**International Guidelines for Management of Sepsis and Septic Shock**

**Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2021**

**Appendix 3. Hemodynamic Management**

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# In patients with septic shock requiring vasopressors, should we recommend invasive monitoring of arterial blood pressure versus non-invasive monitoring?

## Complication rate of radial arterial lines

|  |  |  |
| --- | --- | --- |
| **Complication type** | **N events/N cases** | **Incidence** |
| Permanent ischemic damage | 4/4217 | 0.09% |
| Temporary occlusion | 831/4217 | 19.7% |
| Sepsis | 8/6245 | 0.13% |
| Local infection | 45/6245 | 0.72% |
| Pseudoaneurysm | 14/15623 | 0.09% |
| Hematoma | 418/2903 | 14.40% |
| Bleeding | 2/375 | 0.53% |

## Complication rate of femoral arterial lines:

|  |  |  |
| --- | --- | --- |
| **Complication type** | **N events/N cases** | **Incidence** |
| Permanent ischemic damage | 3/1664 | 0.18% |
| Temporary occlusion | 10/688 | 1.45% |
| Sepsis | 13/2923 | 0.44% |
| Local infection | 5/642 | 0.78% |
| Pseudoaneurysm | 6/2100 | 0.3% |
| Hematoma | 28/461 | 6.1% |
| Bleeding | 5/316 | 1.58% |

Reference: Scheer et al, Clinical review: Complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine, Critical Care, 2002

## Accuracy of non-invasive blood pressure measurement:

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Design** | **Intervention** | **Results** |
| Araghi 2006 | Prospective observational study  54 overweight critically ill patients (BMI >25), 8 on vasopressors  Medical ICU | Arterial line  vs.  aneroid manometer (auscultatory technique)  vs.  oscillometric technique | Mean overall biases for MAP:  Auscultatory: 7.9 +/- 2.7 mmHg  Oscillometric: -4.6 +/-2.5 mmHg |
| Bur 2000 | Prospective  38 critically ill patients, 31 on vasopressors  Emergency department | Radial arterial line  vs.  oscillometric technique | Discrepancy for MAP with proper size cuff:  -6.7 +/- 9.7 mmHg  Discrepancy ranged from -60 mmHg to +25 mmHg |
| Ellis 2015 (abstract) | Retrospective, random selection from database  54 patients with severe sepsis requiring vasopressors > 24 hours | With and without arterial line | Patients with arterial line had higher APACHE II  No significant difference in survival: 45% (art line) vs. 52% (no art line)  Patients with arterial line had more days on vasopressors, longer ICU stay, more days on mechanical ventilation |
| Franchi 2012 (abstract) | 75 consecutive ICU patients with arterial line | Simultaneous invasive and non-invasive measurements in periods of hemodynamic stability | Mean bias for MAP: 0.37 mmHg; limits of agreement -21.0 to 21.7 mmHg |
| Kaur 2019 | Prospective observational  36 ICU patients with arterial line receiving vasopressors; obese excluded | Radial arterial line vs. oscillometric technique | Mean bias:  SBP 2.3 +/- 16.9 mmHg  DBP 0.7 +/- 10.6 mmHg |
| Kumasawa 2015 (abstract) | Cross sectional  111 consecutive patients in shock at ICU admission | Radial arterial line vs. oscillometric technique | Mean difference in BP: -3.4 +/- 11.4 mmHg |
| Lakhal 2012 | Prospective observational  150 medical surgical ICU patients with arterial line; 83 with circulatory failure | Arterial line (59% radial, 41% femoral)  vs. arm, ankle and thigh oscillometric | Mean bias (arm vs. art line): 3.4 +/- 5.0 mmHg  Mean bias (ankle vs. art line): 3.1 +/- 7.7 mmHg  Mean bias (thigh vs. art line): 5.7 +/- 6.8 mmHg  In acute circulatory failure: non-invasive BP allowed detection of MAP<65 mmHg with area under the curve 0.98 95%CI(0.92-1) for arm, 0.93 95%CI(0.85-0.97) for ankle and 0.93 95%CI(0.85-0.98) for thigh |
| Lehman 2013 | Retrospective, ICU database  852 randomly selected patients from 7 Boston ICUs  Vital signs derived from the monitors  Pairwise comparison of arterial line vs. non-invasive measurements; randomly selected pairs | Arterial line vs. oscillometric technique | Non-invasive MAP vs. invasive MAP in the hypotensive range 50-60mmHg: -2.32 mmHg, limits of agreement -20.41, 15.76 |
| Macedo 2010 (abstract) | Prospective  52 patients | Arterial line  vs. oscillometric upper and lower limbs | Right arm: >20 mmHg difference in MAP in 8.7% of patients  Left arm: >20 mmHg difference in MAP in 4.2% of patients  Left leg: >20 mmHg difference in MAP in 17.8% of patients  Right leg: >20 mmHg difference in MAP in 17.4% of patients |
| Riley 2017 | Prospective observational  31 patients admitted with septic shock on stable dose of vasopressor | Radial arterial line  vs. oscillometric | Mean bias for MAP:  2.5 +/- 6.1 mmHg |

## EtD Summary of Judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

## 

# In patients in septic shock, is it safe to start vasopressors peripherally rather than waiting until a central venous access is secured?

