South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Critical care

MEDICINE REVIEW

1. Executive Summary

Date: 24 April 2023 (Updated: 6 October 2023)
Medicine (INN): Vasopressors, inotropes as monotherapy or in combination
Medicine (ATC): H01BA, C01CA
Indication (ICD10 code): Septic shock
Patient population: Adult patients
Prevalence of condition: 677.5 (535.7 to 876.1) cases of sepsis per 100 000 in 2017 globally (Rudd, 2017). Septic shock prevalence in Europe and North America among those diagnosed at any time was 6.5% (95% CI 5.6 to 7.5%) using sepsis-3 criteria (Vincent, 2019).
Prescriber Level: Hospital level
Motivator/reviewer name(s): R Mpofu, TD Leong, S Dadan, R Griesel
PTC affiliation: Red Cross War Memorial Children's Hospital pharmacy therapeutics committee (RM)

Key findings

- Internationally, noradrenaline is recommended as a first-line vasopressor for the management of septic shock. This review assessed the evidence for vasopressor agents in the treatment of adults with septic shock. The quality of evidence included in the current, Surviving Sepsis 2021, guidelines were assessed to be low, and adaptation/adolopment approach was therefore not appropriate.
- We sourced and appraised systematic reviews, of which one was assessed as good quality (Gamper, 2016) using the AMSTAR 2 tool. We also reviewed historical Surviving Sepsis guidelines to identify additional studies of relevance. Five relevant primary RCTs were extracted from the systematic review and risk-of-bias appraised and synthesised with meta-analysis of homogenous data as appropriate.
- Noradrenaline (norepinephrine), with/without other catecholamines, probably does not reduce mortality compared to adrenaline in the management of septic shock: 131/289 (45.3%) vs 124/271 (45.8%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%), *low certainty evidence.*
- It is uncertain whether noradrenaline (norepinephrine), with/without other catecholamines, may have an effect on time to mean arterial pressure goal (24 hours without vasopressor use), time to MAP stabilisation (MAP 70 to 80 mmHg) or effect on vasopressor free days (28 days), compared to adrenaline (epinephrine), very *low certainty evidence.*
- Noradrenaline (norepinephrine), with/without other catecholamines, may not reduce mean change in lactate concentration from baseline, at 24 hours, compared to adrenaline (epinephrine), *very low certainty evidence.* The mean difference was MD - 0.16 mmol/l (95% CI -1.14 fewer to 0.82 more). This change is not considered clinically significant.
- There was no difference in supra- or ventricular-tachyarrhythmias between the adrenaline (epinephrine) [31/176 (17.6%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [30/184(16.3%)], RR 0.92 (95% CI 0.59 to 1.45), *very low certainty evidence.*
- In conclusion, this review found that adrenaline (epinephrine) monotherapy is associated with similar clinical outcomes as noradrenaline (norepinephrine) when used as monotherapy or in combination with other vasopressors.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW RECOMMENDATION (Updated Electronically: 6 OCTOBER 2023):

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for management of septic shock.

Rationale:. Furthermore, noradrenaline (norepinephrine) is cost-prohibitive compared to adrenaline at present, and is unlikely to have generic agents available for the foreseeable future.

Level of Evidence: Low to very low certainty evidence
Review indicator: Price reduction, availability of cost-effective noradrenaline products, or any new evidence of efficacy or harm.

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):

Although the available evidence was of low to very low certainty, NEMLC did not recommend noradrenaline over adrenaline for the initial management of septic shock that is unresponsive to a fluid challenge, due to the absence of clinically significant advantages in mortality or safety.

Monitoring and evaluation considerations

Research priorities

Prospero registration: CRD42022368373

2. **Name of author(s)/motivator(s):** R Mpofu, TD Leong, S Dadan, R Griesel

3. **Author affiliation and conflict of interest details**

RM (Division of Clinical Pharmacology, University of Cape Town), TDL (South African Medical Research Council), SD (University of Cape Town), RG (South African Medical Research Council) and have no interests related to vasopressors or inotropes.

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4. **Introduction/ Background**

Sepsis is a global, public health problem with a risk of mortality greater than 20% (Rudd, 2020). Sepsis is defined as life threatening organ dysfunction due to a dysregulated host response to infection (Singer, 2016). This condition is frequently complicated by septic shock, characterized by a failure to maintain mean arterial pressures (MAP) ≥65 mmHg without the use of vasopressor agents and a serum lactate concentration greater than 2 mmol/L (Singer, 2016). Septic shock is associated with an in-hospital mortality risk greater than 40%. Treatment principles for septic shock include early diagnosis and recognition, fluid resuscitation, antibiotic administration in addition to infection source control, and vasopressor therapy (Surviving sepsis, 2021).

Various drugs with vasopressor activity have been recommended for the treatment of septic shock, but adrenaline (also known as epinephrine), noradrenaline (also known as norepinephrine), dopamine, and vasopressin agonists are commonly used. Adrenaline, noradrenaline, and dopamine are endogenous catecholamines that act on α, ß, and dopamine (D) receptors to varying degrees, with clinical effects that are mediated by relative stimulatory effects on these receptors. Adrenaline is a non-selective α-adrenergic and ß-adrenergic receptor agonist that increases cardiac rate, contractility, and systemic vascular resistance, particularly at doses used in the treatment of septic shock (Shields, 2016). However, high doses and prolonged use have been associated with potentially significant arrhythmias and splanchnic vasoconstriction due to $ß_1$-adrenergic receptor stimulation (Overgaard, 2008). Noradrenaline, a more selective catecholamine compared to adrenaline, predominantly stimulates α-adrenergic receptors and results in peripheral vasoconstriction with reduced arrhythmogenic potential due to decreased ß-adrenergic receptor effects (Overgaard, 2008). Dopamine is an endogenous, centrally acting neurotransmitter that also serves as a precursor in the synthesis of noradrenaline. At low doses (0.5 to 3 $mg.kg^{-1}.min^{-1}$), dopamine stimulates postsynaptic, dopaminergic D_1 receptors in the coronary, renal, mesenteric, and cerebral beds, while also stimulating presynaptic D_2 receptors in the vasculature and renal tissues to promote vasodilation and improve organ perfusion. Effects at higher infusion rates (10 to 20 $mg.kg^{-1}.min^{-1}$) are largely mediated by α_1-adrenergic receptor vasoconstriction (Overgaard, 2008). Dopamine has fallen out of favour as a first-line vasopressor agent in the treatment of septic shock based on data demonstrating an increased risk of arrhythmias and mortality compared with other vasopressors like noradrenaline. However, it may still have utility in a select group of patients, e.g., low risk of tachyarrhythmias or absolute/relative bradycardia (Shields, 2016). Vasopressin is an endogenous, non-adrenergic vasopressor that exerts its circulatory effects through V_{1a} receptor mediated vascular smooth muscle constriction and V_2 receptor mediated water reabsorption by enhancing renal collecting duct permeability (Overgaard, 2008). Vasopressin has minimal inotropic or chronotropic effects on the heart (Shields, 2016).

The South African standard treatment guidelines (STGs) for Adult Hospital Level, 2019 edition, have previously recommended adrenaline for the treatment of septic shock that is unresponsive to a fluid challenge, however, most international guidelines consider noradrenaline as first-choice for vasopressor therapy, followed by other vasopressor agents (which are sometimes recommended in combination) that have not previously been considered for the South African Essential Medicines List (EML). This review assessed the evidence for vasopressor agents in the treatment of adults with septic shock.

5. Methods:

We conducted a review of clinical practice guidelines (CPGs), systematic reviews of randomised controlled trials (RCTs) and RCTs that compared noradrenaline (norepinephrine), with/without other catecholamines to adrenaline (current standard of care) for management of septic shock in adults in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicine List, 2019 edition (NDoH, 2019). Review characteristics are included in **Table 1**.

Table 1: Purpose/Objective i.e., PICO

Population	Critically ill adult patients (age ≥18) with septic shock
Intervention	Noradrenaline (norepinephrine) as monotherapy, or in combination with Dopamine OR Vasopressin
Control	Adrenaline (epinephrine)
Outcomes	1. Clinical cure – time to shock reversal 2. Mortality 3. Safety: adverse effects, including ischaemic complications and dysrhythmias
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

A stepwise methodological approach was used: appraising current good quality guidelines for adaptation/adolopment to local context, followed by screening and selection of systematic reviews and health technological assessments (HTAs) for data extraction and analysis and then extraction of RCTs from systematic reviews as appropriate.

a. **Data sources**: Clinical Practice Guidelines were searched on the Guidelines International Network (GIN) Library database and google scholar. Health Technology Assessments (HTAs) were sought on Nice Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), International HTA Database and the European network for Health Technology Assessment (EUnetHTA). Systematic reviews and randomised controlled trials were searched in Epistemonikos, Cochrane Library, PubMed. To identify planned and ongoing studies, World Health Organization's International Clinicals Trials Registry Platform (ICTRP) as well as ClinicalTrials.gov were also searched.

b. **Search strategy:**
Search strategies were developed for PubMed and Epistemonikos (

Appendix 1). Search terms used for other databases were adapted from the above listed strategies.

c. Screening, data extraction and analysis, evidence synthesis:

Guidelines: Eligible clinical guidelines were sourced (RM) and appraised in duplicate, using the AGREE II tool (Brouwers, 2010) (RG, RM, TL, SD). To minimise duplication of efforts, where up-to-date guidelines that answers the review question are assessed to be of sufficient quality, the guidelines will be adapted using the GRADE-ADOLOPMENT approach, proposed by the GRADE working group (Schünemann, 2017). This approach considers the populated GRADE Evidence-To-Decision table (Moberg, 2018) for the specific clinical guideline on the GRADEPro website, and the categories are then contextualized for South Africa.

Health Technology Assessments: Eligible HTAs were sourced (TL) with appraisal in duplicate, using the AMSTAR 2 checklist (RM, TL, SD), as required.

Systematic reviews: A stepwise approach was taken, first screening and selecting systematic reviews and HTAs for data extraction and analysis. Records were uploaded into the reference management software, COVIDENCE (Covidence, 2023). Titles and abstracts were screened independently and in duplicate (RG, RM, SD, TDL). Thereafter, full text screening was done by two reviewers (RG, RM, SD, TDL) with conflicts resolved by a third reviewer. Eligible systematic reviews were appraised using the AMSTAR 2 Checklist (Shea, 2017) (TDL, RM, SD) and the most relevant studies was identified through consensus for data extraction. Reasons for excluding full texts at full-text stage were agreed in duplicate with a third reviewer finalizing any disputes. The PRISMA flowchart provides an overview of the review process (see **Appendix 2**).

Randomised controlled trials: Following the selection of the relevant systematic review(s), eligible RCTs were extracted from the systematic review(s). We screened for any additional RCTs that were not included in the eligible systematic review(s). Eligible RCTs were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool (Higgins, 2019), with data extraction. For dichotomous outcomes, we reported relative risk (RR) with 95% confidence intervals (95% CI) and results from the review or trial where possible. The mean difference (MD) with 95% CI were reported where the standard deviations (SDs) of outcomes were observed in two groups. SDs were calculated for normally distributed interquartile ranges using the formula proposed by Wan et al (2014) and described by Higgins et al (2019). Where available, we reported on the GRADE (level of certainty) of the evidence, considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness.

Data from multiple studies (considered to be sufficiently homogenous in terms of design, population, interventions and comparators reporting the same outcome) were combined and summarized through a meta-analysis using the Mantel-Haenzel method and a random-effects model to account for further between-study heterogeneity. The data was analysed using RevMan 5 (Review Manager version 5.4). Estimates were summarized using risk ratios (RR) and 95% CIs for dichotomous data, and mean differences and standard deviations for continuous data. Where appropriate, absolute effects with numbers needed to treat (NNT) have been calculated and reported. For any outcomes where insufficient data were found for a meta-analysis, a narrative synthesis has been presented.

Ongoing clinical trials: Clinical registries were screened (SD) to identify any relevant planned or ongoing clinical trials.

6. Results

a. Guidelines

We identified 3 guidelines, the Surviving Sepsis guidelines (2021), Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock (2020) and the clinical practice guidelines for sepsis and septic shock in adults in the Philippines

(2020). These guidelines were all assessed using the AGREE II tool to be of moderate quality (see **Table 2** and **Appendix 3**).

Table 2. AGREE II assessments of the sepsis guidelines

Guideline citation and website	Recommendations	AGREE II Appraisal
Surviving Sepsis Guidelines, 2021	**Recommendation:** For adults with septic shock, we recommend using noradrenaline (norepinephrine) as the first-line agent over other vasopressors. *Strong* • Dopamine: *High-quality evidence* • Vasopressin. *Moderate-quality evidence* • Epinephrine. *Low quality of evidence* • Selepressin. *Low quality of evidence* • Angiotensin II. *Very low-quality evidence* **Recommendation:** For adults with septic shock on norepinephrine with inadequate MAP levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine. *Weak, moderate quality evidence* **Recommendation:** For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine. *Weak, low quality of evidence* **Recommendation:** For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone. *Weak, low quality of evidence*	Overall assessment 67% See Appendix 3.
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock, 2020	**Recommendation:** Between noradrenaline and dopamine, we suggest administering noradrenaline as a first-line vasopressor in adult patients with sepsis *(GRADE 2D: certainty of evidence = "very low")* **Recommendation:** We suggest against using adrenaline as a second-line vasopressor in patients with sepsis/septic shock (*GRADE 2D: certainty of evidence = "very low").* **Recommendation:** We suggest using vasopressin as a second-line vasopressor in patients with sepsis/septic shock *(GRADE 2D: certainty of evidence = "very low").* **Recommendation:** We suggest administering inotropes (adrenaline, dobutamine) in adult patients with septic shock accompanied by cardiac dysfunction *(expert consensus: insufficient evidence).*	Overall assessment 67% See Appendix 3
Clinical practice guidelines for sepsis and septic shock in adults in the Philippines, 2020	**Question 15.** In patients with septic shock requiring vasopressors, should we use norepinephrine over other agents?	Overall assessment 58% See Appendix 3.

