilator Free Days (less important)	**Low**		not estimable	(1 observational study)	⨁◯◯◯ VERY LOW [e]
	0 per 1,000	**0 per 1,000** (0 to 0)			
Hyperglycemia requiring insulin (all shock cohort)	38 per 1,000	**174 per 1,000** (21 to 671)	**OR 5.26** (0.54 to 51.00)	49 (1 RCT)	⨁⨁⨁◯ MODERATE [b,e]
Ventilator Days (all shock cohort)	The mean ventilator Days (all shock cohort) was **0** days	The mean ventilator Days (all shock cohort) in the intervention group was 4 days higher (2 higher to 6 higher)	-	94 (1 observational study)	⨁◯◯◯ VERY LOW [d,e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Pilot RCTs, 1 RCT abstract
b. RCT in patients not specifically in septic shock
c. High risk of bias
d. Retrospective chart review
e. Shock, not specifically septic patients

Supplemental Table 20: Evidence Profile for Glucose Control, Recommendation 46

Author(s): Michael Agus
Date:
Question: TGC < 140 mg/dl with Insulin therapy compared to Usual care for Children with Sepsis/Septic Shock
Setting: TGC glucose goal < 140 mg/dl using insulin treatment vs usual care (insulin treatment and Glucose goals vary)
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TGC < 140 mg/dl with Insulin therapy**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital Mortality												
6	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	110/1974 (5.6%)	113/2047 (5.5%)	**OR 0.95** (0.62 to 1.45)	**3 fewer per 1,000** (from 20 fewer to 23 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Any Hypoglycemia (<60ml/dl)												
5	randomised trials	not serious	serious [c]	serious [b]	not serious	none	371/1925 (19.3%)	116/1910 (6.1%)	**OR 4.39** (2.39 to 8.06)	**160 more per 1,000** (from 73 more to 282 more)	⨁⨁◯◯ LOW	CRITICAL
Neurodevelopmental outcome												
									not estimable		-	CRITICAL
MODS (PELOD, NPMODS or similar)												
									not estimable		-	
Severe Hypoglycemia (< 40 ml/dl)												
5	randomised trials	not serious	not serious	serious [b]	not serious	none	109/1925 (5.7%)	27/1910 (1.4%)	**OR 4.11** (2.67 to 6.32)	**42 more per 1,000** (from 23 more to 69 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Explanations

a. Interventions not blinded across studies, majority of trials were low risk of bias. SR was of low risk of bias
b. We downgraded by one level for serious indirectness of population, critically ill children admitted to Cardiac ICU, med-surg, preterm)
c. Significant Statistical Heterogeneity detected

Supplemental Table 21. Evidence Profile for GRV, Recommendation 55

Summary of findings:

GRV compared to no GRV for Children with Sepsis/Septic shock

Patient or population: Children with Sepsis/Septic shock
Setting: Enterally fed children
Intervention: GRV
Comparison: no GRV

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
Mortality № of participants: (studies)	not estimable	0.0%	**0.0%** (0.0 to 0.0)	**0.0% fewer** (0 fewer to 0 fewer)	-	
ICU LOS № of participants: (studies)	not estimable	0.0%	**0.0%** (0.0 to 0.0)	**0.0% fewer** (0 fewer to 0 fewer)	-	
VAP № of participants: 88 (1 RCT)	not estimable	6.7%	**0.0%** (0.0 to 0.0)	**6.7% fewer** (6.7 fewer to 6.7 fewer)	⨁◯◯◯ VERY LOW a,b,c	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of Bias downgraded for Observational cohort study with some ROB (2 high risk, 2 unclear risk)
b. Downgraded for indirectness of population - non-septic, mechanically ventilated children
c. Downgraded for small sample size, and indirect outcome (not deemed critical)

Supplemental Table 22: Evidence Profile for Selenium, Recommendation 58

Author(s):
Date:
Question: Selenium compared to no Selenium for Children with sepsis/septic shock
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Selenium**	**no Selenium**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
12	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	148/482 (30.7%)	180/483 (37.3%)	**RR 0.83** (0.70 to 0.99)	**63 fewer per 1,000** (from 4 fewer to 112 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Ventilator Days												
1	randomised trials	not serious	serious [c]	not serious	serious [c]		7.9	9.4	-	**0** (0 to 0)	-	CRITICAL
ICU LOS												
1	randomised trials	not serious	serious [c]	not serious	serious [c]		12	13.8	-	**0** (0 to 0)	-	CRITICAL
Serious adverse events												
1	randomised trials	not serious	serious [c]	not serious	serious [c]		39/148 (26.4%)	37/139 (26.6%)	not estimable		-	NOT IMPORTANT