## Complication rate from central lines:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Complication type** | | |  |
| **Insertion site** | Mechanical | Symptomatic DVT | Bloodstream infection | **Total** |
| Subclavian | 2.1% | 0.5% | 0.5% | 3.4% |
| Jugular | 1.4% | 0.9% | 1.4% | 3.7% |
| Femoral | 0.7% | 1.4% | 1.2% | 3.3% |

Parienti et al, Intravascular Complications of Central Venous Catheterization by Insertion Site, NEJM 2015.

## Complication rate when giving vasopressors through peripheral lines

**Summary of the studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Design** | **Intervention** | **Results** | **Complications** |
| **Tian 2019** | Systematic review | Vasopressors via peripheral intravenous catheters | 7 studies; 1382 patients  702 patients: noradrenaline  547 patients: phenylephrine  108 patients: dopamine  Mean duration of infusion 22 hrs | Extravasation occurred in 3.4% (95%CI 2.5-4.7)  No reported episode of tissue necrosis or limb ischemia |
| **Surrey 2019**  **(abstract)** | Retrospective observational study  Emergency department  2016-2018 | Peripheral norepinephrine up to 20 mcg/min through an 18 gauge or larger antecubital or external jugular for a max of 4 hours | 93 patients  63% distributive shock  87% antecubital catheter  Median duration in emergency department 44 minutes (IQR 28, 89)  19% continued in ICU 169 minutes (IQR 69, 252) | 3 (3.2%) episodes of peripheral extravasation  No treatment required beyond monitoring |
| **Delaney 2019** | Post-hoc analysis of ARISE trial  Emergency department | Vasopressor infusion through a peripheral versus central catheter  Majority norepinephrine | 937 patients  Adjusted OR for 90-day mortality with peripheral catheter initiation of vasopressors 1.26 (0.95-1.67)  Shorter median time to commencement of vasopressors with peripheral catheter (2.4hrs [1.3-3.9] vs. 4.9 hrs [3.5-6.6], p<0.001)  Requirement for mechanical ventilation or RRT with peripheral catheter initiation of vasopressors: adjusted OR 1.22 (0.85-1.76)  Duration of peripheral infusion 1.33 hr (IQR 0.6, 2.5) | Not reported |
| **Tyler 2019** | Retrospective observational study  Academic centre ICU  2015-2016 | Vasopressor infusion through a peripheral > 1hr | 202 patients  73% sepsis  72% forearm catheter  54 % antecubital fossa catheter  40% hand catheter  72% norepinephrine, 36% phenylephrine, 2% vasopressin, 1% epinephrine, 1% dopamine  Median duration for norepinephrine 7.5 hrs (IQR 3, 23) | 8 (4%) extravasation episodes  Median 21 hours (IQR 12, 30) until extravasation  25% antecubital  25% hand  50% other  25% <20 gauge  75% >/= 20 gauge  All managed conservatively  No ulceration/necrosis |
| **Medlej 2018** | Prospective observational study  Academic centre emergency department  2013-2015 | Vasopressor initiated through a peripheral IV  Max norepinephrine 30 mcg/min  Max dopamine 15 mcg/kg/min | 55 patients  84% sepsis  91% norepinephrine, 9% dopamine; 5% 2 vasopressors  Median duration 14 hrs (IQR 7, 40)  40% antecubital fossa, 36% hand  51% 20 gauge; 36% 18 gauge | 2 episodes of extravasation, no intervention required  1 local thrombophlebitis (unrelated to extravasation) |
| **Patel 2018**  **(abstract)** | Retrospective observational study  16-bed ICU | Confirmation of intraluminal IV placement by US | 14 patients  Mean duration 11.3 hrs (range 3 to 47)  Most common vasopressor was norepinephrine | 1 episode of extravasation, no complication after per-protocol use of phentolamine |
| **Datar 2018** | Retrospective observational study  Neuro ICU  2012-2015 | Peripheral phenylephrine 120 mcg/mL | 277 patients  40% hemodynamic augmentation,  32% transient post-op hypotension, 22% other, 6% sepsis  50% proximal upper extremity  32% wrist or hand  40% 16/18 gauge, 41% 20 gauge  Average max phenyl infusion 1.04 mcg/kg/min (SD 0.74), mean duration 19 hrs (SD 18) | 9 (3%) episodes of extravasation  No ischemia, tissue necrosis or compartment syndrome.  No patient required phentolamine or surgical consultation |
| **Hallengren 2017** | Retrospective observational study  Stepdown unit | Peripheral norepinephrine up to 0.2 mcg/kg/min  Seselepresptic shock | 79 patients  Most patients achieved MAP >65 mmHg within 1 hr (range 0.25 – 10)  Median duration of infusion 13 hrs (range 0.5-72 hrs) | No patient showed signs of ischemia or necrosis around the area of infusion |
| **Delgado 2016** | Retrospective observational study  Neuro ICU  2013-2014 | Peripheral phenylephrine (40mcg/mL) at a max dose 2 mcg/kg/min  18 gauge or larger peripheral IV in the upper extremity, proximal to the wrist | 20 patients  Mean dose 0.53 mcg/kg/min  Average infusion 14 hrs (range 1 to 54) | 1 possible minor complication (pain, erythema and swelling), IV replaced in a new site |
| **Loubani 2014** | Systematic review |  | 85 articles; 270 patients  73 articles before year 2000  75% norepinephrine  17% sepsis | 318 local tissue injury and extravasation events from peripheral IV infusion; 204 (64%) with local tissue injury, 179 with skin necrosis, 63 required skin graft, 9 required amputation  90% of 204 events had vasopressor administered in site distal to antecubital fossae  Duration of infusion 56 hrs (SD 68) |
| **Ricard**  **2013** | Multicentre RCT  3 ICUs  2004-2006  \*patients were not necessarily septic and did not have to require vasopressors | Systematic insertion of a central venous catheter vs. initial use of a peripheral venous access | 135 allocated to central venous catheter  128 allocated to peripheral catheter  \*67 crossover from peripheral to central | Infectious complications  23 with peripheral vs. 18 with central  Thrombotic complications  5 with peripheral vs. 1 with central  Extravasation 19 with peripheral vs. 2 with central |

