Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-274 Angiotensin II

Stand: Februar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Angiotensin II
[zur Behandlung von Hypotonie bei Erwachsenen mit distributivem Schock]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*II. Zugelassene Arzneimittel im Anwendungsgebiet*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	-
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (laut Beratungsanforderung)
Zu bewertendes Arzneimittel:	
Angiotensin II C01CX09 GIAPREZA	GIAPREZA ist für die Behandlung der refraktären Hypotonie bei Erwachsenen mit einem septischen oder anderen distributiven Schock indiziert, die trotz einer angemessenen Wiederherstellung des Volumens und der Anwendung von Katecholaminen oder anderen verfügbaren gefäßverengenden Therapien hypotensiv bleiben (siehe Abschnitt 5.1).
Norepinephrin C01CA03 Arterenol®	**Septischer Schock**, wenn durch alleinige Volumentherapie keine Kreislaufstabilisierung erreicht werden kann.
Dopamin C01CA04 Dopamin-Fresenius®	Schockzustände bzw. drohende Schockzustände, z. B. bei: – Herzversagen, auch infarktbedingt (kardiogener Schock) – postoperativen Schockzuständen – **schweren Infektionen (infektiös-toxischer Schock**) – **Überempfindlichkeitsreaktionen (anaphylaktischer Schock)** – starkem Blutdruckabfall (schwere Hypotensionen) – beginnendem bzw. manifestem akuten Nierenversagen.
Epinephrin C01CA24 Suprarenin®	– Herz-Kreislauf-Stillstand (kardiopulmonale Reanimation), – **anaphylaktischer Schock,** – schwere anaphylaktische Reaktionen (Stadium III und IV), – **nicht primäre Therapie beim septischen Schock**, – lokal zur Gefäßverengung (z. B. bei Blutungen), nicht jedoch bei chirurgischen Eingriffen am Auge oder am verletzten Ohr bzw. vor einem chirurgischen Eingriff am Ohr.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Argipressin H01BA06 Empressin®	Zur Behandlung der katecholaminrefraktären Hypotonie im Rahmen **septischer Schockzustände** bei Patienten über 18 Jahre. Eine katecholaminrefraktäre Hypotonie besteht bei einem Patienten dann, wenn trotz adäquater Volumentherapie und Einsatz von Katecholaminen der mittlere arterielle Blutdruck nicht auf Werte von 65-75 mm Hg stabilisiert werden kann. Hinweise zu den Anwendungsgebieten - Das Arzneimittel darf nur unter engmaschiger Kontrolle und kontinuierlichem Monitoring der hämodynamischen und organspezifischen Parameter angewendet werden. - Die Therapie mit Argipressin sollte nur begonnen werden, wenn trotz adäquater Volumenssubstitution und Applikation katecholaminerger Vasopressoren kein ausreichender Perfusionsdruck beibehalten werden kann.
Dexamethason-dihydrogenphos-phat-Dinatrium H02AB02 Dexa inject Jenapharm®	Systemische Anwendung (Dexa 40/100 mg inject JENAPHARM): […] – Polytraumatischer Schock/Prophylaxe der posttraumatischen Schocklunge – **Anaphylaktischer Schock** (nach primärer Epinephrin-Injektion).
Dimetindenmaleat R06AB03 Histakut	Zur symptomatischen Akutbehandlung allergischer Erkrankungen, wie z. B. juckende Dermatosen, allergischer Schnupfen, Nahrungs- und Arzneimittelallergien, Urtikaria (Nesselsucht), Neurodermitis (endogenes Ekzem), Quincke-Ödem (angioneurotisches Ödem). Bei anaphylaktoiden Reaktionen sowie als Adjuvans bei **anaphylaktischem Schock**. Zur Prämedikation in Kombination mit einem H2-Rezeptor-Antagonisten zur Vermeidung von durch Histaminfreisetzung ausgelosten klinischen Reaktionen wie z. B. vor Narkosen und vor parenteraler Gabe von Röntgenkontrastmitteln oder Plasmasubstituten.
Triamcinolon-acetonid ATC Code nicht vorhanden Volon A solubile	Volon A solubile enthält den Wirkstoff Triamcinolonacetonid, ein abgewandeltes Nebennierenrindenhormon mit u. a. entzündungs- und allergiehemmenden Eigenschaften (Glukokortikoid). Volon A solubile wird angewendet, wenn eine sehr schnell einsetzende Wirkung erzielt werden soll oder wenn aus besonderen Gründen eine parenterale Anwendung erforderlich ist: […] ***Notfallbehandlung*** Kreislaufversagen in Folge einer starken allergischen Reaktion, nach Injektion eines blutdrucksteigernden Mittels (Epinephrin, Adrenalin)

Quellen: AMIS-Datenbank, Fachinformationen (Stand: 02/2019)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-274 (Angiotensin II)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Januar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACCP/SCCP	Consensus Conference Panel: American College of Chest Physicians/Society of Critical Care Medicine
AKI	acute Kidney Injury
APACHE	acute physiology and chronic health evaluation
AUC	area under the curve
BPS	best practice statement
CVP	central venous pressure
DO_2	oxygen delivery
EN	enteral nutrition
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HRQoL	health-related quality of life
ICU	intensive care unit
CI	confidence interval
LAC	Lactid acid
LoE	level of evidence
LOS	length of stay
MAP	mean arterial pressure
MD	mean difference
NICE	National Institute for Health and Care Excellence
NPVDs	non-protocol vasoactive drugs
OR	odds ratio
PN	parenteral nutrition
RCT	randomized controlled trial
RR	risk ratio
RRT	renal replacement therapy

SAPS	simplified acute physiology score
SOFA	sequential organ failure assessment
SoR	strength of Recommendation
SVRI	systematic vascular resistance index
VO_2	oxygen consumption

1 Indikation

Indikation der Synopse: Zur Behandlung von Hypotonie bei Erwachsenen mit distributivem Schock, die trotz adäquater Flüssigkeitstherapie, Gabe von Katecholaminen und anderen verfügbaren Vasopressoren hypotensiv bleiben.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *distributiver Schock* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.01.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 993 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert werden.

3.2 Cochrane Reviews

Annane D et al., 2015 [1].

Corticosteroids for treating sepsis.

Fragestellung

To examine the effects of corticosteroids on death at one month in patients with sepsis, and to examine whether dose and duration of corticosteroids influence patient response to this treatment.

Methodik

Population:

- Children and adults with sepsis defined by the following criteria (ACCP/SCCM 1992; Vincent 2013):

  (…)

  - Septic shock defined by a combination of these criteria and the presence of hypotension (persisting systolic arterial pressure <90 mm Hg) that is refractory to fluid resuscitation and requires vasopressor support, that is, more than 5 µg/kg of body weight per minute of dopamine or any dose of epinephrine or norepinephrine.

Intervention:

- Systemic treatment with any type of corticosteroid preparation (e.g. cortisone, hydrocortisone, methylprednisolone, betamethasone, dexamethasone).

Komparator:

- Standard therapy (which may have included antibiotics, fluid replacement, inotropic or vasopressor therapy, mechanical ventilation or renal replacement therapy) or placebo.

Endpunkte:

- Primary outcome:
  - 28-Day all-cause mortality
- Secondary outcomes:
  - ICU mortality
  - Hospital mortality
  - Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at day seven and at day 28
  - Number of organs affected and severity of organ dysfunction at day seven, as measured by the sequential organ failure assessment (SOFA) score (Vincent 1996)

- Length of stay in the ICU (for all participants and for survivors only)
- Length of hospital stay (for all participants and for survivors only)
- Adverse events (i.e. gastrointestinal bleeding and superinfection or any other adverse effects or complications of corticosteroid treatment)

Recherche/Suchzeitraum:

- Central Register of Controlled Trials (CENTRAL; 2014, Issue 10), MEDLINE (October 2014), EMBASE (October 2014), Latin American Caribbean Health Sciences Literature (LILACS; October 2014) and reference lists of articles

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool & GRADE approach

Studienergebnisse

Anzahl eingeschlossener Studien:

- 33 RCTs
- Corticosteroids were compared with placebo in 28 trials, and were compared with standard therapy (which may have included antibiotics, fluid replacement, inotropic or vasopressor therapy, mechanical ventilation or renal replacement therapy) in 5 trials.
  - 2 trials: corticosteroid therapy vs. standard therapy (antibiotics, fluid resuscitation and vasopressor when needed) (Hu 2009, Rinaldi 2006)
  - 1 trial: only one of two centres used a placebo (Sprung 1984)
  - 1 trial: hydrocortisone vs. hydrocortisone plus fludrocortisone (Annane 2010) → has been excluded from data analysis
  - 1 trial: Comparison of duration of hydrocortisone treatment (i.e. three vs. seven days) (Huh 2007) → has been excluded from data analysis

Charakteristika der Population:

- 4268 participants included
- One study enrolled both children and adults. Two trials included only children. All remaining trials included only adults.
- Seven trials included both participants with sepsis and individuals with septic shock.
- 18 trials focused only on participants with septic shock treated by a vasopressor. Two of them included only participants with septic shock with adrenal insufficiency as defined by a cortisol increment less than 9 µg/dL after a corticotropin bolus.

Qualität der Studien:

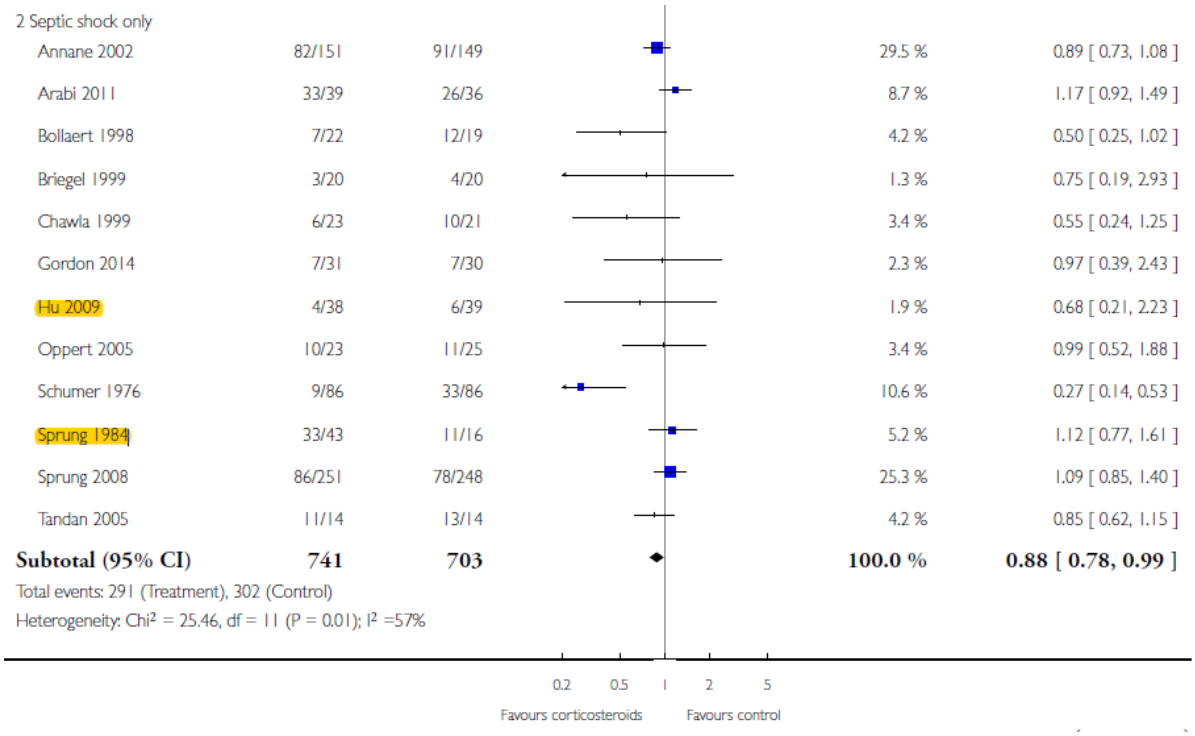
- Low risk of bias studies: 7
- Random sequence generation (selection bias):
  - 26 of 33 trials reported adequate random sequence generation (low risk)
  - 6 of 33 trials did not describe the method for generation of allocation sequence sufficiently (unclear risk), in 1 of 33 trials randomization was inappropriate to minimize selection bias (high risk)
- Allocation concealment (selection bias):

  - 23 of 33 trials at low risk of selection bias
  - 8 trials did not describe the method used (unclear risk), 2 of 33 trials at high risk of bias
- Blinding (performance and detection bias)
  - 22 of 33 trials at low risk of performance and detection bias
  - 6 trials did not report the method used to ensure blinding (unclear risk), 5 trials at high risk (4x method inadequate, 1x blinding was not possible for all of the participants included)
- Incomplete outcome data (attrition bias):
  - 27 of 33 trials at low risk of attrition bias
  - there were unexplained discrepancies and/or a lack of information in 4 trials (unclear risk); 2 trials at high risk of bias due to selective reporting for only a part of all participants
- Selective reporting (reporting bias):
  - 15 trials at low risk of reporting bias
  - 17 trials at unclear risk of bias due to lack of access to the study protocol or lack of information; 2 of 33 trials were stopped prematurely (high risk)
- Other potential sources of bias:
  - 13 trials at low risk of bias
  - 18 of 33 trials at unclear risk due to lack of access to data or lack of information; 2 trials were terminated prematurely and included significantly fewer people than planned

Studienergebnisse:

28-Day all-cause mortality

- In studies of only participants with septic shock, the RR for dying at 28 days was 0.88 (95% CI 0.78 to 0.99; 12 trials; n = 1444; I^2 statistic = 57%). → *including placebo-controlled trials*



Trials focussing on patients with septic shock without comparing with placebo:

- Annane 2010 (comparing hydrocortisone alone versus hydrocortisone plus fludrocortisone): HR of death was 0.94 (95% CI 0.73 to 1.21)
- Hu 2009 (comparing corticosteroids vs. standard therapy): RR for dying at 28 days was 0.68 (95% CI 0.21 to 2.23, see above)
- Sprung 1984 (comparing corticosteroids vs. no treatment (standard therapy; one centre) or placebo (one centre): RR for dying at 28 days was 1.12 (95%CI 0.77-1.61, see above)

ICU mortality

Trial focussing on patients with septic shock without comparing with placebo:

- Rinaldi 2009 (comparing corticosteroids vs. standard therapy): RR for dying in the ICU was 0.83 (95% CI 0.29 to 2.39)

Hospital mortality

- A total of 383 of 1041 participants in the treated group compared with 402 of 973 in the control group died in hospital. Heterogeneity in the results was significant (Chi^2 test = 30.11, P value = 0.02, I^2 statistic = 47%). The RR for dying in hospital was 0.85 (95% CI, 0.73 to 0.98; P value = 0.03, random-effects model)

Trial focussing on patients with septic shock:

- Annane 2010 (comparing hydrocortisone alone versus hydrocortisone plus fludrocortisone): RR of death was 0.94 (95% CI 0.77 to 1.14)

Shock reversal at day 7

- 10 trials studied treatment with a long course of low-dose corticosteroids. Analysis of these 10 trials (n = 1258) revealed no greater heterogeneity in the results (I^2 statistic = 0%). Then, 422 of 633 participants in the treated group and 306 of 625 participants in the control

group had shock reversed at day seven. The RR for having shock reversed was 1.34 (95% CI 1.22 to 1.46; P value < 0.00001) in favour of the corticosteroid group.

Trial focussing on patients with septic shock without comparing with placebo:

- Hu 2009 (comparing corticosteroids vs. standard therapy): RR for having shock reversed was 1.25 (95% CI 0.98 to 1.60)

Number of organs affected and intensity of organ dysfunction according to SOFA score at day seven

- Eight studies (n = 1132) reported the SOFA score at seven days post randomization. The MD in the SOFA score at day seven was -1.53 (95% CI -2.04 to -1.03; P value < 0.00001, random-effects model) in favour of corticosteroids. Moderate heterogeneity across studies was noted (Chi^2 test = 10.80, P value = 0.15, I^2 statistic = 35%)

Trial focusing on patients with septic shock without comparing with placebo:

- Rinaldi 2006 (comparing corticosteroids vs. standard therapy): MD in the SOFA score at day seven was -1.00 (95% CI -3.48 to 1.48)

Length of stay in the intensive care unit (ICU)

- In 12 trials (n = 1384), the MD for ICU length of stay for all participants was -1.68 (95% CI -3.27 to -0.09; P value = 0.04, random-effects model) with some heterogeneity evident across studies (Chi^2 test = 16.03, P value = 0.14, I^2 statistic = 31%)

Trials focussing on patients with septic shock without comparing with placebo:

- Hu 2009 (comparing corticosteroids vs. standard therapy): MD for ICU length of stay was -1.18 (95% CI -2.28 to 0.02)
- Rinaldi 2006 (comparing corticosteroids vs. standard therapy): MD for ICU length of stay was -2.00 (95% CI -12.89 to 8.89)

Adverse events:

- Hyperglycaemia

  13 trials (n = 2081). Moderate heterogeneity was noted in the results (Chi^2 test = 13.60, P value = 0.19; I^2 statistic = 26%). The RR for hyperglycaemia was 1.26 (95% CI 1.16 to 1.37; P value < 0.00001, fixed-effect model).

Trials focussing on patients with septic shock without comparing with placebo:

- Annane 2010: One trial comparing tight glucose control versus standard care found no benefit in normalizing blood glucose levels among corticosteroid-treated septic shock participants.
- Sprung 1984 (comparing corticosteroids vs. no treatment (standard therapy; one centre) or placebo (one centre): RR for hyperglycaemia was 3.48 (95%CI 0.20 to 61.18)

Anmerkung/Fazit der Autoren

Summary of main results

Patients with more severe forms of sepsis, such as those with vasopressor-dependent septic shock and those with acute respiratory distress syndrome (ARDS), may be more likely to derive a survival benefit from corticosteroids than patients with less severe sepsis.

Implications for practice

Overall, corticosteroids may favourably impact all-cause mortality at 28 days, and at ICU and hospital discharge, in patients with sepsis. Subgroup analyses have suggested that corticosteroids should be given at a low dose (of ≤ 400 mg per day, of hydrocortisone or equivalent) for three or more days at full dose, and preferably in patients with septic shock, sepsis and ARDS, community-acquired pneumonia or critical illness-related corticosteroid insufficiency. Evidence from this review is insufficient to support an abrupt or gradual interruption in treatment, or to support intravenous bolus or continuous infusion of treatment. Evidence accumulated from five trials uniformly does not support use of a short course of high dose corticosteroids in patients with sepsis.

Implications for research

The criteria for critical illness-related corticosteroid insufficiency in septic shock remain to be defined.

Kommentare zum Review

- Pooled analyses including both placebo and non-placebo-controlled trials
- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

Gamper G et al., 2016 [5].

Vasopressors for hypotensive shock

Fragestellung

To compare the effect of one vasopressor regimen (vasopressor alone, or in combination) versus another vasopressor regimen on mortality in critically ill participants with shock.

Methodik

Population:

Acutely and critically ill adult and paediatric participants (without pre-term infants with hypotension).

Intervention:

The intervention consisted of administration of different vasopressors.

Komparator:

- intravenous fluids
- placebo alone
- placebo plus non-protocol vasoactive drugs (NPVDs)

Endpunkte

- Primary outcome: Total mortality (in the ICU, in hospital and at one year)
  Secondary outcomes: Morbidity, given as:
  - ICU length of stay (LOS);

- hospital LOS;
- duration of vasopressor treatment;
- duration of mechanical ventilation;
- renal failure (as defined by study authors, such as oliguria or need for renal replacement therapy); and other.
- Health-related quality of life; Anxiety and depression (together or separately)

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015 Issue 6), MEDLINE, EMBASE, PASCAL BioMed, CINAHL, BIOSIS and PsycINFO (from inception to June 2015)

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool & GRADE approach

Studienergebnisse

Anzahl eingeschlossener Studien:

- 28 RCTs included; 18 of 28 trials were performed in participants with septic shock

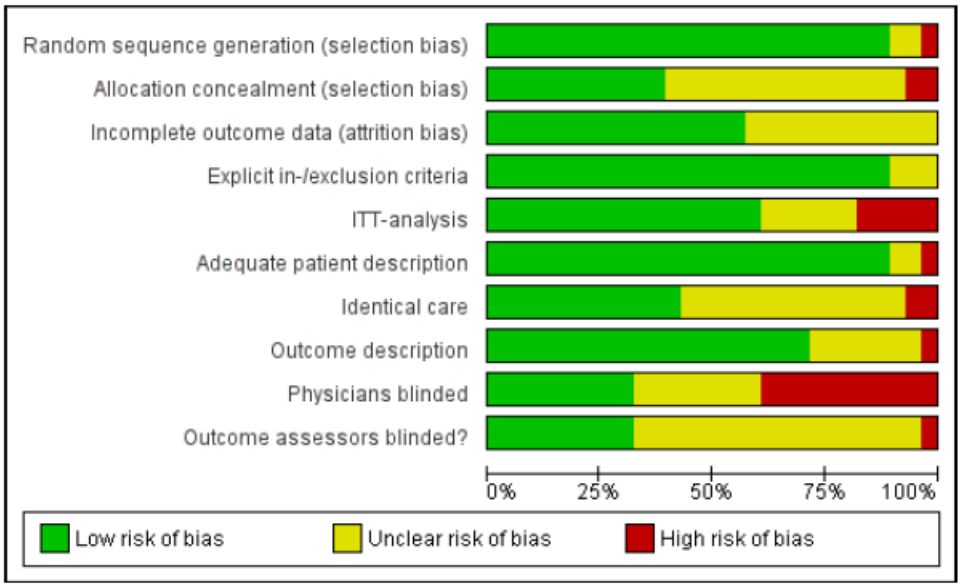
Charakteristika der Population:

- 28 RCTs: 3497 participants
- 18 trials were performed in participants with septic shock
  - Albanese 2005: Norepinephrine vs. Terlipressin
  - Annane 2007: Epinephrine vs. Norepinephrine
  - Han 2012: Pituitrin vs. standard vasopressors (dopamine or norepinephrine)
  - Jain 2010: Norepinephrine vs. Phenylephrine
  - Lauzier 2006: Arginine-vasopressin vs. Norepinephrine
  - Malay 1999: Vasopressin vs. Placebo
  - Marik 1994: Norepinephrine vs. Dopamine
  - Martin 1993: Dopamine vs. Norepinephrine
  - Morelli 2008a: Norepinephrine vs. Terlipressin and Norepinephrine vs. Terlipressin and Dobutamine
  - Morelli 2008b: Norepinephrine vs. Phenylephrine
  - Morelli 2009: Terlipressin vs. Arginine-vasopressin vs. Norepinephrine
  - Patel 2010: Dopamine vs. Norepinephrine
  - Ruokonen 1993: Norepinephrine vs. Dopamine
  - Russell 2008: Vasopressin vs. Norepinephrine
  - Seguin 2002: Epinephrine vs. Norepinephrine plus fixed Dobutamine
  - Seguin 2006: Dopexamine and Norepinephrine vs. Epinephrine
  - Svoboda 2012: Terlipressin vs. “no Terlipressin”
  - Yildizdas 2008: Terlipressin vs. Placebo

Qualität der Studien:

- Low risk of bias studies: 4

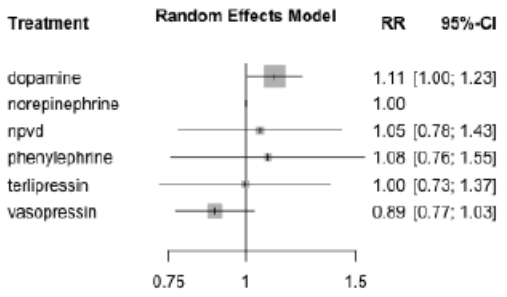
Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse

Mortality (subgroup septic shock)

Figure 11. Subgroup analysis in patients with septic shock: network forest plot comparing 7 vasopressor regimens vs norepinephrine (reference) from 18 studies with 20 pair-wise comparisons. Heterogeneity/inconsistency: tau2 < 0.0001; I2 statistic = 0%. Test of heterogeneity/inconsistency: Q = 5.21, d.f. = 14, P value = 0.98; 'NPVD' denotes non-protocol vasoactive drugs with or without placebo. RR denotes risk ratio, as calculated by a fixed-effect model. RR > 1 indicates increased mortality risk; RR < 1 indicates reduced mortality risk vs norepinephrine (reference).