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

Explanations

a. Some risk of Bias in included RCTs - variable reporting of allocation concealment, blinding adequate in 5 of 12. However, low risk of detection bias for mortality
b. 8 of 12 of these trials were all conducted exclusively in adults (>/= 18 years)with SIRS or SEPSIS
c. Single RCT, intervention is not restricted to selenium

Supplemental Table 23: Evidence Profile for Glutamine, Recommendation 59

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Glutamine	With Glutamine	Difference		
Mortality № of participants: 442 (3 RCTs)	**RR 1.60** (0.85 to 3.01)	Study population			⨁⨁⨁◯ MODERATE [a]	
		6.4%	**10.3%** (5.5 to 19.3)	**3.9% more** (1 fewer to 12.9 more)		
Ventilator days № of participants: 128 (2 RCTs)	-	The mean ventilator days without glutamine was **0** days	-	**MD 1.17 days higher** (0.06 lower to 2.4 higher)	⨁⨁⨁◯ MODERATE [a]	
ICU LOS № of participants: 128 (2 RCTs)	-	The mean ICU LOS without glutamine was **0** days	-	**MD 1.85 days lower** (4.43 lower to 0.74 higher)	⨁⨁◯◯ LOW [a]	
Inotrope Days № of participants: 98 (1 RCT)	-	The mean inotrope Days without glutamine was **0** days	-	**MD 0.1 days higher** (0.85 lower to 1.05 higher)	⨁⨁◯◯ LOW [b,c]	
Secondary Infection № of participants: 30 (1 RCT)	**OR 0.42** (0.06 to 2.77)	Study population			⨁⨁◯◯ LOW [c]	
		26.7%	**13.2%** (2.1 to 50.2)	**13.4% fewer** (24.5 fewer to 23.5 more)		

a. Different Interventions for Glutamine
b. Risk of Bias unclear in multiple domains
c. Single trial

Supplemental Table 24. Evidence Profile for Vitamin C, Recommendation 62

Summary of findings:

Vitamin C compared to No Vitamin C for Children with Sepsis/Septic Shock

Patient or population: Children with Sepsis/Septic Shock
Setting:
Intervention: Vitamin C
Comparison: No Vitamin C

Outcomes	h No Vitamin C	Risk with Vitamin C			
Mortality	40 per 100	**8 per 100** (3 to 25)	**OR 0.13** (0.04 to 0.48)	94 (1 observational study)	⨁◯◯◯ VERY LOW a,b,c
Vasoactive/inotropic infusion days assessed with: Days under inotropic use where lower indicates a better outcome	The mean vasoactive/inotropic infusion days was **54.9** days	The mean vasoactive/inotropic infusion days in the intervention group was 36.6 days fewer (27.9 fewer to 45.3 fewer)	-	94 (1 observational study)	⨁◯◯◯ VERY LOW b,c,d
ICU LOS	The mean ICU LOS was **4** days	The mean ICU LOS in the intervention group was 0 days (1.37 fewer to 1.37 more)	-	94 (1 observational study)	⨁◯◯◯ VERY LOW b,c,d
MODS/NPMODS assessed with: Renal replacement therapy	37 per 100	**10 per 100** (3 to 31)	**RR 0.26** (0.08 to 0.85)	61 (1 observational study)	⨁◯◯◯ VERY LOW c,d
MODS/NPMODS assessed with: change in SOFA score from baseline at 72h, where higher score indicates better outcome in favour of the intervention.	The mean MODS/NPMODS was **33** units	The mean MODS/NPMODS in the intervention group was 3.9 units higher (2.85 higher to 4.94 higher)	-	94 (1 observational study)	⨁◯◯◯ VERY LOW b,c,d

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

Supplemental Table 25: Evidence Profile for Thiamine, Recommendation 63

Thiamine compared to No Thiamine for Children with Sepsis/Septic Shock

Patient or population: Children with Sepsis/Septic Shock
Setting:
Intervention: Thiamine
Comparison: No Thiamine