## EtD Summary of Judgements for peripheral vasopressors

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# In patients with septic shock requiring vasopressors, should we recommend the use of angiotensin 2 vs. norepinephrine?

## Evidence Profile: Angiotensin 2 versus norepinephrine

**Bibliography**: Chawla LS, Busse L, Brasha-Mitchell E, Davison D, Honiq J, Alotaibi Z, Seneff MG. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Critical care. 2014 Oct;18(5):534. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT. Angiotensin II for the treatment of vasodilatory shock. New England Journal of Medicine. 2017 Aug 3;377(5):419-30.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **angiotensin** | **noradrenaline** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (follow up: 28-30 days)** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | very serious b | none | 80/173 (46.2%) | 91/168 (54.2%) | **RR 0.85** (0.69 to 1.06) | **81 fewer per 1,000** (from 168 fewer to 33 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Peripheral ischemia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 5/163 (3.1%) | 3/158 (1.9%) | **RR 1.62** (0.39 to 6.65) | **12 more per 1,000** (from 12 fewer to 107 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Intestinal ischemia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 1/163 (0.6%) | 3/158 (1.9%) | **RR 0.32** (0.03 to 3.07) | **13 fewer per 1,000** (from 18 fewer to 39 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Ventricular tachycardia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 5/163 (3.1%) | 3/158 (1.9%) | **RR 1.62** (0.39 to 6.65) | **12 more per 1,000** (from 12 fewer to 107 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Ventricular fibrillation** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 2/163 (1.2%) | 0/158 (0.0%) | **RR 4.85** (0.23 to 100.18) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Arrhythmia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 3/163 (1.8%) | 0/158 (0.0%) | **RR 6.79** (0.35 to 130.34) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Atrial fibrillation** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 5/163 (3.1%) | 5/158 (3.2%) | **RR 0.97** (0.29 to 3.28) | **1 fewer per 1,000** (from 22 fewer to 72 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Acute myocardial infarction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 2/163 (1.2%) | 2/158 (1.3%) | **RR 0.97** (0.14 to 6.80) | **0 fewer per 1,000** (from 11 fewer to 73 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Deep vein thrombosis** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 3/163 (1.8%) | 0/158 (0.0%) | **RR 6.79** (0.35 to 130.34) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

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

#### Explanations

a. The ATHOS trial investigates the effects of angiotensin 2 + norepinephrine vs. norepinephrine rather than angiotensin alone.

b. The confidence interval includes both clinically important benefit and harm.

c. There are too few events to reliably estimate an effect.

# In patients with septic shock requiring vasopressors, should we recommend the use of selepressin versus norepinephrine?