	Recommendation: We recommend norepinephrine as a first–line agent in septic shock requiring vasopressors (*strong recommendation, high quality of evidence*). **Question 16.** In patients with septic shock requiring a second vasopressor, which agent should be added to norepinephrine? **Recommendation:** We recommend the use of vasopressin (titrated up to 0.03 U/min) as the second vasopressor of choice on top of norepinephrine in patients with septic shock, with the intent of raising MAP to target or decreasing norepinephrine dosage *(conditional recommendation, low quality of evidence).*	

As the current international guidelines recommend noradrenaline (norepinephrine) as the vasopressor of choice and not adrenaline (epinephrine), noting the low quality, the GRADE-ADOLOPMENT approach was not relevant. To identify additional studies that may have been eligible for inclusion, historic Surviving Sepsis Guidelines (2001, 2004, 2008, 2012, 2016 and 2021) were also reviewed (see **Appendix 4**). However, no additional studies were identified.

b. Health technology assessments

We did not identify any health technology assessments relevant to the review.

c. Systematic reviews and randomised controlled trials

Description of included studies:

Ten systematic reviews were eligible and were critically appraised. Using the AMSTAR 2 tool, only one study (Gamper, 2016) was assessed to be of sufficient quality and the rest were of low to critically low quality (see **Appendix 5**). Five primary RCTs (Annane 2007; Myburgh 2008; Levy 2011; Seguin 2002, Seguin 2006) that compared adrenaline (epinephrine) to other vasopressors, included in the systematic review, were then further reviewed. One RCT which was included in the systematic review (Levy 2011) enrolled participants with cardiogenic shock rather than septic shock, and the population and disease differences in this indication may have important implications in the analysis and interpretation of results. Therefore, we excluded this study in the meta-analysis to minimize the potential effect of selection bias.

- ***Systematic review:***

Gamper 2016: Systematic review of 28 RCTs (n=3497) that compared the effect of one vasopressor regimen (vasopressor alone, or in combination) versus another vasopressor regimen on mortality amongst the critically ill with hypotensive shock. Six vasopressors (alone or in combination) were studied in 12 different comparisons.

For adrenaline (epinephrine) compared with noradrenaline (norepinephrine), as monotherapy or combination therapy (six RCTs; n=703 participants), 298 deaths were observed among the 703 participants (see **Figure 1**). No significant difference was found in either comparison. Participants had septic shock (Annane 2007; Levy 1997; Seguin 2002; Seguin 2006), cardiogenic shock (Levy 2011) or were categorized as critically ill patients (Myburgh 2008).

For the comparison of noradrenaline (norepinephrine) and adrenaline (epinephrine) monotherapy, one moderately large RCT of critically ill patients (n=269) showed a 90-day mortality rate of 380 per 1000 compared to 334 per 1000, respectively with a RR 0.88 (0.63 to 1.25), graded as low certainty evidence as the effect is from a single RCT (Myburgh 2008)
The systematic review was assessed as high quality using the AMSTAR 2 tool (see **Table 3** and **Appendix 5**).

Table 3. AMSTAR 2 assessment of the systematic review by Gamper et al, 2016.

Systematic review	Recommendation	AMSTAR 2 appraisal
Gamper, 2016: Vasopressors for hypotensive shock. Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2016 Feb 15;2(2):CD003709.	No differences in total mortality in any comparisons of different vasopressors or combinations in any of the pre‐defined analyses (evidence quality ranging from high to very low). More arrhythmias were observed in participants treated with dopamine than in those treated with norepinephrine (high-quality evidence). Authors suggest that major changes in clinical practice are not needed, but that selection of vasopressors could be better individualised and could be based on clinical variables reflecting hypoperfusion.	High Quality Review. See **Appendix 5**.

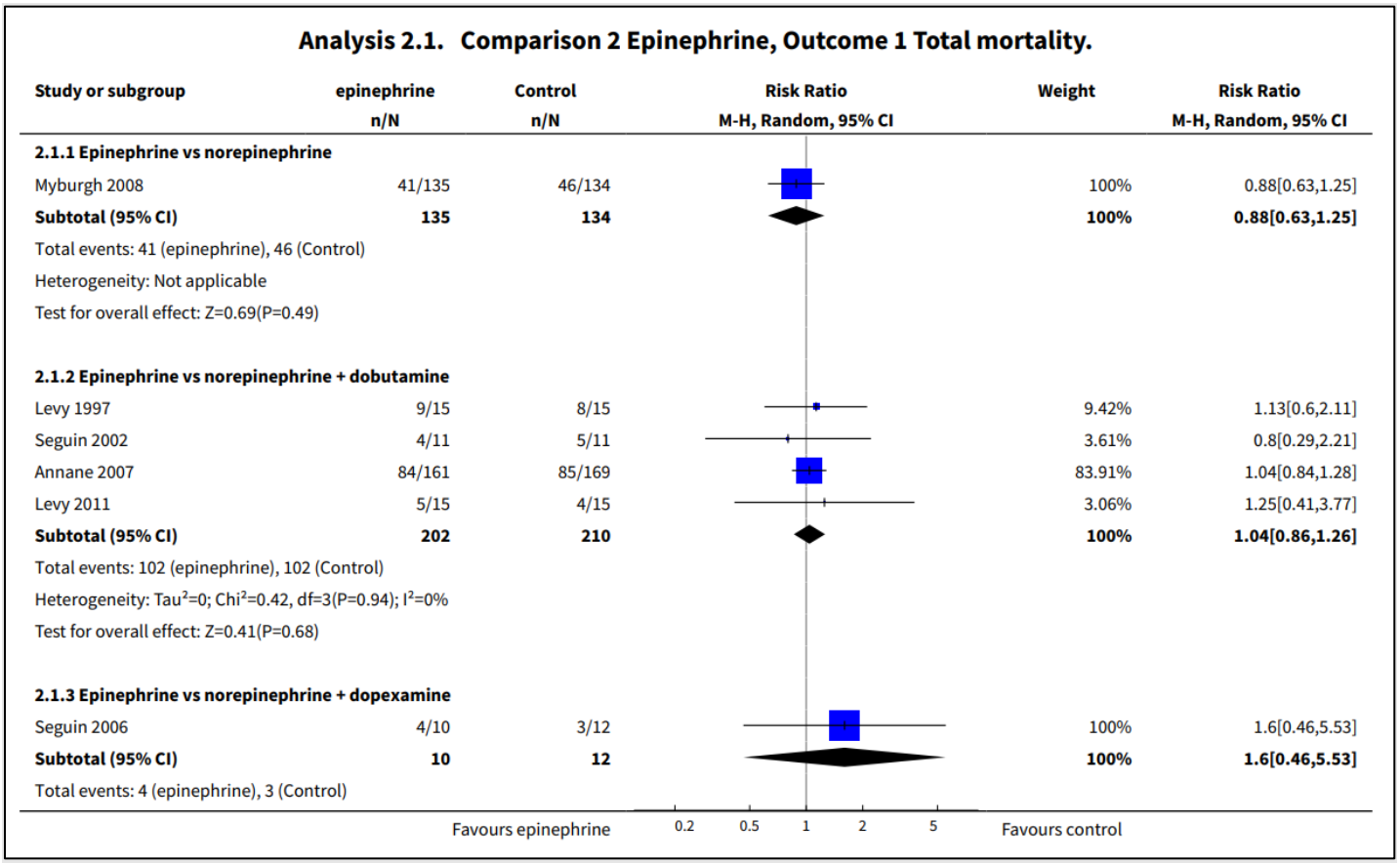


Figure 1. Forest plot comparing epinephrine (adrenaline) to other vasopressors (alone or in combination) amongst critically ill patients with hypotensive shock, including cardiogenic and septic shock (Gamper, 2016)

- ***Randomised controlled trials:***

We further reviewed the primary RCTs that informed the Gamper *et al*. (2016) systematic review that included adrenaline (epinephrine) as a study drug specifically for the management of septic shock. These RCTs were appraised using the Cochrane risk of bias tool (RoB 2) (Higgins, 2019) to independently assess the risk of bias in duplicate (RM, TL) for each outcome in the included studies, resolving any disagreements through discussion (See **Figure 2 and Table 5**).

Monotherapy

Adrenaline (epinephrine) vs noradrenaline (norepinephrine)

One double-blind RCT (Myburgh 2008) conducted at 4 Australian university hospital ICUs of critically ill, adult patients (n=280) with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 22 at study entry who required

vasopressors compared adrenaline (epinephrine) as monotherapy to noradrenaline (norepinephrine). Patients were mostly elderly (mean age of 60 years) and presented with either septic shock (n=158) or acute respiratory failure (n=192) randomized to either adrenaline (epinephrine) or noradrenaline (norepinephrine) to achieve a MAP ≥70 mmHg without vasopressors as the primary outcome. Secondary outcomes included 28- and 90-day mortality.

Combination therapy

Adrenaline (epinephrine) vs noradrenaline (norepinephrine) + dobutamine

Three RCTs that compared adrenaline (epinephrine) with noradrenaline (norepinephrine) and dobutamine in septic shock, were reviewed (Annane 2007, Levy 1997, Seguin 2002). Double blinding was conducted in one trial of 330 participants (Annane 2007), but it is uncertain whether investigators, study participants or outcome assessors were blinded in two trials (Levy 1997: n=30, Seguin 2002: n=22). Participants were predominantly male and elderly, with ages ranging from 44 to 83 years. In one trial, participants had a McCabe classification of class 0 (no fatal underlying disease at the time of admission) (Annane 2007) and in the trial by Levy *et al.,* the mean APACHE II scores were 23 and 24 between the two respective treatment groups (Levy 1997). All trials reported on mortality, which was a primary outcome in one RCT (Annane 2007). Primary endpoints for one RCT (Levy 1997) was hemodynamic measures (also measured in the other RCTs) and another RCT was gastric mucosal blood flow (Seguin 2002). Additional outcomes included time to MAP stabilisation (MAP 70 to 80 mmHg), hepatic function and adverse events (including arrythmias and lactate concentrations).

Adrenaline (epinephrine) vs noradrenaline (norepinephrine) + dopexamine

One open-label RCT (n=22) compared adrenaline (epinephrine) to noradrenaline (norepinephrine) with dopexamine combination therapy (Seguin 2006) on gastric mucosal blood flow (GMBF). Mortality rates and haemodynamic parameters (including heart rate, arterial pressures, pulmonary capillary wedge pressure, cardiac output, and others) were also assessed. GMBF and other haemodynamic parameters were measured at various time points: before vasopressor administration, once MAP target had been obtained, 2 hours after attainment of target MAP, and 6 hours after attainment of target MAP. Participants, mostly male, had a mean age of 67 years and 65 years in the respective study arms, with Simplified Acute Physiology Score II (SAPS II) scores of 8 and 9, respectively. Treatment was titrated to maintain a MAP between 70 and 80 mmHg and the time to target MAP was measured.

QUALITY ASSESMENT

Amstar 2 assessment

The quality of nine systematic reviews, critically appraised using the AMSTAR 2 tool, were assessed to be of low to critically low quality (see **Appendix 4**) for the following reasons. There was no explicit statement that the review methods were established a prior or justification for major protocol deviations in four review reports (Cheng 2019, Avni 2015, Zhou 2015, Chen 2019). Ruslan et al did not use a comprehensive literature search strategy (Ruslan 2019). List of excluded studies with the rationale for exclusion was omitted in eight review reports (Oba 2015, Nagendran 2016, Cheng 2019, Raslan 2021, Cheng 2019, Avni 2015, Zhou 2015, Chen 2019). Statistical methods for meta-analysing data were inappropriate in one review (Chen 2019). In six review reports, review authors did not account for RoB in individual RCTs when interpreting/ discussing the results of the review (Cheng 2019, Ruslan 2019, Avni 2015, Zhou 2015, Chen 2019, Jiang 2019). And, lastly, for quantitative synthesis, review authors had not carried out adequate investigation of publication bias (small study bias) and had not discussed its likely impact on the results of the review in three reports (Oba 2015, Nagendran 2016, Zhou 2015).

Only one study (Gamper, 2016) was appraised to be of sufficient quality and five primary RCTs that informed the Gamper *et al* (2016) systematic review that included adrenaline (epinephrine) as a study drug specifically for the management of septic shock was quality assessed using the Cochrane ROB 2 tool.

ROB 2 assessment

We assessed the following domains of risk of bias by using the RoB 2 tool for various outcomes (See **Figure 2**).

Bias arising from the randomisation process

We judged three RCTs as low risk of bias for this domain, as randomisation was performed using a computer-generated list (Annane 2007, Myburgh 2008, Seguin 2006). Two trials did not adequately report allocation concealment (Levy 1997, Seguin 2002).

Bias arising from deviation from the intended interventions

Three RCTs were double blinded (Annane 2007, Myburgh 2008, Seguin 2002). However, only two were judged as low risk as adrenaline-associated lactic acidosis arm may have informed treatment allocation in the trial conducted by Myburgh et al (Myburgh 2008). One trial (Seguin 2006) was open label, whilst three RCTs did not provide adequate information to judge for selection bias (Levy 1997, Seguin 2002, Seguin 2006). Appropriate intention-to-treat analyses were performed to estimate the effect of assignment to intervention in only two RCTs (Annane 2007, Myburgh 2008), and no information was provided for the other three RCTs (Levy 1997, Seguin 2002, Seguin 2006).