Morbidity

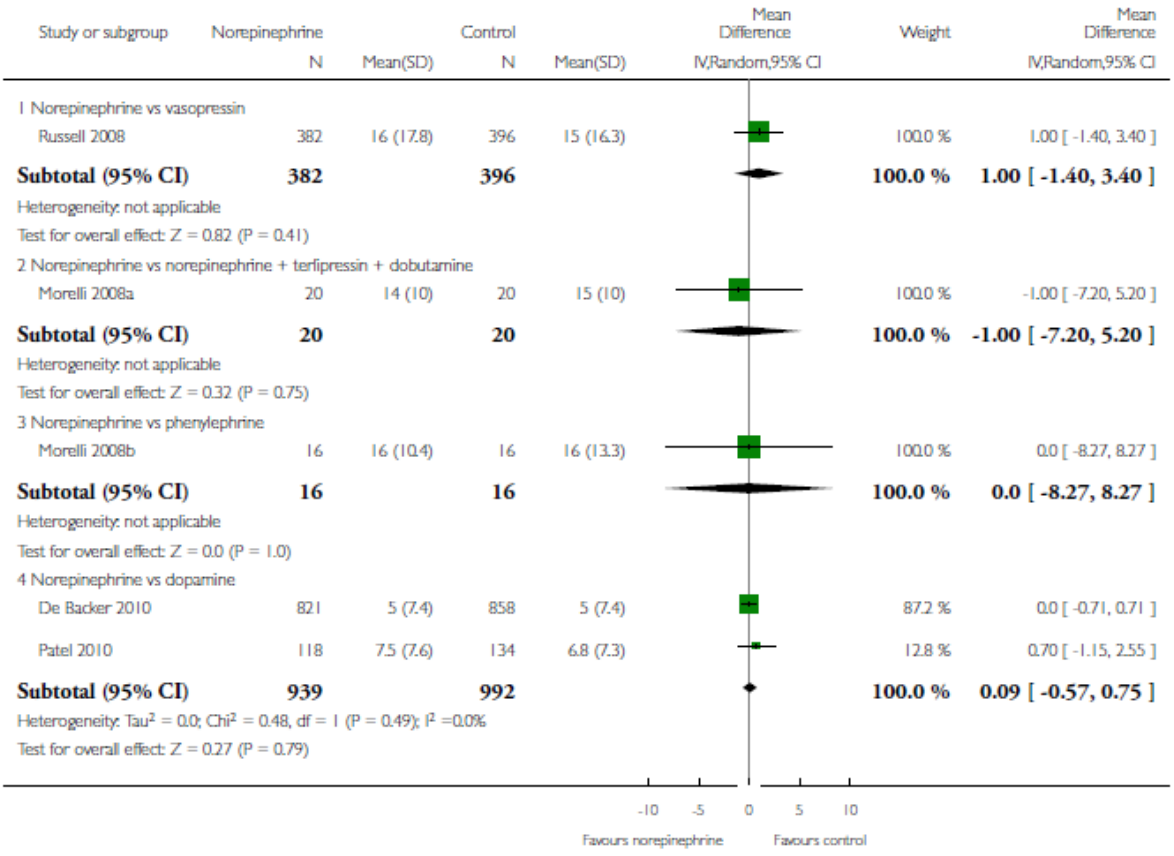
- ICU length of stay (LOS) & hospital LOS
  - Norepinephrine was compared with dopamine, vasopressin, phenylephrine and norepinephrine + terlipressin + dobutamine: no significant differences in ICU LOS (4 of 5 studies: septic shock patients) and hospital LOS (2 studies: 1 with septic shock patients)
  - No significant difference concerning ICU LOS In comparison between epinephrine vs. norepinephrine + dobutamine (one study, septic shock patients)
  - Vasopressin was compared with placebo (non-protocl vasoactive drugs), terlipressin and norepinephrine (four studies: 3x septic shock, 1x vasodilatory shock; 1046 participants): no significant differences in ICU LOS and hospital LOS

Analysis 1.2. Comparison 1 Norepinephrine, Outcome 2 LOS ICU.

Review: Vasopressors for hypotensive shock

Comparison: 1 Norepinephrine

Outcome: 2 LOS ICU



- duration of vasopressor treatment
  - no significant differences in vasopressor use (17, interquartile range (IQR) 0 to 24 vs 19, IQR 0 to 24; P value = 0.61) (one study, septic shock patients)
  - the number of vasopressor-free days until day 90 was reported as a median 53 days (IQR 0 to 86) in the epinephrine group and 66 days (IQR 6 to 86) in the norepinephrine + dobutamine group (P value = 0.18) (one study, septic shock patients)

- vasopressin vs. norepinephrine: no significant differences in vasopressor use (19, IQR 0 to 24 vs 17, IQR 0 to 24; P value = 0.61) (one study, septic shock patients)

- duration of mechanical ventilation
  - vasopressin vs. norepinephrine: no significant differences in days alive free of mechanical ventilation (six, IQR 0 to 20 vs 9, IQR 0 to 20; P value = 0.24) (one study, septic shock patients)

Health-related quality of life: In no studies were measures of HRQoL assessed.

Anxiety and depression: In no studies were measures of anxiety and depression assessed.

Anmerkung/Fazit der Autoren

Implications for practice: Several different vasopressors are available, and for six vasopressors, the effect was assessed in randomized controlled trials. The quality of evidence differs greatly between several comparisons, but, in summary, evidence is insufficient to prove that any of the vasopressors at assessed doses are superior over others in terms of mortality. Dopamine increases the risk for arrhythmia and might confer a mortality disadvantage versus norepinephrine. Most available data involve norepinephrine. The choice of the specific vasopressor may therefore be individualized and left to the discretion of the treating physician. Factors such as experience, physiological effects (e.g. heart rate, intrinsic inotropic effects, splanchnic perfusion), drug interaction with other therapeutics (especially vasopressin and concomitant use of corticosteroids) (Russell 2009), availability and cost should be considered.

Kommentar zum Review:

- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

3.3 Systematische Reviews

McIntyre WF et al., 2018 [8].

Association of Vasopressin plus Catecholamine Vasopressors vs Catecholamines Alone with Atrial Fibrillation in Patients with Distributive Shock: A Systematic Review and Meta-analysis.

Fragestellung

To determine whether treatment with vasopressin + catecholamine vasopressors compared with catecholamine vasopressors alone was associated with reductions in the risk of adverse events.

Methodik

Population:

- Adult patients with distributive shock

Intervention:

- Vasopressin in combination with catecholamine vasopressors

Komparator:

- Catecholamines alone

Endpunkte:

- Primärer Endpunkt: atrial fibrillation
- Sekundäre Endpunkte: mortality, requirement for renal replacement therapy (RRT),myocardial injury, ventricular arrhythmia, stroke, and LOS in the intensive care unit and hospital

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and CENTRAL were searched from inception to February 2018

Qualitätsbewertung der Studien:

- Risk of bias assessment: In each trial, reviewers evaluated the following domains: sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. The results were compared and disagreements resolved by discussion. Performance and detection bias were assessed separately. All open-label studies were classified as being at high risk of performance bias. A priori, the decision was made to classify open-label designs as “likely low risk of bias” for detection bias for mortality, stroke, and LOS in the absence of other concerns, but to judge “likely high risk of bias” for detection bias for atrial fibrillation, RRT, digital ischemia, myocardial injury, and ventricular arrhythmia. For analysis and presentation purposes, risk of bias was dichotomized as high (or likely high) or low (or likely low). For subgroup analyses, the study-level risk of bias was assessed for each outcome. If a study was at risk of selection, performance, detection, or reporting bias for that outcome, it was categorized as high risk of bias. Additionally, studies at risk of attrition bias were categorized as high risk of bias for mortality / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty-three randomized clinical trials were identified (3088 patients; mean age, 61.1 years [14.2]; women, 45.3%). Five trials were multicenter. Twenty-two studies included patients with septic shock. Two studies evaluated patients with post–cardiac surgery vasoplegia. Vasopressin was the intervention in 13 trials, whereas 9 studied terlipressin, 1 studied selepressin, and 1 studied pituitrin (a mixture of vasopressin and oxytocin). One 3-group study compared vasopressin vs terlipressin vs norepinephrine alone. Five studies were published only as abstracts.

Qualität der Studien:

- Fifteen of 23 trials were not blinded. Performance bias due to lack of blinding was judged to have an important effect on all outcomes; patients with distributive shock are critically ill and receiving many concomitant interventions that could be influenced by choice of concomitant vasopressor. Atrial fibrillation, myocardial injury, and digital ischemia are vulnerable to detection bias from differential capture and subjective interpretation; lack of blinding of clinicians and outcome assessors may influence these outcomes. The decision to start RRT could also be subjective. Other outcomes were judged to be at low risk of detection bias in the absence of blinding. Two studies were assessed to be at risk of selection bias due to inadequate randomization; they did not describe their randomization process and had significant between-group imbalances. Nine studies (39%) reported the information necessary to make a definitive judgment for selection bias. Authors relied on imbalances between groups and overall methodological quality of the study to make this judgment. Attrition was found in 7 studies, and judged as having an effect on mortality. Reporting bias was not detected. “Other bias” was judged to be present when studies were published as abstracts only. Prespecified sensitivity analyses were performed to assess the robustness of estimates to risk of bias if studies were dichotomized according to their risk of bias.

Studienergebnisse:

- High-quality evidence supported a lower risk of atrial fibrillation associated with vasopressin treatment (RR, 0.77 [95%CI, 0.67 to 0.88]; risk difference [RD], −0.06 [95%CI, −0.13 to 0.01]).
- For mortality, the overall RR estimate was 0.89 (95%CI, 0.82 to 0.97; RD, −0.04 [95%CI, −0.07 to 0.00]); however, when limited to trials at low risk of bias, the RR estimate was 0.96 (n.s.).
- The overall RR estimate for RRT was 0.74 (n.s.; RD, −0.07 [95%CI, −0.12 to −0.01]). However, in an analysis limited to trials at low risk of bias, RR was 0.70 (95%CI, 0.53 to 0.92, P for interaction = .77).
- There were no significant differences in the pooled risks for other outcomes.

Table 2. Association of Vasopressin + Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock and Sensitivity Analyses

Group	No. With Events/Total No. of Patients		Risk Difference, % (95% CI)[a]	Relative Risk[a]			Quality of Evidence
	Vasopressin + Catecholamines	Catecholamines Alone		Risk Ratio (95% CI)	*P* Value	I^2 %	
All studies[18,20,24,26-28,30,33-35,39-41]	159/739	215/723	−6 (−13 to 1)	0.77 (0.67 to 0.88)	<.001	1	High
Low risk of bias[18,24,30,34,39,40]	136/559	182/554	−7 (−20 to 5)	0.77 (0.68 to 0.88)	<.001	0	
High risk of bias[20,26-28,33,35,41]	23/180	33/169	−3 (−10 to 4)	0.73 (0.40 to 1.34)	.31	36	
Sepsis[20,24,26-28,30,33-35,39-41,b]	60/580	84/563	−3 (−7 to 1)	0.76 (0.55 to 1.05)	.09	8	
Cardiac surgery[18,28,c]	99/159	131/160	−19 (−29 to −10)	0.77 (0.67 to 0.88)	<.001	0	
Vasopressin[18,24,27,28,30,33-35,39,b,c]	151/621	201/626	−7 (−17 to 3)	0.77 (0.68 to 0.88)	<.001	0	
Vasopressin analogues[20,26,35,40,41,c]	8/118	18/112	−0.05 (−11 to 1)	0.52 (0.18 to 1.51)	.23	28	
Fixed-effect analysis[18,20,24,26-28,30,33-35,39-41,b,c]	159/739	215/723	−7 (−11 to −4)	0.75 (0.65 to 0.86)	<.001	1	

[a] Relative risk <1.0 and risk difference <0.0 favors vasopressin + catecholamines.

[b] Dünser et al, 2003,[28] included patients with both sepsis and post–cardiac surgery vasoplegia, but subgroup data were obtained for atrial fibrillation only. This study was excluded from other outcomes when sepsis and post–cardiac surgery vasoplegia were compared.

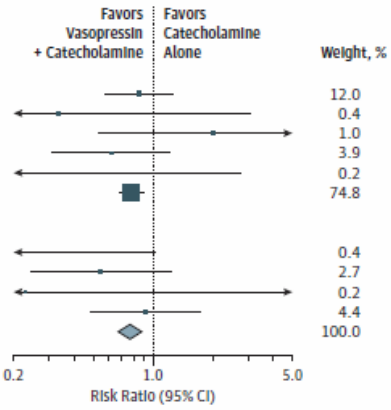
[c] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

Figure 2. Relative Risks of All Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone for Patients With Distributive Shock

A Atrial fibrillation

Source	Vasopressin + Catecholamine[a]		Catecholamine Alone		Risk Ratio (95% CI)	Weight, %
	No. With Events	Total No. of Patients	No. With Events	Total No. of Patients		
Abdullah et al,[25] 2012	0	17	0	17	Not estimable	
Capoletto et al,[38] 2017	34	125	40	125	0.85 (0.58-1.25)	12.0
Choudhury et al,[29] 2016	1	42	3	42	0.33 (0.04-3.08)	0.4
Clem et al,[30] 2016	6	41	3	41	2.00 (0.54-7.46)	1.0
Dünser et al,[39] 2003	8	24	13	24	0.62 (0.31-1.21)	3.9
Gordon et al,[20] 2016	0	205	3	204	0.14 (0.01-2.73)	0.2
Hajjar et al,[18] 2017	95	149	124	151	0.78 (0.67-0.89)	74.8
Lauzier et al,[21] 2006	0	13	0	13	Not estimable	
Malay et al,[33] 1999	0	5	0	5	Not estimable	
Morelli et al,[35] 2009	1	30	4	15	0.13 (0.02-1.02)	0.4
Russell et al,[22] 2008	7	44	14	48	0.55 (0.24-1.23)	2.7
Russell et al,[23] 2017	0	31	1	21	0.23 (0.01-5.37)	0.2
Svoboda et al,[37] 2012	7	13	10	17	0.92 (0.48-1.74)	4.4
Total events (95% CI)	159	739	215	723	0.77 (0.67-0.88)	100.0

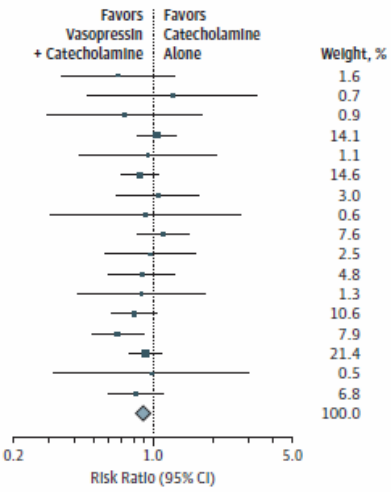
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 9.10$ ($P = .43$); $I^2 = 1\%$
Overall effect: $z = 3.79$ ($P < .001$)



B 28-d or 30-d mortality

Source	Vasopressin + Catecholamine[a]		Catecholamine Alone		Risk Ratio (95% CI)	Weight, %
	No. With Events	Total No. of Patients	No. With Events	Total No. of Patients		
Acevedo et al,[26] 2009	6	12	9	12	0.67 (0.35-1.28)	1.6
Albanese et al,[27] 2005	5	10	4	10	1.25 (0.47-3.33)	0.7
Barzegar et al,[28] 2014	5	15	7	15	0.71 (0.29-1.75)	0.9
Capoletto et al,[38] 2017	71	125	68	125	1.04 (0.84-1.30)	14.1
Chen et al,[40] 2017	9	31	8	26	0.94 (0.43-2.09)	1.1
Choudhury et al,[29] 2016	31	42	36	42	0.86 (0.69-1.07)	14.6
Clem et al,[30] 2016	19	41	18	41	1.06 (0.65-1.70)	3.0
Fonseca Ruiz et al,[34] 2013	4	14	5	16	0.91 (0.30-2.75)	0.6
Gordon et al,[20] 2016	63	204	56	204	1.13 (0.83-1.52)	7.6
Hajjar et al,[18] 2017	23	149	24	151	0.97 (0.57-1.64)	2.5
Han et al,[31] 2012	27	66	34	73	0.88 (0.60-1.28)	4.8
Hua et al,[32] 2013	7	16	8	16	0.88 (0.42-1.84)	1.3
Oliveira et al,[36] 2014	65	191	83	196	0.80 (0.62-1.04)	10.6
Prakash et al,[41] 2017	37	91	57	93	0.66 (0.49-0.89)	7.9
Russell et al,[22] 2008	144	404	154	395	0.91 (0.76-1.09)	21.4
Russell et al,[23] 2017	6	29	4	19	0.98 (0.32-3.03)	0.5
Svoboda et al,[37] 2012	10	13	16	17	0.82 (0.59-1.13)	6.8
Total events (95% CI)	532	1453	591	1451	0.89 (0.82-0.97)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{16} = 11.29$ ($P = .79$); $I^2 = 0\%$
Overall effect: $z = 2.62$ ($P = .009$)



The relative risks were calculated using a random-effects model with Mantel-Haenszel weighting. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs.

[a] Vasopressin (or analogue [ie, terlipressin, selepressin, or pituitrin]) + catecholamine vasopressors.

Table 3. Binary Outcomes and Sensitivity Analyses for Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock

Group	No. With Events/Total No. of Patients		Relative Risk[a]				Quality of Evidence (Reason for Judgment)
	Vasopressin + Catecholamines	Catecholamines Alone	Risk Difference % (95% CI)[a]	Risk Ratio (95% CI)	P Value	I^2 %	
28-d or 30-d Mortality							
All studies[18,21-27,29-32,36,38-41]	532/1453	591/1451	−4 (−7 to 0)	0.89 (0.82 to 0.97)	.009	0	Low (risk of bias)
Low risk of bias[24,29]	215/529	222/520	−2 (−8 to 4)	0.96 (0.84 to 1.11)	.6	0	
High risk of bias[18,21-23,25-27,29-32,36,38,40,41]	317/924	369/931	−4 (−8 to 0)	0.86 (0.77 to 0.95)	.004	0	
28-d or 30-d or ICU mortality[18,21-36,38-41,b,c]	567/1525	623/1505	−4 (−7 to −1)	0.89 (0.83 to 0.97)	.006	0	
Full text only[18,22,23,25,26,29-32,39-41,d]	334/993	356/984	−2 (−6 to 2)	0.91 (0.82 to 1.01)	.09	0	
Vasopressin[23,24,27,29,30,36,39,41,b]	404/1156	431/1160	−2 (−6 to 2)	0.94 (0.85 to 1.04)	.21	0	
Vasopressin analogues[21,22,25,26,31,32,38,40,41,b]	128/297	160/291	−10 (−18 to −3)	0.81 (0.70 to 0.94)	.005	0	
Sepsis[21-27,29-32,36,38-41]	509/1304	567/1300	−4 (−8 to −1)	0.89 (0.82 to 0.97)	.008	0	
Cardiac surgery[18]	23/149	24/151	−0 (−9 to 8)	0.97 (0.57 to 1.64)	.91	NA	
Requirement for Renal Replacement Therapy							
All studies[23,24,28,30,33,35,b,e]	97/412	125/393	−7 (−12 to −1)	0.74 (0.51 to 1.08)	.12	70	Moderate (imprecision)
Low risk of bias[24,30]	62/330	89/329	−7 (−13 to −2)	0.70 (0.53 to 0.92)	.01	0	
High risk of bias[23,28,33,35,b,c]	35/82	36/64	−5 (−16 to 7)	0.77 (0.42 to 1.43)	.41	67	
AKI as outcome[18,21,24,28,30,b]	154/515	204/516	−8 (−21 to 6)	0.73 (0.46 to 1.17)	.19	91	
Vasopressin[23,24,28,30,33,35,b,e]	93/397	125/393	−6 (−11 to −1)	0.76 (0.53 to 1.10)	.15	68	
Vasopressin analogues[35,b,e]	4/15	8/15	−27 (−60 to 7)	0.50 (0.19 to 1.31)	.16	NA	
Digital Ischemia							
All studies[18,23,24,26,29,30,39-41]	41/990	17/973	2 (−1 to 4)	2.38 (1.37 to 4.12)	.002	0	Moderate (post hoc outcome)
Low risk of bias[18,24,30,39,40]	23/906	9/883	1 (−1 to 3)	2.45 (1.10 to 5.43)	.03	0	
High risk of bias[23,26,29,41]	18/84	8/90	10 (0 to 19)	2.31 (1.08 to 4.94)	.03	0	
Defined as digital ischemia[18,23,29,30,33,39,40,f]	25/810	8/789	2 (0 to 3)	2.73 (1.27 to 5.87)	.01	0	
Vasopressin[18,23,24,29,30,33,39,b]	24/904	10/893	1 (−1 to 3)	2.35 (1.10 to 5.05)	.03	0	
Vasopressin analogues[26,40,41,b]	17/86	7/80	10 (−4 to 25)	2.40 (1.09 to 5.31)	.03	0	
Myocardial Injury							
All studies[18,20,24,28,30,33,34,37,39-41,b]	62/991	71/966	0 (−2 to 2)	0.86 (0.63 to 1.17)	.34	0	Low (indirectness, imprecision)
Low risk of bias[18,24,30,34,37,39,40]	61/924	66/899	1 (−1 to 3)	0.89 (0.64 to 1.25)	.52	4	
High risk of bias[20,28,33,41,b]	1/67	5/67	−5 (−12 to 3)	0.37 (0.07 to 1.95)	.24	0	
Sepsis[20,24,28,30,33,34,37,39-41,b]	51/818	51/791	1 (−1 to 2)	0.94 (0.67 to 1.32)	.71	0	
Cardiac surgery[18]	11/149	17/151	−4 (−10 to 3)	0.66 (0.32 to 1.35)	.25	NA	
Vasopressin[18,24,28,30,33,34,37,39,b]	61/930	70/912	0 (−3 to 2)	0.87 (0.61 to 1.23)	.42	6	
Vasopressin analogues[20,40,41,b]	1/61	1/54	1 (−6 to 7)	0.91 (0.10 to 8.33)	.93	0	
Ventricular Arrhythmia							
All studies[18,20,24,26,27,33,34,37,41]	39/418	48/419	0 (−2 to 1)	0.93 (0.73 to 1.19)	.55	0	Low (indirectness, imprecision)
Low risk of bias[18,34,37]	27/167	32/167	−2 (−10 to 5)	0.86 (0.54 to 1.35)	.50	NA	
High risk of bias[20,24,26,27,33,41]	12/251	16/252	0 (−1 to 1)	0.96 (0.72 to 1.28)	.78	0	
Vasopressin[18,24,27,33,34,37,b]	28/346	32/343	0 (−1 to 2)	0.88 (0.56 to 1.38)	.57	0	
Vasopressin analogues[20,26,41,b]	11/72	16/76	−2 (−7 to 3)	0.95 (0.71 to 1.27)	.73	0	
Stroke							
All studies[18,24,39,41]	11/683	6/675	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	Moderate (imprecision)
Low risk of bias[18,24,39]	11/670	6/658	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	
High risk of bias[41]	0/13	0/17	0 (−12 to 12)	NA	NA	NA	
Vasopressin[18,24,39,b]	11/670	6/658	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	
Vasopressin analogues[41,b]	0/13	0/17	0 (−12 to 12)	NA	NA	NA	

Abbreviation: AKI, acute kidney injury.

[a] Relative risk <1.0 and risk difference <0.0 favors vasopressin + catecholamines.