## Evidence Profile: selepressin versus norepinephrine

**Bibliography**: Laterre PF et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. JAMA, 2019, 322 (15): 1476-1485. Russell JA et al. Selepressin, a Novel Selective Vasopressin V1A Agonist, Is an Effective Substitute for Norepinephrine in a Phase IIa Randomized Placebo-controlled Trial in Septic Shock Patients. Critical Care, 2017, 21: 213.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **selepressin** | **noradrenaline** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | not serious | none | 247/591 (41.8%) | 120/297 (40.4%) | **RR 0.99** (0.84 to 1.18) | **4 fewer per 1,000** (from 65 fewer to 73 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Cardiovascular dysfunction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b | none | 17/562 (3.0%) | 4/266 (1.5%) | **RR 2.01** (0.68 to 5.92) | **15 more per 1,000** (from 5 fewer to 74 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Coagulation dysfunction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 359/562 (63.9%) | 155/266 (58.3%) | **RR 1.09** (0.97 to 1.24) | **52 more per 1,000** (from 17 fewer to 140 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Liver dysfunction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 301/562 (53.6%) | 123/266 (46.2%) | **RR 1.00** (0.86 to 1.18) | **0 fewer per 1,000** (from 65 fewer to 83 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Acute kidney injury** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 248/562 (44.1%) | 114/266 (42.9%) | **RR 1.02** (0.87 to 1.22) | **9 more per 1,000** (from 56 fewer to 94 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Respiratory dysfunction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 225/562 (40.0%) | 122/266 (45.9%) | **RR 0.87** (0.74 to 1.03) | **60 fewer per 1,000** (from 119 fewer to 14 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Vasopressor-free days** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 369 | 175 | - | mean **0.5 days lower** (2.87 lower to 1.87 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| **Peripheral ischemia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | very serious d | none | 14/591 (2.4%) | 8/297 (2.7%) | **RR 0.88** (0.37 to 2.08) | **3 fewer per 1,000** (from 17 fewer to 29 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Gastrointestinal ischemia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | very serious d | none | 21/591 (3.6%) | 7/297 (2.4%) | **RR 1.43** (0.63 to 3.25) | **10 more per 1,000** (from 9 fewer to 53 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Cardiac arrhythmia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 209/562 (37.2%) | 87/266 (32.7%) | **RR 1.14** (0.93 to 1.39) | **46 more per 1,000** (from 23 fewer to 128 more) | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. The PICO question in the included trials is different from our PICO question

b. The confidence interval includes both no effect and appreciable benefit. There are too few events to reliably estimate an effect.

c. The confidence interval includes both appreciable harm and benefit.

d. The confidence interval includes both appreciable benefit and harm. There are too few events to reliably estimate an effect.

# In patients with septic shock requiring vasopressors, should we recommend the use of terlipressin versus norepinephrine?

## Table: Evidence Profile: terlipressin versus norepinephrine

**Bibliography**: Acevedo, JG et al. Clinical Efficacy and Safety of Terlipressin Administration in Cirrhotic Patients With Septic Shock. Journal of Hepatology, 2009, 50:S73. https://doi.org/10.1016/S0168-8278(09)60176-8. Albanèse J et al. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Critical Care Medicine, 2005, 33:1897–1902. Chen Z et al.Comparison of effect of norepinephrine and terlipressin on patients with ARDS combined with septic shock: a prospective single-blind randomized controlled trial. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue , 2017, 29:111–116. Choudhury A et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int, 2017, 37:552–561. https://doi.org/10.1111/liv.13252 Morelli A et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Critical Care, 2009, 13:R130. https://doi.org/10.1186/cc7990. Prakash V et al. Early introduction of a combination of low dose terlipressin and noradrenaline as vaso- pressors is superior to high dose noradrena- line alone in patients of cirrhosis with septic shock (NCT02468063). In: Hepatology, 2017, Washington, DC, USA. Svoboda P et al. Terlipressin in the treatment of late phase catecholamine-resistant septic shock. Hepatogastroenterology, 2012, 59:1043–1047. https://doi.org/10.5754/hge10550. Liu Z-M et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Medicine, 2018, 44:1816–1825. https://doi.org/10.1007/s00134-018-5267-9 Xiao X et al. Effects of terlipressin on patients with sepsis via improving tissue blood flow. J Surg Res, 2016, 200:274–282. https://doi.org/10.1016/j.jss.2015.07.016

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| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **terlipressin** | **noradrenaline** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 9 | randomised trials | not serious | not serious | serious a | serious b | none | 200/466 (42.9%) | 237/484 (49.0%) | **RR 0.89** (0.70 to 1.13) | **54 fewer per 1,000** (from 147 fewer to 64 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **New organ dysfunction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor-free days** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious b | none | 260 | 266 | - | MD **0.84 days higher** (1.09 lower to 2.77 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| **Digital ischemia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | 33/260 (12.7%) | 1/266 (0.4%) | **RR 33.76** (4.65 to 245.04) | **123 more per 1,000** (from 14 more to 917 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Cardiac arrhythmia/Life-threatening arrhythmia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | very serious c | none | 7/302 (2.3%) | 7/308 (2.3%) | **RR 1.05** (0.38 to 2.90) | **1 more per 1,000** (from 14 fewer to 43 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mesenteric ischemia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious c | none | 3/260 (1.2%) | 1/266 (0.4%) | **RR 3.07** (0.32 to 29.32) | **8 more per 1,000** (from 3 fewer to 106 more) | ⨁◯◯◯ VERY LOW | CRITICAL |

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

#### Explanations

a. The PICO question in the included trials was different from our PICO question

b. The confidence interval includes both appreciable benefit and harm.

c. The confidence interval includes both appreciable benefit and harm. There are too few events to reliably estimate the effect.

# In patients with septic shock requiring vasopressors, should we recommend the use of vasopressin and noradrenaline vs. noradrenaline alone?