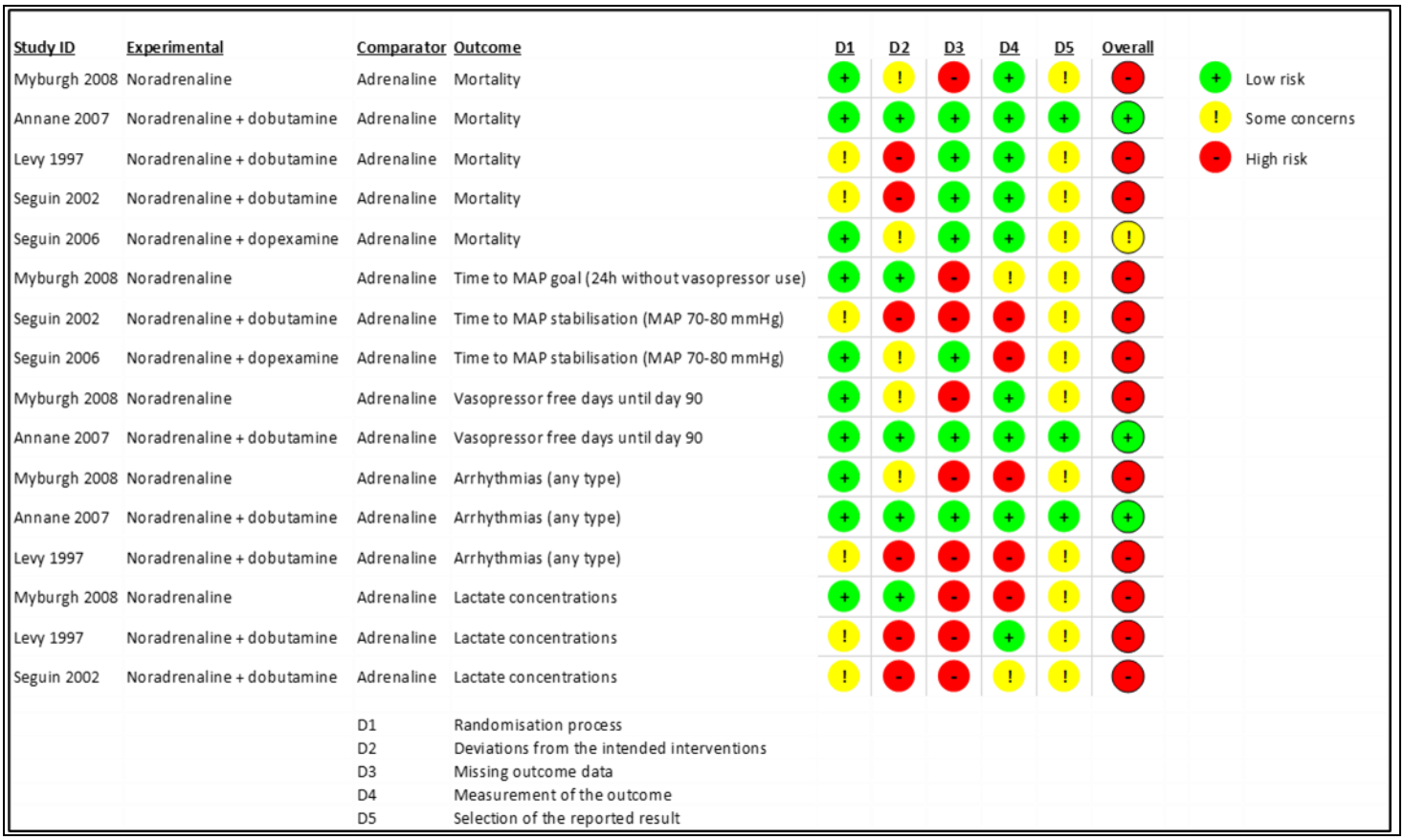


Figure 2: Methodological quality summary - review authors' judgements for each outcome per included study

Bias due to missing outcome data

For most outcomes, it was not reported whether outcome data were available for all, or nearly all participants who underwent randomisation. Only Annane *et al.* reported on availability of outcome data for all outcomes (Annane 2007). Mortality is an observer-reported outcome not involving judgement, assessed as low risk except for RCT by Myburgh *et al*. as there is uncertainty of the time when patients were switched from adrenaline to open-label noradrenaline due to adrenaline-associated lactic acidosis (Myburgh 2008).

Bias in measurement of the outcome

For mortality, we judged all trials as low risk of bias for this domain. For the other outcomes, one trial was open-label (Seguin 2006) and in another two trials there was insufficient information to judge blinding in another (Levy 1997, Seguin 2002). We judged that outcome assessors in one "double-blinded" RCT (Myburgh 2008) were probably aware that adrenaline was received by study participants due to clinically evaluated adrenaline-associated lactic acidosis that caused clinicians to withdraw participants from the adrenaline group, with subsequent receipt of open-labelled noradrenaline. Some concerns were also noted with the Seguin *et al* trials, as there was no clear definition of MAP stabilisation (Seguin 2002, Seguin 2006).

Bias due to selection of the reported result

Only one trial had a protocol registered in a trial registry (Annane 2007). Published protocols, detailing pre-specified outcome(s), and statistical analysis plans were not available for the other four trials.

OUTCOMES

Effectiveness:

- **Mortality (Day 28) – overall (mono- and combination therapy)**

Noradrenaline (norepinephrine), with/without other catecholamines, probably does not increase/reduce mortality compared to adrenaline (epinephrine), in septic shock – evidence assessed as *low certainty* due to serious risk of bias and concerns of blinding of investigators and assessors (refer to **Table 4: GRADE summary of findings**).

Mortality was assessed at an undetermined time point in two RCTs (Levy 1997, Seguin 2002), so we assumed this to be at 28-days, based on other studies with similar study designs involving the same authors (Levy 2011, Seguin 2006). Levy 2011 (performed in participants with cardiogenic shock rather than septic shock) was excluded and five studies were meta-analysed (Levy 1997; Seguin 2002; Seguin 2006; Annane 2007; Myburgh 2008; See

Table 6). Adrenaline (epinephrine) was shown to be comparable to noradrenaline (norepinephrine) monotherapy/combination therapy (with another catecholamine vasopressor), 124/271 (45.8%) vs 131/289 (45.3%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%; **Figure 3**) and an absolute difference of 5 fewer deaths per 1000 patients treated (from 78 fewer to 82 more).

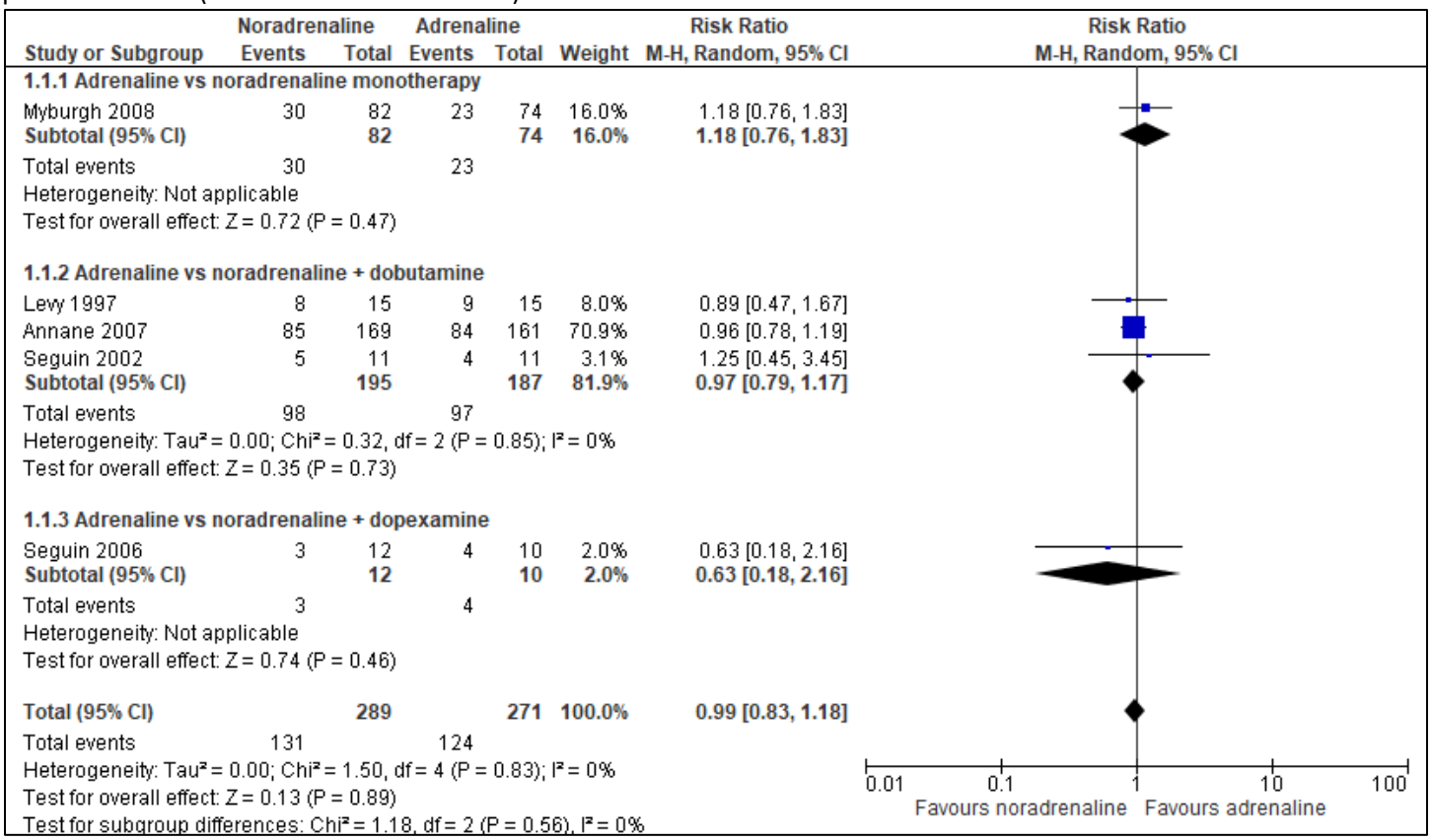


Figure 3. Forest plot comparing adrenaline vs noradrenaline monotherapy or noradrenaline-dopamine derivative (dobutamine or dopexamine) combination therapy in septic shock, for the outcome: mortality.

- **Mortality - monotherapy**

There is probably no difference in mortality between noradrenaline (norepinephrine) [30/82 (36.6%)] compared to adrenaline (epinephrine) [23/74 (31.1%)] RR 1.18 95% CI 0.76 to 1.83 (**Figure 4**). However, 22 patients (12.9%) were withdrawn from their blinded treatment allocation (either adrenaline or noradrenaline) to open-label noradrenaline (norepinephrine) due to associated adverse effects of transient increase in lactate concentrations and heart rate.

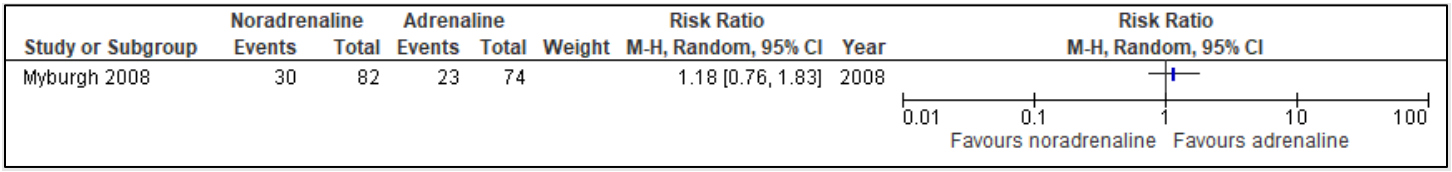


Figure 4. Forest plot comparing adrenaline to noradrenaline in septic shock, for the outcome: mortality.

- **Mortality - combination therapy**

Similarly, there was no mortality difference for noradrenaline (norepinephrine) with dopamine derivative (dobutamine or dopexamine) combination therapy [101/207 (48.8%) compared to adrenaline (epinephrine) monotherapy [101/197 (51.3%)] ,RR 0.96 (95% CI 0.79 to 1.16; I^2=0%; **Figure 5**).