[b] Dünser et al, 2003,[28] included patients with both sepsis and post-cardiac surgery vasoplegia, but subgroup data were obtained for atrial fibrillation only. This study was excluded from other outcomes when sepsis and post-cardiac surgery vasoplegia were compared.

[c] Added 4 studies that reported on ICU mortality.

[d] "Full text only" refers to studies not published only as abstracts.

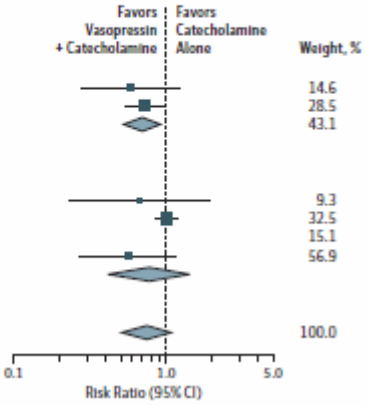
[e] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

[f] Includes only studies in which the authors described the outcome as digital ischemia. Peripheral cyanosis and limb ischemia were excluded.

Figure 3. Relative Risks of All Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone for Patients With Distributive Shock

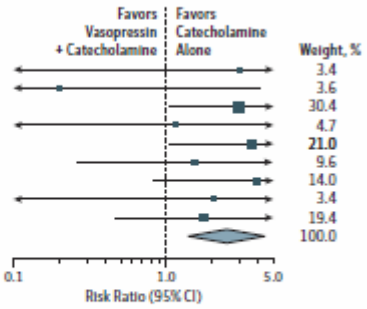
A Requirement of renal replacement therapy

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Low risk of bias[b]						
Capoletto et al,[38] 2017	10	125	17	125	0.59 (0.28-1.23)	14.6
Gordon et al,[20] 2016	52	205	72	204	0.72 (0.53-0.97)	28.5
Total events (95% CI)	62	330	89	329	0.70 (0.53-0.92)	43.1
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = .24$ ($P = .62$); $I^2 = 0\%$						
Overall effect: $z = 2.53$ ($P = .01$)						
High risk of bias[b]						
Barzegar et al,[28] 2014	4	15	6	15	0.67 (0.23-1.89)	9.3
Dünser et al,[39] 2003	22	24	22	24	1.00 (0.84-1.19)	32.5
Lauzier et al,[21] 2006	0	13	0	10	Not estimable	15.1
Morelli et al,[35] 2009	9	30	8	15	0.56 (0.27-1.16)	56.9
Total events (95% CI)	35	82	36	64	0.77 (0.42-1.43)	
Heterogeneity: $\tau^2 = 0.19$; $\chi^2_3 = 5.99$ ($P = .05$); $I^2 = 67\%$						
Overall effect: $z = 0.82$ ($P = .41$)						
Total (95% CI)	97	412	125	393	0.74 (0.51-1.08)	100.0
Heterogeneity: $\tau^2 = 0.10$; $\chi^2_5 = 13.51$ ($P = .009$); $I^2 = 70\%$						
Overall effect: $z = 1.56$ ($P = .12$)						
Subgroup differences: $\chi^2_1 = 0.09$ ($P = .77$); $I^2 = 0\%$						



B Digital Ischemia

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Barzegar et al,[28] 2014	1	15	0	15	3.00 (0.13-68.26)	3.4
Capoletto et al,[38] 2017	0	125	2	125	0.20 (0.01-4.12)	3.6
Choudhury et al,[29] 2016	12	42	4	42	3.00 (1.05-8.55)	30.4
Fonseca Ruiz et al,[34] 2013	1	14	1	16	1.14 (0.08-16.63)	4.7
Gordon et al,[20] 2016	**11**	**205**	**3**	**204**	**3.65 (1.03-12.89)**	**21.0**
Hajjar et al,[18] 2017	3	149	2	151	1.52 (0.26-8.97)	9.6
Russell et al,[22] 2008	8	396	2	382	3.86 (0.82-18.05)	14.0
Russell et al,[23] 2017	1	31	0	21	2.06 (0.09-48.34)	3.4
Svoboda et al,[37] 2012	4	13	3	17	1.74 (0.47-6.47)	19.4
Total events (95% CI)	41	990	17	973	2.38 (1.37-4.12)	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 4.36$ ($P = .82$); $I^2 = 0\%$						
Overall effect: $z = 3.09$ ($P = .002$)						



The relative risks were calculated using a random-effects model with Mantel-Haenszel weighting. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs.

[a] Vasopressin (or analogue [ie, terlipressin, selepressin, or pitulrin]) + catecholamine vasopressors.

[b] Risk of bias categories for requirement for renal replacement therapy are the same as those for atrial fibrillation, as summarized in Table 1.

Table 4. Continuous Outcomes and Sensitivity Analyses for Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock

Group	Mean Length of Stay in Days (SD)[a] Vasopressin + Catecholamines	Mean Length of Stay in Days (SD)[a] Catecholamines Alone	Mean Difference (95% CI), d[b]	P Value	I^2 %	Quality of Evidence (Reason for Judgment)
Hospital Length of Stay						
All studies[18,20,22,29,32,34,38,40]	21.3 (23.0)	22.6 (22.9)	−1.14 (−3.60 to 1.32)	.36	75	Low (imprecision, inconsistency)
Low risk of bias[18,24,30,39]	22.0 (24.1)	23.3 (23.8)	−1.83 (−4.47 to 0.81)	.17	69	
High risk of bias[29,32,34,40]	15.7 (8.6)	16.6 (11.1)	−0.45 (−4.40 to 3.50)	.82	62	
Vasopressin[18,24,29,30,39,c]	21.8 (24.0)	23.4 (23.7)	−2.33 (−5.05 to 0.40)	.09	67	
Vasopressin analogs[29,32,40,c]	16.1 (7.7)	14.9 (8.5)	1.03 (−1.48 to 3.53)	.42	22	
Intensive Care Unit Length of Stay						
All studies[18,20,22,28,29,31,32,35,38,39]	11.1 (12.2)	11.6 (13.4)	−0.40 (−1.05 to 0.25)	.23	24	Moderate (imprecision)
Low risk of bias[18,24,30,39]	11.2 (12.7)	12.2 (14.1)	−0.54 (−1.33 to 0.25)	.18	34	
High risk of bias[28,29,31,32,35,39,40]	10.4 (10.2)	9.4 (8.5)	−0.12 (−1.37 to 1.13)	.85	22	
Vasopressin[18,23,24,28,30,35,39,c]	11.8 (13.0)	12.4 (14.0)	−0.24 (−1.27 to 0.79)	.65	44	
Vasopressin analogues[29,31,32,35,40,c]	7.9 (7.0)	7.9 (7.0)	−0.38 (−1.33 to 0.58)	.44	0	

[a] Mean length of stay was weighted by the number of patients.

[b] Mean difference <0.0 favors vasopressin + catecholamines.

[c] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

Anmerkung/Fazit der Autoren

In this meta-analysis, the addition of vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation. However, findings for secondary outcomes varied.

Rodriguez R et al., 2018 [16].

Novel Vasopressors in the Treatment of Vasodilatory Shock: A Systematic Review of Angiotensin II, Selepressin, and Terlipressin.

Fragestellung

To summarize the efficacy and safety of these novel vasopressors and to offer guidance on their appropriate use

Methodik

Population:

- Adults with shock

Intervention/Komparator:

- AT2, selepressin, or terlipressin with any agent

Endpunkte:

- effect on BP, hemodynamic measures (cardiac output or index, central venous oxygen saturation [ScVO2], lactate, oxygen delivery, and extraction), mortality, severity and duration of illness (e.g., organ dysfunction, length of mechanical ventilation, length of hospital, and ICU stay), concomitant vasopressor utilization, and adverse effects

Recherche/Suchzeitraum:

- Medline (via PubMed), EMBASE, International Pharmaceutical Abstracts, and the Cochrane Central Register of Controlled Trials
- published through April 13, 2018

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions to assess risk of bias, including the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to assess the quality of the body of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen controlled trials were assessed after exclusion of 2 dated trials of a distinct AT2 formulation. Trials are limited for AT2 (n = 2) and selepressin (n = 1), while terlipressin was investigated in 11 small trials.

Qualität der Studien:

- The overall quality rating for the body of evidence was determined to be low.

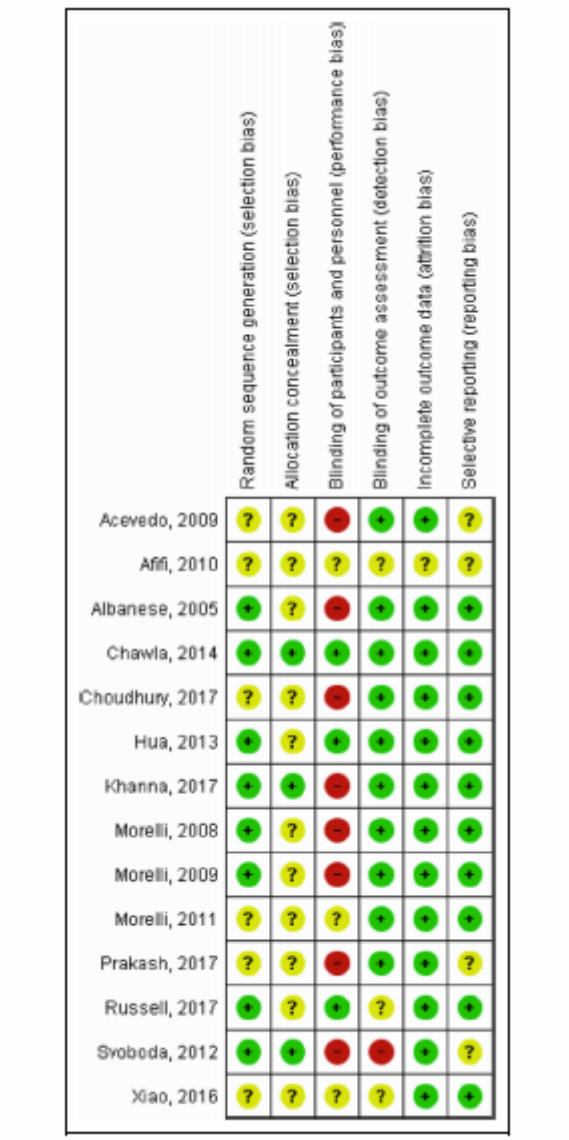


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Studienergebnisse:

- Most report mean arterial pressure (MAP) as primary endpoint and all indicate novel vasopressors increase MAP compared to placebo and to a similar degree as with catecholamine vasopressors.
- Mortality findings are preliminary, as they have been limited to specific subgroups in trials of terlipressin and post hoc analyses of one trial of AT2.
- Trials reported safety concerns for each agent including thromboembolism with AT2 and ischemia with terlipressin/selepressin.

Anmerkung/Fazit der Autoren

This systematic review assessed contemporary controlled trials of AT2 (n = 2), selepressin (n = 1), and terlipressin (n = 11) to be at unclear risk of bias and the body of evidence to be of low quality. Generally, these novel vasopressors appear to increase MAP while also decreasing catecholamine requirements. Angiotensin II may improve survival in certain

subgroups based on 5 post hoc analyses from one trial, but these findings should be considered preliminary. Findings for selepressin lack precision based on the single assessed trial. Data on terlipressin are heterogeneous in light of the various dosing regimens studied, but are strongest in cirrhotic patients with septic shock (with or without HRS). Safety concerns exist for all novel vasopressors, including the risk of thromboembolic events with AT2 and ischemia with terlipressin and selepressin. Larger well-designed and active-controlled studies would provide more direct evidence, address limitations of available trials, and help determine the value of their novel characteristics, including the distinct mechanism of AT2 and the pharmacologic differences between selepressin and terlipressin compared to AVP.

Nedel WL et al., 2019 [13].

Renal Outcomes of Vasopressin and Its Analogs in Distributive Shock: A Systematic Review and Meta-Analysis of Randomized Trials

Fragestellung

To systematically review the literature and synthesize evidence concerning the effects of vasopressin and its analogs compared with other vasopressors in distributive shock, focusing on renal outcomes.

Methodik

Population:

- adult patients with distributive shock

Intervention:

- Vasopressin and its analogues

Komparator:

- other vasopressors

Endpunkte:

- Renal outcomes related to acute renal failure (e.g. need for RRT, incidence of AKI, or AKI-free days

Recherche/Suchzeitraum:

- EMBASE, Cochrane Central, and Clinicaltrials.gov databases from inception through June 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 studies comprising a total of 2,833 subjects: 1,448 who received VA and 1,385 who received standard vasopressors (mainly noradrenaline)

- Vasopressors were used to treat septic shock in 14 studies, comprising 2,311 patients, and to treat postoperative vasoplegic shock in three studies, comprising 474 patients (83% and 17% of the study population, respectively).
- In one study with 48 patients (2.3% of the study population), the authors included patients with distributive shock without discriminating between septic or vasoplegic shock.
- Vasopressin was the vasopressor of choice in 13 studies, and terlipressin was used in six studies. One study used both.
- 11 studies (2,691 individuals) were suitable for quantitative meta-analysis

Qualität der Studien:

- Overall, the evidence was of low to moderate quality.

Studienergebnisse:

- Patients who received vasopressin and its analogues had a reduced need for renal replacement therapy (odds ratio, 0.59 [0.37–0.92]; p = 0.02; I^2 = 49%) and a lower acute kidney injury incidence (odds ratio, 0.58 [0.37–0.92]; p = 0.02; I^2 = 63%). → These results should be interpreted with caution, due to excessive heterogeneity.
- Acute kidney injury-free data was not pooled, since the small number of studies and extreme heterogeneity.
- Subgroup Analysis:

  RRT

  - Septic Shock or Vasoplegic Shock: RRT: VA reduced the need for RRT in vasoplegic but not in septic shock. Four studies evaluated the use of RRT in septic shock. RRT was used in 213 of 647 patients in VA group versus 234 of 616 in the control group (OR, 0.75 [0.54–1.04]; p = 0.08; I^2 = 27%; p for heterogeneity = 0.25).
  - Two studies evaluated RRT in vasoplegic shock. RRT was used in six of 189 patients in VA group versus 25 of 193 in the control group (OR, 0.23 [0.09–0.61]; p = 0.31; I^2 = 4%; p for heterogeneity = 0.003). This analysis demonstrated that the type of shock was a major source of heterogeneity for the outcome need for RRT, as heterogeneity decreases when we separate studies by the type of shock (septic or vasoplegic). However, the p value for subgroup interaction was 0.07, suggesting the presence of potentially meaningful subgroup effects.

  AKI incidence:

  - Despite the association between VA and lower AKI incidence in distributive shock, VA did not reduce AKI incidence when patients with septic shock and patients with vasoplegic shock were analysed separately. Six studies evaluated the effect of VA on AKI incidence in patients with septic shock: 370 of 673 in the VA group versus 383 of 645 in the control group (OR, 0.83 [0.66–1.05]; no heterogeneity). Three studies evaluated patients with vasoplegic shock. In this subgroup, the use of VA was not associated with lower AKI incidence: 30 of 236 in the VA group versus 68 of 238 in the control group (OR, 0.50 [0.13–1.95]; I^2= 81%; p for heterogeneity = 0.005). The p value for subgroup interaction was 0.75.

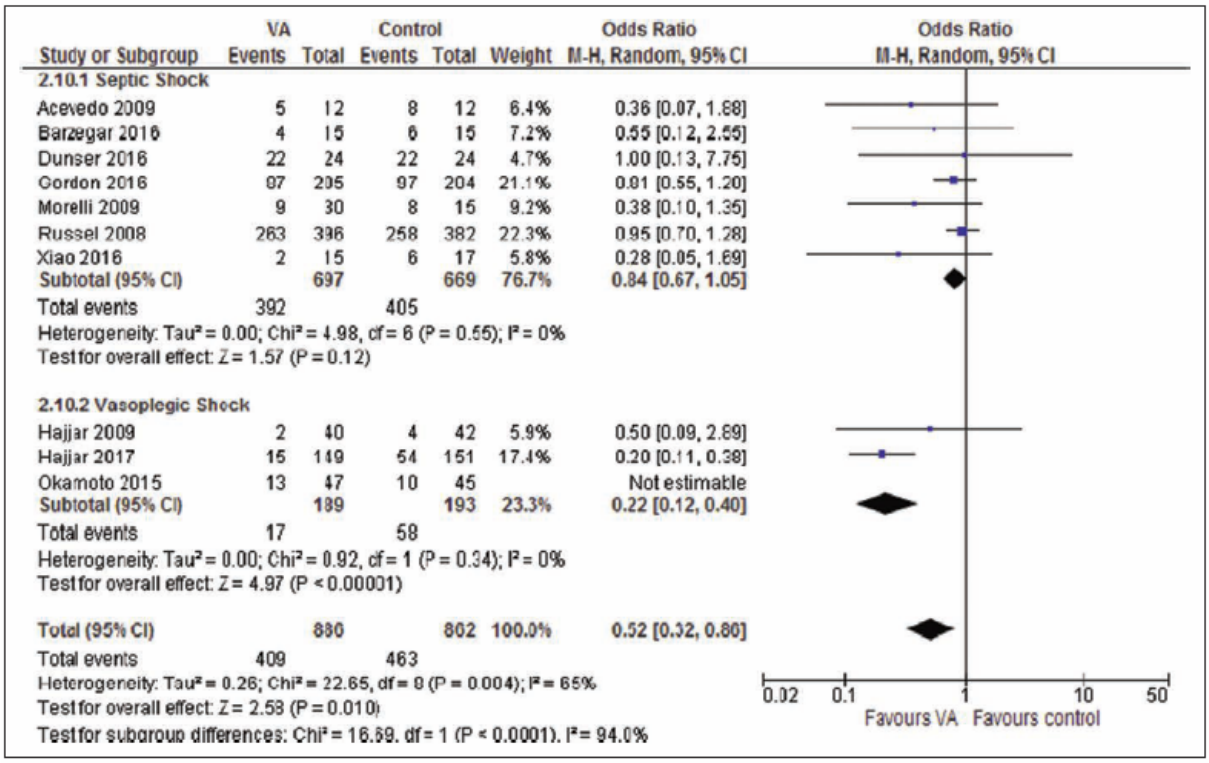


Figure 3. Forest plot of studies evaluating the effects of vasopressin or analogs (VA) on the incidence of acute kidney injury in patients with distributive shock. *df* = degrees of freedom, M-H = Mantel-Haenszel.

Vasopressin or Terlipressin vs. Catecholamines.

- Eight of the trials included in the quantitative synthesis (1,678 patients) reported using vasopressin, and another three (101 patients) reported using terlipressin as a VA. One trial compared three groups (vasopressin, terlipressin, and noradrenaline) and was then included in both subgroup analyses, according to treatment allocation.
- Vasopressin was associated with a reduced need for RRT (OR, 0.60 [0.39– 0.94]; p = 0.02; I2 = 46%; p for heterogeneity = 0.09), whereas terlipressin was associated with a lower incidence of AKI (OR, 0.32 [0.12–0.83]; I2 = 0%; p for heterogeneity = 0.98).

Anmerkung/Fazit der Autoren

The present data provide weak evidence based on high risk of bias studies in favor of using VA, showing that this therapy may be associated with a reduced need for RRT and lower AKI incidence in patients with distributive shock. These results are of major relevance to critical care practice in view of the high morbidity, mortality, and costs associated with AKI and RRT. Then, the effects of vasopressin on renal outcomes should be confirmed in blinded, large prospective RCTs before more solid conclusions can be drawn.

Belletti A et al., 2017 [3].

The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials.

Fragestellung

To indirectly compare and grade all the vasoactive drugs ever tested in randomized controlled trials (RCTs) in septic patients to identify the treatment associated with the highest survival rate.

Methodik

Population:

- Adult patients with sepsis, severe sepsis, or septic shock

Intervention:

- Inotrope or vasopressor treatment

Komparator:

- No restriction on type of control treatment (e.g., other vasoactive agents, placebo, or standard treatment without placebo)

Endpunkte

- mortality

Recherche/Suchzeitraum

- PubMed, EMBASE, BioMed Central, and the Cochrane Central register; last updated June 30, 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Studienergebnisse

Anzahl eingeschlossener Studien:

- 33 trials: 3470 patients in 16 treatment groups

Table 1
Characteristics of included trials

First author (study acronym)	Year	Treatment 1	Treatment 2	Treatment 3	Overall mortality/N. patients group 1	Overall mortality/N. patients group 2	Overall mortality/N. patients group 3	Longest follow-up
Albanèse J [26]	2005	Norepinephrine	Terlipressin		4/10	5/10		Hospital stay
Annane D (CATS) [27]	2007	Epinephrine	Nor + Dbt		84/161	85/169		90 d
De Backer D (SOAP-II) [7]	2010	Norepinephrine	Dopamine		249/502	291/542		12 mo
Fang M [28]	2014	Dobutamine	Levosimendan		8/18	7/18		28 d
Hernández G [29]	1999	Dobutamine	Amrinone		4/7	2/7		At least ICU stay
Hua F [30]	2013	Dopamine	Terlipressin		8/16	7/16		28 d
Jain G [31]	2010	Norepinephrine	Phenylephrine		15/27	16/27		ICU stay
Kern H [32]	2001	Dobutamine	Enoximone		12/24	13/24		ICU stay
Kirov MY [33]	2001	Methylene blue	Control		5/10	7/10		28 d
Lauzier F [34]	2006	Norepinephrine	Vasopressin		3/10	3/13		ICU stay
Levy B [35]	1997	Epinephrine	Nor + Dbt		9/15	8/15		At least 24 h
Luckner G [36]	2006	Vasopressin	Control		8/10	7/8		ICU stay
Mahmoud KM [37]	2012	Epinephrine	Dobutamine		16/30	15/30		28 d
Malay MB [38]	1999	Vasopressin	Control		0/5	2/5		24 h
Marik PE [39]	1994	Norepinephrine	Dopamine		5/10	6/10		ICU stay
Martin C [40]	1993	Norepinephrine	Dopamine		7/16	10/16		Hospital stay
Mathur SK [41]	2007	Norepinephrine	Dopamine		14/25	19/25		ICU stay
Memis D [42]	2012	Dobutamine	Levosimendan		5/15	2/15		ICU stay
Memis D [43]	2002	Methylene blue	Control		4/15	4/15		Hospital stay
Morelli A (TERLIVAP) [10]	2009	Norepinephrine	Vasopressin	Terlipressin	10/15	8/15	7/15	ICU stay
Morelli A [44]	2005	Dobutamine	Levosimendan		9/15	7/15		30 d
Morelli A [45]	2010	Dobutamine	Levosimendan		15/20	13/20		ICU stay
Morelli A (DOBUPRESS) [46]	2008	Terlipressin	Ter + Dbt	Control	12/20	14/20	14/20	ICU stay
Morelli A [11]	2008	Norepinephrine	Phenylephrine		9/16	10/16		ICU stay
Myburgh JA (CAT) [8]	2008	Norepinephrine	Epinephrine		30/82	23/76		90 d
Patel GP [47]	2010	Norepinephrine	Dopamine		51/118	67/134		28 d
Ruokonen E[48]	1993	Norepinephrine	Dopamine		4/5	3/5		ICU stay
Russell JA (VASST) [9]	2008	Norepinephrine	Vasopressin		188/382	172/396		90 d
Schmoelz M [49]	2006	Dopamine	Dopexamine	Control	4/22	5/21	7/21	28 d
Seguin P [50]	2002	Epinephrine	Nor + Dbt		4/10	5/11		ICU stay
Seguin P [51]	2006	Epinephrine	Nor + Dpx		4/10	3/12		90 d
Svoboda P [52]	2012	Terlipressin	Control		12/15	16/17		90 d
Torraco A [53]	2014	Levosimendan	Control		6/13	11/13		28 d

Dbt indicates dobutamine; Dpx, dopexamine; Nor, norepinephrine; Ter, terlipressin.