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Thiamine	Risk difference with Thiamine
mortality (Adult RCT)	88 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.05** (0.66 to 1.60)	419 per 1,000	**21 more per 1,000** (142 fewer to 251 more)
ICU LOS (ICU LOS) assessed with: days	15 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean ICU LOS was **0**	**0** (0 to 0)
24h SOFA score (MODS) Scale from: 1 to 30 follow up: median 28 days	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean 24h SOFA score was **0**	**0** (0 to 0)
Mortality, Thiamine Deficient Subgroup	28 (1 RCT)	⨁⨁◯◯ LOW [a]	not estimable	462 per 1,000	**462 fewer per 1,000** (462 fewer to 462 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Adult Septic Shock RCT
b. Single Adult RCT

Supplemental Table 26: Evidence Profile for Vitamin D, Recommendation 64

Vitamin D3 Non-Deficient compared to Vitamin D deficient Children with Sepsis/Septic Shock

Patient or population:
Setting: Children who are 25(OH)D Deficient
Intervention: Vitamin D Non-deficient
Comparison: Vitamin D deficient

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D deficient	Risk difference with Vitamin D Non-deficient
Mortality assessed with: all cause mortality	590 (7 observational studies)	⨁◯◯◯ VERY LOW a,b	**RR 0.70** (0.48 to 1.03)	193 per 1,000	**58 fewer per 1,000** (100 fewer to 6 more)
Vasoactive/Inotropic days assessed with: days of inotropic use	347 (5 observational studies)	⨁◯◯◯ VERY LOW a	-	The mean vasoactive/Inotropic days was **0** days	MD **0.66 days fewer** (1.15 fewer to 0.17 fewer)
ICU days assessed with: days in the PICU	429 (5 observational studies)	⨁◯◯◯ VERY LOW a,c	-	The mean ICU days was **0** days	MD **2.05 days fewer** (3.51 fewer to 0.59 fewer)
Secondary infections	124 (1 observational study)	⨁◯◯◯ VERY LOW d,e	**RR 0.96** (0.51 to 1.82)	238 per 1,000	**10 fewer per 1,000** (117 fewer to 195 more)
Organ dysfunction (NPMODS)	124 (1 observational study)	⨁◯◯◯ VERY LOW d,e	**RR 0.83** (0.52 to 1.32)	397 per 1,000	**67 fewer per 1,000** (190 fewer to 127 more)
Motor Strength - not reported	-	-	-	-	-
Osteopenia - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one further level due to critical risk of bias in 2 studies which did not use methods to properly adjust for critical confounders and also had risk of selection bias
b. Downgraded one level because of confidence intervals that include an appreciable threshold of benefit and the null.
c. One study with high risk of bias (providing 24% of weight in the meta-analysis) could explain the heterogeneity.
d. No adjustment of critical (or any) confounders and risk of selection of participants.
e. Downgraded one level because of wide confidence intervals that include appreciable thresholds of benefit and harm.

Supplemental Table 27: Evidence Profile for Restrictive Transfusion, Recommendations 65 and 66

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a restrictive transfusion strategy, defined as transfusion for a hemoglobin concentraton < 7g/dL,**	**a threshold of < 9 g/dL (adults) or 9.5 g/dL (pediatrics)**	**Relative (95% CI)**	**Absolute (95% CI)**		
90-day mortality (adults with shock)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	216/502 (43.0%)	223/506 (44.1%)	**RR 0.94** (0.78 to 1.09)	**26 fewer per 1,000** (from 40 more to 97 fewer)	⊕⊕◯◯ LOW	CRITICAL
New or progressive multiple organ dysfunction syndrome (hemodynamically stabilized pediatric patients)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	13/69 (18.8%)	13/68 (19.1%)	not estimable		⊕⊕◯◯ LOW	IMPORTANT
28-day mortality (hemodynamically stabilized pediatric patients)												
1	randomised trials	not serious	not serious	not serious	very serious [d]	none	7/69 (10.1%)	2/68 (2.9%)	not estimable		⊕⊕◯◯ LOW	CRITICAL
Volume of blood transfused (hemodynamically stabilized pediatric patients)												
1	randomised trials	not serious	not serious	not serious	serious [e]	none	69	68	-	mean **8.1 mL/kg higher** (0 to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pediatric intensive care unit length of stay												
1	randomised trials	not serious	not serious	not serious	serious [e]	none	69	68	-	mean **0.4 days lower** (2.6 lower to	⊕⊕⊕◯ MODERATE	IMPORTANT

										1.9 higher)		

CI: Confidence interval; RR: Risk ratio

Explanations

a. Study was in adult patients.
b. 95% confidence interval includes possibility of modest harm.
c. 26 total events.
d. 9 total events.
e. Small study (n=137).