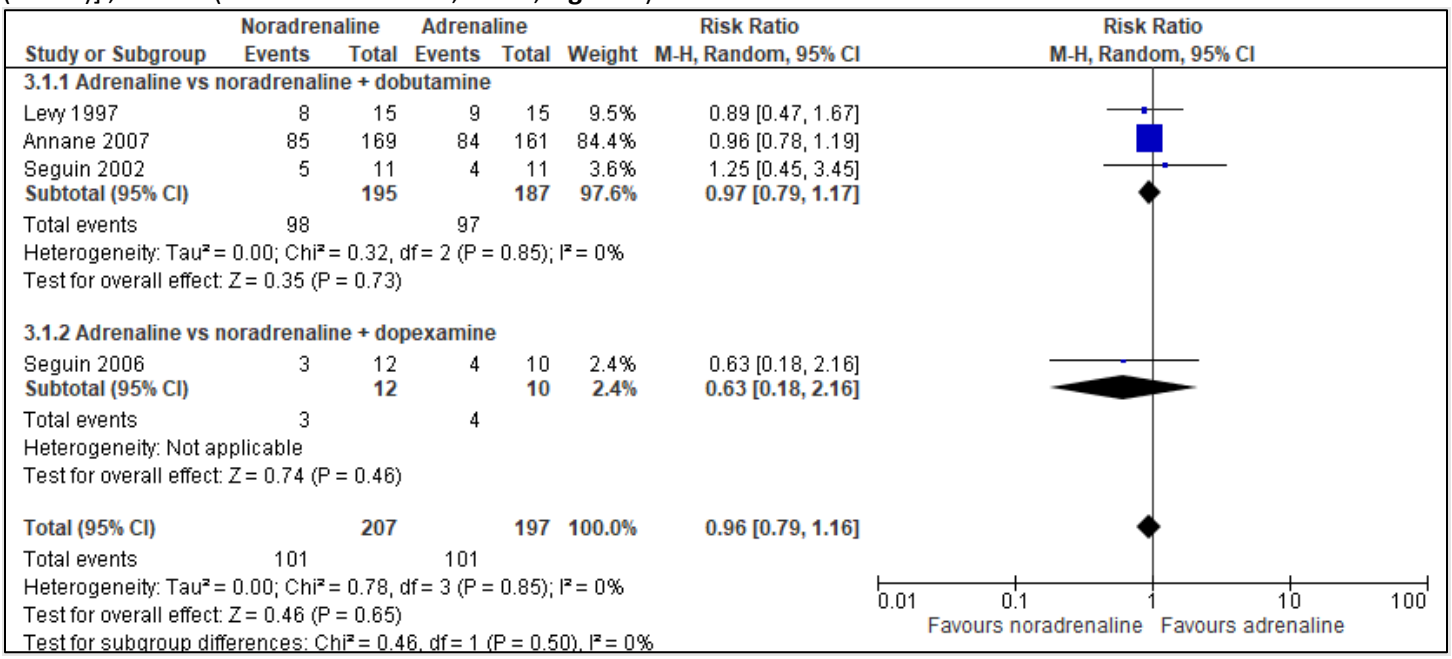


Figure 5. Forest plot comparing adrenaline to noradrenaline + dopamine derivative in septic shock, for the outcome: mortality.

- **Time to MAP goal (24h without vasopressor use)**

Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on time to mean arterial pressure goal (24 hours without vasopressor use) but the evidence is very uncertain – assessed as *very low certainty* due to possible attrition and for serious imprecision in this sub analysis (**Table 4**). In the Myburgh et al (2008) trial, *a priori* severe sepsis subgroup at baseline (158/277), there was no difference in the median time to achieve target MAP between adrenaline (epinephrine) (35.1 h; IQR 16.7 to 75 h; n=76) and noradrenaline (norepinephrine) — 50.0 h(IQR 18.2 to 127.5 h; n=82), with a hazards ratio (HR) of 0.81; 95% CI 0.59 to 1.12; p= 0.18). Based on a probability of 63.9% to achieve the MAP goal by 48 hours with adrenaline (epinephrine), 77 per 1000 fewer patients (from 187 fewer to 82 more) would reach the MAP goal when treated with noradrenaline (norepinephrine) compared to adrenaline (epinephrine) — refer to Kaplan-Meier plot for all critically ill patients in **Figure 6**.

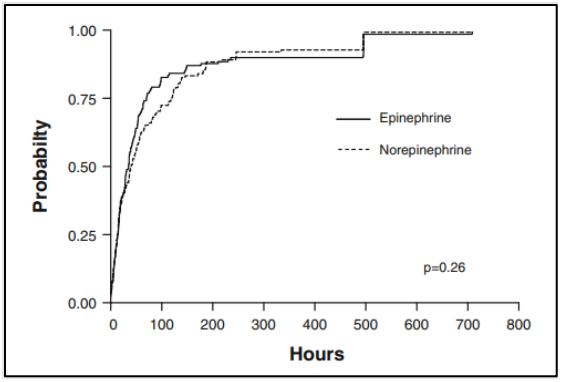


Figure 6. Kaplan-Meier estimates for probability of achieving MAP - adrenaline (epinephrine) vs noradrenaline (norepinephrine) in critically ill adults

- **Time to MAP stabilisation:**

Noradrenaline (with/without other catecholamines) may increase/have little to no effect on time to MAP stabilisation (MAP 70 to 80 mmHg) but the evidence is very uncertain, MD 7.17 minutes (95% CI -16.74 to 31.08; **Figure 7**). Evidence

was judged as *very low certainty* due to serious risk of measurement bias, inconsistency as uncertainty and very serious imprecision (**Table 4**).

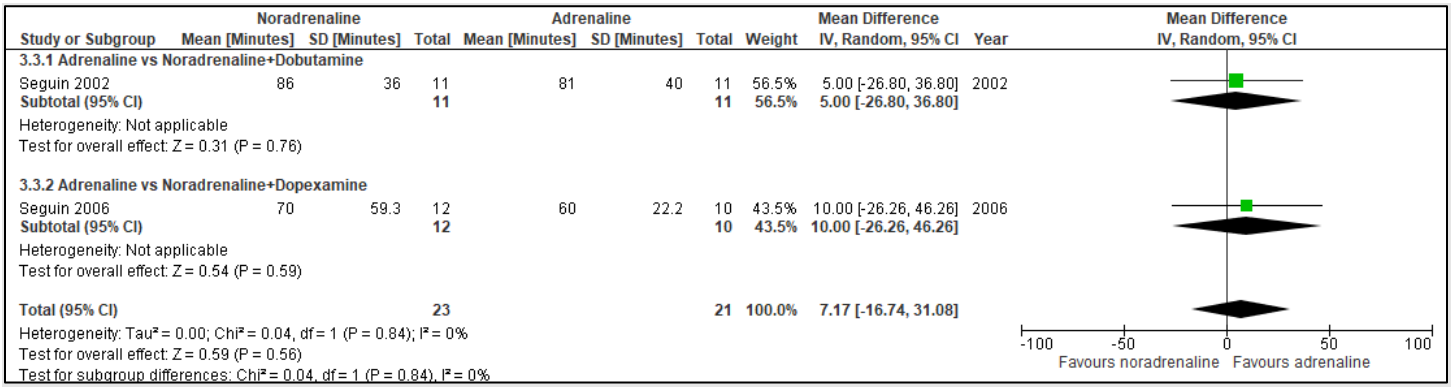


Figure 7. Forest plot comparing adrenaline vs noradrenaline + dopamine derivative in septic shock, for the outcome: Time to MAP stabilisation (70 to 80 mmHg) [minutes].

- **Vasopressor free days (Day 28)**

Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on vasopressor free days (from beginning of treatment to 28 days post treatment initiation) compared to adrenaline (epinephrine), MD of -0.05, 95% CI -4.07 to 3.96; I^2=63% (**Figure 8**), but there was *very low certainty* of evidence due to serious imprecision, possible attrition and inconsistent comparators.

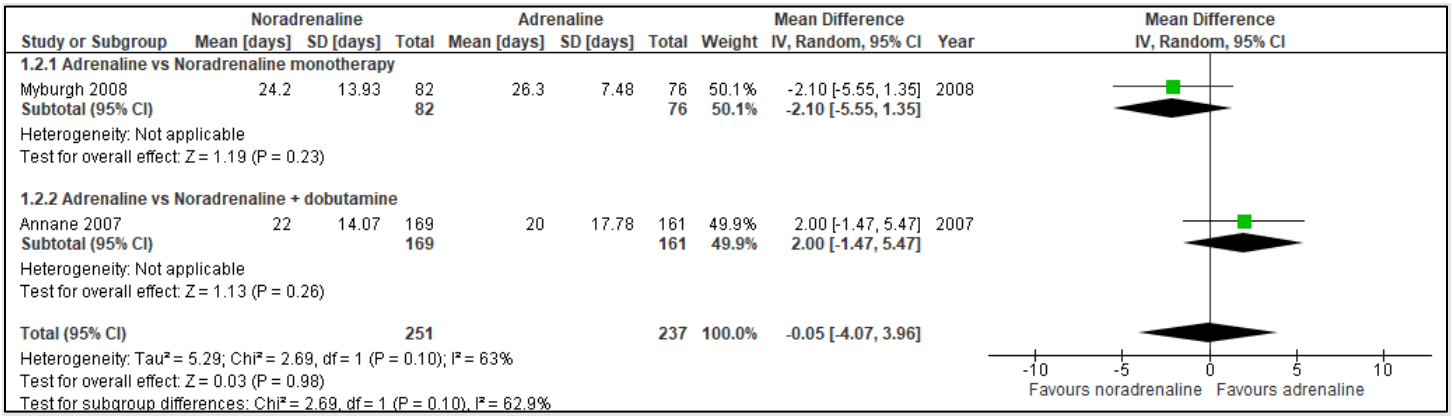


Figure 8: Forest plot comparing adrenaline vs noradrenaline in septic shock, for outcome: vasopressor free days (Day 28)

Safety:

- **Lactate concentrations**

Noradrenaline (norepinephrine), with/without other catecholamines, may not reduce the mean change in lactate concentration, compared to adrenaline (epinephrine). Certainty of evidence was downgraded to *very low certainty* due to serious imprecision and very serious risk of bias (**Table 4**). Two studies (Levy 1997 and Seguin 2002) assessed arterial lactate concentrations during treatment and reported data suitable for inclusion in a meta-analysis. Including 52 patients, the mean difference between the intervention and control groups was -0.16 mmol/L (95% CI -1.14 to 0.82; I^2=4%; **Figure 9**) between the epinephrine monotherapy and the norepinephrine+dobutamine combination therapy groups, which is considered to be clinically insiginificant.

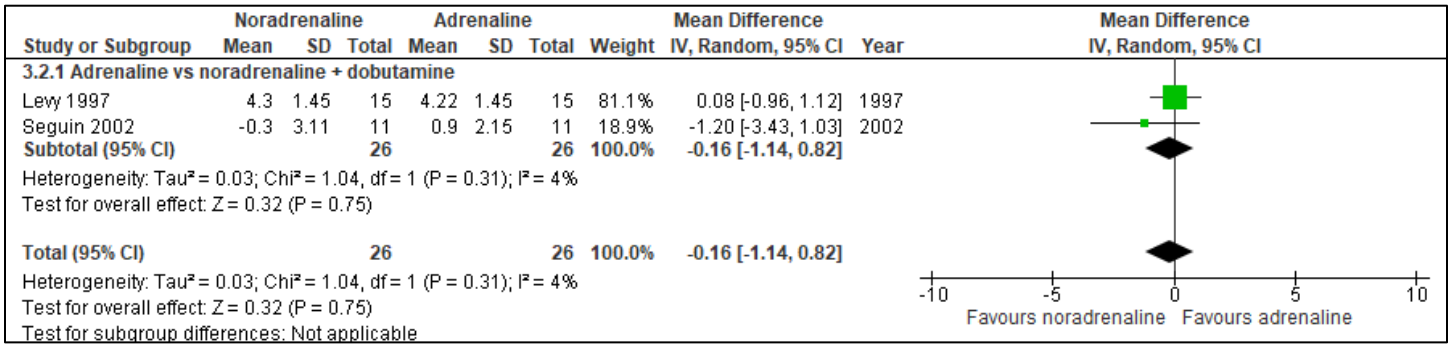


Figure 9. Forest plot comparing adrenaline vs noradrenaline+dobutamine combination in septic shock, on arterial lactate concentrations after 24 hours

- **Arrhythmias (any type)**

Noradrenaline (with/without other catecholamines) may not reduce arrhythmias (any type), certainty of evidence assessed as *very low* due to attrition and very serious imprecision (**Table 4**). Two trials (Levy 1997, Annane 2007) reported on arrhythmias, with no arrythmias reported in either treatment group by Levy *et al.* (1997), whilst Annane *et al.* (2007) reported no difference in supra- or ventricular-tachyarrhythmias between the adrenaline (epinephrine) [31/176 (17.6%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [30/184 (16.3%)], RR 0.92 (95% CI 0.59 to 1.45), absolute difference of 14 patients with arrhythmias per 1000 patients treated (from 72 fewer to 79 more; **Figure 10)**.

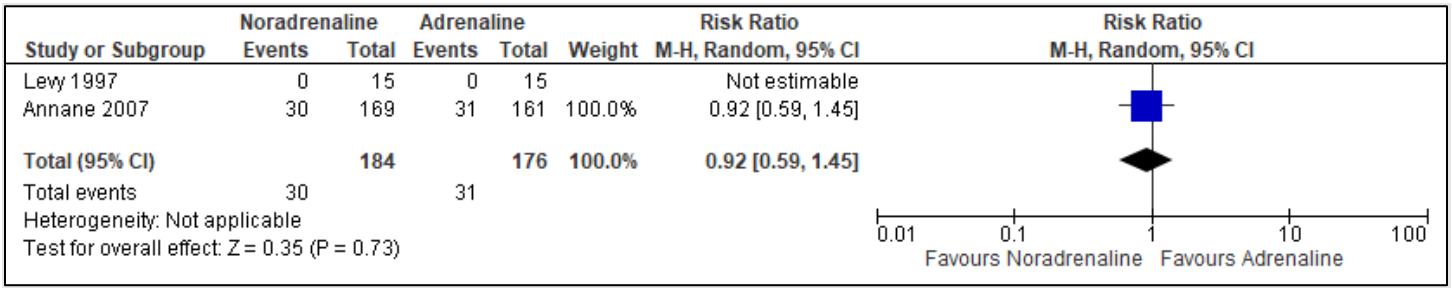


Figure 10. Forest plot of adrenaline compared to noradrenaline + dopamine derivative in septic shock, for the outcome: Arrhythmias.