Charakteristika der Population:

- See table 1 (above)
- Patients with septic shock
- Most frequently investigated comparators:
  - Norepinephrine (1218 patients, 13 studies)
  - Dopamine (1141 patients, 8 studies)
  - Vasopressin (424 patients, 5 studies)
  - Epinephrine (302 patients, 6 studies)
  - Norepinephrine plus dobutamine (195 patients, 3 studies)
  - Dobutamine (129 patients, 6 studies)

Qualität der Studien:

- RCTs
- Trials were on average of moderate quality, with a total of 10 studies judged to carry a low risk of bias, 21 a moderate risk of bias, and 2 a high risk of bias.

Studienergebnisse:

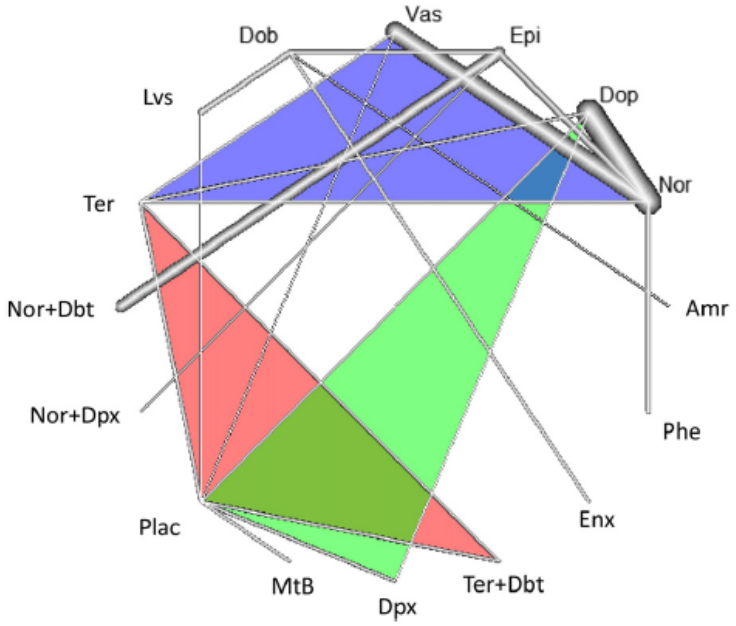


Fig. 2. Network configuration. Amr indicates amrinone; Dbt, dobutamine; Dop, dopamine; Dpx, dopexamine; Enx, enoximone; Epi, epinephrine; Lvs, levosimendan; MtB, methylene blue; Nor, norepinephrine; Phe, phenylephrine; Plac, placebo/standard treatment; Ter, terlipressin; Vas, vasopressin.

- There was no significant heterogeneity/inconsistency among comparisons investigated (I2 = 0%; Q statistics P value whole network, P = .99; within designs, P = .99; between designs, P = .94).
- Dopamine was associated with a significantly increased mortality when compared with other agents such as norepinephrine (OR for dopamine vs norepinephrine, 1.23; 95% CI, 1.00-1.52), vasopressin (OR for dopamine vs vasopressin, 1.56; 95% CI, 1.11-2.19), and levosimendan (OR for dopamine vs levosimendan, 3.67; 95% CI, 1.04- 10.97).

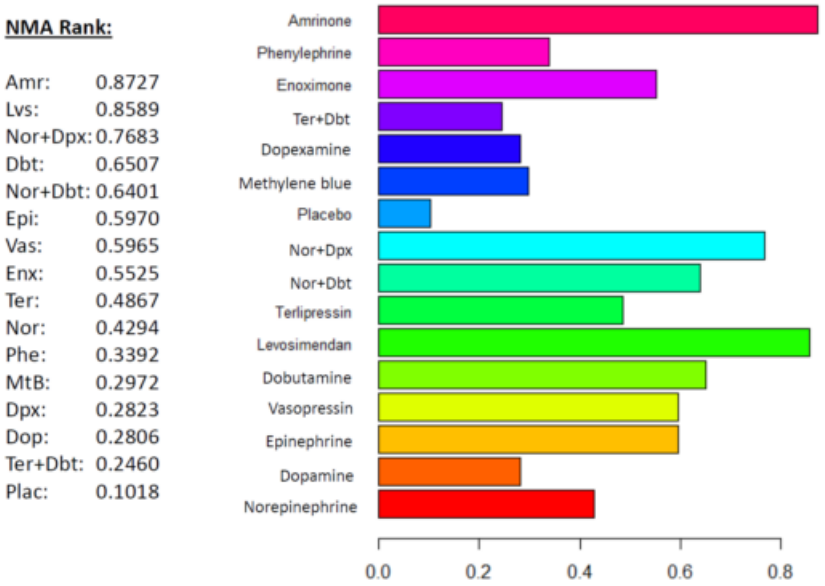
Table 2
. Results of head-to-head comparisons of the network analysis

Comparison	Nor	Dop	Epi	Vas	Dbt	Lvs	Ter	Nor + Dbt	Nor + Dpx	Plac	MtB	Dpx	Ter + Dbt	Enx	Phe	Amr
Nor	–	0.81 (0.66-1.00)	1.35 (0.71-2.56)	1.26 (0.26-1.66)	1.58 (0.55-4.58)	2.73 (0.85-8.79)	1.08 (0.52-2.26)	1.45 (0.68-3.09)	2.69 (0.39-18.52)	0.47 (0.20-1.10)	0.68 (0.15-3.00)	0.67 (0.18-2.54)	0.61 (0.13-2.35)	1.34 (0.28-6.33)	0.82 (0.35-1.95)	5.28 (0.45-61.87)
Dop	1.23 (1.00-1.52)	–	1.66 (0.85-3.25)	1.56 (1.11-2.19)	1.95 (0.67-5.73)	3.67 (1.04-10.97)	1.33 (0.63-2.80)	1.79 (0.82-3.91)	3.32 (0.48-23.07)	0.58 (0.25-1.36)	0.84 (0.19-3.70)	0.83 (0.22-3.11)	0.76 (0.20-2.90)	1.65 (0.35-7.89)	1.02 (0.42-2.46)	6.51 (0.55-76.80)
Epi	0.74 (0.39-1.41)	0.70 (0.31-1.18)	–	0.94 (0.47-1.88)	1.18 (0.47-3.97)	2.03 (0.69-5.99)	0.80 (0.31-2.09)	1.08 (0.72-1.61)	2.00 (0.32-12.33)	0.35 (0.13-0.96)	0.51 (0.10-2.45)	0.50 (0.12-2.13)	0.46 (0.11-1.97)	1.00 (0.23-4.31)	0.61 (0.21-1.79)	3.92 (0.45-43.51)
Vas	0.79 (0.60-1.04)	0.64 (0.46-0.90)	1.06 (0.53-2.13)	–	1.25 (0.42-3.73)	2.16 (0.65-7.13)	0.85 (0.40-1.83)	1.15 (0.51-2.56)	2.13 (0.30-14.92)	0.37 (0.16-0.89)	0.54 (0.12-2.40)	0.53 (0.14-2.05)	0.49 (0.13-1.89)	1.06 (0.22-5.11)	0.65 (0.27-1.61)	4.18 (0.35-49.57)
Dbt	0.63 (0.22-1.82)	0.51 (0.17-1.50)	0.85 (0.34-2.15)	0.80 (0.27-2.37)	–	1.72 (0.86-3.47)	0.68 (0.20-2.35)	0.92 (0.33-2.51)	1.70 (0.22-13.09)	0.30 (0.09-0.99)	0.43 (0.08-2.38)	0.43 (0.08-2.17)	0.39 (0.08-1.99)	0.85 (0.27-2.63)	0.52 (0.13-2.04)	3.33 (0.36-30.70)
Lvs	0.37 (0.11-1.18)	0.30 (0.09-0.97)	0.49 (0.17-1.46)	0.46 (0.14-1.53)	0.58 (0.29-2.37)	–	0.40 (0.11-1.47)	0.53 (0.17-1.69)	0.99 (0.12-8.19)	0.17 (0.05-0.60)	0.25 (0.04-1.42)	0.25 (0.05-1.32)	0.23 (0.04-1.20)	0.49 (0.13-1.86)	0.30 (0.07-1.29)	1.93 (0.19-0.82)
Ter	0.93 (0.44-1.93)	0.75 (0.36-1.58)	1.25 (0.48-3.24)	1.17 (0.55-2.51)	1.47 (0.43-5.06)	2.53 (0.68-9.41)	–	1.34 (0.48-3.79)	2.49 (0.32-19.46)	0.44 (0.18-1.05)	0.63 (0.14-2.82)	0.62 (0.15-2.56)	0.57 (0.16-1.97)	1.24 (0.23-6.66)	0.76 (0.25-2.37)	4.89 (0.38-62.18)
Nor + Dbt	0.69 (0.32-1.47)	0.56 (0.26-1.22)	0.93 (0.62-1.39)	0.87 (0.39-1.94)	1.09 (0.40-3.00)	1.88 (0.59-5.98)	0.74 (0.26-2.10)	–	1.86 (0.29-11.96)	0.32 (0.11-0.96)	0.47 (0.09-2.39)	0.46 (0.10-2.09)	0.42 (0.09-1.93)	0.92 (0.20-4.22)	0.57 (0.18-1.79)	3.64 (0.32-41.77)
Nor + Dpx	0.37 (0.05-2.55)	0.30 (0.04-2.09)	0.50 (0.08-3.08)	0.47 (0.07-3.29)	0.59 (0.08-4.53)	1.01 (0.12-8.43)	0.40 (0.05-3.13)	0.54 (0.08-3.47)	–	0.17 (0.02-1.40)	0.25 (0.02-2.81)	0.25 (0.02-2.56)	0.23 (0.02-2.35)	0.50 (0.05-5.14)	0.31 (0.04-2.53)	1.96 (0.10-40.04)
Plac	2.13 (0.91-4.98)	1.72 (0.74-4.04)	2.86 (1.05-7.85)	2.69 (1.13-6.43)	3.37 (1.01-11.28)	5.81 (1.67-20.24)	2.30 (0.96-5.52)	3.08 (1.04-9.13)	5.73 (0.72-45.82)	–	1.45 (0.43-4.88)	1.43 (0.40-5.11)	1.31 (0.37-4.56)	2.85 (0.54-14.95)	1.76 (0.53-5.88)	11.24 (0.90-140.72)
MtB	1.47 (0.33-6.46)	1.19 (0.27-5.24)	1.98 (0.41-9.57)	1.86 (0.42-8.27)	2.33 (0.42-12.89)	4.01 (0.70-22.87)	1.59 (0.35-7.08)	2.13 (0.42-10.85)	3.95 (0.36-43.91)	0.69 (0.21-2.32)	–	0.99 (0.17-5.74)	0.90 (0.16-5.15)	1.97 (0.25-15.35)	1.21 (0.22-6.72)	7.75 (0.47-128.03)
Dpx	1.48 (0.39-5.59)	1.20 (0.32-4.50)	2.00 (0.47-8.51)	1.88 (0.49-7.20)	2.35 (0.46-11.98)	4.05 (0.76-21.64)	1.60 (0.39-6.58)	2.15 (0.48-9.68)	3.99 (0.39-40.86)	0.70 (0.20-2.49)	1.01 (0.17-5.86)	–	0.91 (0.16-5.12)	1.99 (0.27-14.46)	1.23 (0.25-5.95)	7.83 (0.50-122.99)
Ter + Dbt	1.63 (0.43-6.22)	1.32 (0.34-5.05)	2.19 (0.51-9.43)	2.06 (0.53-7.97)	2.58 (0.50-13.19)	4.44 (0.83-23.77)	1.76 (0.51-6.08)	2.36 (0.52-10.72)	4.38 (0.43-45.11)	0.76 (0.22-2.67)	1.11 (0.19-6.33)	0.20 (1.10-6.16)	–	2.18 (0.30-15.92)	1.34 (0.27-6.60)	8.59 (0.55-135.21)
Enx	0.75 (0.16-3.52)	0.60 (0.13-2.89)	1.00 (0.23-4.34)	0.94 (0.20-4.55)	1.18 (0.38-3.67)	2.04 (0.54-7.72)	0.81 (0.15-4.32)	1.08 (0.24-4.94)	2.01 (0.19-20.74)	0.35 (0.07-1.84)	0.51 (0.07-3.96)	0.50 (0.07-3.66)	0.46 (0.06-3.35)	–	0.62 (0.10-3.63)	3.94 (0.33-47.65)
Phe	1.21 (0.51-2.86)	0.98 (0.41-2.37)	1.63 (0.56-4.76)	1.53 (0.20-4.55)	1.92 (0.49-7.51)	3.31 (0.78-14.10)	1.31 (0.42-4.05)	1.76 (0.56-5.51)	3.26 (0.40-26.91)	0.57 (0.17-1.90)	0.82 (0.15-4.57)	0.82 (0.17-3.96)	0.74 (0.15-3.66)	1.62 (0.28-9.57)	–	6.40 (0.47-86.64)
Amr	0.19 (0.02-2.22)	0.15 (0.01-1.81)	0.25 (0.02-2.83)	0.24 (0.02-2.84)	0.30 (0.03-2.76)	0.52 (0.05-5.30)	0.20 (0.02-2.60)	0.27 (0.02-3.15)	0.51 (0.02-10.41)	0.09 (0.01-1.11)	0.13 (0.01-2.13)	0.13 (0.01-2.00)	0.12 (0.01-1.83)	0.25 (0.02-3.07)	0.16 (0.01-2.12)	–

Data presented as OR (95% CI). Amr indicates amrinone; Dop, dopamine; Enx, enoximone; Epi, epinephrine; Lvs, levosimendan; MtB, methylene blue; Phe, phenylephrine; Plac, placebo/standard treatment; Vas, vasopressin.

- Rank analysis showed that among treatments found to be significantly associated with reduced mortality, levosimendan showed the highest probability to be the best (85%) followed by dobutamine (65%), the combination of norepinephrine plus dobutamine (64%), epinephrine (60%), and vasopressin (59%).

Supplementary Figure 2. Ranking of the different treatment, expressed as probability of being the best.



NMA: network meta-analysis; Amr: amrinone; Dbt: dobutamine; Dop: dopamine; Dpx: dopexamine; Enx: enoximone; Epi: epinephrine; Lvs: levosimendan; MtB: methylene blue; Nor: norepinephrine; Phe: phenylephrine; Plac: placebo/standard treatment; Ter: terlipressin; Vas: vasopressin.

Anmerkung/Fazit der Autoren

In patients with septic shock, use of inodilators is associated with the highest survival probability. Among 16 different treatment regimens, levosimendan is the most promising, followed by dobutamine and a combination of dobutamine plus norepinephrine. Nevertheless, available evidence is still insufficient to recommend such treatment because of lack of high-quality, multicenter RCTs. Future RCTs focusing on the role of inodilators in septic shock are warranted.

Kommentar zum Review:

- Studies investigating drugs currently not available on the market either in Europe or in the United States were excluded.
- In the study selection there were no restrictions regarding the severity of sepsis, leading to inclusion of studies of sepsis, severe sepsis and septic shock. Even though the results (and the title of the meta-analysis) have been described as if they were exclusively for patients with septic shock. The study populations of the included trials have not been described.
- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

Chidambaram S et al., 2019 [4].

Vasopressin vs. noradrenaline: Have we found the perfect recipe to improve outcome in septic shock?

Fragestellung

to compare the outcomes of noradrenaline against vasopressin in managing patients with septic shock.

Methodik

Population:

- Adult patients ≥16 years with sepsis (at least two of the systematic inflammatory response criteria due to known or suspected infection)
- vasopressor requirement despite adequate intravenous fluid resuscitation as assessed by clinical examination, central venous pressure, oxygen saturation, or other physiological parameters using repeated fluid challenges
- no previous continuous infusion of vasopressors during current admission
- no known end-stage renal disease, mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis or other vasospastic disease
- non-pregnant

Intervention:

- Noradrenaline (Norepinephrine)

Komparator:

- Vasopressin

Endpunkte

- Primary outcome:
  - 28-day mortality rate
- Secondary outcomes:
  - days alive
  - rate of organ dysfunction
  - length of stay in the intensive care unit (ICU)
  - rate of adverse events

Recherche/Suchzeitraum

- The following databases were searched: a) MEDLINE (1946 till April week 1 2018) via OvidSP, last search on 4th April 2018; b) MEDLINE in process and other non-indexed citations (latest issue) via OvidSP, last search on 4th April 2018; c) Ovid EMBASE (1974 to latest issue), last search 4th April 2018; d) Scopus (1996 till present), last search on 4th April 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

- Quality of evidence was assessed using GRADE

Studienergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs: 1039 patients (range 23-779)
  - Vasopressin group: 529 patients
  - Noradrenaline group: 510 patients

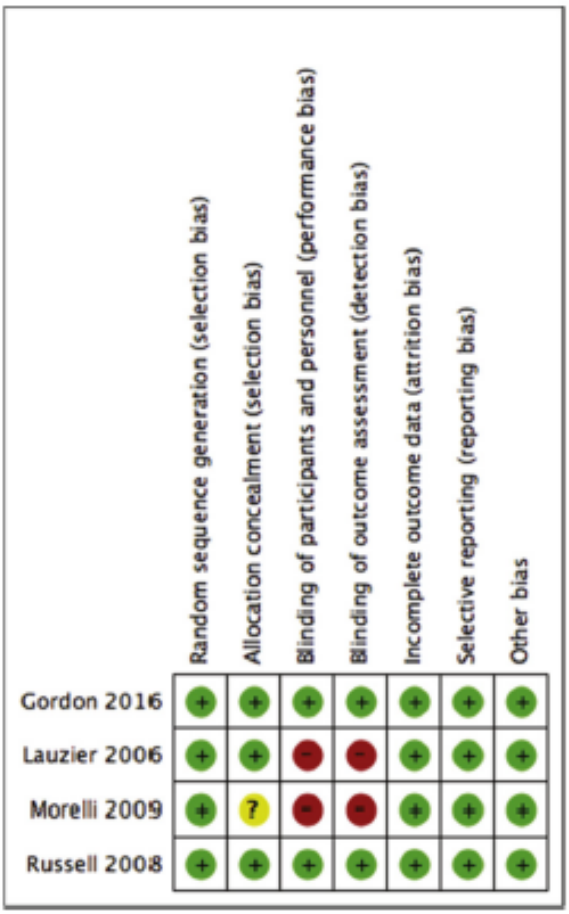
Charakteristika der Population:

Table 1
Study characteristics.

Study	Number of patients (*n*)		Age		M:F ratio		Severity score system	Baseline severity score		Duration of therapy
	VP	NE	VP	NE	VP	NE		VP	NE	
Lauzier 2006	13	10	51.2 (17.2)	58.1 (17.5)	6:7	8:2	APACHE II	22.8 (3.4)	23.5 (4.2)	Up to 48 h
Russell 2008	397	382	59.3 (16.4)	61.8 (16.0)	246:151	229:153	APACHE II	27.0 (7.7)	27.1 (6.9)	As required
Morelli 2009	15	15	67.3 (6.5)	65.5 (6.5)	10:5	12:3	SAPS II	58.2 (13.9)	59.5 (13.1)	Up to 48 h
Gordon 2016	104	103	68.2 (7.5)	66.0 (7.5)	52:52	65:37	APACHE II	24.0 (7.5)	23.7 (9.0)	As required

Qualität der Studien:

- Risk of bias of included studies:



Studienergebnisse:

- Mortality rate
  - Four studies evaluated the mortality rate at different time-points throughout the study. Overall, vasopressin treatment was associated with a marginally lower 28-day mortality rate compared to noradrenaline treatment, with a RR of 0.92 (95% CI: 0.78, 1.08, p=.32, I2=0%). No evidence of heterogeneity was present and the quality of evidence was deemed high.

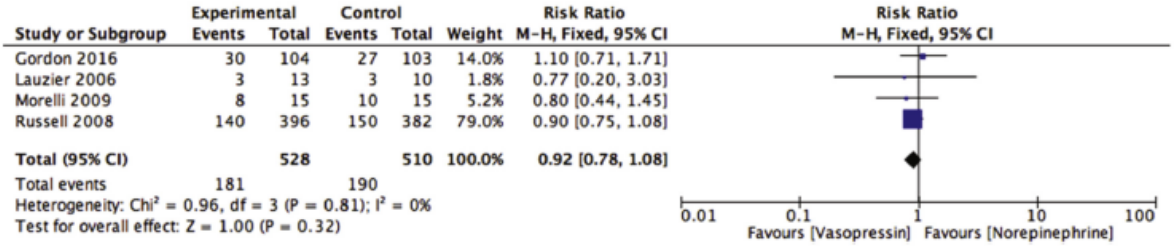


Fig. 4. 28-day mortality rate.

- ICU length of stay
  - The duration of stay in the ICU was reported by three studies. There was a slightly increased ICU length of stay in the vasopressin group compared to the noradrenaline group, with a MD of 0.14 (95% CI: -1.37, 1.65, p = .86, I2 = 46%). Moderate heterogeneity was present and the quality of evidence was deemed moderate.
- Adverse events
  - Three studies documented the incidence of adverse events following treatment with vasopressin and noradrenaline. Patients treated with vasopressin had a marginally increased risk of adverse events compared to those treated with noradrenaline, with a RR of 1.19 (95% CI: 0.83, 1.70, p = .35, I2 = 13%). There was low heterogeneity present and the quality of evidence was deemed to be moderate.
- Additional outcome measures
  - Additional outcome measures reported included regional hemodynamics, sequential organ failure assessment (SOFA) score, organ dysfunction/ failure and use of inotropes. Due to significant heterogeneity in the data, a pooled meta-analysis could not be performed. A qualitative assessment demonstrated comparable outcomes between both groups.

Anmerkung/Fazit der Autoren

In conclusion, it can be suggested that there is no significant difference in 28-day survival or length of ICU stay between a regime of only noradrenaline compared to a combination of noradrenaline and vasopressin. However, there is a role for vasopressin in selected patients experiencing less severe septic shock beyond a 36-h period. Further work is necessary to characterize an optimal regime, and to determine whether initial vasopressin usage as well as additional patient factors that have a similar predictive role on whether vasopressin will play a role.

Kommentar zum Review:

- Only 4 studies, of which one accounts for a major proportion of the sample size (Russel 2008)
- Primary studies did not measure vasopressin levels and the dose and regime of vasopressors used were not standardized across studies.
- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

Nagendran M et al., 2016 [11].

Comparative safety and efficacy of vasopressors for mortality in septic shock: a network meta-analysis.

Fragestellung

The aim of this review was to compare the safety and relative efficacy of different vasopressor agents on 28-day mortality and arrhythmia incidence in septic shock patients.

Methodik

Population:

- patients with septic shock

Intervention:

- vasopressor

Komparator:

- another type of vasopressor
- no active intervention

Endpunkte

- 28-day mortality
- arrhythmia incidence

Recherche/Suchzeitraum:

- The following databases were searched from inception to September 2014: MEDLINE, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Studienergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs:
  - 28-day mortality: 3146 patients
  - arrhythmias: 2198 patients

Characteristics of population:

Table 1. Characteristics of included trials.

References	No. of patients	Intervention in group 1	Intervention in group 2	Age	Female (%)	Severity score system	Baseline severity score	Therapy duration
Annane et al. 2007[26]	330	EPI	NOREPI + DOB	63	39	SAPS II	53	As required to day 28
De Backer et al.[3]	1044	DOPA	NOREPI	NR	NR	NR	NR	As required to day 28
Lauzier et al. 2006[27]	23	VASO	NOREPI	54	39	APACHE II	23	Up to 48 h
Mahmoud & Ammar 2012[28]	60	NOREPI + DOB	NOREPI + EPI	51	48	SOFA	15	NR
Morelli et al. 2008[29]	32	NOREPI	PHENYL	70	34	SAPS II	56	Up to 12 h
Morelli et al.[30]	45	NOREPI	VASO/TERLI	66	27	SAPS II	60	Up to 48 h
Myburgh et al. 2008[31]	158	EPI	NOREPI	NR	NR	NR	NR	Until target MAP without vasopressor
Oliveira et al. 2014[32]	407	NOREPI	VASO	NR	NR	NR	NR	NR
Patel et al. 2002[33]	24	NOREPI	VASO	68	25	APACHE II	23	Up to 4 h
Patel et al. 2010[34]	252	DOPA	NOREPI	NR	54	APACHE II	28	As required to day 28
Russell et al.[4]	802	NOREPI	VASO	61	38	APACHE II	27	As required
Svoboda et al. 2012[35]	32	TERLI	NOREPI	73	38	SOFA	18	Up to 72 h
Zambolim et al.[36]	107	VASO	NOREPI	NR	NR	NR	NR	NR

APACHE: acute physiology and chronic health evaluation; DOB: dobutamine; DOPA: dopamine; EPI: epinephrine; MAP: mean arterial pressure; NOREPI: norepinephrine; NR: not reported; PHENYL: phenylephrine; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; TERLI: terlipressin; VASO: vasopressin.