Supplemental Table 28: Evidence Profile for Prophylactic Platelet Transfusion, Recommendation 67

Bibliography: Du POnt-Thibodeau G. Pediatric Critical Care Medicine 2016.17(9):e420-e429

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic platelet transfusion	no platelet transfusion	Relative (95% CI)	Absolute (95% CI)		
Mortality (PICU)												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	11/60 (18.3%)	17/765 (2.2%)	OR 10.10 (4.48 to 22.70)	164 more per 1,000 (from 70 more to 318 more)	⨁◯◯◯ VERY LOW	CRITICAL
total length of mechanical venitalation												
1	observational studies	not serious	not serious	serious [a]	not serious	none	60	782	-	MD 9.3 days more (0 to 69.2 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Mortality (hospital)												
1	observational studies	not serious	not serious	serious [a]	serious [c]	none	12/107 (11.2%)	30/765 (3.9%)	OR 0.98 (0.13 to 7.59)	1 fewer per 1,000 (from 34 fewer to 197 more)	⨁◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. 260/842 patients with a diagnosis of sepsis.

b. 28 total events

c. 42 total events, counting 28 in PICU plus 14 charted as "Hospital mortality."

Supplemental Table 29: Evidence profile for Prophylactic FFP transfusion, Recommendation 68

Bibliography: Yang, et al., Transfusion 2012;52(8):1673, Pieters, et al., Peediatric Anaesthesia 2015;25(3):279

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic frozen plasma transfusion	no transfusion	Relative (95% CI)	Absolute (95% CI)		
24-hour postoperative blood loss (mostly adults)												
9	randomised trials	not serious [a]	serious [b]	serious [c]	serious [d]	none	199	201	-	MD 35.24 mL lower (84.16 lower to 13.68 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Blood volume lost (craniosynostosis repair)												
1	randomised trials	not serious [e]	not serious	serious [f]	very serious [g]	none	40	39	-	MD 19.56 % blood volume higher (103.6 lower to 64.47 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

a. Only 2 trials fulfilled all criteria of study quality assessment, most uncertain.
b. I-squared 55%. Forest plot shows dispersion of confidence intervals.
c. Mostly adult patients.
d. Confidence interval includes higher and lower blood loss volumes.
e. Uncertainties around blinding, but not likely to bias outcome.
f. Not children with sepsis-associated organ dysfunction
g. 81 total patients, confidence intervals embrace substantially higher and lower blood loss.

Supplemental Table 30: Evidence Profile for Plasma Exchange, Recommendations 69 and 70

Bibliography: Rimmer E, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Critical Care, 2014. 18:699

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**plasma exchange**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (28 days or at undefined time interval)												
3	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	13/35 (37.1%)	10/31 (32.3%)	**RR 0.96** (0.28 to 3.38)	**13 fewer per 1,000** (from 232 fewer to 768 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. Long and Reeves studies judged at high risk bias by Cochrane tool ("significant baseline imbalances").
b. I-square 60%.
c. 23 total events. 95% CI embraces significant benefit and harm.

Supplemental Table 31: Evidence Profile for RRT for Volume Overload, Recommendation 71

Bibliography: Gulla KM, Gupta D, Gipta N, et al. Continuous renal replacement therapy in children with severe sepsis and multiorgan dysfunction - a pilot study on timing of initiation. Indian J Crit Care Med, 2015. 19(10): 613-7

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**renal replacement therapy (RRT)**	**no renal replacement therapy (studied as late RRT)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	7/18 (38.9%)	6/9 (66.7%)	**OR 0.58** (0.15 to 2.26)	**130 fewer per 1,000** (from 152 more to 436 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
% decrease in inotropic score												
1	observational studies	not serious	not serious	serious [a]	serious [c]	none	21.6	21.5	-	**0** (0 to 0)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; OR: Odds ratio

Explanations

a. Observational study of patients looking at early versus late initiation of renal replacement therapy.
b. 13 total events.
c. 27 total subjects