Table 4. GRADE Summary of findings: Noradrenaline (with/without other catecholamines) compared to adrenaline for septic shock

Patient or population: Septic shock
Setting: Hospital
Intervention: Noradrenaline (with/without other catecholamines)
Comparison: Adrenaline

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Noradrenaline (with/without other catecholamines)	With Noradrenaline (with/without other catecholamines)	Difference		
Mortality follow-up: 28 days n = 560 (5 RCTs)	**RR 0.99** (0.83 to 1.18)	45.8%	**45.3%** (38 to 54)	**0.5% fewer** (7.8 fewer to 8.2 more)	⊕⊕◯◯ Low[a,b]	Noradrenaline (with/without other catecholamines) probably does not increase/reduce mortality.
Time to mean arterial pressure goal (24 hours without vasopressor use) (Time to MAP goal) n = 158 (1 RCT)	**HR 0.81** (0.59 to 1.12) [Time to mean arterial pressure goal (24 hours without vasopressor use)]	**Moderate**			⊕◯◯◯ Very low[c,d]	Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on time to mean arterial pressure goal (24 hours without vasopressor use) but the evidence is very uncertain.
		63.9%	**56.2%** (45.2 to 68.1)	**7.7% fewer** (18.7 fewer to 4.2 more)		
Time to MAP stabilisation (MAP 70 to 80 mmHg) assessed with: minutes n = 44 (2 RCTs)	-	The mean time to MAP stabilisation (MAP 70 to 80 mmHg) was **0**	-	MD **7.17 more** (16.74 fewer to 31.08 more)	⊕◯◯◯ Very low[e,f,g]	Noradrenaline (with/without other catecholamines) may increase/have little to no effect on time to MAP stabilisation (MAP 70 to 80 mmHg) but the evidence is very uncertain.
Vasopressor free days (28 days) n = 488 (2 RCTs)	-	The mean vasopressor free days (28 days) was **0**	-	MD **0.05 fewer** (4.07 fewer to 3.96 more)	⊕◯◯◯ Very low[b,c,h]	Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on vasopressor free days (28 days) but the evidence is very uncertain.
Arrhythmias (any type) n = 360 (2 RCTs)	**RR 0.92** (0.59 to 1.45)	17.6%	**16.2%** (10.4 to 25.5)	**1.4% fewer** (7.2 fewer to 7.9 more)	⊕◯◯◯ Very low[c,g]	Noradrenaline (with/without other catecholamines) may not reduce arrhythmias (any type).
Mean change in lactate concentration assessed with: mmol/l n = 52 (2 RCTs)	-	The mean change in lactate concentration was **0** mmol/l	-	MD **0.16 mmol/l fewer** (1.14 fewer to 0.82 more)	⊕⊕◯◯ Low[b,i]	Noradrenaline (with/without other catecholamines) may not reduce mean change in lactate concentration.

*__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; **HR:** hazard Ratio; **MD:** mean difference; **n**: sample size; **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. Downgraded by one level for serious risk of bias as one trial was open-label (Seguin 2006) and compromised blinding due to adrenaline-specific lactic acidosis toxicity in another trial (Myburgh 2008).
b. Downgraded by one level for serious imprecision as the CI includes appreciable benefit and harm.
c. Downgraded by one level for serious risk of bias due to possible attrition (Myburgh 2008).
d. Downgraded by one level for serious imprecision as OIS criterion in sub-analysis not met.
e. Downgraded by one level for serious risk of measurement bias.
f. Downgraded by one level for serious inconsistency as uncertainty regarding the definition of MAP stabilisation.
g. Downgraded by two levels for very serious imprecision as few events and the CI includes appreciable benefit and harm.
h. Downgraded by one level for serious inconsistency due to different comparators (Annane 2007, Myburgh 2008).
i. Downgraded by one level for serious risk of bias as insufficient information to assess selection and measurement risk (Levy 1997, Seguin 2002).

d. Planned or ongoing clinical trials

A search was conducted on Clinical Trials and WHO ICTRP databases, and we identified no planned or ongoing trials relevant to the PICO of this review.

7. Conclusion:

Our review showed that there is little difference in the effectiveness and safety of noradrenaline (norepinephrine) and adrenaline (epinephrine) for managing septic shock. The latest Surviving Sepsis guidelines recommend noradrenaline (norepinephrine) as first-line therapy, but the evidence cited to support this recommendation is limited and suggests little difference between the two agents (Evans 2021). Our review found that the risk of mortality and the time required to stabilize blood pressure without vasopressors were similar for both agents, although the certainty of the evidence was low or very low.

While adrenaline (epinephrine) has been associated with a potentially higher risk of adverse outcomes, such as arrhythmias, tachycardia, and elevated lactate concentrations, our review found that these risks were similar for both agents. It has been suggested that increased lactate concentrations may be an indicator of increased tissue hypoxia and anaerobic metabolism, but this did not translate to an increase in adverse clinical outcomes in the studies included in this review and meta-analysis. While it is possible that adrenaline (epinephrine) may be associated with elevated lactate concentrations, these changes are likely transient as was shown in one RCT (Myburgh, 2008) and may not negatively impact clinical outcomes (Belletti, 2021). Clinicians should be aware of this potential adverse effect when monitoring patients' clinical progress using blood gas investigations such as arterial blood pH and lactate concentrations.

Thus, it could be inferred that noradrenaline (norepinephrine) can safely be used as an alternative to adrenaline (epinephrine) but may not be affordable. A direct comparison of per-milligram drug prices suggest a seven to twenty fold increase in treatment costs with noradrenaline compared with adrenaline. Therefore, the choice of vasopressor therapy will most likely depend on cost, feasibility, and availability.

In conclusion, this review found that adrenaline (epinephrine) monotherapy is associated with similar clinical outcomes as noradrenaline (norepinephrine) used as monotherapy or in combination with other vasopressors.

Table 5. Characteristics of included studies

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
A: SYSTEMATIC REVIEW					
Gamper, 2016	Systematic review of 28 RCTs 6 RCTs compared epinephrine to other vasopressors (alone or in combination)	N=3497; critically ill patients with hypotensive shock N=703; epinephrine comparisons, (compared with norepinephrine, norepinephrine + dobutamine and norepinephrine + dopexamine) Participants with septic shock (Annane 2007; Levy 1997; Seguin 2002; Seguin 2006), participants with cardiogenic shock (Levy 2011) and critically ill participants (Myburgh 2008).	Epinephrine Vs Norepinephrine; Norepinephrine + dobutamine; and Norepinephrine + dopexamine	Overall/Total mortality	• Systematic review of high quality (High AMSTAR rating – see **Appendix 4.** • Systematic review reviewed all vasopressors alone or in combination, and only 6 of the 28 RCTs were eligible for review (PICO criteria) • Population included all critically ill patients with hypotensive shock – this review focuses specifically on patients with septic shock
B: RANDOMISED CONTROLLED TRIALS					
Epinephrine vs norepinephrine					
Myburgh 2008	Multi-centre double-blind randomized controlled trial, 4 multi-disciplinary university hospital ICUs; Australia Funding for statistical analysis of this study from the Australian and New Zealand College of Anaesthetists (Project grant: 06/024). Financial contribution from participating institutions that provided substantial support from internal funds Conflict of interest: none declared	N=280 Adult ICU participants requiring vasopressors for any reason Subgroup analysis: septic shock, circulatory failure Mean age = 60 years 39% female APACHE II score = 22	Switch from the vasopressor at inclusion to : Epinephrine (no dosing scheme reported) Or Norepinephrine (no dosing scheme reported) no restriction on other vasopressors except study drugs	• To achieve MAP > 70 mm Hg (or individualized by treating physicians) • Time to achieve MAP goal • Drug-free days from randomization (primary) • Mortality at days 28, 90	• For the mortality analysis: used data on 90-day mortality • Risk of bias assessment – see figure 2
Epinephrine vs norepinephrine + dobutamine					
Annane, 2007	Multi-centre double-blind randomized controlled trial in 19 ICUs (CATS study); France	n=330 Adult participants with septic shock (study authors' definition)	Epinephrine infusion 0.2 µg/kg/min (n = 161) Vs	• 28-day mortality (primary); 7-, 14-, 90-day ICU • Hospital mortality • Duration of vasopressor therapy	• For the mortality analysis, 90-day mortality was used.

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
	Funding: The French Ministry of Health provided financial support (1997 Clinical Research Hospital Programme PHRC 1997, AOM 97123) *Declarations of interest:* None reported	Mean age = 63 years, 39% female SAPS II score = 53, SOFA score = 11	Norepinephrine infusion 0.2 µg/kg/min and dobutamine 5 µg/kg/min (N = 169) Both adjusted according to MAP, pulmonary arterial wedge pressure, cardiac index and response to fluid challenge	• Time to haemodynamic success • Adverse events	• Risk of bias assessment – see figure 2
Levy, 1997	Single-centre randomized controlled trial, University hospital; France *Funding:* Supported by "Commi-tee of Clinical Research of Nancy Universi-ty Hospital" and by a grant of Lilly France(Saint-Cloud, France) *Declarations of interest:* Not declared	n = 30 Mean age = 54 years (Epinephrine group); 56 years (Norepinephrine/dobutamine group) Predominantly pulmonary infection APACHE II score: epinephrine group = 23; Norepinephrine/dobutamine group = 24 Adult surgical and medical participants with septic shock	Epinephrine and norepinephrine started at 0.3mg/kg per min and titrated to MAP > 80 mmHg Dobutamine was infused at a fixed dose of 5 µg/kg/min	• Mortality • Haemodynamics • Tonometry	• Risk of bias assessment – see figure 2 • Reporting error for arterial pH at 24 hours between groups found. No correction available on journal article webpage.
Seguin 2002	Single-centre randomized controlled trial, University hospital; France *Funding:* Not reported *Declarations of interest:* Not reported	n = 22 Adult participants with septic shock; unclear whether medical or surgical	Goal-directed epinephrine vs norepinephrine + fixed dobutamine (5 mcg/kg/min)	• Death	• For the mortality analysis: used data on undetermined mortality • It is unclear when participants died • Risk of bias assessment – see figure 2
Epinephrine vs norepinephrine + dopexamine					
Seguin 2006	Single-centre randomized controlled trial, University hospital; France *Funding:* Supported by Grant from Rennes University Hospital and Rennes 1 University, 2001 Clinical	n =22 Adult participants with septic shock (study authors' definition) Mean age = 66 years, 23% female SAPS II score = 54 SOFA score = 10	Norepinephrine (NE) infusion 0.2 mcg/kg/min ***plus*** Dopexamine (DX) infusion 0.5 mcg/kg/min • If cardiac index > 3 L/kg/min, NE increased by 0.2 mcg/kg/min every 3 minutes until MAP 70 to 80 mmHg	• Primary: Gastromucosal blood flow • Haemodynamics • 28-day mortality • 90-day mortality	• For the mortality analysis, 90-day mortality was used. • Risk of bias assessment – see figure 2

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
	Research Program, Rennes, France *Declarations of interest:* Not reported		• If cardiac index < 3 L/kg/min, DX increased by 0.5 mcg/kg/min every 3 minutes until MAP 70 to 80 mmHg vs Epinephrine infusion 0.2 mcg/kg/min. Increased by 0.2 mcg/kg/min every 3 minutes until MAP 70 to 80mm Hg		