Charakteristika der Population:

Table 2. Risk of bias in included trials.

References	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome data	Selective outcome reporting	Source of funding
Annane et al. 2007[26]	Low	Low	Low	Low	Low	Low	Low
De Backer et al.[3]	Low	Low	Low	Low	Low	Low	Unclear
Lauzier et al. 2006[27]	Low	Low	High	High	High	Unclear	Low
Mahmoud & Ammar 2012[28]	Low	Low	Unclear	Low	Low	Unclear	Low
Morelli et al. 2008[29]	Low	Low	Low	Low	Undear	Low	Low
Morelli et al.[30]	Low	Low	Low	Low	Undear	Low	Low
Myburgh et al. 2008[31]	Low	Low	Low	Unclear	High	Unclear	Low
Oliveira et al. 2014[32]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
Patel et al. 2002[33]	Low	Unclear	Unclear	Unclear	Undear	Unclear	Unclear
Patel et al. 2010[34]	High	High	High	High	Low	Low	Low
Russell et al.[4]	Low	Low	Low	Low	High	Low	Low
Svoboda et al. 2012[35]	Low	Low	Unclear	Unclear	High	Unclear	Low
Zambolim et al.[36]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear

Studienergebnisse:

28-day mortality

- Direct comparison:
  - Two studies compared norepinephrine versus dopamine. There was no significant difference in mortality (odds ratio (OR) 0.83 (95% CI 0.67 to 1.03)).
  - Three studies compared norepinephrine with vasopressin analogues. There was no significant difference in mortality (OR 1.13 (95% CI 0.86 to 1.48)).

  [no visual or statistical evidence of heterogeneity]
- Network meta-analysis:
  - Vasopressin was superior to dopamine (OR 0.68 (95% CI 0.5 to 0.94)).

Table 3. 28-day mortality effect estimates from network meta-analysis.

	Norepinephrine	Dopamine	Epinephrine	Vasopressins	Norepinephrine and epinephrine	Norepinephrine and dobutamine
Norepinephrine	–	OR 1.2; 95% CI 0.97 to 1.5	OR 0.69; 95% CI 0.34 to 1.42	OR 0.82; 95% CI 0.66 to 1.03	OR 0.63; 95% CI 0.17 to 2.37	OR 0.55; 95% CI 0.23 to 1.27
Dopamine	–	–	OR 0.58; 95% CI 0.27 to 1.22	**OR 0.68; 95% CI 0.5 to 0.94**	OR 0.52; 95% CI 0.14 to 2	OR 0.45; 95% CI 0.19 to 1.09
Epinephrine	–	–	–	OR 1.19; 95% CI 0.56 to 2.52	OR 0.91; 95% CI 0.2 to 4.1	OR 0.79; 95% CI 0.26 to 2.39
Vasopressins	–	–	–	–	OR 0.76; 95% CI 0.2 to 2.93	OR 0.66; 95% CI 0.28 to 1.59
Norepinephrine and epinephrine	–	–	–	–	–	OR 0.87; 95% CI 0.18 to 4.21
Norepinephrine and dobutamine	–	–	–	–	–	–

Note: The odds ratio represents the odds of mortality in the agent at the top of the table relative to the agent in the first column of the table.
CI, 95% credible intervals (equivalent to 95% confidence intervals); OR: odds ratio.

Arrhythmias

- Direct comparison:
  - Two studies compared norepinephrine versus dopamine. There were significantly more arrhythmias in the dopamine group compared to norepinephrine (OR 2.69 (95% CI 2.08 to 3.47).
  - Three studies compared norepinephrine with vasopressin analogues. There was no significant difference in arrhythmias between the groups (OR 1.36 (95% CI 0.56 to 3.31).

  [evidence of substantial heterogeneity in the vasopressin comparison]
- Network meta-analysis:
  - There were no statistically significant differences. Most of the confidence intervals were extremely wide.

Anmerkung/Fazit der Autoren

In this network meta-analysis, vasopressin was superior to dopamine for 28-day mortality in septic shock. Existing pairwise information supports the use of norepinephrine over dopamine. Our findings suggest that dopamine should be avoided in patients with septic shock and that other vasopressor agents should continue to be based on existing guidelines and clinical judgement of the specific presentation and circumstances of the patient.

Kommentar zum Review:

- Results from direct comparisons based on a small number of studies
- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

Zhou F et al., 2015 [17].

Vasopressors in septic shock: a systematic review and network meta-analysis

Fragestellung

To compare the effects among different types of vasopressor agents.

Methodik

Population:

- adult patients (at least 18 years) with septic shock

Intervention:

- vasopressor

Komparator:

- another vasopressor

Endpunkte

- mortality
- cardiac events
- hemodynamic and metabolic parameters

Recherche/Suchzeitraum:

- PubMed (US National Library of Medicine, Bethesda, MD, USA) and Cochrane Library databases and EMBASE from database inception to December 2014

Qualitätsbewertung der Studien:

- Jadad scale

Studienergebnisse

Anzahl eingeschlossener Studien:

- 21 RCTs: 3819 patients
  - 14 single-center studies
  - 7 multi-center studies

Source	Interventions
Mahmoud and Ammar[11]	NE+DB vs NE+EN
Gordon et al[30]	NE vs VP
De Backer et al[35]	NE vs DA
Patel et al*	NE vs DA
Gordon et al[30]	NE vs VP
Jain and Singh[32]	NE vs PE
Morelli et al[31]	NE vs VP vs TP
Morelli et al[9]	NE vs PE
Morelli et al[29]	NE vs TP+NE vs TP+DB
Myburgh[28]	NE vs EN
Russell et al[10]	NE vs VP
Annane et al[27]	NE+DB vs EN
Mathur et al[26]	NE vs DA
Lauzier et al[25]	NE vs VP
Seguin et al[24]	NE+DX vs EN
Albanese et al[23]	NE vs TP
Seguin et al[22]	NE+DB vs EN
Levy et al[21]	NE+DB vs EN
Marik and Mohedin[18]	NE vs DA
Martin et al[20]	NE vs DA
Ruokonen et al[19]	NE vs DA

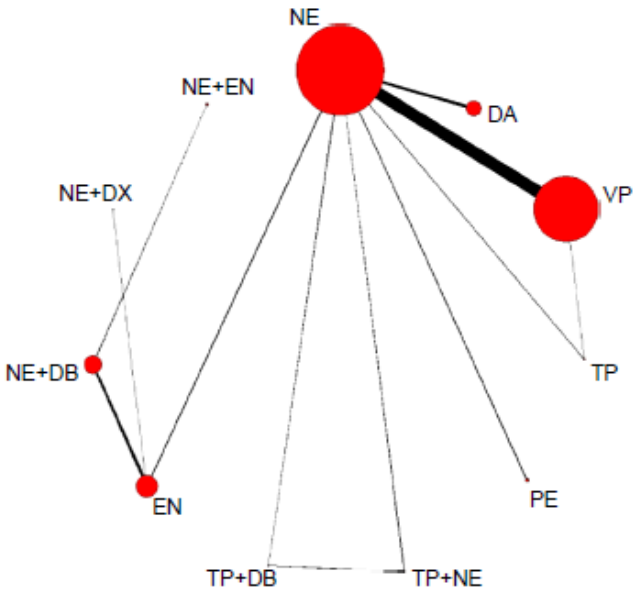


Figure 2 Network of eligible comparisons for the multiple-treatment meta-analysis for mortality.
Notes: The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomized participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.
Abbreviations: DA, dopamine; DB, dobutamine; DX, dopexamine; EN, epinephrine; NE, norepinephrine; PE, phenylephrine; TP, terlipressin; VP, vasopressin.

Charakteristika der Population:

- See Appendix (table 1) for characteristics of the randomized trials.
- Mean age ranged from 18 years to 70 years, and the proportion of male patients ranged from 46% to 77.3%. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 23.8.

Qualität der Studien:

- Sequence of randomisation reported in 19 of 21 studies
- Blinding conducted in 9 of 21 studies
- Mean Jada Score 3.3

Studienergebnisse:

Mortality

- When compared to norepinephrine, dopamine was associated with increased mortality (OR: 1.24, 95% CI: 1.01, 1.53).
- no significant difference in mortality in direct or indirect comparisons between other different vasopressor agents and vasopressor combinations
- for the probability of mortality, the possible rank from low to high was norepinephrine + dobutamine (area under the curve [AUC]: 0.2648), epinephrine (AUC: 0.3473), terlipressin (AUC: 0.379), norepinephrine + epinephrine (AUC: 0.3943), terlipressin + norepinephrine (AUC: 0.3967), vasopressin (AUC: 0.4212), terlipressin + dobutamine (AUC: 0.5423), norepinephrine (AUC: 0.5752), phenylephrine (AUC: 0.6796), norepinephrine + dopexamine (AUC: 0.7279), and dopamine (AUC: 0.7718)

NE	1.24 (1.01, 1.53)	0.91 (0.75, 1.11)	0.73 (0.24)	1.21 (0.51, 2.86)	0.73 (0.19, 2.79)	1.00 (0.26, 3.87)	0.70 (0.34, 1.43)	—	—	—
1.3 (0.96, 1.84)	DA	—	—	—	—	—	—	—	—	—
0.86 (0.61, 1.16)	0.68 (0.4, 1.003)	VP	0.77 (0.18)	—	—	—	—	—	—	—
0.85 (0.25, 2.12)	0.67 (0.19, 1.71)	1.003 (0.3, 2.53)	TP	—	—	—	—	—	—	—
1.36 (0.48, 3.03)	1.08 (0.34, 2.51)	1.63 (0.53, 3.77)	2.16 (0.4, 6.996)	PE	—	—	—	—	—	—
0.98 (0.17, 3.29)	0.77 (0.13, 2.66)	1.17 (0.19, 3.93)	1.55 (0.17, 5.803)	0.89 (0.11, 3.43)	TP+NE	1.36 (0.36, 5.17)	—	—	—	—
1.31 (0.23, 4.18)	1.03 (0.17, 3.48)	1.56 (0.26, 5.08)	2.03 (0.23, 7.86)	1.2 (0.15, 4.86)	1.76 (0.32, 5.66)	TP+DB	—	—	—	—
0.77 (0.31, 1.62)	0.61 (0.22, 1.33)	0.92 (0.34, 1.99)	1.22 (0.25, 3.53)	0.71 (0.17, 2.02)	1.38 (0.18, 4.98)	1.04 (0.14, 4.04)	EN	0.86 (0.57, 1.30)	2.14 (0.28, 16.37)	—
0.71 (0.24, 1.71)	0.56 (0.17, 1.36)	0.84 (0.27, 2.11)	1.11 (0.21, 3.45)	0.65 (0.14, 1.99)	1.27 (0.15, 4.86)	0.96 (0.11, 3.81)	0.91 (0.54, 1.501)	NE+DB	—	1.14 (0.41, 3.15)
4.95 (0.19, 24.21)	3.95 (0.14, 18.85)	5.92 (0.22, 28.96)	8.04 (0.18, 40.1)	4.38 (0.13, 23.88)	9.52 (0.16, 55.39)	7.23 (0.13, 39.79)	6.62 (0.3, 29.21)	7.57 (0.32, 36.73)	NE+DX	—
0.95 (0.18, 3.09)	0.74 (0.13, 2.45)	1.14 (0.21, 3.82)	1.5 (0.17, 5.82)	0.87 (0.11, 3.39)	1.72 (0.13, 7.78)	1.28 (0.1, 5.78)	1.24 (0.33, 3.32)	1.36 (0.41, 3.35)	0.87 (0.03, 4.77)	NE+EN

Treatment | Direct comparison | NMA comparison

Figure 3 Mortality of different vasopressors in direct comparison and network meta-analysis in terms of mortality.
Notes: Results are the ORs and CIs in the row-defining treatment compared with the ORs and CIs in the column-defining treatment. For mortality, ORs >1 favor the row-defining treatment. Network meta-analysis results are at the bottom-left of the figure, while direct comparison results are at the upper-right of the figure.
Abbreviations: CI, confidence interval; DA, dopamine; DB, dobutamine; DX, dopexamine; EN, epinephrine; NE, norepinephrine; NMA, network meta-analysis; OR, odds ratio; PE, phenylephrine; TP, terlipressin; VP, vasopressin.

Cardiac adverse events

- cardiac events mainly consisted of arrhythmias and tachycardia
- norepinephrine decreased cardiac adverse events significantly compared to dopamine
- no significant difference in cardiac adverse events was found between other vasopressor agents and vasopressor combinations.

Table 3 Direct comparison of different vasopressors on cardiac adverse events

	Number of studies	Number of patients	OR (95% CI)	Heterogeneity I^2 (*P*-value)	Test for effect (*P*-value[a])
NE vs DA	1[24]	252	0.15 (0.05, 0.43)	–	0.0005
NE vs VP	3[10,25,31]	831	1.30 (0.73, 2.32)	0% (0.48)	0.38
NE vs TP	1[21]	30	12.13 (0.59, 248.49)	–	0.11
NE vs PE	1[9]	32	0.47 (0.04, 5.73)	–	0.55
TP+NE vs TP+DB	1[27]	330	0.88 (0.53, 1.45)	–	0.61
TP+DB vs EN	1[11]	60	0.66 (0.18, 2.36)	–	0.52

Note: [a]Fixed-effect model.
Abbreviations: CI, confidence interval; DA, dopamine; DB, dobutamine; EN, epinephrine; NE, norepinephrine; PE, phenylephrine; TP, terlipressin; VP, vasopressin; vs, versus.

Hemodynamic and metabolic parameters

- norepinephrine vs. dopamine:
  - norepinephrine decreased heart rate (SMD: -2.10; 95% CI: -3.95, -0.25; P=0.03) and cardiac index (SMD: -0.73; 95% CI: -1.14, -0.03; P=0.004) and increased SVRI (SMD: 1.03; 95% CI: 0.61, 1.45; P<0.0001), but there was no significant difference on MAP, oxygen delivery (DO2), oxygen consumption (VO2), and lactate.
- Vasopressin vs. Norepinephrine:
  - vasopressin significantly decreased heart rate (SMD: 0.21; 95% CI: 0.07, 0.34; P=0.003).
- epinephrine vs. norepinephrine + dobutamine combination:
  - epinephrine did not show a significant difference in heart rate, MAP, cardiac index, pulmonary MAP, DO2, VO2, and lactate
- epinephrine vs. norepinephrine + epinephrine combination:
  - norepinephrine + epinephrine combination was more effective in reversing the abnormalities of cardiovascular parameters
  - norepinephrine + epinephrine combination had significantly higher MAP, heart rate, central venous pressure (CVP), cardiac index, SVRI, ejection fraction, left ventricular end diastolic volume, DO2, lactate, and urine output

Table 4 Direct comparison of different vasopressors on hemodynamic and metabolic parameters

	Number of studies	Number of patients	SMD IV (95% CI)	Heterogeneity I^2 (*P*-value)	Test for effect (*P*-value)
NE vs DA					
HR	4[18–20,26]	105	−2.10 (−3.95, −0.25)	91% (<0.0001)	0.03[a]
MAP	3[18–20]	55	0.64 (−1.09, 2.38)	87% (0.0004)	0.47[a]
Cardiac index	4[18–20,26]	105	−0.73 (−1.14, −0.03)	43% (0.15)	0.004[b]
SVRI	4[18–20,26]	105	1.03 (0.61, 1.45)	26% (0.25)	<0.0001[b]
DO_2	4[18–20,26]	105	−0.54 (−1.50, 0.42)	79% (0.003)	0.27[a]
VO_2	4[18–20,26]	105	−0.49 (−1.37, 0.39)	75% (0.008)	0.27[a]
Lactate	3[18–20]	55	0.01 (−0.53, 0.56)	23% (0.27)	0.96[a]
NE vs VP					
HR	3[10,25,31]	831	0.21 (0.07, 0.34)	0% (0.96)	0.003[b]
MAP	3[10,25,31]	831	−0.07 (−0.21, 0.07)	0% (0.70)	0.76[b]
Cardiac index	3[25,30,31]	294	−0.04 (−0.26, 0.19)	0% (0.93)	0.76[b]
SVRI	2[25,31]	53	0.15 (−0.39, 0.70)	0% (0.91)	0.58[b]
DO_2	2[25,31]	53	−0.06 (−0.62, 0.49)	0% (0.42)	0.82[b]
VO_2	2[25,31]	53	0.03 (−0.52, 0.59)	0% (0.44)	0.91[b]
Lactate	2[25,31]	53	0.25 (−0.31, 0.80)	0% (0.95)	0.38[b]
NE+DB vs EN					
HR	2[21,22]	52	0.33 (−0.22, 0.89)	49% (0.16)	0.24[b]
MAP	2[21,22]	52	−0.24 (−0.78, 0.31)	0% (0.99)	0.90[b]
Cardiac index	2[21,22]	52	−0.04 (−0.59, 0.51)	48% (0.17)	0.90[b]
MPAP	2[21,22]	52	−0.09 (−0.63, 0.45)	0% (0.71)	0.75[b]
DO_2	2[21,22]	52	−0.19 (−0.74, 0.36)	47% (0.17)	0.50[b]
VO_2	2[21,22]	52	−0.13 (−0.67, 0.42)	0% (0.41)	0.65[b]
Lactate	2[21,22]	52	−0.11 (−0.66, 0.43)	0% (0.59)	0.69[b]

Notes: [a]Random-effects model; [b]fixed-effect model.

Abbreviations: CI, confidence interval; DA, dopamine; DB, dobutamine; DO_2, oxygen delivery; EN, epinephrine; HR, heart rate; IV, inverse variance method; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; NE, norepinephrine; SMD, standardized mean difference; SVRI, systemic vascular resistance index; VO_2, oxygen consumption; VP, vasopressin; vs, versus.

Anmerkung/Fazit der Autoren

In terms of survival, norepinephrine may be superior to dopamine. Otherwise, there is insufficient evidence to suggest that any other vasopressor agent or vasopressor combination is superior to another. When compared to dopamine, norepinephrine is associated with decreased cardiac adverse events, heart rate, and cardiac index, as well as increased SVRI. The effects of vasopressor agents or vasopressor combinations on patients with septic shock require further investigation by larger-scale RCTs.

Kommentar zum Review

- See Appendix (table 1) for characteristics of the randomized trials.
- Jadad Scores for each study not presented.
- Aussagen möglich zum septischen Schock, keine Untersuchungen zu weiteren Subtypen des distributiven Schocks (Anaphylaktischer Schock, neurogener Schock)

3.4 Leitlinien

Annane D et al., 2017 [2].

Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM)

Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I)

Leitlinienorganisation/Fragestellung

To update the 2008 consensus statements for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adult and pediatric patients.

Methodik

Grundlage der Leitlinie

- A multispecialty task force of 16 international experts in Critical Care Medicine, endocrinology, and guideline methods, all of them members of the Society of Critical Care Medicine and/or the European Society of Intensive Care Medicine.
- All members were allowed to participate in all discussions and had equal weight in formulating the statements or in voting. All were allowed equal involvement in data extraction and writing the rationales.
- Some research questions had been previously addressed in the 2008 guidelines and required updates of the evidence summaries, whereas others required de novo systematic reviews.
- Systematic methods to identify relevant research:
  - Databases: The Cochrane Database of Systematic Reviews, DARE, CENTRAL, and Medline for all PICO questions on diagnosis and treatment. All searches were updated through May 2017.
  - If a previous meta-analysis of high quality was identified which addressed one of the PICO questions, this was used or updated to incorporate new evidence since its publication.
  - The methods chair also searched guideline databases and organizations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Health and Care Excellence, and professional critical care and endocrinology societies for guidelines in order to screen the reference lists.
- All recommendations were developed based on the GRADE evidence profiles for each recommendation. Each of the following factors was considered in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the patient's values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation.
- Recommendation approval required the agreement of at least 80% of the task force members.

- For each intervention question a list of outcomes was compiled, reflecting both benefits and harms of alternative management strategies. Outcomes (from the perspective of a patient) were ranked from “low” to “critical” importance and agreed by consensus of the task force members.

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- According to the GRADE approach the strength of each recommendation was classified as strong or conditional (strong: we recommend, conditional: we suggest)
- The quality of evidence was rated from high to very low based on factors including the individual study design, the risk of bias, the consistency of the results, and the directness and precision of the evidence.

Hinweis:

- Sources cited in the respective background text on recommendations
- Funding: There was no input or funding from industry to produce this guideline.

Empfehlungen

For corticosteroid use in critical care conditions:

Recommendation B:

We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).

Recommendation C:

If using corticosteroids for septic shock, we suggest using long course and low dose (e.g., IV hydrocortisone <400 mg/day for at ≥3 days at full dose) rather than high dose and short course in adult patients with septic shock (conditional recommendation, low quality of evidence).

Rationale:

- The latest Cochrane systematic review of the use of low-dose hydrocortisone for treating septic shock, including 33 RCTs with a total of 4268 patients [42], showed that corticosteroids significantly reduced the risk of death at 28 days compared with placebo.
- A network meta-analysis of 22 trials suggested no clear evidence for the superiority of one type of corticosteroids over another in adult patients with septic shock [43].
- Given the consistent effect of corticosteroids on shock reversal and the low risk for superinfection with low-dose corticosteroids, the task force suggests the use of low-dose IV hydrocortisone <400 mg/day for at least 3 days at full dose, or longer in adult patients with septic shock that is not responsive to fluid and moderate to high-dose (>0.1 µg/kg/min of norepinephrine or equivalent) vasopressor therapy.
- The task force panel was unable to comment on pediatric patients with septic shock as the meta-analyses reviewed did not include enough patients in this age group.
- Since the publication of the Cochrane meta-analysis in 2015, a few small studies of early corticosteroid therapy in patients with pediatric septic shock and adult patients with sepsis-associated ARDS have been published [45–47] but the results are consistent with the current recommendations.

42. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y (2015) Corticosteroids for treating sepsis. Cochrane Database Syst Rev. 12:CD002243 43. Gibbison B, López-López JA, Higgins JP, Miller

T, Angelini GD, Lightman SL, Annane D (2017) Corticosteroids in septic shock: a systematic review and network meta-analysis. Crit Care 21(1):78
45. Menon K, McNally D, O'Hearn K, Canadian Critical Care Trials Group et al (2017) A randomized controlled trial of corticosteroids in pediatric septic shock: a pilot feasibility study. Pediatr Crit Care Med 18(6):505–512
46. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU (2016) Hydrocortisone treatment in early sepsisassociated acute respiratory distress syndrome: results of a randomized controlled trial. Crit Care 20(1):329
47. El-Nawawy A, Khater D, Omar H, Wali Y (2017) Evaluation of early corticosteroid therapy in management of pediatric septic shock in pediatric intensive care patients: a randomized clinical study. Pediatr Infect Dis J 36(2):155–159

Kommentar zur Leitlinie

- Keine Empfehlungen zu weiteren Subtypen des distributiven Schocks (z.B. anaphylaktischer oder neurogener Schock)

Joannidis M et al., 2017 [6].

Working Group on Prevention, AKI section, European Society of Intensive Care Medicine

Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017

Leitlinienorganisation/Fragestellung

To determine and update previous recommendations for the prevention of AKI, specifically the role of fluids, diuretics, inotropes, vasopressors/vasodilators, hormonal and nutritional interventions, sedatives, statins, remote ischaemic preconditioning and care bundles.

Methodik

Grundlage der Leitlinie

- Systematic literature search: MEDLINE (1966 through March 2017), EMBASE (1980 through March 2017), CINAHL (1982 through March 2017), Web of Science (1955 through March 2017) and PubMed/PubMed CENTRAL
- clinical conditions considered: major surgery, critical illness, sepsis, shock, exposure to potentially nephrotoxic drugs and radiocontrast
- Clinical endpoints included incidence or grade of AKI, the need for renal replacement therapy and mortality
- Delphi process

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- GRADE

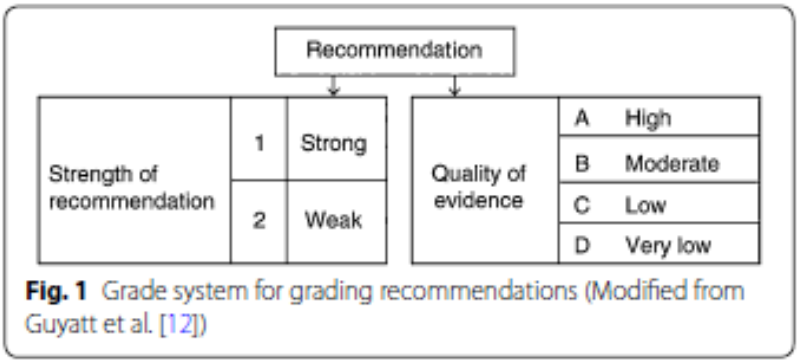


Fig. 1 Grade system for grading recommendations (Modified from Guyatt et al. [12])

- best practice statements (BPSs), which represent ungraded strong recommendations

Table 1 Criteria for best practice statements (Modified from Guyatt et al. [14])

	Criteria for best practice statements
1	Is the statement clear and actionable?
2	Is the message necessary?
3	Is the net benefit (or harm) unequivocal?
4	Is the evidence difficult to collect and summarize?
5	Is the rationale explicit?
6	Is this better to be formally GRADEd?

GRADE Gradings of Recommendations, Assessment, Development, and Evaluation

Hinweis

- Process of study selection not described
- Sources cited in the respective background text on recommendations
- Funding: Open access funding provided by University of Innsbruck and Medical University of Innsbruck.

Empfehlungen

Volume expansion

6. We suggest using human serum albumin if a colloid is deemed necessary for the treatment of patients with septic shock (Grade 2C).

Rationale:

- Post-hoc analysis showed survival benefit in septic shock[74], confirmed by meta-analyses[76,77]

74. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ALBIOS Study Investigators (2014) Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 370:1412–1421

76. Wiedermann CJ, Joannidis M (2014) Albumin replacement in severe sepsis or septic shock. N Engl J Med 371:83

77. Patel A, Laffan MA, Waheed U, Brett SJ (2014) Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ 349:g4561

Vasopressors

1. We recommend titrating vasopressors to a mean arterial pressure (MAP) of 65–70 mmHg (Grade 1B) rather than a higher MAP target (80–85 mmHg) in patients with septic shock. However, for patients with chronic hypertension we recommend aiming for a higher target (80–85 mmHg) for renal protection in septic shock (Grade 1C).

3. If vasopressors are needed for treatment of hypotension, we recommend norepinephrine (along with correction of hypovolaemia) as the first-choice vasopressor to protect kidney function (Grade 1B) and suggest vasopressin in patients with vasoplegic shock after cardiac surgery (Grade 2C).

Rationale:

- large open-label multicentre RCT (patients with septic shock to resuscitation with a MAP target of either 80–85 mmHg or 65–70 mmHg[125]):
  - no difference in mortality, incidence of AKI stage 2 or need for RRT, but more atrial fibrillation in the high target group
  - patients with known chronic hypertension: a higher MAP → lower incidence of AKI stage 2, less RRT
- in comparison with dopamine norepinephrine was associated with less tachycardia in the first hours and was superior regarding survival in cardiogenic shock patients; trend towards more RRT-free days through day 28 in the norepinephrine group [127]
- in comparison with norepinephrine vasopressin was associated with a reduced need for RRT, while the proportion of patients who never developed AKI stage 3, the number of AKI stage 3-free days or the incidence of AKI stage 3 was not affected[132]

125. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, Herve F, du Cheyron D, Guerin C, Mercat A, Teboul JL, Radermacher P, Investigators S (2014) High versus low blood-pressure target in patients with septic shock. N Engl J Med 370:1583–1593

127. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators (2010) Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 362:779–789

132. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ, VANISH Investigators (2016) Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA 316:509–518

Use of vasodilators

- We recommend against low-dose dopamine for protection against AKI (Grade 1A).
- We recommend not using levosimendan for renal protection in patients with sepsis (Grade 1B) and recommend against its use for renal protection in cardiac surgery patients with poor preoperative left ventricular function or needing postoperative haemodynamic support (Grade 1B).
- We suggest not using fenoldopam or natriuretic peptides for renal protection in critically ill or cardiovascular surgery patients at risk of AKI (Grade 2B).

Metabolic interventions

1. We recommend not using high-dose IV selenium for renal protection in critically ill patients (1B).

2. We suggest not using N-acetylcysteine to prevent contrast-associated AKI in critically ill patients because of conflicting results and possible adverse effects (Grade 2B).

3. We suggest that all patients with or at risk of acute kidney injury have adequate nutritional support preferably through the enteral route (BPS).

Rationale:

- In addition IV NAC may be harmful leading to allergic reactions [247] and decreased cardiac output or survival in patients with septic shock [248, 249].

247. Sandilands EA, Bateman DN (2009) Adverse reactions associated with acetylcysteine. Clin Toxicol (Phila) 47:81–88.

248. Molnar Z, Shearer E, Lowe D (1999) N-Acetylcysteine treatment to prevent the progression of multisystem organ failure: a prospective, randomized, placebo-controlled study. Crit Care Med 27:1100–1104

249. Peake SL, Moran JL, Leppard PI (1996) N-acetyl-l-cysteine depresses cardiac performance in patients with septic shock. Crit Care Med 24:1302–1310

Kommentar zur Leitlinie

- Keine Empfehlungen zu weiteren Subtypen des distributiven Schocks (z.B. anaphylaktischer oder neurogener Schock)

McClave SA et al., 2016 [7].

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

Leitlinienorganisation/Fragestellung

This particular report is an update and expansion of guidelines published by A.S.P.E.N. and SCCM in 2009

Methodik

Grundlage der Leitlinie

- Committee of multidisciplinary experts in clinical nutrition composed of physicians, nurses, pharmacists, and dietitians was jointly convened by the 2 societies.
- The literature search included MEDLINE, PubMed, Cochrane Database of Systemic Reviews, the National Guideline Clearinghouse, and an Internet search using the Google search engine for scholarly articles through an end date of December 31, 2013 (including ePub publications).
- Since release of the 2009 A.S.P.E.N. and SCCM Clinical Guidelines, the concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group have been adopted.

- Achievement of consensus was arbitrarily set at 70% agreement of authors with a particular recommendation.

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- According to GRADE:
  - LoE: high, moderate, low and very low
  - SoR: strong or weak (online appendix)
- When no RCT or observational study was available to answer a question directly, consensus of the author group on the best clinical practice approach was used, and the recommendation was designated “based on expert consensus” (ungraded).

Hinweis:

- Process of formulating research questions not described.
- Sources cited in the respective background text on recommendations
- Conflict of Interest: All authors completed both an A.S.P.E.N. and SCCM conflict-of interest form for copyright assignment and financial disclosure.
- Funding: There was no input or funding from industry, nor were any industry representatives present at any of the committee meetings.

Empfehlungen

N1. Based on expert consensus, we suggest that critically ill patients receive EN [enteral nutrition] therapy within 24–48 hours of making the diagnosis of severe sepsis/septic shock as soon as resuscitation is complete and the patient is hemodynamically stable. [ungraded]

Rationale:

- Studies specifically addressing nutrition therapy in the population of patients with severe sepsis/septic shock are lacking
- It is widely believed that patients with severe sepsis and septic shock have GI dysfunction at a rate of up to 60%.[70,101,400,401] The combination of compromised GI function and hypermetabolism from an exaggerated acute phase response[402] likely leads to greater risk for malnutrition in this subpopulation of critically ill patients. Nutrition therapy, therefore, would be expected to offer a benefit for improved clinical outcomes.[403]
- Initiating EN within 24–48 hours of resuscitation or when hemodynamic stability is reached is associated with improved outcomes.[404]

70. Stechmiller JK, Treloar D, Allen N. Gut dysfunction in critically ill patients: a review of the literature. *Am J Crit Care*. 1997;6(3):204-209.

101. Caddell KA, Martindale R, McClave SA, Miller K. Can the intestinal dysmotility of critical illness be differentiated from postoperative ileus? *Curr Gastroenterol Rep*. 2011;13(4):358-367.

400. Swank GM, Deitch EA. Role of the gut in multiple organ failure: bacterial translocation and permeability changes. World J Surg. 1996;20(4):411-417.

401. Chapman MJ, Nguyen NQ, Deane AM. Gastrointestinal dysmotility: clinical consequences and management of the critically ill patient. Gastroenterol Clin North Am. 2011;40(4):725-739.

402. Liu MJ, Bao S, Napolitano JR, et al. Zinc regulates the acute phase response and serum amyloid A production in response to sepsis through JAK-STAT3 signaling. PLoS One. 2014;9(4):e94934.

403. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012;12(12):919-924.

404. Ortiz Leyba C, Montejo Gonzalez JC, Vaquerizo Alonso C; Spanish Society of Intensive Care Medicine and Coronary Units–Spanish Society of Parenteral and Enteral Nutrition. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus of the Spanish Society of Intensive Care Medicine and Coronary Units–Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE): patient with sepsis. Med Intensiva. 2011;35(suppl 1):72-76.

N2. We suggest not using exclusive PN [parenteral nutrition] or supplemental PN in conjunction with EN early in the acute phase of severe sepsis or septic shock, regardless of patients' degree of nutrition risk. [LoE: very low, SoR: weak]

Rationale:

- There is a lack of studies addressing the use of exclusive or supplemental PN early in the acute phase of sepsis.
- The EPaNiC study by Casaer et al, in which one-fifth of patients had a sepsis diagnosis, reported that early supplemental PN added to hypocaloric EN resulted in longer hospital and ICU stays, longer durations of organ support, and a higher incidence of ICU-acquired infection than late supplementation. [240] Because this patient population has an exaggerated stress response and handles exogenous fuels poorly, the wide risk/benefit ratio with PN may be problematic.[405]
- Experience from 2 observational studies emphasizes the risk of early PN in this particular patient population [406, 407]

240. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506-517.

405. Puleo F, Arvanitakis M, Van Gossum A, Preiser JC. Gut failure in the ICU. Semin Respir Crit Care Med. 2011;32(5):626-638.

406. Elke G, Schadler D, Engel C, et al. Current practice in nutritional support and its association with mortality in septic patients—results from a national, prospective, multicenter study. Crit Care Med. 2008;36(6):1762-1767.

407. Elke G, Kuhnt E, Ragaller M, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis: a secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed. 2013;108(3):223-233.

Kommentar zur Leitlinie

- Keine Empfehlungen zu weiteren Subtypen des distributiven Schocks (z.B. anaphylaktischer oder neurogener Schock)

Møller MH et al., 2016 [9].

Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI)

Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure

Leitlinienorganisation/Fragestellung

The aim of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) task force for Acute Circulatory Failure was to present clinically relevant, evidence-based treatment recommendations on this topic.

Methodik

Grundlage der Leitlinie

- The Clinical Practice Committee of SSAI appointed national members of the guideline task force for Acute Circulatory Failure.
- Systematic literature search: PubMed (January 1966 to December 2015) and the Cochrane Library (Issue 12, December 2015)

Table 1 Clinical research questions and PICO questions used to assess evidence relevant to this guideline statement.

	PICO Question			
Clinical question	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
Should norepinephrine or other vasopressors be used as first-line treatment for adult patients with acute circulatory failure?	Adult patients with acute circulatory failure divided into the following subgroups: 1. Shock in general 2. Septic shock 3. Cardiogenic shock 4. Hypovolemic shock 5. Other types of shock, including vasodilatory shock	1. Dopamine 2. Epinephrine 3. Vasopressin analogues 4. Phenylephrine	Norepinephrine	1. Short-term mortality 2. Long-term mortality 3. Quality-of-life 4. Ischaemic events 5. Renal replacement therapy 6. Acute kidney injury 7. Dysrhythmias 8. Length of hospital stay

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- When moving from evidence to recommendations, four factors were considered and integrated: benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations.
- GRADE approach:
  - LoE: High, moderate, low, very low
  - SoR: strong (“we recommend”), weak (“we suggest”)

Hinweis:

- Search strategy not presented
- Process of study selection not described.
- Sources cited in the respective background text on recommendations
- Conflict of Interest: The authors declare no relevant conflict of interest.
- Funding: initiated and supported by SSAI

Empfehlungen

Population: The population of interest was adult patients (as defined in the original trials) with acute circulatory failure/shock (as defined in the original trials) receiving vasopressors in a highdependency setting in hospital, including the emergency department, ICU, operating room,

and recovery room. The following subpopulations were assessed: patients with (1) shock in general, (2) septic shock, (3) cardiogenic shock, (4) hypovolemic shock, and (5) other types of shock, including vasodilatory shock.

Vasopressors in patients with shock in general

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason (s) for downgrading	Comments
Vasopressor treatment of patients with shock in general				
1. We recommend using norepinephrine rather than dopamine	Strong	No difference in short-term mortality, long-term mortality, ischaemic events or hospital LOS. Increased risk of dysrhythmias in patients treated with dopamine	Moderate due to imprecision	
2. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of epinephrine has been inadequately assessed	Low due to imprecision and risk of bias	
3. We suggest using norepinephrine rather than vasopressin analogues	Weak	The potential harm associated with use of vasopressin analogues has been inadequately assessed	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock
4. We suggest using norepinephrine rather than phenylephrine	Weak	The potential harm associated with use of phenylephrine has been inadequately assessed	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock

Vasopressors in patients with septic shock

1. We recommend using norepinephrine rather than dopamine	Strong	Increased risk of dysrhythmias and short-term mortality in patients treated with dopamine	Moderate due to imprecision
2. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of epinephrine has been inadequately assessed	Low due to imprecision and risk of bias
3. We suggest using norepinephrine rather than vasopressin analogues	Weak	No difference in short-term mortality, ischaemic events, dysrhythmias or use of renal replacement therapy. The potential harm associated with use of vasopressin analogues has been inadequately assessed	Low due to imprecision and risk of bias
4. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of phenylephrine has been inadequately assessed	Low due to imprecision and risk of bias

Rationale recommendation 1:

- 2012 systematic review comparing norepinephrine vs. dopamine: increased risk of mortality and dysrhythmias with dopamine[13]

  13. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis*. Crit Care Med 2012; 40: 725 –30.

Rationale recommendation 2:

- Small RCT 2008 comparing norepinephrine vs. epinephrine: no difference in short-term mortality[12]
- Authors believe the potential harm associated with systematic epinephrine treatment in patients with septic shock has been inadequately assessed, which is why they suggest using norepinephrine.

  12. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, Investigators CATS. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 2008; 34: 2226 – 34.

Rationale recommendation 3:

- In an updated meta-analysis comprising five trials [16–20], there were no differences in short-term mortality, ischaemic events, dysrhythmias, or use of renal replacement therapy in patients with septic shock treated with norepinephrine vs. vasopressin analogues
- Authors believe the potential harm associated with systematic vasopressin treatment in patients with septic shock has been inadequately assessed, which is why they suggest using norepinephrine.

  16. Morelli A, Ertmer C, Lange M, Dunser M, Rehberg S, Van Aken H, Pietropaoli P, Westphal M. Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. Br J Anaesth 2008; 100: 494 – 503.
  17. Albanese J, Leone M, Delmas A, Martin C. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Crit Care Med 2005; 33: 1897 – 902.
  18. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D, Investigators V. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008; 358: 877–87.
  19. Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Med 2006; 32: 1782–9.
  20. Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Bachetoni A, D'Alessandro M, Van Aken H, Pietropaoli P, Westphal M. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 2009; 13:R130.

Rationale recommendation 4:

- Small RCT[21]: no difference in short-term mortality between norepinephrine vs. phenylephrine
- Authors believe the potential harm associated with systematic phenylephrine treatment in patients with septic shock has been inadequately assessed, which is why they suggest using norepinephrine.

  Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Laderchi A, Bachetoni A, D'Alessandro M, Van Aken H, Pietropaoli P, Westphal M. Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. Crit Care 2008; 12: R143.

Vasopressor treatment of patients with other types of shock, including vasodilatory shock

1. Norepinephrine vs. dopamine	Weak	The harm associated with dopamine treatment in patients with shock in general and those with septic shock, cautions use in other subgroups, including patients with other types of shock, including vasodilatory shock	Low due to imprecision, and indirectness	No data available for this population; data extrapolated from patients with septic shock

Hinweis zur Leitlinie:

- Keine spezifischen Empfehlungen nach Vasopressor-Versagen
- See Appendix (Figure 1) for Forest plot of (A) short-term all-cause mortality, (B) ischaemic events, (C) renal replacement therapy, (D) dysrhythmias, and (E) hospital length of stay in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with septic shock

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Møller MH et al., 2018 [10].

Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI)

Scandinavian SSAI clinical practice guideline on choice of inotropic agent for patients with acute circulatory failure

Leitlinienorganisation/Fragestellung

The aim of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) task force for Acute Circulatory Failure was to present patient-important treatment recommendations on this topic.

Methodik

Grundlage der Leitlinie

- The Clinical Practice Committee of SSAI appointed national members of the guideline task force for Acute Circulatory Failure.
- Systematic literature search: PubMed (January 1966 to 25 September 2017) and the Cochrane Library (Issue 4, September 2017), Epistemonikos (25 September 2017)
- guideline prepared according to AGREE statement

Table 1 Clinical research questions and PICO questions used to assess evidence relevant to this guideline statement.

	PICO Question			
Clinical question	**Population (P)**	**Intervention (I)**	**Comparator (C)**	**Outcomes (O)**
Should dobutamine or other inotropes be used for adult patients with acute circulatory failure?	Adult patients with acute circulatory failure divided into the following subgroups: 1. Shock in general 2. Septic shock 3. Cardiogenic shock 4. Hypovolemic shock 5. Shock after cardiac surgery 6. Other types of shock, including vasodilatory shock	1. Levosimendan 2. Milrinone 3. Epinephrine 4. Dopamine 5. Placebo/no treatment	Dobutamine	1. Short-term mortality 2. Long-term mortality 3. Quality of life 4. Ischemic events 5. Renal replacement therapy 6. Acute kidney injury 7. Dysrhythmias 8. Length of hospital stay

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- When moving from evidence to recommendations, four factors were considered and integrated: benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations.
- GRADE approach:
  - LoE: High, moderate, low, very low
  - SoR: strong (“we recommend”), weak (“we suggest”)

Hinweis:

- Process of study selection not described.
- Sources cited in the respective background text on recommendations
- Conflict of Interest: The authors declare no relevant conflict of interest.
- Funding: initiated and supported by SSAI

Empfehlungen

Shock in general:

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Comments
A) Use of inotropes in patients with shock in general				
1. We suggest using dobutamine rather than levosimendan	Weak	No difference in short-term mortality. Potential harm of levosimendan[25]	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock. The defined daily dose price of levosimendan is about 22 times higher than dobutamine
2. Dobutamine vs. milrinone	None	–	–	No data available; no relevant populations to extrapolate data from. The defined daily dose price of milrinone is about 100 times higher than dobutamine
3. We suggest using dobutamine rather than epinephrine	Weak	No difference in short-term mortality, ischemic events, and dysrhythmias. Excessive vasoconstriction and tachycardia of epinephrine may affect cardiac output adversely[6]	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock
4. Dobutamine vs. dopamine	None	–	–	No data available; no relevant populations to extrapolate data from
5. We suggest against the use of dobutamine as compared to placebo/no treatment	Weak	Potential harm of dobutamine[19]	Very low due to serious risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock (observational study)
B) Use of inotropes in patients with septic shock				
1. We suggest using dobutamine rather than levosimendan	Weak	No difference in short-term mortality. Potential harm of levosimendan[25]	Very low due to imprecision, risk of bias, and indirectness	The defined daily dose price of levosimendan is about 22 times higher than dobutamine
2. Dobutamine vs. milrinone	None	–	–	No data available; no relevant populations to extrapolate data from. The defined daily dose price of milrinone is about 100 times higher than dobutamine
3. We suggest using dobutamine rather than epinephrine	Weak	No difference in short-term mortality, ischemic events, and dysrhythmias. Excessive vasoconstriction and tachycardia of	Very low due to imprecision, risk of bias, and indirectness	

Table 2 (Continued)

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Comments
		epinephrine may affect cardiac output adversely[6]		
4. Dobutamine vs. dopamine	None	–	–	No data available; no relevant populations to extrapolate data from
5. We suggest against the use of dobutamine as compared to placebo/no treatment	Weak	Potential harm of dobutamine[19]	Very low due to serious risk of bias, and indirectness	No data available; no relevant RCT populations to extrapolate data from. Observational study suggests harm from dobutamine

Rationale recommendation 1:

- In an updated meta-analysis comprising five trials, [20–24] there were no statistically significant difference in short-term mortality in patients with septic shock treated with dobutamine vs. levosimendan.
- In the recently published LEOPARDS trial, in which adult patients with sepsis were randomized to levosimendan or placebo, levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher rate of supraventricular tachyarrhythmia compared to placebo.[25] This should caution the use of levosimendan in patients with sepsis, which is why the panel suggest using dobutamine rather than levosimendan in patients with septic shock.

20. Alhashemi JA, Alotaibi QA, Abdullah GM, Shalabi SA. Levosimendan vs dobutamine in septic shock. J Crit Care 2009; 24: e14–5.

21. Memis D, Inal MT, Sut N. The effects of levosimendan vs dobutamine added to dopamine on liver functions assessed with noninvasive liver function monitoring in patients with septic shock. J Crit Care 2012; 27: 318. e1–6.

22. Morelli A, Donati A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Landoni G, Pelaia P, Pietropaoli P, Van Aken H, Teboul JL, Ince C, Westphal M. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care 2010; 14: R232.

23. Vaitsis J, Michalopoulou H, Thomopoulos C, Massias S, Stamatis P. Use of levosimendan inmyocardial dysfunction due to sepsis. Crit Care 2009; 13(Suppl. 1): P165.

24. Hajjej Z, Meddeb B, Sellami W, Labbene I, Morelli A, Ferjani M. Effects of levosimendan on cellular metabolic alterations in patients with septic shock: a randomized controlled pilot study. Shock 2017; 48: 307–12.

25. Gordon AC, Perkins GD, Singer M, McAuley DF,Orme RM, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J, Brealey D, Nutt CL, McNamee JJ, Reschreiter H, Breen A, Liu KD, Ashby D. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med 2016; 375: 1638–48.

Rationale recommendation 3:

- Small RCT: no difference in short-term mortality, ischemic events, and dysrhythmias between patients treated with dobutamine vs. epinephrine[26.]
- As excessive vasoconstriction and tachycardia may affect cardiac output adversely in most patients where an inotropic agent is deemed indicated[6] we suggest using dobutamine rather than epinephrine in patients with septic shock.

6. Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015; 20: 249–60.

26. Mahmoud KM, Ammar AS. Norepinephrine supplemented with dobutamine or epinephrine for the cardiovascular support of patients with septic shock. Indian J Crit Care Med 2012; 16: 75–80.