## Evidence Profile: vasopressin and noradrenaline vs. noradrenaline alone

**Bibliography**: Barzegar E et al. The therapeutic role of vasopressin on improving lactate clearance during and after vasogenic shock: microcirculation, is it the black box? Acta Med Iran, 2016, 15–23. Clem O et al. Norepinephrine and Vasopressin vs Norepinephrine Alone for Septic Shock: Randomized controlled trial. Critical Care Medicine, 2016, 44 (12): 143. Fonseca-Ruiz N et al (2013) Uso de vasopresina en pacientes con choque séptico refractario a catecolaminas. Acta Colombiana de Cuidado Intensivo, 2013, 13 (2): 114-123. Lauzier F et al.. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Medicine, 2006, 32:1782–1789. https://doi.org/10.1007/s00134-006-0378-0 Malay MB et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma, 1999, 47: 699-703-705. https://doi.org/10.1097/00005373-199910000-00014 Morelli A et al.Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Critical Care, 2009, 13:R130. https://doi.org/10.1186/cc7990. Oliveira S et al. Early Vasopressin Application in Shock study. Critical Care, 2014, 18:P158. https://doi.org/10.1186/cc13348 Russell JA et al. Vasopressin versus norepinephrine infusion in patients with septic shock. New England Journal of Medicine, 2008, 358:877–887. https://doi.org/10.1056/NEJMoa067373 Hammond DA et al. Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2018, 38:531–538. Hajjar LA et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. Anesthesiology, 2017, 126:85–93. https://doi.org/10.1097/ALN.0000000000001434

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| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **vasopressin + noradrenaline** | **noradrenaline** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 10 | randomised trials | not serious | not serious | serious a | not serious | none | 389/860 (45.2%) | 434/856 (50.7%) | **RR 0.91** (0.83 to 0.99) | **46 fewer per 1,000** (from 86 fewer to 5 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **New organ dysfunction** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | 94/191 (49.2%) | 74/196 (37.8%) | **RR 0.79** (0.62 to 0.99) | **79 fewer per 1,000** (from 143 fewer to 4 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Digital ischemia** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | serious a | very serious b | none | 9/536 (1.7%) | 4/522 (0.8%) | **RR 1.81** (0.33 to 9.84) | **6 more per 1,000** (from 5 fewer to 68 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Arrhythmia/Life-threatening arrhythmia** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | serious a | serious c | none | 52/618 (8.4%) | 58/604 (9.6%) | **RR 0.88** (0.63 to 1.23) | **12 fewer per 1,000** (from 36 fewer to 22 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mesenteric ischemia** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b | none | 9/396 (2.3%) | 13/382 (3.4%) | **RR 0.67** (0.29 to 1.54) | **11 fewer per 1,000** (from 24 fewer to 18 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Atrial fibrillation - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Myocardial infarction** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | very serious b | none | 3/149 (2.0%) | 8/149 (5.4%) | **RR 0.41** (0.12 to 1.40) | **32 fewer per 1,000** (from 47 fewer to 21 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Vasopressor-free days** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | There was no difference in median [IQR] vasopressor-free days: Noradrenaline 12 [ 1-24]; Varopressor 10 [1-23] p=0.669 | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Renal replacement therapy/Dialysis** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | serious a | serious c | none | 54/592 (9.1%) | 66/578 (11.4%) | **RR 0.79** (0.57 to 1.10) | **24 fewer per 1,000** (from 49 fewer to 11 more) | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. There were differences in the thresholds that were used to administer vasopressin.

b. Confidence interval includes both appreciable harm and benefit. There are too few events to reliably estimate a treatment effect.

c. Confidence interval includes both appreciable harm and benefit.

# In patients with sepsis or septic shock, should we use balanced solutions for resuscitation versus saline?

## Evidence Profile balanced solutions for resuscitation versus saline

**Bibliography**: Young P. et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA, 2015, 314 (16): 1701-1710. Brown RM et al. Balanced Crystalloids Versus Saline for Adults with Sepsis or Septic Shock. American Journal of Respiratory and Critical Care Medicine. 2018, 197: A6188. Brown RM et al. Balanced Crystalloids Versus Saline in Sepsis: A Secondary Analysis of the SMART Trial. American Journal of Respiratory and Critical Care Medicine, 2019, 200 (12), 1487-1495. Semler MW et al. Balanced Crystalloids Versus Saline in Critically Ill Adults. New England Journal of Medicine, 2018, 378: 829-839.