Supplemental Table 32: Evidence Profile for High-volume hemofiltration, Recommendation 72

Bibliography: 1. Miao H, Wang F, Xiong X, Wang C, Zhang Y. Clinical benefits of high-volume hemofiltration in critically ill pediatric patients with severe sepsis: a retrospective cohort study. Blood Purif 2018;45:18-27 2. Borthwick EMJ, Hill CJ, Radindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults (Review) Cochrane Databse of Systematic Reviews 2017, Issue 1. Art. No.: CD008075

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**high-volume hemofiltration**	**standard hemofiltration**	**Relative (95% CI)**	**Absolute (95% CI)**		
28 day mortality, pediatric patients (follow up: 28 days)												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	23/93 (24.7%)	21/62 (33.9%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
28 day mortality, Cochrane adults (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	very serious [b]	none	28/75 (37.3%)	34/81 (42.0%)	**RR 0.89** (0.60 to 1.32)	**46 fewer per 1,000** (from 134 more to 168 fewer)	⊕⊕◯◯ LOW	CRITICAL
Dopamine dose, pediatric patients												
1	observational studies	not serious	not serious	not serious	not serious	none	93	62	-	SMD **0.9 SD higher** (0 to 4.5 higher)	⊕⊕◯◯ LOW	IMPORTANT
ICU Length of stay, Cochrane adults												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	66	71	-	median **1 day higher** (0 to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
Organ dysfunction, Cochrane adults												
2	randomised trials	not serious	not serious	not serious	very serious [d]	none	Ghani 2006: SOFA scores fell by day seven in both groups, statistically significant in both. Joannes-Boyau 2013: no difference in median SOFA scores in either group at days four and twenty-eight.				⊕⊕◯◯ LOW	IMPORTANT
Vasopressor dose, Cochrane adults: decreased norepinephrine > 75% in 24 hours (Ghani 2006)												
1	randomised trials	not serious	not serious	not serious	very serious [e]	none	8/9 (88.9%)	4/10 (40.0%)	**RR 2.22** (1.01 to 4.51)	**488 more per 1,000**	⊕⊕◯◯ LOW	IMPORTANT

										(from 4 more to 1,000 more)		
Norepinephrine dose, Cochrane adults (Cole 2001)												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none			-	median **9.5 mcg/min higher** (0 to 0)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

Explanations

a. 40 total events
b. 62 total events. Confidence intervals embrace significant harm and benefit.
c. No data provided about precision. 137 total patients.
d. Cochrane authors: "We downgraded the evidence to low quality owing to imprecision."
e. 12 total events
f. Proportional decrease of 68% (IQR 28%) versus 7% (IQR 59%). Downgrade two levels by Cochrane authors.

Supplemental Table 33: Evidence profile for Recommendation 73

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ECLS**	**No ECLS**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	observational studies	not serious	not serious	not serious	serious [a]	none	15/61 (24.6%)	18/61 (29.5%)	**OR 0.80** (0.34 to 1.83)	**44 fewer per 1,000** (from 139 more to 170 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

a. We downgraded the quality of evidence by one level for serious imprecision, the CI included both significant benefit and harm

Supplemental Table 34: Evidence Profile for VA-ECMO, Recommendation 74

Bibliography: Oberender F, Ganeshalingham A, Fortenberry JD, et al. Veno-arterial extracorporeal membrane oxygenation versus conventional therapy in severe pediatric septic shock. Pediatric Critical Care medicine, 2018 ():- (PCCM-D-17-00516R2)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**veno-arterial ECMO**	**no ECMO**	**Relative (95% CI)**	**Absolute (95% CI)**		
mortality at hospital discharge												
1	observational studies	not serious	not serious	not serious	serious [a]	none	22/44 (50.0%)	72/120 (60.0%)	**RR 0.83** (0.63 to 1.25)	**100 more per 1,000** (from 100 fewer to 300 more) [b]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. 94 total events (72 in control, 22 in VA ECMO groups
b. Absolute calculation based on the published confidence intervals of the absolute effects: "95% CI -30%, 10%; p=0.25"

Supplemental Table 35: Evidence profile for IVIG, Recommendation 75

Bibliography: Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates (Review). Cochrane Review, 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous immunoglobulin	control	Relative (95% CI)	Absolute (95% CI)		
Mortality from any cause												
9	randomised trials	serious [a]	not serious [b]	serious [c]	serious [d]	none	216/1268 (17.0%)	226/1259 (18.0%)	**RR 0.95** (0.80 to 1.13)	**9 fewer per 1,000** (from 23 more to 36 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Death or major disability (follow up: 2 years)												
1	randomised trials	not serious	not serious	serious [e]	serious [d]	none	686/1759 (39.0%)	677/1734 (39.0%)	**RR 1.00** (0.92 to 1.09)	**0 fewer per 1,000** (from 31 fewer to 35 more)	⊕⊕◯◯ LOW	CRITICAL
Hospital Length of Stay												
3	randomised trials	serious [f]	serious [g]	serious [c]	serious [h]	none			-	MD **4.08 days fewer** (6.47 fewer to 1.69 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
All cause mortality (IgM-enriched IVIG)- subgroup)												
4	randomised trials	serious [i]	not serious	serious [c]	very serious [j]	none	16/131 (12.2%)	25/135 (18.5%)	**RR 0.68** (0.39 to 1.20)	**59 fewer per 1,000** (from 37 more to 113 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. Unclear random sequence generation in many studies. Unclear selective reporting in most studies.
b. I-squared 23%, wide CIs that overlap. No downGRADE.
c. Neonates only. Suspected infection.
d. 95% CI embraces modest harm and benefit.
e. Neonates only. Suspected and proven infection.
f. Uncertain sequence generation in 2/3 trials. Selective outcome reporting in 1/3, uncertain in 2/3.
g. I-squared 33%, but CI overlap on Forest plot.
h. 160 total participants.
i. No random sequence generation: 1/4, uncertain in 3/4 trials. Selective reporting in 1/4, uncertain 2/4 trials.
j. 41 total events

Supplemental Table 36: Evidence Profile for Stress Ulcer Prophylaxis, Recommendation 76

Bibliography: Reveiz L, Guerrero-Lozano R, Camacho A, et al. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. Pediatri Crit Care Med 2010;11(1):124-32 Jimenez J, Drees M, Loveridge-Lenza B, et al. Exposure to gastric acid-suppression therapy is associated with health care- and community-associated Clostridium dificile infection in children. J Pediatr Gastroenterol Nutr 2015;61:208-11

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress ulcer prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
1	observational studies	serious [b]	not serious	serious [a,c]	not serious	none			**OR 5.5** (2.9 to 10.4)	**6 fewer per 1,000** (from 3 fewer to 10 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Clinically important bleeding												
2	randomised trials	not serious [d]	not serious	serious [e]	serious [f]	none	12/223 (5.4%)	10/77 (13.0%)	**RR 0.41** (0.19 to 0.91)	**77 fewer per 1,000** (from 12 fewer to 105 fewer)	⊕⊕◯◯ LOW	CRITICAL
Clostridium dificile infection												
1	observational studies	not serious	not serious	serious [g]	not serious	none	138 cases	276 controls	**OR 1.76** (1.01 to 3.10)	-	⊕◯◯◯ VERY LOW	IMPORTANT
							-	0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio

Explanations

a. Very low birth weight infants, not necessarily with sepsis
b. From the meta-analysis by More K, et al., Terrin et al. data used: the authors judged a moderate risk because of no adjustment for confounders.
c. All infections, not just pneumonia.
d. Per the meta analysis authors, "open" design with unclear risk of bias
e. Pediatric ICU patients, not necessarily with sepsis
f. Twenty two total events
g. Children in any inpatient setting, not necessarily with sepsis

Supplemental Table 37: Evidence Profile for DVT prophylaxis, Recommendation 77

Bibliography: Massicote 2003, cited in Brandao 2014 for the Cochrane Collaboration

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**mechanical or pharmacological DVT prophylaxis**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Thrombosis (symptomatic and asymptomatic)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	11/78 (14.1%)	10/80 (12.5%)	**RR 1.13** (0.51 to 2.50)	**16 more per 1,000** (from 61 fewer to 188 more)	⊕⊕◯◯ LOW	IMPORTANT
Major bleeding												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	0/78 (0.0%)	1/80 (1.3%)	**RR 0.34** (0.01 to 8.26)	**8 fewer per 1,000** (from 12 fewer to 91 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Study specific to children with central venous catheters who may or may not have had sepsis, and may not apply to general thromboembolism risk in children with sepsis.
b. Wide confidence intervals embrace significant harm and benefit.