Patients with other types of shock, including vasodilatory shock:

F) Use of inotropes in patients with other types of shock, including vasodilatory shock					
1.	We suggest using dobutamine rather than levosimendan	Weak	No difference in short-term mortality. Potential harm of levosimendan[25]	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock. The defined daily dose price of levosimendan is about 22 times higher than dobutamine

Hinweis:

- See Appendix (Figure 2) for Forest plot of (A) short-term mortality, (B) long-term mortality, (C) quality of life, (D) ischemic events, (E) renal replacement therapy, (F) acute kidney injury, (G) dysrhythmias, and (H) hospital length of stay in randomised trials of doputamine vs. other inotropes for patients with septic shock

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NICE, 2016 [12].

Sepsis: recognition, assessment and early management.

Leitlinienorganisation/Fragestellung

The guideline aims to consider the clinical evidence to help healthcare professionals and the public recognise when and in whom to suspect sepsis, how to identify the source of infection, what should be part of the clinical risk assessment including the evidence for the use of existing scoring tools and blood tests, initial fluid management and the timing of the escalation of care and senior staff involvement, and early disease monitoring and information and support for patients and their relatives or carers.

Methodik

Grundlage der Leitlinie:

- PICO questions
- Systematic literature search
  - Clinical literature search in MEDLINE, EMBASE, and the Cochrane Library; for one question: CINAHL and PsychINFO (updated on 9 October 2015)
  - Health economic literature search in NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA), and the Health Economic Evaluation Database (HEED) without date restrictions + MEDLINE and EMBASE using an economic filter (from 2012)

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- GRADE approach: overall quality rated as high, moderate, low, or very low
- Risk of bias assessment of included studies
- strength of the recommendation: strong (“offer” etc.), weak (“consider”)

Hinweis

- Funding: The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

Empfehlungen

IV Fluid administration

8.5.5 Evidence statements

- Clinical
  - The evidence included in this review was of moderate to very low quality.
  - Adults with sepsis, severe sepsis or septic shock: Evidence from eight studies on head-to-head comparison of different types of IV fluids found that there was no clinically important difference for the outcomes of mortality and hospital length of stay. A multivariable analysis in one study indicated that patients receiving albumin had a lower chance of death at 28 days compared to those receiving saline, while another study did not find any difference in mortality between those who had received albumin and those who had received crystalloids.
  - Children with sepsis, severe sepsis or septic shock: The evidence from one study did not show any clinically important difference for mortality at 72 hours between different dosages of IV fluids.

Inotropic agents and vasopressors

9.5 Evidence statements

- Clinical
  - The evidence in this review ranged from high to very low quality for the outcomes. Adults with septic shock:
  - RCT evidence from sixteen studies on head to head comparisons of inotropic agents or vasopressors found that there was no clinically important difference for the outcomes of mortality, length of stay in hospital and ICU settings, the number of organs supported, and adverse events.
  - One retrospective cohort study assessing the effect of a delay in inotrope or vasopressor therapy suggested that a delay might increase mortality. A second retrospective study found a trend for increased mortality with therapy delay.
  - One RCT study indicated that a norepinephrine dose greater than 1 µg/kg/min might be an independent predictor of death.
  - Children with septic shock: One RCT study in children indicated that epinephrine might be potentially more clinically effective than dopamine for the outcome of mortality. However, children in the dopamine group had a significantly longer resuscitation period and were more likely to receive renal replacement therapy than children in the epinephrine group.

“No specific recommendation was made for use of inotropes or vasopressors.”

Hinweis:

- Keine Empfehlungen spezifisch den Subtypen des distributiven Schocks (z.B. septischer Schock, anaphylaktischer oder neurogener Schock)

Penack O et al., 2014 [14].

Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO)

Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO)

Leitlinienorganisation/Fragestellung

The aim is to give evidence-based recommendations for haematologist, oncologists and intensive care physicians on how to manage adult patients with neutropenia and sepsis.

Methodik

Grundlage der Leitlinie

- panel of 13 experts in the field of infectious diseases in haematology and oncology
- systematic literature search: Medline (up to June 2013)
- consensus process: email- and meeting-based discussion group

Level of Evidence (LoE) / Strength of Recommendation (SoR):

Table 1 Categories of evidence used in this guideline [88]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Hinweis:

- Sources cited in the respective background text on recommendations

- Funding: The AGIHO received no sponsoring for the preparation of these guidelines. Travel expenses were covered by the German Society of Hematology and Medical Oncology
- Conflict of interest: All remaining authors have declared no conflicts of interest.

Empfehlungen

Antimicrobial treatment

Taken together, a combination treatment with an aminoglycoside may be considered in neutropenic patients with septic shock and severe sepsis (BIII).

Rationale:

- combination treatment with aminoglycosides increased renal toxicity without improving efficacy in neutropenic patients with bacteraemia [125–127].
- use of β-lactam antibiotic/aminoglycoside combinations were associated with superior outcome, as compared with single-agent antimicrobial treatment, in neutropenic patients with severe sepsis and septic shock [95]
- reduced hospital mortality in non-neutropenic patients with severe bacterial sepsis after combination therapy comprising at least two antibiotics of different mechanisms versus antibiotic monotherapy [92]

125. PaulM, Benuri-Silbiger I, Soares-Weiser K et al (2004) Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ 328:668

126. PaulM, Dickstein Y, Schlesinger A et al (2013) Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. Cochrane Database Syst Rev 6, CD003038

127. Paul M, Soares-Weiser K, Leibovici L (2003) Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. BMJ 326:1111

95. Legrand M, Max A, Peigne Vet al (2012) Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 40:43–49

92. Kumar A, Zarychanski R, Light B et al (2010) Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 38:1773–1785

Cardiovascular insufficiency

Albumin-containing solutions may be used for fluid resuscitation of patients with sepsis and septic shock (CII).

Rationale:

- the use of albumin-containing solutions for fluid resuscitation of patients with sepsis was associated with lower mortality compared with crystalloids [40]
- the use of albumin therapy did not significantly reduce 28-day mortality compared to saline solution [50]

40. Delaney AP, Dan A,Mccaffrey J et al (2011) The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 39:386–391

50. Finfer S, Bellomo R, BoyceNet al (2004) Acomparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256

Not named as a recommendation: To restore adequate cardiac filling pressures and to maintain adequate organ perfusion (goal, mean arterial pressure 65 mmHg, central venous

pressure 8–12 mmHg, pulmonary wedge pressure 12–15 mmHg, urinary output 0.5 mL/kg/h and central venous or mixed venous oxygen saturation 70 %), crystalloid fluids are recommended as the initial fluid of choice in severe sepsis and septic shock.

Rationale:

- Compared to crystalloids, randomized controlled trials did not show beneficial effects of colloids, especially hydroxyethyl starches for fluid resuscitation in sepsis 32, 62, 128.

32. Brunkhorst FM, Engel C, Bloos F et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl JMed 358:125–139

62. Guidet B, Martinet O, Boulain T et al (2012) Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care 16:R94

128. Perner A, Haase N, Guttormsen AB et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134

"…and there is currently poor evidence to support the use of vasopressin in septic shock (CI)[54]

54. Flowers CR, Seidenfeld J, Bow EJ et al (2013) Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol Off J Am Soc Clin Oncol 31:794–810

Nutrition and control of metabolic functions: We do not recommend general use of arginine, omega-3 fatty acids and combined formulations in patients with severe sepsis and septic shock (DII).

Rationale:

- Reproducible mortality benefits for supplementation are lacking (arginine[31,56]; omega-3 fatty acids[24,130,131]; combined formulations[27,56,68])

27. Bertolini G, Iapichino G, Radrizzani D et al (2003) Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. Intensive Care Med 29:834–840

56. Galban C, Montejo JC, Mesejo A et al (2000) An immuneenhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit CareMed 28:643–648.

86. Kielstein JT, Burkhardt O (2011) Dosing of antibiotics in critically ill patients undergoing renal replacement therapy. Curr Pharm Biotechnol 12:2015–2019.

Glutamine substitutions cannot be recommended in patients with severe sepsis and septic shock (EI).

Rationale:

- Substitution of glutamine did not positively affect the primary survival endpoint in two randomized trials including together over 1,000 patients with sepsis [9, 66] and significantly increased in-hospital and 6-month mortality[66]

9. Andrews PJ, Avenell A, NobleDWet al (2011) Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ 342:d1542.

66. Heyland D, Muscedere J, Wischmeyer PE et al (2013) A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 368:1489–1497

Rhodes A et al., 2017 [15].

Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)

Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock; 2016

Leitlinienorganisation/Fragestellung

To provide an update to "Surviving Sepsis Campaign Guidelines for Management of Sepsis and Septic Shock: 2012".

Methods

Grundlage der Leitlinie

- 55 international experts representing 25 international organizations was convened
- Methodologic expertise was provided by the GRADE Methodology Group
- Questions from the last version of the SSC guidelines were reviewed; those that were considered important and clinically relevant were retained. Questions that were considered less important or of low priority to clinicians were omitted, and new questions that were considered high priority were added (by discussion and consensus)
- Literature search: conducted of a minimum of two major databases (e.g. Cochrane Registry, MEDLINE, or EMBASE)

Level of Evidence (LoE) / Strength of Recommendation (SoR):

- Acceptance of a statement required votes from 75% of the panel members with an 80% agreement threshold.
- GRADE approach

Table 3 Comparison of 2016 grading terminology with previous alphanumeric descriptors

	2016 Descriptor	2012 Descriptor
Strength	Strong	1
	Weak	2
Quality	High	A
	Moderate	B
	Low	C
	Very Low	D
Ungraded strong recommendation	Best Practice Statement	Ungraded

Hinweis:

- Sources cited in the respective background text on recommendations
- Funding: Funding for the development of these guidelines was provided by SCCM and ESICM. In addition, sponsoring organizations provided support for their members' involvement.
- Conflict of interest:

- o No industry input into guidelines development occurred, and no industry representatives were present at any of the meetings. No member of the guidelines committee received honoraria for any role in the guidelines process.
- o Five were judged as having conflicts that were managed through reassignment to another group as well as the described restrictions on voting on recommendations in areas of potential COI. One individual was asked to step down from the committee.

Empfehlungen

A. INITIAL RESUSCITATION

6. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).

Rationale:

- High MAP is associated with raised cardiac index, but does not affect arterial lactate levels, oxygen consumption, renal function, urinary flow, gastric mucosal Pco2, RBC velocity, or skin capillary flow[26,27]

26. LeDoux D, Astiz ME, Carpati CM, Rackow EC (2000) Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 28(8):2729–2732

27. Bourgoin A, Leone M, Delmas A, Garnier F, Albanese J, Martin C (2005) Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. Crit Care Med 33(4):780–786

D. ANTIMICROBIAL THERAPY

2. We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).

Rationale:

- Failure to initiate appropriate empiric therapy → substantial increase in morbidity and mortality [79, 95–97].
- increased probability of progression from gram-negative bacteremic infection to septic shock is increased [98]

79. Barie PS, Hydo LJ, Shou J, Larone DH, Eachempati SR (2005) Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. Surg Infect. 6(1):41–54

95. Kumar A, Ellis P, Arabi Y et al (2009) Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Chest 136(5):1237–1248

96. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000). The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118(1):146–155

97. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L (2010) Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 54(11):4851–4863

98. Kreger BE, Craven DE, McCabe WR (1980) Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 68(3):344–355

6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).

Rationale:

- The phrase “combination therapy” in the context of this guideline connotes the use of two different classes of antibiotics (usually a β-lactam with a fluoroquinolone, aminoglycoside, or macrolide) for a single putative pathogen expected to be sensitive to both, particularly for purposes of accelerating pathogen clearance. The term is not used where the purpose of a multidrug strategy is to strictly broaden the range of antimicrobial activity (e.g., vancomycin added to ceftazidime, metronidazole added to an aminoglycoside or an echinocandin added to a β-lactam).
- combination therapy leads to higher survival in severely ill septic patients with a high risk of death, particularly in those with septic shock [167-172]
- Despite the overall favorable evidence for combination therapy in septic shock, direct evidence from adequately powered RCTs is not available to validate this approach definitively.

167. Kumar A, Safdar N, Kethireddy S, Chateau D (2010) A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a metaanalytic/ meta-regression study. Crit Care Med 38(8):1651–1665

168. Kumar A, Zarychanski R, Light B et al (2010) Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 38(9):1773–1785

169. Al-Hasan MN, Wilson JW, Lahr BD et al (2009) Beta-lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by gram-negative bacilli. Antimicrob Agents Chemother (Bethesda). 53(4):1386–1394

170. Delannoy PY, Boussekey N, Alfandari S et al (2012) Impact of combination therapy with aminoglycosides on the outcome of ICU-acquired bacteraemias. Eur J Clin Microbiol Infect Dis 31(9):2293–2299

171. Diaz-Martin A, Martinez-Gonzalez ML, Ferrer R et al (2012) Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mechanisms of action reduces mortality. Crit Care 16(6):R223

172. Martin-Loeches I, Lisboa T, Rodriguez A et al (2010) Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 36(4):612–620

F. FLUID THERAPY

2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).

3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).

6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

Rationale:

- absence of any clear benefit following the administration of colloid compared to crystalloid solutions in the combined subgroups of sepsis, in conjunction with the expense of albumin
- no direct comparisons have been made between isotonic saline and balanced salt solutions in patients with sepsis
- No studies comparing balanced and unbalanced crystalloid solutions
- ALBIOS trial[249]: no mortality benefit of albumin in combination with crystalloids compared to crystalloids alone; subgroup analysis suggested that the albumin group was associated with lower 90-day mortality in patients with septic shock
- HES use resulted in higher risk of death and a higher risk of RRT compared to other fluids in low risk of bias studies (high-quality evidence) [250]
- high-quality studies comparing gelatins to other fluids in patients with sepsis or septic shock are lacking

249. Caironi P, Tognoni G, Masson S et al (2014) Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 370(15):1412–1421

250. Haase N, Perner A, Hennings LI et al (2013) Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ 346:f839

G. VASOACTIVE MEDICATIONS

1. We recommend **norepinephrine as the first choice vasopressor** (strong recommendation, moderate quality of evidence).

2. 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) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.

3. We suggest using **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) (weak recommendation, low quality of evidence).

4. We recommend **against using low-dose dopamine for renal protection** (strong recommendation, high quality of evidence).

5. We suggest using **dobutamine in patients who show evidence of persistent hypoperfusion** despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

Rationale:

- Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine [262]. It may also influence the endocrine response via the hypothalamic pituitary axis and may have immunosuppressive effects [263].
- Guideline authors conducted an updated meta-analysis to include the results of the VANISH trial. Data from nine trials (n = 1324 patients with septic shock), comparing norepinephrine with vasopressin (or terlipressin) demonstrated no significant difference in mortality [268, 271, 272, 277–279].

- RCT (low-dose dopamine vs. placebo) found no difference in need for RRT, urine output, time to renal recovery, survival, ICU stay, hospital stay, or arrhythmias [282, 283]

262. Regnier B, Rapin M, Gory G, Lemaire F, Teisseire B, Harari A (1977) Haemodynamic effects of dopamine in septic shock. Intensive Care Med 3(2):47–53

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268. Dunser MW, Mayr AJ, Ulmer H et al (2003) Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation 107(18):2313–2319

271. Malay MB, Ashton RC, Landry DW, Townsend RN (1999) Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 47(4):699–703

272. O'Brien A, Clapp L, Singer M (2002) Terlipressin for norepinephrineresistant septic shock. Lancet 359(9313):1209–1210 277. Albanese J, Leone M, Delmas A, Martin C (2005) Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Crit Care Med 33(9):1897–1902

278. Morelli A, Ertmer C, Lange M et al (2008) Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. Br J Anaesth 100(4):494–503

279. Morelli A, Ertmer C, Rehberg S et al (2009) Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 13(4):R130

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Rationale:

- absence of convincing evidence and/or contradictory results

J. IMMUNOGLOBULINS

1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).

Rationale:

- absence of convincing evidence and/or contradictory results

L. ANTICOAGULANTS

1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).

2. We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.

Rationale:

- absence of convincing evidence and/or contradictory results

T. NUTRITION

7. We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence)

Rationale:

- prokinetic agent use was associated with lower risk of feeding intolerance (RR 0.73; 95% CI 0.55–0.97; moderate-quality evidence) and did not significantly increase mortality (RR 0.97; 95% CI 0.81–1.1; low-quality evidence) [606]

606. Lewis K, Alqahtani Z, McIntyre L et al (2016) The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. Crit Care 20(1):259

9. We recommend against the use of IV selenium to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).

10. We suggest against the use of arginine to treat sepsis and septic shock (weak recommendation, low quality of evidence).

11. We recommend against the use of glutamine to treat sepsis and septic shock (strong recommendation, moderate quality of evidence)

12. We make no recommendation about the use of carnitine for sepsis and septic shock.

Rationale:

- absence of convincing evidence and/or contradictory results

Hinweis:

- Process of study selection not described

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2019) am 03.01.2019

#	Suchfrage
1	MeSH descriptor: [Shock] this term only
2	MeSH descriptor: [Shock, Septic] explode all trees
3	MeSH descriptor: [Anaphylaxis] explode all trees
4	((distributive OR vasodilatory) NEXT shock):ti,ab,kw
5	(septic OR endotoxic OR toxic OR sepsis):ti,ab,kw AND shock:ti,ab,kw
6	(anaphylaxis OR (anaphylactic NEXT (reaction* OR shock))):ti,ab,kw
7	(neurogenic NEXT shock):ti,ab,kw
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	#8 with Cochrane Library publication date from Jan 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 03.01.2019

#	Suchfrage
1	shock[mh:noexp]
2	shock, septic[mh]
3	anaphylaxis[mh]
4	distributive shock[tiab] OR vasodilatory shock[tiab]
5	(septic[tiab] OR endotoxic[tiab] OR toxic[tiab] OR sepsis[tiab]) AND shock[tiab]
6	anaphylaxis[tiab] OR (anaphylactic[tiab] AND (reaction*[tiab] OR shock[tiab]))
7	neurogenic shock[tiab]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic review[pt] OR ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR

	scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
10	((#9) AND ("2014/01/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[mh:noexp] NOT (Humans[mh] AND animals[mh:noexp]))
11	(#10) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 03.01.2019

#	Suchfrage
1	shock[mh:noexp]
2	sepsis[mh:noexp]
3	shock, septic[mh]
4	anaphylaxis[mh]
5	distributive shock[tiab] OR vasodilatory shock[tiab]
6	(septic[tiab] OR endotoxic[tiab] OR toxic[tiab] OR sepsis[tiab]) AND shock[tiab]
7	sepsis[ti] NOT medline[sb]
8	anaphylaxis[tiab] OR (anaphylactic[tiab] AND (reaction*[tiab] OR shock[tiab]))
9	neurogenic shock[tiab]
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
12	((#11) AND ("2014/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp])
13	(#12) NOT retracted publication[ptyp]

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2. **Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al.** Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 2017;43(12):1751-1763.
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Anhang

Table 1: Characteristics of included randomized trials (Zhou et al. 2015 [17])

Table 1 Characteristics of the included randomized trials

Source	Number of patients	Mean age (years)	Male (%)	Center	Mean APACHE II/SAPS II/SOFA score	Blood pressure (mmHg)	Inclusion criteria
Mahmoud and Ammar[21]	60	51.4	31 (51.7)	S	NR/NR/14.8	MAP <70	Sepsis plus hypotension refractory to an initial fluid challenge
Gordon et al[20]	241	62.0	146 (60.6)	M	28.2/NR/NR	MAP =72.4	Septic shock with two or more criteria of the systemic inflammatory response syndrome, infection, dysfunction of one or more organs
De Backer et al[23]	1,044	67.5	NR	M	NR/NR/NR	MAP <70	MAP <70 mmHg or the SBP <100 mmHg after adequate amount of fluids used and signs of tissue hypoperfusion
Patel et al[24]	252	≥18	116 (46.0)	S	27.5/NR/12	MAP <60 and/or SBP <90	Septic shock requiring vasopressors after adequate fluid used (clinical examination and/or CVP >8 mmHg)
Gordon et al[22]	778	61.8	475 (61.0)	M	27.1/NR/NR	MAP =72.7 (NE maintaining)	Septic shock with two or more criteria for the systemic inflammatory response syndrome
Jain and Singh[25]	54	44.1	28 (51.9)	S	18.4/NR/NR	SBP =74.1	SBP <90 mmHg or MAP <60 mmHg and CVP >12 mmHg or PAOP >18 mmHg despite adequate fluid used and continuous dopamine for 1 hour; evidence of one or more end-organ dysfunction, infection with special criteria
Morelli et al[21]	45	65.7	33 (73.3)	S	NR/60/NR	MAP <65	MAP <65 mmHg despite appropriate volume resuscitation
Morelli et al[9]	32	70	21 (65.5)	S	NR/56/NR	MAP <65	MAP <65 mmHg despite appropriate volume resuscitation
Morelli et al[26]	59	66.3	43 (72.3)	S	NR/60/NR	MAP =70 (NE maintaining)	MAP <65 mmHg despite appropriate volume resuscitation
Myburgh et al[28]	158	≥18	NR	M	NR/NR/NR	MAP ≤60	Clinician judged patients to require either epinephrine or norepinephrine
Russell et al[10]	778	60.6	475 (61.1)	M	27.1/NR/NR	MAP =72.5 (vasopressors maintaining)	Septic shock with two or more criteria of the systemic inflammatory response syndrome, infection, one or more organ dysfunction
Annane et al[27]	330	62.5	202 (61)	M	NR/53/11	MAP <60 and/or SBP <90	Two or more of the systemic inflammatory response syndrome, organ dysfunction, or two or more signs of tissue hypoperfusion
Mathur et al[14]	50	53.7	32 (64)	S	25.1/NR/NR	SBP =75.6	SBP <90 mmHg and two or more of the systemic inflammatory response syndrome
Lauzier et al[13]	23	54.7	14 (60.9)	M	23.2/NR/8.9	MAP <60	Septic shock with MAP <60 mmHg after >1,000 mL crystalloid resuscitation, vasopressors used <12 hours, PAOP ≥12 mmHg, cardiac index ≥3 L/min/m²
Seguin et al[24]	22	66	17 (77.3)	S	NR/54/10	SBP <90	SBP <90 mmHg; infection; three or more of the systemic inflammatory response syndrome; two or more following criteria: plasma lactate >2 mmol/L or pH <7.3, hypoxemia, urine output <30 mL/hour, platelet count <100,000/mm³, or a decrease of 50% from a previous value or unexplained coagulopathy
Albanese et al[12]	20	65.5	13 (65)	S	28.5/NR/NR	MAP <60	MAP <60 mmHg and two or more organ dysfunctions
Seguin et al[15]	22	67.5	12 (54.5)	S	NR/59.5/10	SBP <90	SBP <90 mmHg; infection; three or more of the systemic inflammatory response syndrome; two or more following criteria: plasma lactate >2 mmol/L or pH <7.3, hypoxemia, urine output <30 mL/hour, platelet count <100,000/mm³ or a decrease of 50% from a previous value or unexplained coagulopathy
Levy et al[11]	30	55	21 (70)	S	23.5/NR/NR	MAP <60	After optimal fluid resuscitation and dopamine up to a dose of 20 μg/kg/min, the patients still have the following criteria: MAP <60 mmHg, urine output <30 mL/hour, increased lactate level (>2.5 mmol/L, cardiac index ≥3.5 L/min/m²
Marik and Mohedin[18]	20	46	11 (55)	S	17.5/NR/NR	MAP <60	After optimal fluid resuscitation, the patients with sepsis still had cardiac index >3.2 L/min/m² or SVRI <1,200 dyne·s·cm⁻⁵·m² or MAP <60 mmHg
Martin et al[20]	32	52.5	24 (75)	S	30.5/NR/NR	SBP <90	SBP <90 mmHg, cardiac index >4 L/min/m², decreased organ perfusion, lactate levels of arterial blood >2.5 mmol/L, and infection
Ruokonen et al[19]	10	45.1	NR	S	13.3/NR/NR	SBP <90	SBP <90 mmHg with PAOP of 8 mmHg to 12 mmHg, infection

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CVP, central venous pressure; DBP, diastolic blood pressure; M, multicenter trial; MAP, mean arterial pressure; NR, not reported; PAOP, pulmonary artery occlusion pressure; RCT, randomized controlled trial; S, single-center trial; SAPS, simplified acute physiology score; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; SVRI, systemic vascular resistance index; NE, norepinephrine.

Figures

Figure 1: Forest plot of (A) short-term all-cause mortality, (B) ischaemic events, (C) renal replacement therapy, (D) dysrhythmias, and (E) hospital length of stay in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with septic shock (Møller et al. 2016[9]

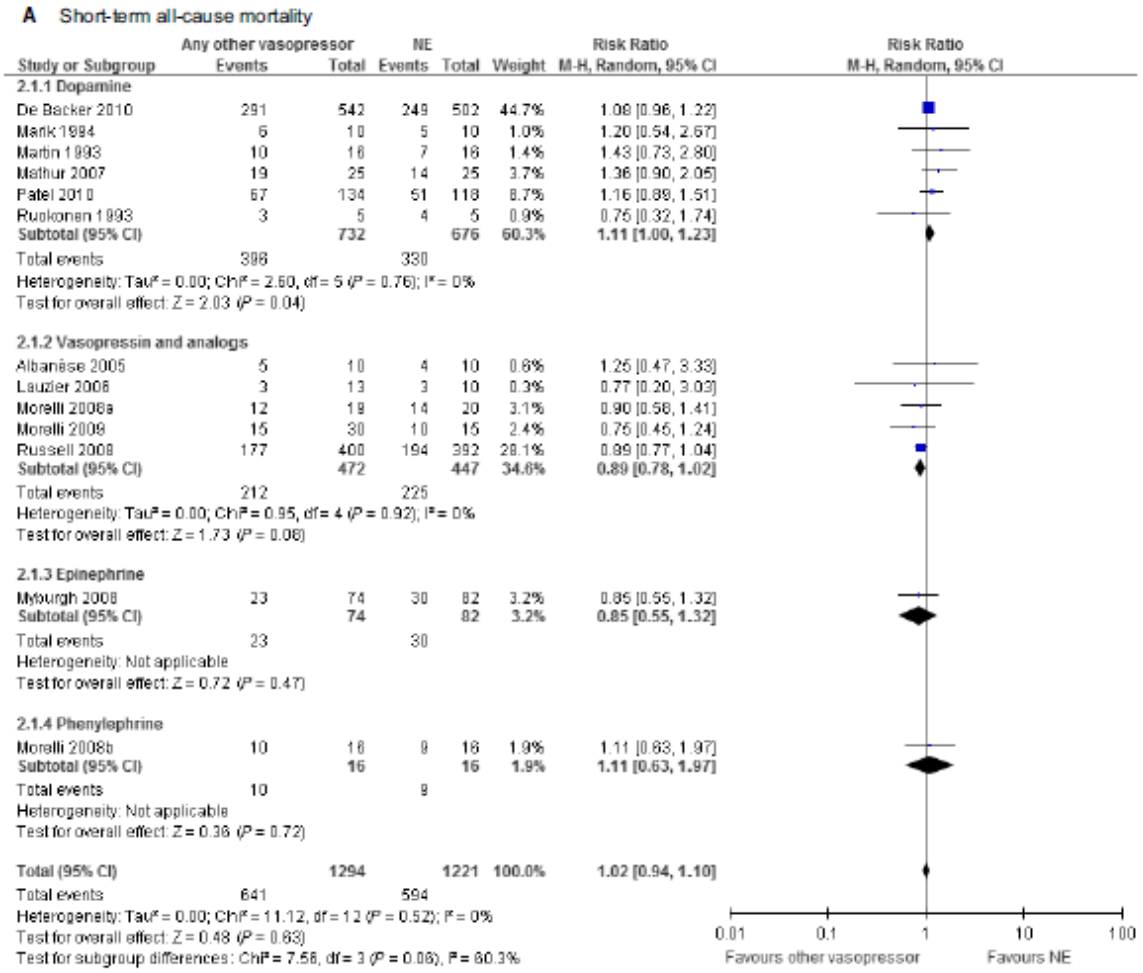


Fig. 2. Forest plot of (A) short-term all-cause mortality, (B) ischaemic events, (C) renal replacement therapy, (D) dysrhythmias, and (E) hospital length of stay in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with septic shock. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

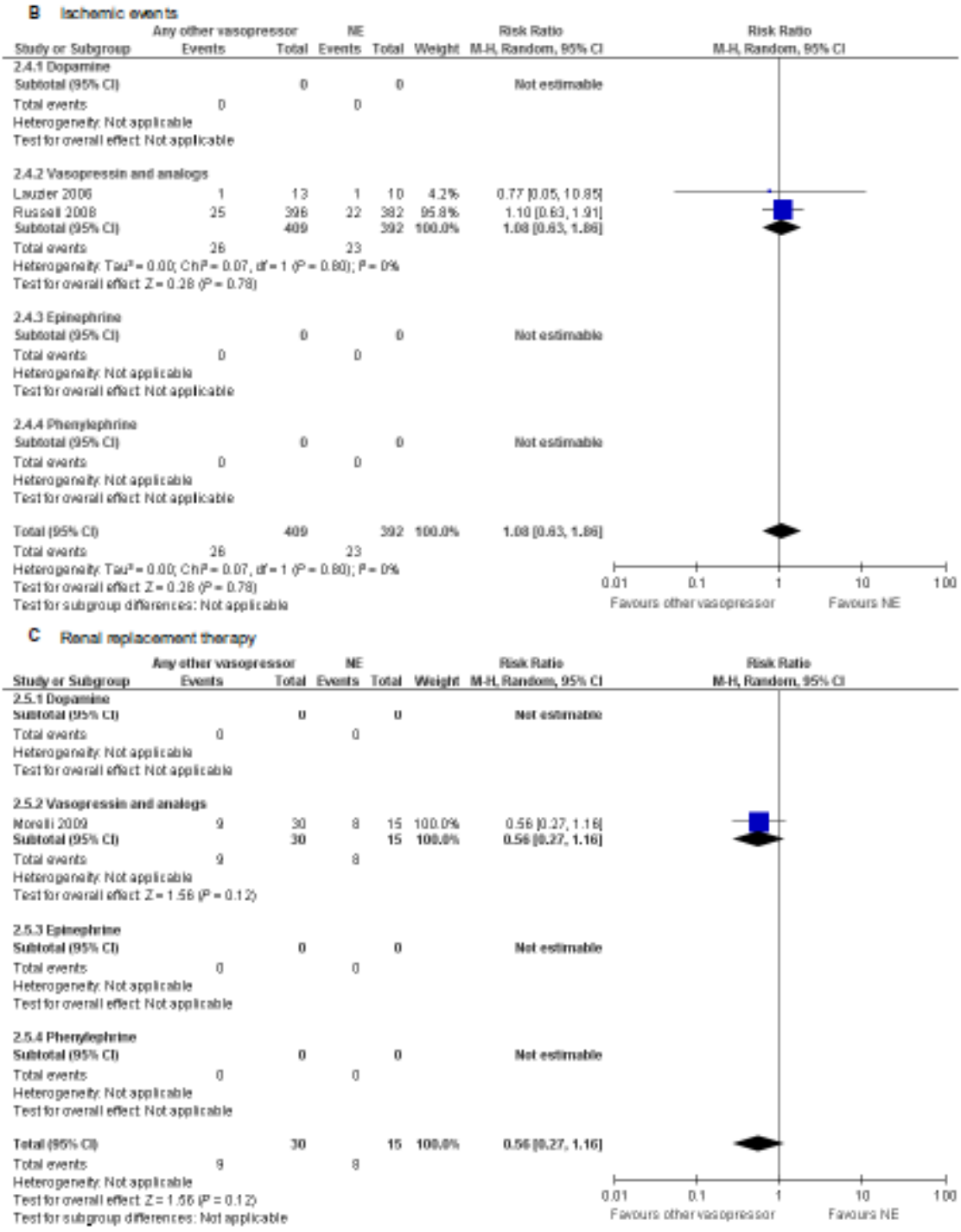
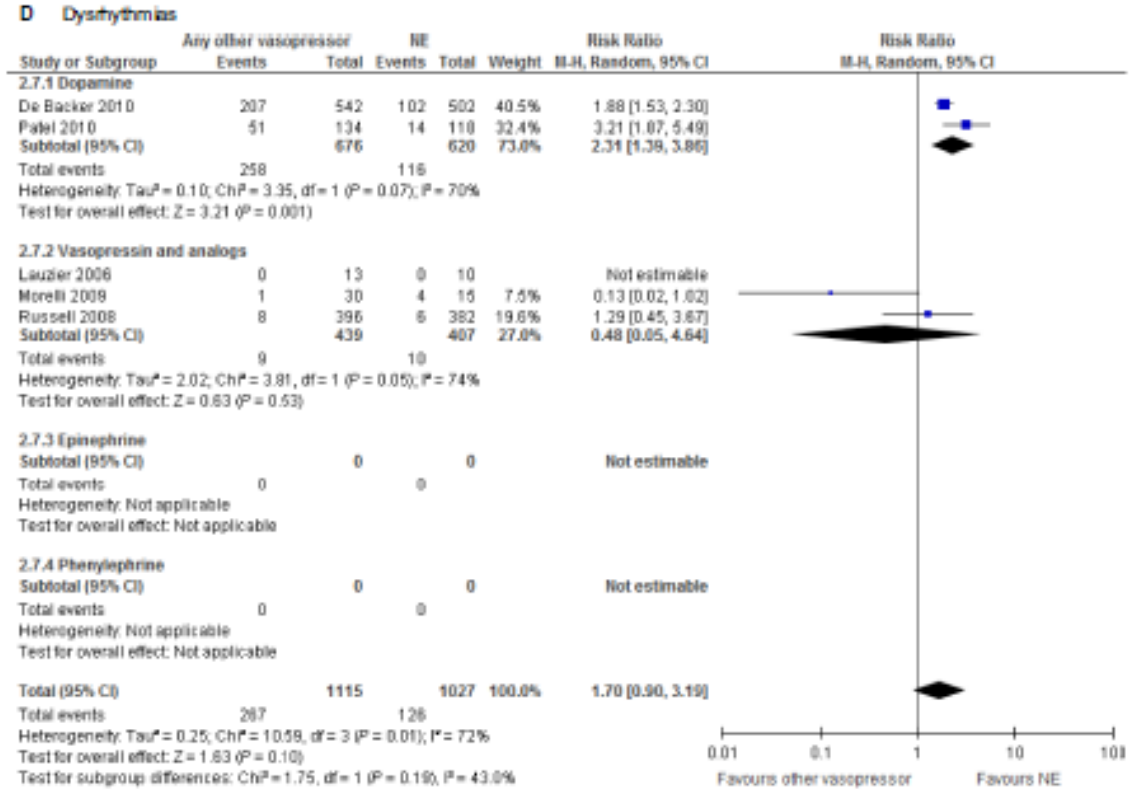


Fig. 2. Continued



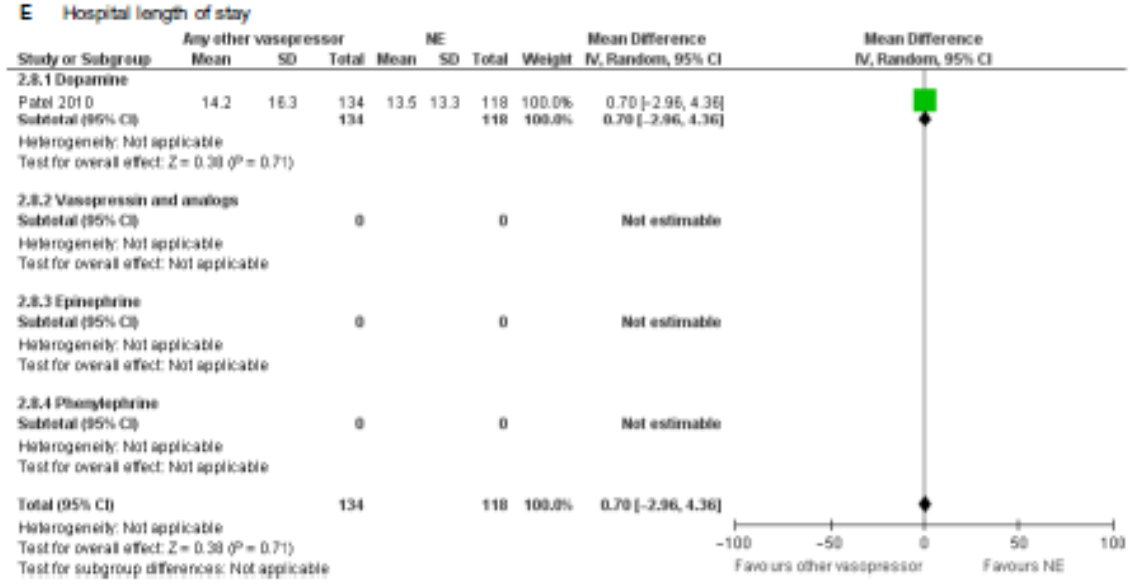


Fig. 2 Continued

Figure 2 Forest plot of (A) short-term mortality, (B) long-term mortality, (C) quality of life, (D) ischemic events, (E) renal replacement therapy, (F) acute kidney injury, (G) dysrhythmias, and (H) hospital length of stay in randomised trials of doputamine vs. other inotropes for patients with septic shock (Møller et al. 2018 [10])

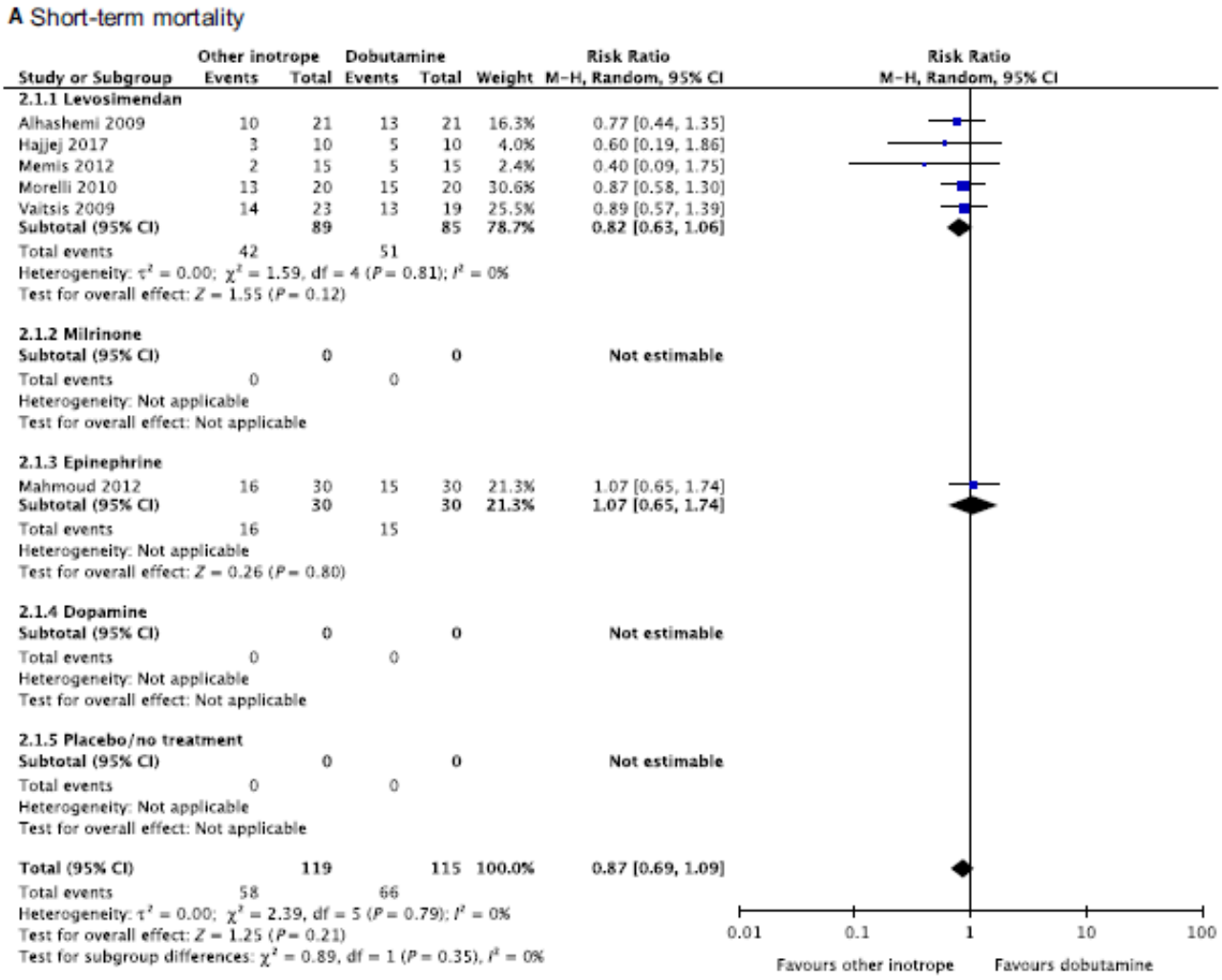
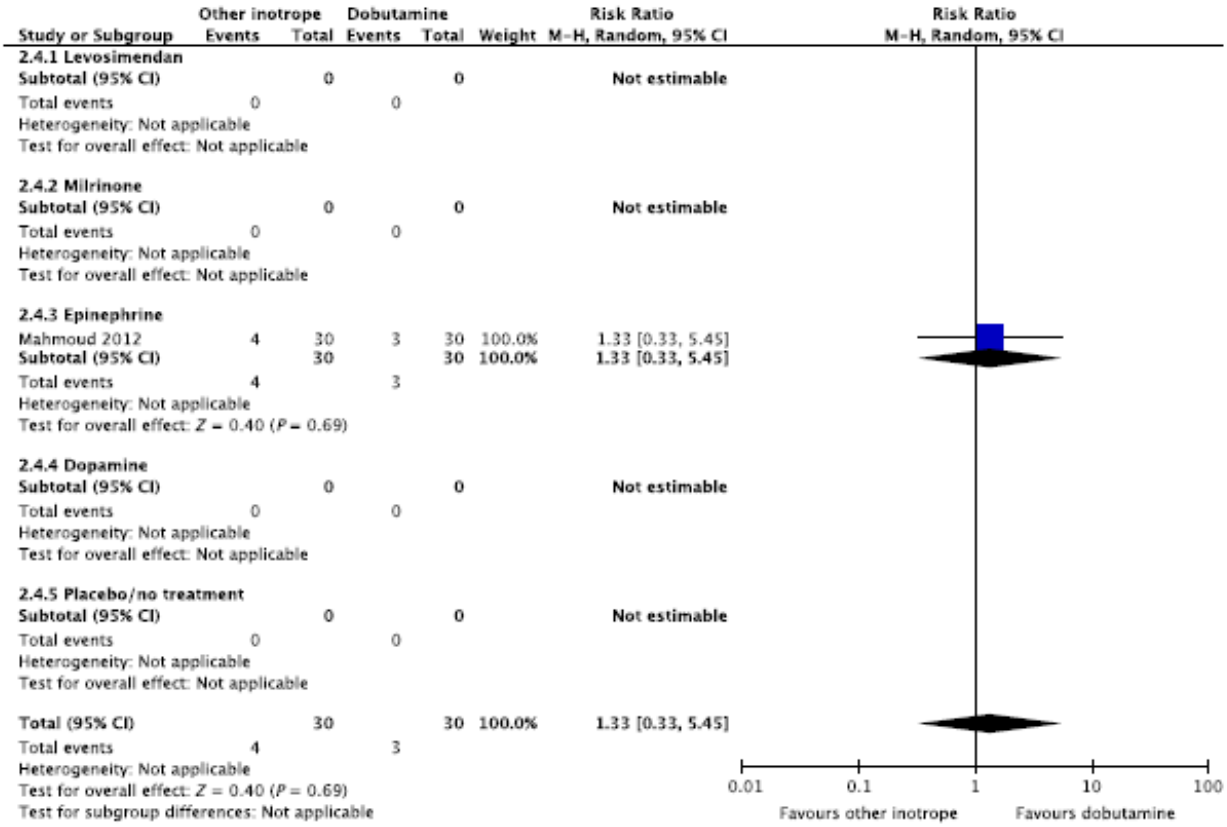


Fig. 2. Forest plot of (A) short-term mortality, (B) long-term mortality, (C) quality of life, (D) ischemic events, (E) renal replacement therapy, (F) acute kidney injury, (G) dysrhythmias, and (H) hospital length-of-stay in randomized trials of dobutamine vs. other inotropes for patients with *septic shock*. [Colour figure can be viewed at wileyonlinelibrary.com]

D Ischemic events



E Renal replacement therapy

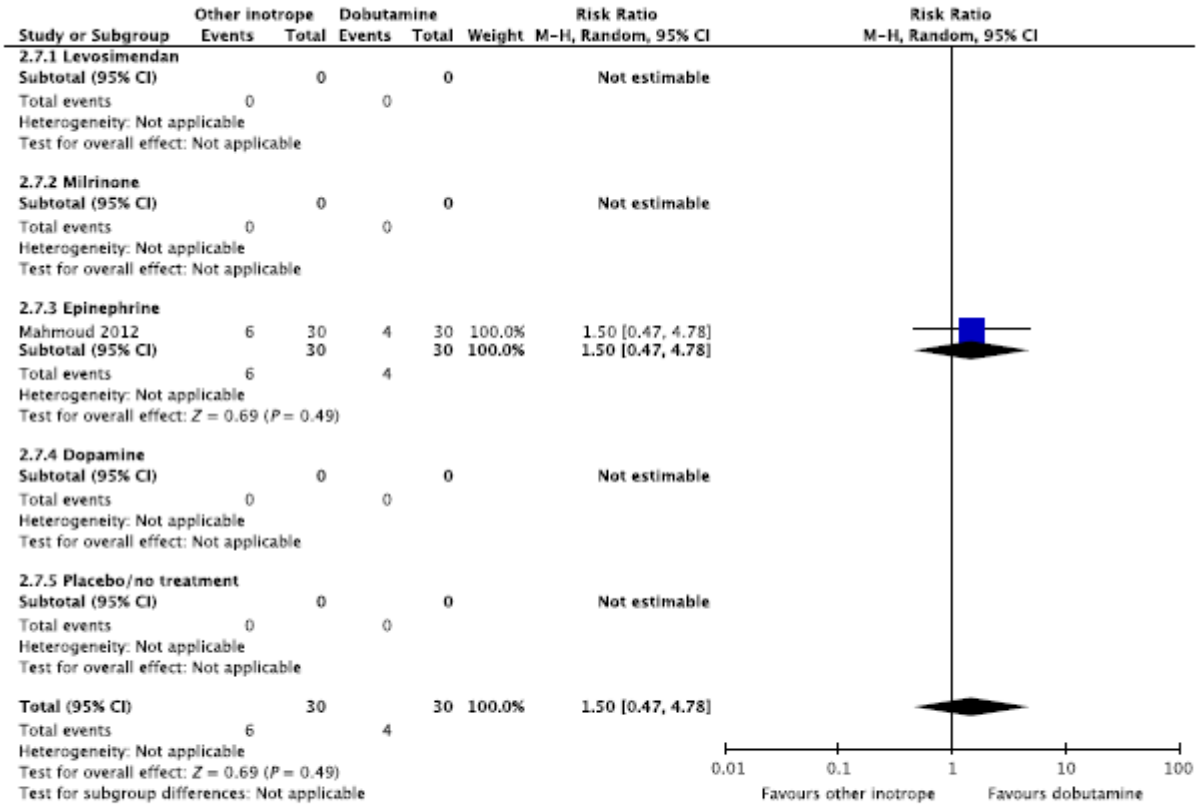
No data.

F Acute kidney injury

No data.

Fig. 2. Continued

G Dysrhythmias



H Hospital length-of-stay

No data.

Fig. 2. Continued