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| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **balanced solutions** | **saline** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (in-hospital)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious a,b | not serious | not serious | not serious | none | 613/2162 (28.4%) | 653/2159 (30.2%) | **RR 0.83** (0.74 to 0.93) | **51 fewer per 1,000** (from 79 fewer to 21 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| **Kidney injury (or failure from SPLIT trial)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious a,b | not serious | not serious | not serious | none | 245/989 (24.8%) | 296/989 (29.9%) | **RR 0.79** (0.65 to 0.96) | **63 fewer per 1,000** (from 105 fewer to 12 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 2 | randomised trials | very serious a,b | not serious | not serious | not serious | none | 79/954 (8.3%) | 82/947 (8.7%) | **RR 0.74** (0.51 to 1.01) | **23 fewer per 1,000** (from 42 fewer to 1 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Ventilator-free days** | | | | | | | | | | | | |
| 1 | randomised trials | very serious a,b | not serious | not serious | not serious | none | The median number of ventilator-free days was statistically significantly higher in the balanced crystalloid group. 27 days [IQR 0 - 28 days] vs 26 days [0 - 28 days] | | | | ⨁⨁◯◯ LOW | CRITICAL |
| **Vasopressor-free days** | | | | | | | | | | | | |
| 2 | randomised trials | very serious a,b | not serious | not serious | not serious | none | Brown, 2018: The median number of vasopressor-free days did not differ significantly between the balanced crystalloid and saline groups (28 days [IQR 12 - 28 days] vs 26 days [0 - 28 days]; P = 0.10).  Brown 2019: The median number of vasopressor-free days was statistically significantly higher in the crystalloid than saline group (27 days [IQR 0 - 28 days] vs 26 days [0 - 28 days]). | | | | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. Large definitive trials are underway

b. Estimates generated from single centre and cluster trials

## EtD: summary of Judgements for balanced crystalloids versus saline

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Type of recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# In patients with sepsis or septic shock, should we use gelatin for resuscitation versus crystalloids?

## Evidence Profile gelatin for resuscitation versus crystalloids

**Bibliography**: Annane et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. Jama. 2013 Nov 6;310(17):1809-17. Rochwerg et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. Intensive care medicine. 2015 Sep 1;41(9):1561-71. Rochwerg et al. Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis. Annals of Internal Medicine. 2014; 161:347-355. Moeller et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. Journal of Critical Care. 2016; 35:75-83.

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| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **gelatin** | **crystalloids** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - non-randomized subgroup of Annane** et al. **(follow up: 90 days)** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious a | none | 47/152 (30.9%) | 213/594 (35.9%) | **RR 0.87** (0.66 to 1.12) | **47 fewer per 1,000** (from 122 fewer to 43 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mortality – Rochwerg** et al. **NMA** | | | | | | | | | | | | |
| b | randomised trials | not serious | not serious | serious b | serious a | none |  |  | **OR 1.24** (0.61 to 2.55) | **1 fewer per 1,000** (from 3 fewer to 1 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| b | randomised trials | not serious | not serious | not serious | serious a | none | 172/1000 (17.2%) | 115/1000 (11.5%) | **RR 1.05** (0.42 to 2.56) | **6 more per 1,000** (from 67 fewer to 179 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **New organ dysfunction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Ventilator-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Anaphylaxis** | | | | | | | | | | | | |
| 10 | randomised trials | not serious | not serious | serious c | not serious | none | 21/314 (6.7%) | 5/292 (1.7%) | **RR 3.01** (1.27 to 7.14) | **34 more per 1,000** (from 5 more to 105 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |

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

#### Explanations

a. Confidence interval includes both appreciable benefit and harm.

b. The effect estimate comes from an NMA with no direct comparisons.

c. Estimate from a meta-analysis of trials in critically ill patients (not specifically sepsis/septic shock)

## EtD Summary of Judgments gelatin for resuscitation versus crystalloids

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | **Favors the comparison** | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
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# In patients with sepsis and septic shock, should we use a restrictive fluid management in the first 24 hours of resuscitation?

## Evidence Profile: restrictive fluid management in the first 24 hours of resuscitation

**Bibliography**: Semler MW et al. Conservative fluid management after sepsis resuscitation: A pilot randomized trial. Journal of Intensive Care Medicine, 2019, in press. Hjortrup PB et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised parallel-group, multicentre feasibility trial. Intensive Care Medicine. 2016, 42, 1695-1705. Chen C et al. Targeted fluid minimization following initial resuscitation in septic shock: A pilot study. Chest, 148 (6), 1462-1469. Cort KA et al. The restrictive IV fluid trial in severe sepsis and septic shock (RIFTS): A randomized pilot study. Critical Care Medicine 2019, 47 (7), 951-959.