Table 6. Excluded studies

Author, date		Title	Study type	Reason for exclusion
1	Zhao, 2012	Dopamine versus norepinephrine for septic shock: A systemic review.	Systematic Review	Wrong comparator
2	Zhou, 2014	Clinical trials comparing norepinephrine with vasopressin in patients with septic shock: a meta-analysis.	Systematic Review	Wrong comparator
3	Lu, 2021	Norepinephrine was superior in death risk reducing and hemodynamics compared to dopamine in treatment of patients with septic shock	Systematic Review	Wrong comparator
4	Yao, 2020	Clinical Efficiency of Vasopressin or Its Analogs in Comparison With Catecholamines Alone on Patients With Septic Shock: A Systematic Review and Meta-Analysis.	Systematic Review	Wrong comparator
5	Kochkin, 2020	Modern vasopressor therapy of septic shock (Review)	Systematic Review	Wrong study design
6	Gordon, 2021	A meta-analysis of early administration of vasopressor in septic shock: Is there mortality benefit?	Systematic Review	Wrong comparator
7	Soong, 2011	Vasopressin and terlipressin in the treatment of vasodilatory septic shock: A systematic review	Systematic Review	Wrong comparator
8	Belletti, 2015	The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials.	Systematic Review	Wrong comparator
9	Tan, 2016	Vasopressin and its analog terlipressin versus norepinephrine in the treatment of septic shock: A meta-analysis.	Systematic Review	Wrong comparator
10	Yin, 2018	Efficacy of norepinephrine, dopamine or vasopressor in the management of septic shock and severe sepsis: A meta-analysis.	Systematic Review	Wrong comparator
11	Serpa Neto, 2012	Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials.	Systematic Review	Wrong comparator
12	Vasu, 2012	Norepinephrine or dopamine for septic shock: systematic review of randomized clinical trials.	Systematic Review	Wrong comparator
13	Teja, 2020	Vasopressor Dosing in Septic Shock Clinical Trials: A Systematic Review and Ecologic Study.	Systematic Review	Wrong outcomes
14	Roumpf, 2019	Does the Addition of Vasopressin to Catecholamine Vasopressors Affect Outcomes in Patients With Distributive Shock?	Systematic Review	Wrong comparator
15	Nagendran, 2019	Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials.	Systematic Review	Wrong comparator
16	Sedhai, 2022	Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis.	Systematic Review	Wrong comparator
17	Rudis, 1996	Is it time to reposition vasopressors and inotropes in sepsis?	Pooled data analysis	Wrong study design
18	Li, 2020	Effect of terlipressin on prognosis of adult septic shock patients: a Meta-analysis	Systematic Review	Wrong intervention
19	Zhou, 2013	Effectiveness of norepinephrine versus dopamine for septic shock: a meta analysis	Systematic Review	Wrong comparator
20	Zhu, 2019	Terlipressin for septic shock patients: a meta-analysis of randomized controlled study.	Systematic Review	Wrong intervention
21	Morelli, 2008a	Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study	RCT in Gamper, 2016	Wrong intervention
22	Morelli, 2008b	Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial.	RCT in Gamper, 2016	Wrong intervention
23	Morelli 2009	Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study.	RCT in Gamper, 2016	Wrong intervention
24	Svoboda 2012	Terlipressin in the treatment of late phase catecholamine-resistant septic shock. Hepato-Gastroenterology	RCT in Gamper, 2016	Wrong intervention
25	Yildizdas 2008	Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. Intensive Care Medicine	RCT in Gamper, 2016	Wrong intervention
26	Hajjar 2019	Vasopressin Versus Norepinephrine for the Management of Septic Shock in Cancer Patients: the VANCS II Randomized Clinical Trial	RCT	Wrong comparator
27	Permpikul 2017	Early norepinephrine administration vs. standard treatment during severe sepsis/septic shock resuscitation: a randomized control trial	RCT	Wrong indication
28	Fe 2017	Vasopressin or epinephrine as a second vasopressor in septic shock: a pilot study	Pilot study	Wrong study design
29	Nadler 2016	Vasopressin as a Single Vasopressor Agent in Patients with Septic Shock	Narrative review	Wrong study design
30	Clem 2016	Norepinephrine and vasopressin vs norepinephrine alone for septic shock: randomized controlled trial	RCT	Wrong comparator
31	Zambolim 2018	Vasopressin versus norepinephrine for the management of septic shock in cancer patients (VANCS II)	RCT	Wrong comparator
32	Roy 2016	Attempting to define and refine vasopressin use in septic shock: the VANISH trial	Narrative review	Wrong study design
33	Du 2015	Comparison of clinical effect of dopamine and norepinephrine in the treatment of septic shock	RCT	Wrong comparator
34	Einav 2021	Vasopressor and inotrope treatment for septic shock: An umbrella review of reviews.	Non-RCT	Wrong study design
35	Young 2019	Vasopressin in septic shock: what we know and where to next?	Non-RCT	Wrong study design
36	Hernández 2019	Norepinephrine in septic shock.	Narrative review	Wrong comparator
37	Ammar 2019	Optimal norepinephrine-equivalent dose to initiate epinephrine in patients with septic shock.	Non-RCT	Wrong study design
38	Teja 2022	First-Line Vasopressor Use in Septic Shock and Route of Administration: An Epidemiologic Study.	Non-RCT	Wrong study design
39	Nguyen 2017	Comparative Effectiveness of Second Vasoactive Agents in Septic Shock Refractory to Norepinephrine.	Non-RCT	Wrong study design
40	Aso 2022	Vasopressin versus epinephrine as adjunct vasopressors for septic shock	Non-RCT	Wrong study design
41	Feldheiser 2021	Vasopressor effects on venous return in septic patients: a review.	Letter	Wrong study design

42	Hammond 2018	Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock.	RCT	Wrong comparator
43	Li 2019	How to use vasoactive drugs in septic shock.	Narrative review	Non- English article
44	Annane 2015	Evidence to Practice Gap: The Case of Dopamine.	Narrative review	Wrong study design
45	Russell 2018	Vasopressin versus norepinephrine in septic shock: a propensity score matched efficiency retrospective cohort study in the VASST coordinating center hospital.	Non-RCT	Wrong study design
46	Sedhai 2022	Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis.	Non-RCT	Wrong study design
47	Mazandaran University of Medical Sciences 2020	Comparison Dopamine and Nor-epinephrine on End tidal carbon dioxide pressure in patients with septic shock	RCT	Wrong outcomes
48	Albanese 2005	Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study	RCT in Gamper, 2016	Wrong intervention
49	Boccara 2003	Terlipressin versus norepinephrine to correct refractory arterial hypotension after general anesthesia in patients chronically treated with renin-angiotensin system inhibitors	RCT in Gamper, 2016	Wrong intervention
50	Choong 2009	Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial	RCT in Gamper, 2016	Wrong intervention
51	De Backer 2010	Comparison of dopamine and norepinephrine in the treatment of shock	RCT in Gamper, 2016	Wrong intervention
52	Dünser 2003	Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study	RCT in Gamper, 2016	Wrong intervention
53	Han 2012	[A clinical study of pituitrin versus norepinephrine in the treatment of patients with septic shock].	RCT in Gamper, 2016	Wrong intervention
54	Han 2013	Terlipressin decreases vascular endothelial growth factor expression and improves oxygenation in patients with acute respiratory distress syndrome and shock	RCT in Gamper, 2016	Wrong intervention
55	Jain 2010	Comparison of phenylephrine and norepinephrine in the management of dopamine-resistant septic shock.	RCT in Gamper, 2016	Wrong intervention
56	Lauzier 2006	Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial	RCT in Gamper, 2016	Wrong intervention
57	Levy 2011	Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study	RCT in Gamper, 2016	Wrong intervention
58	Luckner 2006	Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome	RCT in Gamper, 2016	Wrong intervention
59	Malay1999	Low-dose vasopressin in the treatment of vasodilatory septic shock	RCT in Gamper, 2016	Wrong intervention
60	Marik 1994	The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis	RCT in Gamper, 2016	Wrong intervention
61	Martin 1993	Norepinephrine or dopamine for the treatment of hyperdynamic septic shock	RCT in Gamper, 2016	Wrong intervention
62	Mathur 2007	Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography	RCT in Gamper, 2016	Wrong intervention
63	Patel 2010	Efficacy and safety of dopamine versus norepinephrine in the management of septic shock	RCT in Gamper, 2016	Wrong intervention
64	Ruokonen 1993	Regional blood flow and oxygen transport in septic shock	RCT in Gamper, 2016	Wrong intervention
65	Russell 2008	Vasopressin versus norepinephrine infusion in patients with septic shock	RCT in Gamper, 2016	Wrong intervention
66	Svoboda 2012	Terlipressin in the treatment of late phase catecholamine-resistant septic shock	RCT in Gamper, 2016	Wrong intervention
67	Yildizdas 2008	Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children	RCT in Gamper, 2016	Wrong intervention

Note: The table lists 48 excluded records described in the PRISMA flow diagram (**Appendix 2**) and 19 RCTs excluded from the 2016 Gamper *et al*. systematic review.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** • **Mortality** High [ ] Moderate [ ] Low [X] Very low [ ] • **Time to MAP goal (24h without vasopressor use)** High [ ] Moderate [ ] Low [ ] Very low [X] • **Time to MAP stabilisation** High [ ] Moderate [ ] Low [ ] Very low [X] • **Vasopressor free days (to day 28):** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	• **Mortality:** *low certainty evidence due to serious* risk of bias (concerns of blinding of investigators and assessors) and serious imprecision. • **Time to MAP goal** (24 hours without vasopressor use)**:** *very low certainty evidence* due to serious risk of bias (possible attrition) and for serious imprecision. • **Time to MAP stabilisation** (MAP 70 to 80 mmHg or clinician discretion): *very low certainty* due to serious risk of measurement bias, serious inconsistency (uncertainty regarding the definition of MAP stabilisation) and very serious imprecision. • **Vasopressor free days (to day 28):** *very low certainty evidence* due to serious imprecision, serious risk of bias (possible attrition) and serious inconsistency (inconsistent comparators).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** • **Mortality** Large [ ] Moderate [ ] Small [ ] None [X] • **Time to MAP goal (24h without vasopressor use)** Large [ ] Moderate [ ] Small [X] None [ ] • **Time to MAP stabilisation (70 to 80 mmHg or clinician discretion)** Large [ ] Moderate [ ] Small [X] None [ ] • **Time to MAP goal (24h without vasopressor use)** Large [ ] Moderate [ ] Small [ ] None [X]	• **Mortality:** Noradrenaline (norepinephrine) vs adrenaline (epinephrine) — 131/289 (45.3%) vs 124/171 (45.8%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%; 5 fewer deaths per 1000 patients treated (from 78 fewer to 82 more)), • **Time to MAP goal:** Noradrenaline (norepinephrine) vs adrenaline (epinephrine) — Median 50.0 h vs 35.1 h — HR 0.81; 95% CI 0.59 to 1.12; p= 0.18. Based on a probability of 63.9% to achieve the MAP goal by 48 hours with epinephrine (adrenaline), 77 fewer patients per 1000 (from 187 fewer to 42 more) would achieve MAP goal when comparing noradrenaline (norepinephrine)-treated patients to adrenaline (epinephrine)-treated patients. • **Time to MAP stabilisation (70 to 80 mmHg or clinician discretion):** Noradrenaline may increase/have little to no effect on time to MAP stabilisation — Mean difference (MD) 7.17 minutes (from 16.74 fewer to 31.08 more). • **Vasopressor free days (to day 28):** Noradrenaline may reduce/have little to no effect on vasopressor free days — MD -0.05 days (from 4.07 fewer to 3.96 more)
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** • **Lactate concentrations** High [ ] Moderate [ ] Low [ ] Very low [X] • **Arrhythmias (any)** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• **Lactate concentrations:** *very low certainty evidence* due to very serious risk of bias and serious imprecision, which is considered to be clinically insignificant. • **Arrhythmias (any type):** *very low certainty evidence* due to serious risk of bias (possible attrition) and very serious imprecision.

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
• Lactate concentrations
Large [ ] Moderate [ ] Small [ ] None [X]
• Arrhythmias (any)
Large [ ] Moderate [ ] Small [ ] None [X]</td><td>• Lactate concentrations: Noradrenaline may reduce/have no effect on lactate concentration — MD - 0.16 mmol/l (95% CI -1.14 fewer to 0.82 more).
• Arrhythmias (any type): adrenaline (epinephrine) [30/184 (16.3%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [31/176 (17.6%)], RR 0.92 (95% CI 0.59 to 1.45).</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control or Uncertain [X]</td><td>There is uncertainty as to whether desirable effects outweigh undesirable effects, noting that increase in lactate concentrations may not be clinically important.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available: n/a</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [ ] No [X] Uncertain [ ]</td><td>Noradrenaline has recently been registered with SAHPRA, however, there are concerns regarding cost.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines/ treatment course:
<table>
<tr><th>Medicine</th><th>Tender price *</th><th>SEP 100%</th><th>SEP 60%</th></tr>
<tr><td>Adrenaline (Pharma-Q Adrenaline 1 Amp 1 mg/ml)*</td><td>R 4.00</td><td>R 36.11 (10 units)</td><td>R 21.67</td></tr>
<tr><td>Noradrenaline (BGM-noradrenaline 10 Amps 2mg/ml; Available through S21 process – private sector price**</td><td>n/a</td><td>R 434.70 (10 units)***</td><td>n/a</td></tr>
<tr><td>Noradrenaline (Sinora – noradrenaline 10 Amps 4mg/4ml)***</td><td>n/a</td><td>R 2564.11</td><td>R 1538.40</td></tr>
</table>
* Contract circular HP06-2021SVP
**S21 private sector price sourced from MediKredit
***Noradrenaline-Sinora Single exit price (14 August 2023)
<table>
<tr><th>Medicine</th><th>Days treated (Median & IQR)¥</th><th>Total treatment dose (mg) (Median & IQR)¥</th><th>Per patient cost (Median & IQR) (Rand)</th></tr>
<tr><td>Adrenaline</td><td>2 (1, 11)</td><td>40.3 (23.0, 86.7)</td><td>R 161.28 (R 92.16, R 346.94)</td></tr>
<tr><td>Noradrenaline (BGM-noradrenaline)</td><td>4 (2, 21)</td><td>56.2 (40.3, 130.4)</td><td>R 1 220.64 (R 876.36, R 2 834.59)</td></tr>
<tr><td>Noradrenaline (Sinora)</td><td>4 (2, 21)</td><td>56.2 (40.3, 130.4)</td><td>R 3 600.01 (R 2 584.62, R 8 360.02)</td></tr>
</table>
¥ Based on data from Myburgh et al (2008)

Other resources: n/a</td></tr>
</table>

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no local survey data assessing the preferences and acceptability of healthcare workers or patients. However, it was reported that use of noradrenaline is preferred in the private sector.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	There is no local survey data assessing equity. Additionally, there are concerns regarding price.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	24 April 2023 *(Updated 6 October 2023)*	RM, TDL, SD, RG	The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for the management of septic shock in adults. The evidence is limited and uncertain.

References:

- Agrawal A, Gupta A, Consul S, Shastri P. Comparative study of dopamine and norepinephrine in the management of septic shock. Saudi J Anaesth. 2011 Apr;5(2):162-6. doi: 10.4103/1658-354X.82784.
- Akinaga J, Lima V, Kiguti LR, Hebeler-Barbosa F, Alcántara-Hernández R, García-Sáinz JA, Pupo AS. Differential phosphorylation, desensitization, and internalization of α1A-adrenoceptors activated by norepinephrine and oxymetazoline. Mol Pharmacol. 2013 Apr;83(4):870-81. doi: 10.1124/mol.112.082313. Epub 2013 Jan 30.
- Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007;370(9588):676-84
- Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015 Aug 3;10(8):e0129305. doi: 10.1371/journal.pone.0129305.
- 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. J Crit Care. 2017 Feb;37:91-98. doi: 10.1016/j.jcrc.2016.08.010. Epub 2016 Aug 13.
- Bollaert PE, Bauer P, Audibert G, Lambert H, Larcan A. Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock. Chest. 1990 Oct;98(4):949-53. doi: 10.1378/chest.98.4.949.
- Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010 Dec 14;182(18):E839-42. doi: 10.1503/cmaj.090449.
- Chen C, Pang L, Wang Y, Wen T, Yu W, Yue X, Rong Y, Liao W. Combination era, using combined vasopressors showed benefits in treating septic shock patients: a network meta-analysis of randomized controlled trials. Ann Transl Med. 2019 Oct;7(20):535. doi: 10.21037/atm.2019.09.134.
- Cheng L, Yan J, Han S, Chen Q, Chen M, Jiang H, Lu J. Comparative efficacy of vasoactive medications in patients with septic shock: a network meta-analysis of randomized controlled trials. Crit Care. 2019 May 14;23(1):168. doi: 10.1186/s13054-019-2427-4.
- Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, 2023. Available from www.covidence.org
- Day NP, Phu NH, Bethell DP, Mai NT, Chau TT, Hien TT, White NJ. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. Lancet. 1996 Jul 27;348(9022):219-23. doi: 10.1016/s0140-6736(96)09096-4. Erratum in: Lancet 1996 Sep 28;348(9031):902.
- De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al.. Comparison of Dopamine and Norepinephrine in the Treatment of Shock. New England Journal of Medicine. 2010;362(9):779–89.
- De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med. 2003 Jun;31(6):1659-67. doi: 10.1097/01.CCM.0000063045.77339.B6.
- Desjars P, Pinaud M, Bugnon D, Tasseau F. Norepinephrine therapy has no deleterious renal effects in human septic shock. Crit Care Med. 1989 May;17(5):426-9. doi: 10.1097/00003246-198905000-00010. PMID: 2520533.
- Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD. A reappraisal of norepinephrine therapy in human septic shock. Crit Care Med. 1987 Feb;15(2):134-7. doi: 10.1097/00003246-198702000-00011.
- Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y. Epub 2021 Oct 2.
- Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2016 Feb 15;2(2):CD003709.
- Gregory JS, Bonfiglio MF, Dasta JF, Reilley TE, Townsend MC, Flancbaum L. Experience with phenylephrine as a component of the pharmacologic support of septic shock. Crit Care Med. 1991 Nov;19(11):1395-400. doi: 10.1097/00003246-199111000-00016.
- Hesselvik JF, Brodin B. Low dose norepinephrine in patients with septic shock and oliguria: effects on afterload, urine flow, and oxygen transport. Crit Care Med. 1989 Feb;17(2):179-80. doi: 10.1097/00003246-198902000-00016.

- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.
- Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, Heard SO, Martin C, Napolitano LM, Susla GM, Totaro R, Vincent JL, Zanotti-Cavazzoni S. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004 Sep;32(9):1928-48. doi: 10.1097/01.ccm.0000139761.05492.d6.
- Jiang L, Sheng Y, Feng X, Wu J. The effects and safety of vasopressin receptor agonists in patients with septic shock: a meta-analysis and trial sequential analysis. Crit Care. 2019 Mar 14;23(1):91. doi: 10.1186/s13054-019-2362-4.
- Le Tulzo Y, Seguin P, Gacouin A, Camus C, Suprin E, Jouannic I, Thomas R. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med. 1997 Jun;23(6):664-70. doi: 10.1007/s001340050391.
- Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Medicine 1997;23:282-7
- Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Critical Care Medicine 2011;39(3):450-5
- Mackenzie SJ, Kapadia F, Nimmo GR, Armstrong IR, Grant IS. Adrenaline in treatment of septic shock: effects on haemodynamics and oxygen transport. Intensive Care Med. 1991;17(1):36-9. doi: 10.1007/BF01708407.
- Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA. 1994 Nov 2;272(17):1354-7.
- Martin C, Eon B, Saux P, Aknin P, Gouin F. Renal effects of norepinephrine used to treat septic shock patients. Crit Care Med. 1990 Mar;18(3):282-5. doi: 10.1097/00003246-199003000-00007.
- Martin C, Perrin G, Saux P, Papazian L, Gouin F. Effects of norepinephrine on right ventricular function in septic shock patients. Intensive Care Med. 1994 Jul;20(6):444-7. doi: 10.1007/BF01710657.
- Martin C, Saux P, Eon B, Aknin P, Gouin F. Septic shock: a goal-directed therapy using volume loading, dobutamine and/or norepinephrine. Acta Anaesthesiol Scand. 1990 Jul;34(5):413-7. doi: 10.1111/j.1399-6576.1990.tb03114.x.
- Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. Crit Care Med. 2000 Aug;28(8):2758-65. doi: 10.1097/00003246-200008000-00012.
- Meadows D, Edwards JD, Wilkins RG, Nightingale P. Reversal of intractable septic shock with norepinephrine therapy. Crit Care Med. 1988 Jul;16(7):663-6. doi: 10.1097/00003246-198807000-00003.
- Meier-Hellmann A, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L. Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med. 1997 Mar;25(3):399-404. doi: 10.1097/00003246-199703000-00005. PMID: 9118653.
- Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, et al; GRADE Working Group. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Res Policy Syst. 2018 May 29;16(1):45. doi: 10.1186/s12961-018-0320-2.
- Moran JL, O'Fathartaigh MS, Peisach AR, Chapman MJ, Leppard P. Epinephrine as an inotropic agent in septic shock: a dose-profile analysis. Crit Care Med. 1993 Jan;21(1):70-7. doi: 10.1097/00003246-199301000-00015.
- Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Medicine 2008;34(12):2226-34.
- Nagendran M, Maruthappu M, Gordon AC, Gurusamy KS. Comparative safety and efficacy of vasopressors for mortality in septic shock: A network meta-analysis. J Intensive Care Soc. 2016 May;17(2):136-145. doi: 10.1177/1751143715620203. Epub 2015 Dec 17.
- National Department of Health. Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List, 2019. Available at: https://knowledgehub.health.gov.za/elibrary/hospital-level-adults-standard-treatment-guidelines-and-essential-medicines-list-2nd
- Oba Y, Lone NA. Mortality benefit of vasopressor and inotropic agents in septic shock: a Bayesian network meta-analysis of randomized controlled trials. J Crit Care. 2014 Oct;29(5):706-10. doi: 10.1016/j.jcrc.2014.04.011. Epub 2014 Apr 26.
- Overgaard CB, DžAvíK V. Inotropes and Vasopressors. Circulation. 2008;118(10):1047–56.

- Patel GP, Grahe JS, Sperry M, Singla S, Elpern E, Lateef O, Balk RA. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock. 2010 Apr;33(4):375-80. doi: 10.1097/SHK.0b013e3181c6ba6f.
- Redl-Wenzl EM, Armbruster C, Edelmann G, Fischl E, Kolacny M, Wechsler-Fördös A, Sporn P. The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. Intensive Care Med. 1993;19(3):151-4. doi: 10.1007/BF01720530.
- Regnier B, Rapin M, Gory G, Lemaire F, Teisseire B, Harari A. Haemodynamic effects of dopamine in septic shock. Intensive Care Med. 1977 Aug;3(2):47-53. doi: 10.1007/BF01683060.
- Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
- Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020 Jan 18;395(10219):200-211. doi: 10.1016/S0140-6736(19)32989-7.
- Ruslan MA, Baharuddin KA, Noor NM, Yazid MB, Noh AYM, Rahman A. Norepinephrine in Septic Shock: A Systematic Review and Meta-analysis. West J Emerg Med. 2021 Feb 16;22(2):196-203. doi: 10.5811/westjem.2020.10.47825.
- Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017 Jan;81:101-110. doi: 10.1016/j.jclinepi.2016.09.009. Epub 2016 Oct 3.
- Seguin P, Laviolle B, Guinet P, Morel I, Malledant Y, Bellissant E. Dopexamine and norepinephrine versus epinephrine on gastric perfusion in patients with septic shock: a randomized study [NCT00134212]. Critical Care 2006;10(1)(R32):1-8
- Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008.
- Shields SH, Holland RM. Pharmacology of Vasopressors and Inotropes. In: Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Cline DM. eds. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8e. McGraw Hill; 2016. Accessed March 12, 2023. https://accessemergencymedicine.mhmedical.com/content.aspx?bookid=1658&sectionid=109426988
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287.
- Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care. 2019 May 31;23(1):196. doi: 10.1186/s13054-019-2478-6.
- Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec 19;14:135.
- Wilson W, Lipman J, Scribante J, Kobilski S, Lee C, Krause P, Cooper J, Barr J. Septic shock: does adrenaline have a role as a first-line inotropic agent? Anaesth Intensive Care. 1992 Nov;20(4):470-4. doi: 10.1177/0310057X9202000413.
- Yamazaki T, Shimada Y, Taenaka N, Oshumi H, Takezawa J, Yoshiya I. Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. Crit Care Med. 1982 Jul;10(7):432-5. doi: 10.1097/00003246-198207000-00003.
- Zhou F, Mao Z, Zeng X, Kang H, Liu H, Pan L, Hou PC. Vasopressors in septic shock: a systematic review and network meta-analysis. Ther Clin Risk Manag. 2015 Jul 14;11:1047-59. doi: 10.2147/TCRM.S80060.
- Zhou SX, Qiu HB, Huang YZ, Yang Y, Zheng RQ. Effects of norepinephrine, epinephrine, and norepinephrine-dobutamine on systemic and gastric mucosal oxygenation in septic shock. Acta Pharmacol Sin. 2002 Jul;23(7):654-8.

Appendix 1: Search Strategies

A: PubMed

1) Date: 7 October 2022

Search	Query	Results
#11	Search: #3 AND #6 Filters: Meta-Analysis, Systematic Review	113
#10	Search: #3 AND #6 Filters: Systematic Review	89
#9	Search: #7 AND #8	2,267
#7	Search: #3 AND #6	5,269
#8	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,844,207
#6	Search: #4 OR #5	383,954
#5	Search: noradrenaline[tiab] OR norepinephrine[tiab] OR levonor[tiab] OR levophed[tiab] OR levarterenol[tiab] OR arterenol[tiab] OR epinephrine[tiab] OR dopamine[tiab] OR intropin[tiab] OR adrenaline[tiab] OR vasopressin*[tiab] OR lypressin[tiab] OR felypressin[tiab] OR ornipressin[tiab] OR terlipressin[tiab] OR vasoconstrictor*[tiab] OR pitressin[tiab] OR vasopressor*[tiab]	306,406
#4	Search: norepinephrine[mh] OR vasoconstrictor agents[mh] OR epinephrine[mh] OR dopamine[mh] OR vasopressins[mh]	237,850
#3	Search: #1 OR #2	167,808
#2	Search: septic shock[tiab] OR toxic shock[tiab] OR endotoxin shock[tiab] OR endotoxic shock[tiab] OR severe sepsis[tiab] OR septicemia*[tiab] OR septiceamia*[tiab] OR blood stream infection*[tiab] OR bloodstream infection*[tiab] OR sepsis syndrome[tiab]	68,896
#1	Search: systematic inflammatory response syndrome[mh] OR sepsis[mh] OR shock, septic[mh]	137,718

PubMed

2) Date: 23 September 2022

Search	Query	Results
#10	Search: #3 AND #6 Filters: Meta-Analysis, Systematic Review	37
#9	Search: #7 AND #8	857
#8	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,831,580
#7	Search: #3 AND #6	1,774

Search	Query	Results
#6	Search: #4 OR #5	81,014
#5	Search: septic shock[tiab] OR toxic shock[tiab] OR endotoxin shock[tiab] OR endotoxic shock[tiab] OR severe sepsis[tiab] OR septicemia*[tiab] OR blood stream infection*[tiab] OR bloodstream infection*[tiab]	68,122
#4	Search: shock, sepsis[mh]	34,792
#3	Search: #1 OR #2	127,718
#2	Search: noradrenaline[tiab] OR norepinephrine[tiab] OR levonor[tiab] OR levophed[tiab] OR levarterenol[tiab] OR arterenol[tiab]	98,409
#1	Search: norepinephrine[mh]	87,035

B: Epistemonikos

Date: 7 October 2022

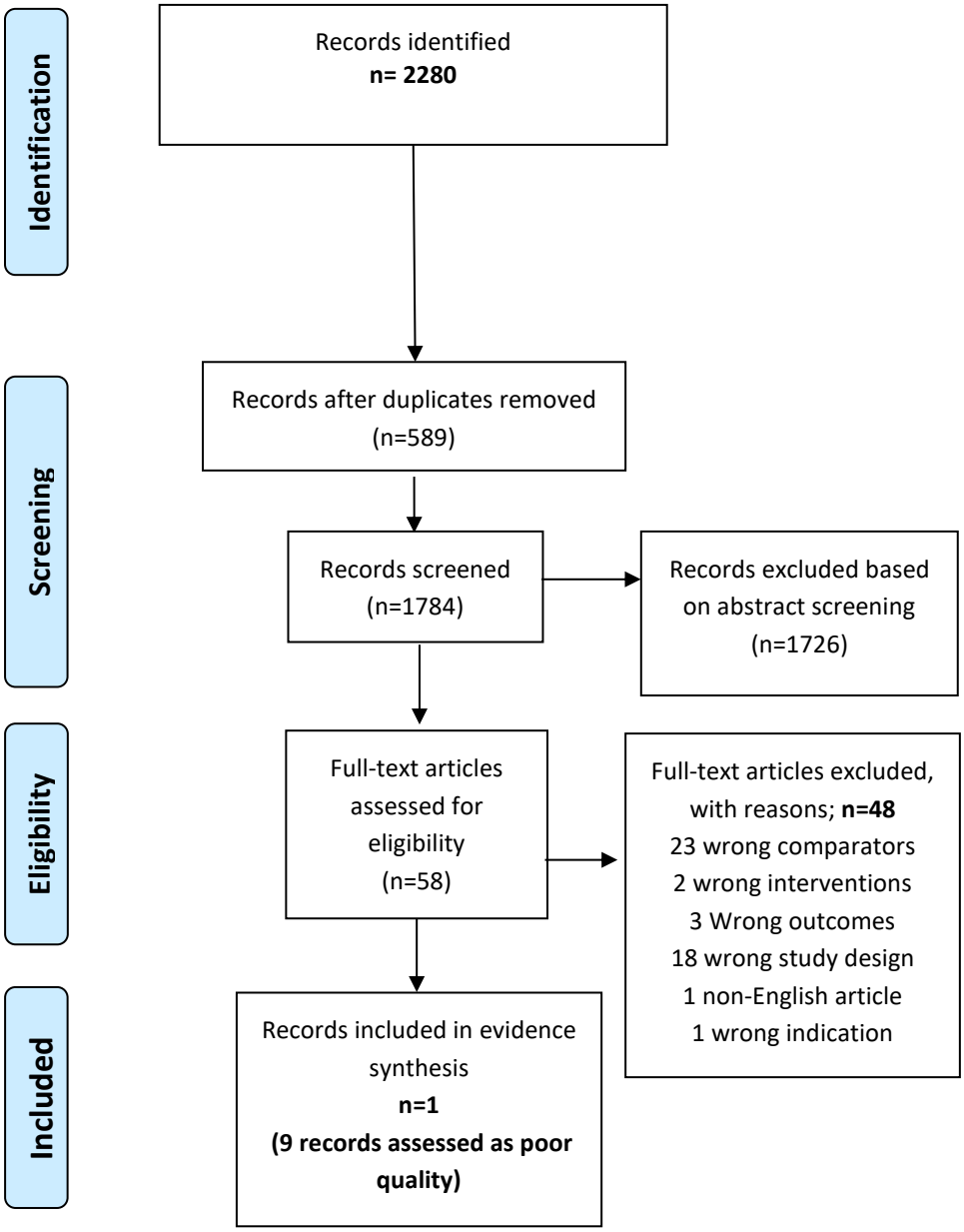
#	Query	Results
5	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*)) **Filters: Publication type = Primary Study**	634
4	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*)) **Filters: Publication type = Systematic Review**	170
3	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR	823

	arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*))	
2	(title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*))	16,934
1	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections"))	22,555

C: Health technology assessment databases

Databases that were searched included NICE, Canada HTA, EUNETHTA and INATHTA, Google scholar.

Appendix 2: PRISMA flowchart



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: AGREE II appraisal summaries

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
Surviving Sepsis Guidelines, 2021	83%	58%	56%	75%	21%	54%	67%
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock, 2020	92%	89%	83%	75%	44%	92%	67%
Clinical practice guidelines for sepsis and septic shock in adults in the Philippines, 2020	72%	56%	39%	78%	60%	38%	58%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 4: Appraisal of previous surviving sepsis campaign guidelines that recommend norepinephrine vs. epinephrine therapy in patients with septic shock

Surviving sepsis guideline title (year published)	Recommendations	Cited evidence	Comment
Hemodynamic support in septic shock (2001)	• "Norepinephrine and dopamine preferred over epinephrine to correct hypotension in septic shock (grade E evidence)".	• "Norepinephrine markedly improves MAP and glomerular filtration. This is particularly true in the high output-low resistance state of many septic shock patients." • "A few studies have used norepinephrine as the only adrenergic agent to correct sepsis-induced hemodynamic abnormalities" – Fukuoka, 1989; Martin, 1990a; Martin, 1993; Ruokonen, 1993; Marik, 1994 • "Renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may effectively optimize renal blood flow and renal vascular resistance" - Redl-Wenzl, 1993; Winslow, 1973; Marik, 1994 • "Norepinephrine is probably more effective than dopamine at reversing hypotension in septic shock patients" - Martin, 1993 • "Other studies, however, have observed no significant changes in either cardiac output or stroke volume index after the use of norepinephrine in the presence of a significant increase in vascular resistance, suggesting that norepinephrine is exerting α_1-receptor agonist effects." - Desjars, 1987; Meadows, 1988; 1989; Hesselvik, 1989; Martin, 1990; Martin, 1994 • "Epinephrine has detrimental effects on splanchnic blood flow and causes transient decreases in pH and increases in the pCO2 gap" - Levy, 1997; Meier-Hellmann, 1997 • "Epinephrine administration has been associated with increases in systemic and regional lactate concentrations." - Levy, 1997; Wilson, 1992; Meier-Hellman, 1997 • "Because of its negative effects on gastric blood flow and blood lactate concentrations its use should be limited."	• Imbalanced presentation of evidence justifying preferred use of norepinephrine over epinephrine. • Low quality evidence informed preferred use of norepinephrine over epinephrine: Grade E evidence = Level IV or V evidence; Non-randomized studies, historical control studies, uncontrolled studies, case series, and expert opinion evidence
Surviving sepsis campaign guidelines (2004)	• "Either norepinephrine or dopamine (through a central line as soon as available) is the first-	• "Although there is no high-quality primary evidence to recommend one catecholamine over another, human and animal studies suggest some	• Preference for norepinephrine over epinephrine appears to depend on differences in metabolic effects like

	choice vasopressor agent to correct hypotension in septic shock."	advantages of norepinephrine and dopamine over epinephrine (potential tachycardia, possibly disadvantageous effects on splanchnic circulation) and phenylephrine (decrease in stroke volume)." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared to dopamine." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003	lactate, as well as relatively preserved splanchnic circulation in patients with severe shock on norepinephrine compared to those on epinephrine. However, none of the referenced studies showed improvements in clinical outcomes or mortality.
Surviving sepsis campaign guidelines (2008)	• "We recommend either norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available) (grade 1C)." • "We suggest that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (grade 2C)." • "We suggest that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine (grade 2B)."	• "There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock." – Martin, 1994; Martin, 2000; De Backer, 2003; Day, 1996; Le Tulzo, 1997; Bollaert, 1990; Zhou, 2002; Mackenzie, 1991; Moran, 1993; Yamazaki, 1982; Gregory, 1991; Annane, 2007 • "Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine." – No references cited	• Recommendation for norepinephrine in preference over epinephrine more nuanced than previous guidelines, and is largely made on theoretical/haemodynamic response data rather than evidence with clinical outcomes. • Strength of recommendation grading: Grade 1 = Strong recommendation, Grade 2 = Weak recommendation. • Quality of evidence grading: High quality = grade A, moderate quality = grade B, low quality = grade C
Surviving sepsis campaign guidelines (2012)	• "We recommend that vasopressor therapy initially target a MAP of 65 mmHg (grade 1C)."	• "Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases MAP due to	• "Reason for preference of norepinephrine over epinephrine is largely based on theoretical

	• "We recommend norepinephrine as the first-choice vasopressor (grade 1B)." • "We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B)." • "Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG)." • "Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsisinduced hypotension, and vasopressin doses higher than 0.03–0.04 U/min should be reserved for salvage therapy (failure to achieve an adequate MAP with other vasopressor agents) (UG)." • "We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C)."	its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock." – • "Information from five randomized trials (n = 1,993 patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock." - Martin, 2000; Ruokonen, 1993; Marik, 1994; Patel, 2010; De Backer, 2010 • "Although some human and animal studies suggest epinephrine has deleterious effects on splanchnic circulation and produces hyperlactatemia, no clinical evidence shows that epinephrine results in worse outcomes, and it should be the first alternative to norepinephrine. Indeed, information from 4 randomized trials (n = 540) comparing norepinephrine to epinephrine found no evidence for differences in the risk of dying (RR, 0.96; CI, 0.77–1.21; fixed effect; I^2 = 0%)." - Levy, 1997; Annane, 2007; Seguin, 2002; Myburgh, 2008 • "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscles' β2-adrenergic receptors and thus may prevent the use of lactate clearance to guide resuscitation." - No references cited	considerations." • "Despite making a "soft" recommendation for norepinephrine over other vasopressors, the recommendation is assessed as grade 1B. The referenced clinical outcome data that congruent with this assessment are from norepinephrine vs dopamine studies." • "Four intervention parallel cohort studies failed to show significant differences between norepinephrine and epinephrine, with no difference in mortality shown by an RR of 0.96."
Surviving sepsis campaign guidelines (2016)	• "We recommend norepinephrine as the firstchoice vasopressor (strong recommendation, moderate quality of evidence)." • We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min)	• "Human and animal studies suggest that the infusion of epinephrine may have deleterious effects on the splanchnic circulation and produces hyperlactatemia. However, clinical trials do not demonstrate worsening of clinical outcomes. One RCT comparing norepinephrine to epinephrine demonstrated no difference in mortality but an increase in adverse drug-related events with epinephrine." - Myburgh, 2008 • "A meta-analysis of four randomized trials (n = 540) comparing norepinephrine to epinephrine found no significant difference in mortality (RR 0.96; CI 0.77–1.21; low-quality evidence)." - Avni, 2015	• Blinding in cited RCT by Myburgh, 2008 may have been at risk of compromise: Epinephrine was already thought to increase heart rate and lactic acidosis compared to norepinephrine prior to study, & these were the two commonest reasons for relative withdrawal from study, after which patients would receive open-label norepinephrine which was preferred and recommended by 3 previous editions of SSC guidelines.

	(weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage."	• "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β2-adrenergic receptors and thus may preclude the use of lactate clearance to guide resuscitation." - No reference cited	
Surviving sepsis campaign guidelines (2021)	• For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors (Strong recommendation)." • "For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine (Weak recommendation, low-quality evidence)."	• "Quality of evidence used to make recommendation by drug: Dopamine - High quality evidence; Epinephrine - Low quality evidence; Vasopressin - Moderate-quality evidence" • "In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine." - No references cited • "Potential adverse effects of epinephrine include arrhythmias and impaired splanchnic circulation." - De Backer, 2003 • "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β-2 adrenergic receptors, making the use of serum lactate to guide resuscitation challenging." - Presumably Myburgh, 2008 (see comment). • "A randomized blinded study comparing epinephrine with norepinephrine in patients with shock showed no difference in 90-day mortality (HR, 0.88; 95% CI, 0.63–1.25) and vasopressor-free days (Myburgh, 2008). The panel issued a strong recommendation for norepinephrine as the first-line agent over other vasopressors." • "Epinephrine has been suggested as second or third-line vasopressor for patients with septic shock...With the use of norepinephrine at elevated concentrations, the α_1 receptors may already be saturated and downregulated." - Akinaga, 2013 • "The use of another drug such as epinephrine that targets the same receptors may be of limited utility and vasopressin could be more adequate in patients with shock unresponsive to norepinephrine. In an indirect comparison, a network meta-analysis did not find any significant difference between epinephrine and vasopressin	• Unclear what evidence/rationale was used to make a strong recommendation for norepinephrine in the absence of long-term, clinically relevant differences in efficacy or safety. • There is no clinical data available to corroborate an increased risk of arrhythmias using epinephrine in septic shock. Cited text by De Backer et al (2003) assess effects of epinephrine, norepinephrine, and dopamine on splanchnic circulation. Epinephrine has improved cardiac index compared to other agents in moderate and severe shock, but impaired splanchnic circulation in severe shock compared to norepinephrine.

		in terms of mortality (RR, 0.94; 95% CI, 0.47–1.88). Epinephrine might be useful in refractory septic shock patients with myocardial dysfunction.” - Belletti, 2017	

Appendix 5: AMSTAR assessment of systematic reviews

No.	Criteria	Yes (Y)/ Partial Yes (PY)/ No (N)									
		Belletti 2017	Oba 2015	Nagendran 2016	Cheng 2019	Ruslan 2021	Gamper 2016	Avni 2015	Zhou 2015	Chen 2019	Jiang 2019
1	Research questions and inclusion criteria for the review included the components of PICO	PY	PY	Y	Y	Y	Y	Y	Y	N	Y
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	PY	PY	PY	N	PY	PY	N	N	N	Y
3	Review authors explained selection of the study designs for inclusion in the review	N	N	N	N	N	N	N	N	N	N
4*	Review authors used a comprehensive literature search strategy	PY	PY	PY	PY	N	Y	PY	PY	PY	Y
5	Review authors perform study selection in duplicate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Review authors perform data extraction in duplicate	Y	N	Y	N	Y	Y	Y	Y	N	Y
7*	Review authors provided a list of excluded studies and justify the exclusions	Y	N	N	N	N	Y	N	N	N	Y
8	Review authors described the included studies in adequate detail	Y	y	PY	Y	Y	Y	Y	PY	N	Y
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Y	PY	Y	Y	Y	Y	Y	PY	PY	Y
10	Review authors reported on the sources of funding for the studies included in the review.	N	N	Y	N	N	Y	N	N	N	N
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	N	N	Y	N	N	Y	N	N	N	N
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Y	PY	Y	N	N	Y	N	N	N	N
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Y	Y	Y	N	N	Y	N	Y	N	Y
15*	For quantitative synthesis, review authors carried out adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Y	N	N	Y	Y	Y	Y	N	Y	Y
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
	OVERALL QUALITY ASSESMENT:	Low to moderate	Critically low	Critically low	Critically low	Critically low	High	Critically low	Critically low	Critically low	Critically Low
	Rationale and conclusion:	See below for respective rating									

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).