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| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **restrictive fluid management** | **non-restrictive fluid management** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | serious a | serious b | none | 69/236 (29.2%) | 71/235 (30.2%) | **RR 0.98** (0.76 to 1.28) | **6 fewer per 1,000** (from 73 fewer to 85 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 4 | randomised trials | not serious c | not serious | serious a | serious b | none | 92/229 (40.2%) | 93/235 (39.6%) | **RR 1.00** (0.91 to 1.10) | **0 fewer per 1,000** (from 36 fewer to 40 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **New onset organ dysfunction - cardiovascular (vasopressor for shock)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious c | not serious | serious a | very serious b | none | 47/55 (85.5%) | 43/54 (79.6%) | **RR 1.07** (0.90 to 1.28) | **56 more per 1,000** (from 80 fewer to 223 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **New onset organ dysfunction - respiratory (new mechanical ventilation)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious c | not serious | serious a | very serious b | none | 15/53 (28.3%) | 17/52 (32.7%) | **RR 0.87** (0.49 to 1.55) | **43 fewer per 1,000** (from 167 fewer to 180 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **New onset organ dysfunction - new hemodialysis** | | | | | | | | | | | | |
| 1 | randomised trials | not serious c | not serious | serious a | very serious b | none | 1/48 (2.1%) | 2/53 (3.8%) | **RR 0.55** (0.05 to 5.90) | **17 fewer per 1,000** (from 36 fewer to 185 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Ventilator-free days** | | | | | | | | | | | | |
| 3 | randomised trials | not serious d | not serious | serious a | very serious e | none | Median (IQR); BALANCE - Restricted fluid: 6 (0 to 12); Control: 6 (0 to 17); RIFTS - Restricted fluid: 26 (0 to 28); Control: 19 (1 to 28); REFRESH - Restricted fluid 28 (28 to 28); Control: 28 (28 to 28) | | | | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Vasopressor-free days** | | | | | | | | | | | | |
| 3 | randomised trials | not serious d | not serious | serious a | very serious f | none | Median (IQR); BALANCE - Restricted fluid: 6 (0 to 10); Control: 5 (0 to 16); RIFTS - Restricted fluid: 28 (26 to 29); Control: 28 (7 to 28); REFRESH - Restricted fluid 26 (25 to 27); Control: 27 (25 to 28) | | | | ⨁◯◯◯ VERY LOW | CRITICAL |

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

#### Explanations

a. There are important variations in the interventions investigated in the trials.

b. Confidence interval includes both appreciable benefit and harm.

c. No blinding of participants or personnel. Downgraded by two levels for both imprecision and risk of bias.

d. No blinding of participants or personnel. Downgraded by one level for both imprecision and risk of bias.

e. Inadequate number of participants to detect an appreciable difference in number of ventilator free days.

f. Inadequate number of participants to detect an appreciable difference in number of vasopressor-free days.

## EtD Summary of Judgments restrictive fluid management in the first 24 hours of resuscitation

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | Moderate | Large |  | Varies | **Don't know** |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **Don't know** |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

## 

# In patients with sepsis or septic shock, should we use crystalloid with supplemental albumin for resuscitation versus crystalloids alone?

## Evidence Profile: crystalloid with supplemental albumin for resuscitation versus crystalloids alone

**Bibliography**: Park CHL et al. Lactated Ringer's Versus 4% Albumin on Lactated RInger's in Early Sepsis Therapy in Cancer Patients: A Pilot Single-Center Randomized Trial, Critical Care Medicine, 2019; 47 (10): e798-e805. Kakaei F et al. Albumin As a Resuscitative Fluid in Patients with Severe Sepsis: A Randomized Clinical Trial, Advances in Bioscience & Clinical Medicine, 2017, 5 (4), 8-16. Philips CA et al. Comparison And Outcomes of 5% Albumin Vs. 0.9% Normal Saline Fluid Resuscitation In Cirrhotics Presenting With Sepsis Induced Hypotension - A Randomized Controlled Trial - Fluid Resuscitation In Septic Shock In Cirrhosis (FRISC Protocol), Hepatology, 62 (1 Suppl): 261A. Caironi P et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. New England Journal of Medicine, 2014, 370 (15): 1412-1421. Annane D et al. Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock. JAMA. 2013, 310 (17): 1809-1917. Finfer S et al. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. New England Journal of Medicine, 2004; 350: 2247-2256. Rackow et al. Fluid Resuscitation in Circulatory Shock: a comparison of the effects of cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Critical Care Medicine. 1983, 11: 839-850. Metildi LA et al. Crystalloid Versus Colloid in Fluid Resuscitation of Patients With Severe Pulmonary Insufficiency. Surgery, Gynecology & Obstetrics, 1984, 158: 207-212.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **supplemental albumin** | **crystalloids** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | not serious | serious a | not serious | none | 751/1913 (39.3%) | 924/2425 (38.1%) | **RR 0.98** (0.89 to 1.08) | **8 fewer per 1,000** (from 42 fewer to 30 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **New organ failure** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | 464/836 (55.5%) | 458/841 (54.5%) | **RR 1.02** (0.93 to 1.11) | **11 more per 1,000** (from 38 fewer to 60 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **RRT-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Ventilator free days - Annane et al.** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | * Median [IQR] for albumin: 28 [7-28] * Median [IQR] for crystalloids: 28 [21-28]   p=0.2 | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Vasopressor free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor free days - Park et al.** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | not serious | none | * Median [IQR] for albumin: 25 [7-27] * Median [IQR] for crystalloids: 25 [21-27] * p=0.7 | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |

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

#### Explanations

a. Some trials compared studied albumin (rather than crystalloids with supplemental albumin).

## EtD Summary of Judgments crystalloid with supplemental albumin for resuscitation versus crystalloids alone

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |

**Type of recommendation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | **●** | ○ | ○ | ○ |

# In patients with septic shock with persistent hypoperfusion, should we recommend using dobutamine versus epinephrine?

## Evidence Profile dobutamine versus epinephrine

**Bibliography**: Belletti et al. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. Journal of critical care. 2017 Feb 1;37:91-8.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **dobutamine** | **epinephrine** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (dobutamine alone)** | | | | | | | | | | | | |
| 1 a | randomised trials | not serious | not serious | serious b | serious c | none | 477/1000 (47.7%) | 518/1000 (51.8%) | **OR 0.85** (0.34 to 2.15) | **41 fewer per 1,000** (from 250 fewer to 180 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality (intervention is +/- norepinephrine)** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | serious b | serious c | none | 500/1000 (50.0%) | 518/1000 (51.8%) | **OR 0.93** (0.62 to 1.39) | **18 fewer per 1,000** (from 118 fewer to 81 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Organ dysfunction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor-free days (follow up: 28 days)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious b | not serious | none | Dobutamine median [IQR]: 22 (6–25)  Epinephrine median [IQR]: 20 (0–24) | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious b | very serious c,d | none | 3/30 (10.0%) | 4/30 (13.3%) | **RR 0.75** (0.18 to 3.07) | **33 fewer per 1,000** (from 109 fewer to 276 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Arrhythmia** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious b | very serious c,d | none | 4/45 (8.9%) | 6/45 (13.3%) | **RR 0.67** (0.21 to 2.13) | **44 fewer per 1,000** (from 105 fewer to 151 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Atrial fibrillation - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Myocardial infarction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

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

#### Explanations

a. Results are from NMA. Number of RCTs with direct comparisons reported.

b. The PICO question in the included trial is not exactly the same as our PICO question

c. The confidence interval includes both appreciable benefit and harm.

d. There are too few events to produce a reliable effect estimate.

# In patients with septic shock with persistent hypoperfusion despite adequate volume loading and the use of vasopressor agents, should we recommend using dobutamine versus no inotropic agents?

## Evidence Profile dobutamine versus no inotropic agents

**Bibliography**: Belletti A, Benedetto U, Biondi-Zoccai G, Leggieri C, Silvani P, Angelini GD, Zangrillo A, Landoni G. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. Journal of critical care. 2017 Feb 1;37:91-8. Wilkman E, Kaukonen KM, Pettilä V, Kuitunen A, Varpula M. Association between inotrope treatment and 90‐day mortality in patients with septic shock. Acta Anaesthesiologica Scandinavica. 2013 Apr;57(4):431-42.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **dobutamine** | **no inotropic agents** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (NMA of RCTs)** | | | | | | | | | | | | |
| 0 a | randomised trials b | not serious | not serious | serious b | serious c | none |  | 564/1176 (48.0%) | **RR 0.69** (0.32 to 1.47) | **149 fewer per 1,000** (from 326 fewer to 225 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality (Observational)** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious c | none | 79/186 (42.5%) | 56/234 (23.9%) | **OR 2.34** (1.36 to 4.02) | **185 more per 1,000** (from 60 more to 319 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **New-onset organ dysfunction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Renal replacement therapy-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Life-threatening arrhythmia - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Atrial fibrillation - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Myocardial infarction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

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

#### Explanations

a. Data come from NMA without direct comparisons

b. 33 trials included in NMA; none directly compared dobutamine + norepinephrine vs. norepinephrine.

c. Confidence interval includes very large harm and benefit.

## EtD Summary of Judgments dobutamine versus no inotropic agents

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# In patients with septic shock with persistent hypoperfusion, should we recommend using levosimendan versus dobutamine?

## Evidence Profile: levosimendan versus dobutamine

**Bibliography**: Bhattacharjee et al. Levosimendan does not provide mortality benefit over dobutamine in adult patients with septic shock: A meta-analysis of randomized controlled trials. Journal of Clinical Anesthesia 2017. 39; 67-72.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **levosimendan** | **dobutamine** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 7 | randomised trials | not serious | not serious | serious a | serious b | none | 59/131 (45.0%) | 63/127 (49.6%) | **OR 0.80** (0.48 to 1.33) | **56 fewer per 1,000** (from 175 fewer to 71 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **New-onset organ dysfunction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Vasopressor-free days - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b,c | none | 3/20 (15.0%) | 3/20 (15.0%) | **RR 1.00** (0.23 to 4.37) | **0 fewer per 1,000** (from 115 fewer to 505 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Life-threatening arrhythmia - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
| **Atrial fibrillation** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious b,c | none | 1/15 (6.7%) | 1/13 (7.7%) | **RR 0.87** (0.06 to 12.52) | **10 fewer per 1,000** (from 72 fewer to 886 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Myocardial infarction - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

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

#### Explanations

a. The PICO question in the included trials is not exactly the same as ours.

b. The confidence interval includes both appreciable harm and benefit.

c. There are too few events to reliably estimate the treatment effect.

## EtD Summary of Judgments levosimendan versus dobutamine

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | **Large costs** | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |