

Adjunctive Vasopressors and Short-Term Mortality in Adults with Septic Shock: A Systematic Review and Meta-Analysis

Seth R. Bauer^{1,2}, Patrick M. Wieruszewski^{3,4}, Brittany D. Bissell Turpin^{5,6}, Siddharth Dugar^{2,7},
Gretchen L. Sacha¹, Ryota Sato⁸, Matthew T. Siuba^{2,7}, Mary Schleicher⁹, Vidula
Vachharajani^{2,7,10}, Yngve Falck-Ytter^{11,12}, Rebecca L. Morgan^{11,13}

¹Department of Pharmacy, Cleveland Clinic, Cleveland, Ohio, United States

²Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western
Reserve University, Cleveland, Ohio, United States

³Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, United States

⁴Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota, United States

⁵Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky,
Lexington, Kentucky, United States

⁶Department of Pharmacy, Ephraim McDowell Regional Medical Center, Danville, Kentucky,
United States

⁷Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland,
Ohio, United States

⁸Division of Critical Care Medicine, The Queen's Medical Center, Honolulu, Hawaii, United
States

⁹The Cleveland Clinic Floyd D. Loop Alumni Library, Cleveland Clinic, Cleveland, Ohio,
United States

¹⁰Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic,
Cleveland, Ohio, United States

¹¹Department of Population and Quantitative Health Sciences, Case Western Reserve
University, Cleveland, Ohio, United States

¹²Division of Gastroenterology and Hepatology, VA Northeast Ohio Healthcare System,
Cleveland, Ohio, United States

¹³Department of Health Research Methods, Evidence and Impact, McMaster University,
Hamilton, Ontario, Canada

Address correspondence to:

Seth R. Bauer
Cleveland Clinic
Department of Pharmacy, Mail Code JJN1-284
9500 Euclid Avenue
Cleveland, OH, United States 44195
E-mail: bayers@ccf.org
Phone: 216-952-2553
Fax: 216-444-8849

Registration: PROSPERO CRD42023427984

Competing interests and Funding: PMW previously served as consultant for La Jolla Pharmaceutical Company. All other authors report no potential conflicts of interest. Supported by the National Institutes of Health, National Institute of General Medical Sciences (SRB: K08GM147806 and VV: R35GM149240). The funding source had no role in study design; data collection, analysis, or interpretation; writing the report; or the decision to submit the report for publication. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Authors' contributions: Conceptualization: SRB, SD, VV. Data curation: SRB, PMW. Formal analysis: SRB, PMW, BDBT, RLM. Investigation: SRB, PMW, SD, GLS, RS, MTS, MS. Methodology: SRB, PMW, BDBT, SD, MS, YF-Y, RLM. Project administration: SRB, PMW, VV, YF-Y, RLM. Resources: MS. Supervision: VV, YF-Y, RLM. Visualization: SRB. Writing – original draft: SRB. Writing – review and editing: SRB, PMW, BDBT, SD, GLS, RS, MTS, MS, VV, YF-Y, RLM. SRB had access to all study data and takes responsibility for the content of the manuscript.

Availability of data and materials: The data generated or analyzed during this study are included in this published article and its supplementary information file.

ACCEPTED

Abstract

Background: Adjunctive vasopressors are added to norepinephrine in one-third of adults with septic shock in the United States. However, effectiveness of this approach is unclear, and treatment recommendations are based on indirect evidence. We sought to synthesize the direct evidence for adjunctive vasopressor administration in adults with septic shock.

Methods: We searched MEDLINE, Embase, and Cochrane Central Register of Controlled Trials from inception to June 7, 2023. We included randomized clinical trials of adults with septic shock comparing adjunctive treatment with a vasopressin analogue, angiotensin II, methylene blue, hydroxocobalamin, or catecholamine analogue to standard care vasopressors. The primary outcome was short-term mortality (at or before 28-30 days or intensive care discharge). Secondary outcomes included kidney replacement therapy, digital/peripheral ischemia, and venous thromboembolism. Random-effects meta-analyses were conducted to derive risk ratios (RRs) and 95% CIs. The certainty of the evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation.

Results: Of 6763 records, 17 trials (3813 participants) were included. Compared with standard care, adjunctive vasopressor administration may reduce short-term mortality risk (RR, 0.92 [95% CI, 0.85 to 1.00], low certainty, 17 trials [18 participants]) and likely reduces kidney replacement therapy receipt (RR, 0.92 [95% CI, 0.84 to 1.01], moderate certainty, 8 trials [2408 participants]). Adjunctive vasopressor treatment may increase risk of digital/peripheral ischemia (RR, 2.44 [95% CI, 1.17 to 5.10], low certainty, 9 trials [2981 participants]) and venous thromboembolism (RR, 16.48 [95% CI, 0.96 to 283.17], low certainty, 1 trial [321 participants]). There was some evidence that the pooled estimate for short-term mortality was different (interaction $P = 0.13$) for trials adjudicated as low risk of bias (RR, 0.95 [95% CI, 0.87 to 1.05]) compared with trials adjudicated as some concerns or high risk of bias (RR, 0.82 [95% CI, 0.69 to 0.97]). The findings were robust to multiple sensitivity and subgroup analyses.

Conclusions: In adults with septic shock, adjunctive vasopressors may lower short-term death risk and likely lower kidney replacement therapy risk, but may increase risk of adverse effects. In the

United States, adjunctive vasopressor use prevalence in septic shock is disconnected from the low evidence certainty for a favorable mortality-to-risk profile.

Registration: PROSPERO CRD42023427984

Key Words: shock, septic; vasoconstrictor agents; vasopressins; systematic review; meta-analysis

ACCEPTED

Background

Sepsis causes over 48 million incident cases and 20% of all deaths worldwide each year.¹ Within the United States, sepsis is the leading cause of death in hospitals.² Consequently, interventions are urgently needed to reduce mortality in patients with sepsis. Septic shock is the most severe sepsis subset where profound circulatory and cellular metabolic derangements lead to substantial mortality.³ Clinically, septic shock is characterized by cardiovascular failure due to vasodilation resulting in hypotension requiring supportive care with vasopressors to maintain adequate blood pressure and organ perfusion. The catecholamine vasopressor norepinephrine is recommended as the first-line vasopressor in adults with septic shock.⁴ Yet, adjunctive vasopressors such as vasopressin are administered in addition to norepinephrine in 33-42% of patients in the United States, with increasing prevalence over time.⁵⁻⁷

Adjunctive vasopressors have pharmacology different from norepinephrine, leading to alternative pathways for increasing blood pressure. Because of the potential for improved end-organ perfusion, large randomized clinical trials have evaluated adjunctive vasopressors in adults with septic shock.⁸⁻¹⁰ These trials have consistently shown adjunctive vasopressors increase blood pressure and lower norepinephrine requirements. However, despite point estimates favoring adjunctive vasopressors, the treatment effect was small enough such that no trial has detected improved mortality with an adjunctive vasopressor over standard care. Furthermore, an improvement in a clinically-important outcome with an adjunctive vasopressor has only been shown in one trial.⁹ These findings have led to large practice variability in adjunctive vasopressor use both globally and within the United States.^{5,11}

Previously published systematic reviews and meta-analyses have sought to inform the use of adjunctive vasopressors in patients with septic shock.^{4,12-17} But each of the published reviews has one or more important limitations that hinder its interpretation. Although designed to assess randomized clinical trials of adjunctive vasopressors in septic shock, multiple reviews have included a historically-controlled study misclassified as a randomized clinical trial, included trials enrolling patients with the broader syndrome of distributive shock (of which septic shock is one of several etiologies), and/or included trials predominantly evaluating the vasopressor(s) of interest as a first-line treatment. These limitations hinder application of the previous reviews to the target population for three reasons. First, simultaneous synthesis of a non-randomized study evaluating

asynchronous cohorts with randomized clinical trials in a pairwise meta-analysis can lead to confounding by selection bias, unexplained heterogeneity, and ambiguous results.^{18,19} Second, patients with septic shock have different hemodynamics and outcomes compared with patients with other distributive shock etiologies such as post-cardiovascular surgery.²⁰⁻²² Lastly, and importantly, trials predominantly evaluating the vasopressor of interest as an initial therapy are not directly applicable to the use of the vasopressor as an adjunctive therapy. Despite their limitations the findings from these reviews are utilized broadly, including in the 2021 Surviving Sepsis Campaign International Guidelines, to support the administration of adjunctive vasopressors in septic shock.⁴ To overcome previous limitations, the objective of this systematic review and meta-analysis was to determine whether adjunctive vasopressor treatment compared with standard care was associated with lower risk for mortality and other important outcomes in adult patients with septic shock based on the direct evidence from randomized clinical trials.

Methods

This systematic review and meta-analysis was conducted with a prespecified published protocol (without subsequent amendments),²³ registered in the International Prospective Register of Systematic Reviews (registration number redacted), followed Cochrane handbook guidance,²⁴ and reported in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁵

Eligibility Criteria

We included randomized clinical trials that recruited adult patients, of whom 75% or more had septic shock, and compared the administration of an adjunctive vasopressor (75% or more receiving a standard care vasopressor at enrollment) to standard care vasopressors. Adjunctive vasopressor drugs of interest were 1) vasopressin and its analogues pituitrin, selepressin, and terlipressin; 2) angiotensin II; 3) the nitric oxide pathway modulators methylene blue and hydroxocobalamin; and 4) the catecholamine (and analogues thereof) vasopressors dopamine, epinephrine, and phenylephrine. Although norepinephrine is currently recommended as the initial vasopressor in patients with septic shock,⁴ previous Surviving Sepsis Campaign International Guidelines iterations published in 2004 and 2008 also recommended dopamine as an initial vasopressor.^{26,27} Because these guidelines may have been current at the time of trial design and

recruitment, administration of norepinephrine or dopamine, with or without adjunctive vasopressor infusion, were considered standard care vasopressor regimens.^{4,26-29} However, no included trial solely utilized dopamine and all included trials utilized norepinephrine. Standard care vasopressor regimens could include placebo with continuation of open-label standard care vasopressors or blinded comparator standard care vasopressor. Studies were excluded if they were published in a non-English language, had a cross-over design, or were missing all outcomes of interest. We included all eligible reports including studies only reported as abstracts.

Search Methods

We systematically searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to June 7, 2023. An information specialist developed and implemented the search strategy. We also conducted manual searches of reference lists of included studies and other systematic reviews. eTable 1 in the Supplement provides details of the electronic search strategy.

Study Selection

We used the Covidence (Melbourne, Australia) reference management system to screen studies. Six reviewers independently and in duplicate screened studies' titles and abstracts for possible inclusion. Two reviewers independently assessed the full text of articles in duplicate to determine eligibility. Disagreements were resolved through discussion.

Data Collection

We extracted data from each included trial using a standardized and piloted data collection form as outlined in the protocol. To optimize completeness, in addition to published study manuscripts we utilized trial protocols, registers, and regulatory documents, when available. Extracted data included characteristics of study design and enrolled population (e.g., demographics, percentage with septic shock), and details of the intervention and comparator. Two reviewers independently and in duplicate extracted data on outcomes. We did not impute missing data; each analysis only included published trial results (a “complete case analysis”) and missingness for participant and intervention characteristics is noted as indicate. Reviewers compared extraction results and resolved disagreements through discussion. We did not contact study investigators to obtain or

confirm data.

Risk of Bias Assessment

Two reviewers independently and in duplicate assessed risk of bias using the Cochrane Risk of Bias 2 tool.³⁰ The data capture tool utilized embedded resources to optimize accuracy and consistency of responses to risk of bias signaling questions. The results were compared, and disagreements resolved through discussion.

Outcomes

The primary outcome was short-term mortality, defined as mortality at or before 28 days, 30 days, or intensive care unit (ICU) discharge. Mortality reported at these three follow-up timepoints was considered equivalent.³¹ Data were also collected for the following secondary outcomes: intermediate-term mortality (at or before 60 days or hospital discharge),³¹ kidney replacement therapy, digital/peripheral ischemia, and venous thromboembolism. Short-term and intermediate-term mortality are considered patient-important outcomes in critically ill patients,^{32,33} kidney replacement therapy receipt was deemed on the causal pathway for mortality,³⁴ and digital/peripheral ischemia and venous thromboembolism are recognized adverse effects of adjunctive vasopressors.³⁵ Secondary outcomes were accepted as defined by study authors. Each of the primary and secondary outcomes was adjudicated as “critical” importance for decision making by panel members for the 2021 Surviving Sepsis Campaign International Guidelines.⁴

Sensitivity and Subgroup Analyses

There were two prespecified sensitivity analysis.²³ We compared trials where the risk of bias was low with trials where there were some concerns for bias or a high risk of bias. We also attempted to restrict studies to those evaluating non-catecholamine adjunctive vasopressors. There were four post hoc sensitivity analyses; 1) we restricted studies to those evaluating currently available vasopressor medications (removing selepressin), 2) we restricted studies to those where the comparison standard care vasopressor regimen did not include an open-label intervention vasopressor of interest, 3) we restricted studies to vasopressin analogues, and 4) we restricted studies to those exclusively enrolling patients with septic shock. There were three prespecified subgroup analyses.²³ We compared trials by the intervention drug class/mechanism of action

grouped as vasopressin analogues, angiotensin II, methylene blue and hydroxocobalamin, or catecholamine analogues. We also compared trials by shock severity, as assessed by baseline norepinephrine dosage above or below the overall median value from all studies. Lastly, we attempted to compare trials by standard care vasopressor comparator, whether norepinephrine or dopamine. In a post hoc subgroup analysis we restricted the analysis of short-term mortality by intervention drug class/mechanism of action to only trials where the risk of bias was low. *P* values for interaction between subgroups were tested.

Data Synthesis

Treatment effect for outcome measures (each dichotomous) was assessed by calculating the risk ratio (RR) with 95% confidence interval (CI) between adjunctive vasopressor and standard care groups. Included studies determined to be sufficiently similar for grouping through tabulation of characteristics were analyzed with meta-analysis conducted using a random-effects model with the DerSimonian and Laird inverse variance method. We a priori chose a random-effects model due to anticipated between-study variation in estimated intervention effects. Heterogeneity among trials was quantified with the I^2 statistic, reflecting the percentage of total variability in effect estimates due to between-study heterogeneity rather than chance. A threshold for interpretation of the I^2 statistic was not utilized.³⁶ Evidence for heterogeneity of the intervention or subgroup effect beyond chance was determined from the *P* value of a chi-square test, with a *P* value threshold below 0.10 utilized to determine statistical significance.³⁶ Funnel plots for outcome measures with at least ten studies were visually inspected for evidence of publication bias. RevMan (Cochrane Collaboration), version 5.4, was used to combine data quantitatively and visually display results.

Certainty of the Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the certainty (i.e., quality or confidence) of the body of evidence that adjunctive vasopressor administration compared with standard care improves each outcome measure.³⁷ The target of our certainty ratings was an effect estimate greater than the minimum clinically important difference (small effect threshold).³⁸ To ensure judgments were systematic and transparent, detailed assessments were provided in evidence profiles with rationale for each factor determining the certainty of evidence for each outcome. A minimum clinically important difference for

mortality in patients with septic shock, or critically ill patients in general, has not been established. Some have utilized an absolute difference of 5% as the minimum clinically important difference based on review of the literature,³⁹ while others have postulated a 1.5% minimum clinically important difference for calculation of statistical power in a trial.⁴⁰ Due to this lack of clarity we considered both of these thresholds when adjudicating imprecision for mortality outcome measures. To adjudicate imprecision, we also estimated the optimal information size for each outcome measure.⁴¹⁻⁴³ We also generated a post hoc evidence profile restricted to adjunctive vasopressin analogues. We used GRADEpro GDT (McMaster University and Evidence Prime) to facilitate certainty of evidence assessment and produce estimates of absolute effect by applying the RRs with 95% CIs to the risk in the control group.

Results

The electronic search resulted in 6763 records and the manual search identified 68 records (**Figure 1** and eTable 2 in the Supplement). After abstract screening and full-text review, 17 trials were included enrolling 3813 participants.^{8-10,44-57} **Table 1** and eTable 3 in the Supplement present the trial and patient characteristics. Sixteen of 17 trials exclusively enrolled subjects with septic shock (81% of subjects had septic shock in one trial⁴⁸). In 12 of 17 trials all subjects enrolled were receiving baseline standard care vasopressors, in three trials some patients (range 12-24%) solely received the intervention or comparison vasopressor,^{9,50,51} and in two trials all patients were receiving a baseline vasopressor but some patients (range 2-14%) were solely receiving a vasopressor other than norepinephrine or dopamine.^{8,48} The included trials had a median of 40 participants (interquartile range [IQR], 22-407), the median age of participants was 63 years (IQR, 60-66), and the median percentage of female participants was 39% (IQR, 37%-42%).

Risk of Bias

eFigure 1 and eTable 3 in the Supplement present risk of bias assessments. The risk of bias was adjudicated as low for 10 of 17 trials. We rated down the evidence certainty due to risk of bias for short-term mortality but not for other outcomes (**Table 2**).

Primary Outcome

There were 17 trials (3618 participants) contributing data to the evaluation of short-term

mortality. Assessment of short-term mortality was at or before 28 days in 12 trials, 30 days in 2 trials, and ICU discharge in 3 trials. The pooled estimated RR for short-term mortality for adjunctive vasopressors was 0.92 (95% CI, 0.85 to 1.00; $I^2 = 0\%$) compared with standard care vasopressors (**Figure 2**). There were serious concerns for imprecision regardless of the minimum clinically important difference threshold used. The certainty in the evidence was adjudicated as low (**Table 2**).

Sensitivity Analysis

Table 3 presents the results of the prespecified sensitivity and subgroup analyses for short-term mortality. There was some evidence that the pooled estimate for short-term mortality was different (P value for the between-subgroup interaction test = 0.13) for trials adjudicated as low risk of bias (RR, 0.95 [95% CI, 0.87 to 1.05]) compared with trials adjudicated as some concerns or high risk of bias (RR, 0.82 [95% CI, 0.69 to 0.97]) as shown in **Table 3** and eFigure 2 in the Supplement. All included trials evaluated non-catecholamine adjunctive vasopressors, therefore a sensitivity analysis restricted to non-catecholamine adjunctive vasopressors was not performed. Results were similar in the post hoc sensitivity analyses of currently available vasopressor medications (eFigure 3 in the Supplement), when studies were restricted to those where the comparison standard care vasopressor regimen did not include an open-label intervention vasopressor of interest (eFigure 4 in the Supplement), and when studies were restricted to those exclusively enrolling patients with septic shock (eFigure 5 in the Supplement). In the post hoc sensitivity analysis of vasopressin analogues, the certainty in the evidence was adjudicated as low (eFigure 6 and eTable 5 in the Supplement). Visual inspection of the funnel plot did not raise concerns for publication bias (eFigure 7 in the Supplement).

Subgroup Analysis

No evidence was detected for a differential estimate of the association of adjunctive vasopressor administration with short-term mortality in trials based on the drug class/mechanism of action (P value for the between-subgroup interaction test = 0.34; eFigure 8 in the Supplement) or baseline shock severity (P value for the between-subgroup interaction test = 0.38; eTable 4 and eFigure 9 in the Supplement). Data were not available to permit an assessment of the potential heterogeneity by comparator standard care vasopressor because no included trial solely utilized dopamine and

all included trials utilized norepinephrine. Findings were similar when the subgroup analysis based on the drug class/mechanism of action was restricted to trials where the risk of bias was low (eFigure 10 in the Supplement).

Secondary Outcomes

Table 2 and eTable 5 and eFigures 11-22 in the Supplement present the results of the secondary outcome assessments. Kidney replacement therapy was assessed in 8 trials (2408 participants), intermediate-term mortality in 1 trial (evaluated at hospital discharge, 408 participants), digital/peripheral ischemia in 9 trials (2981 participants), and venous thromboembolism in 1 trial (321 participants). Compared with standard care, adjunctive vasopressors likely reduce kidney replacement therapy receipt (RR, 0.92 [95% CI, 0.84 to 1.01], $I^2 = 0\%$, moderate certainty), and may increase risk of intermediate-term mortality (RR, 1.13 [95% CI, 0.85 to 1.51], I^2 not applicable, low certainty), digital/peripheral ischemia (RR, 2.44 [95% CI, 1.17 to 5.10], $I^2 = 40\%$, low certainty), and venous thromboembolism (RR, 16.48 [95% CI, 0.96 to 283.17], I^2 not applicable, low certainty). There was no evidence for a differential estimate of the association of adjunctive vasopressor use with any secondary outcome in the sensitivity and subgroup analyses. Publication bias assessment was limited by small numbers of studies for each secondary outcome.

Discussion

In this systematic review and meta-analysis, we found adjunctive vasopressor administration may lower risk for short-term mortality compared with standard care vasopressors alone in adults with septic shock. However, evidence certainty was low due to risk of bias and imprecision, and the 95% confidence interval for the risk ratio included no effect. Short-term mortality reduction was evident only in trials with some concerns or high risk for bias. Kidney replacement therapy receipt is likely reduced with adjunctive vasopressor administration, but this therapy may increase risk for intermediate-term mortality and adverse effects. There was evidence for a higher risk for digital/peripheral ischemia with adjunctive vasopressors.

To our knowledge, this systematic review is the first to evaluate the direct evidence for adjunctive vasopressor treatment in adults with septic shock. Previous reviews have sought to evaluate this topic, but their evaluation of indirect evidence substantially limits application to patients with septic shock. In particular, the review of vasopressin performed for the 2021 Surviving Sepsis

Campaign International Guidelines is limited by inclusion of studies evaluating vasopressin as a first-line vasopressor instead of adjunctive therapy, and inclusion of a trial enrolling patients with distributive shock after cardiac surgery.⁴ Further, they seemed to use any non-null effect instead of a minimum clinically important difference when rating effect estimate imprecision certainty. While our results are generally similar to previous reviews, the direct evidence was of low certainty to support an association of adjunctive vasopressor administration in general (and also with vasopressin analogues specifically) with a benefit on short-term mortality. This level of certainty, along with the adverse effect risks outlined, should be incorporated into the evidence to decision framework in future guidelines.

Adjunctive vasopressor administration is common and increasing in prevalence in adults with septic shock.⁵⁻⁷ The prevalent use of these therapies in clinical practice is juxtaposed by our finding of an uncertain mortality-to-risk profile. Clinicians may be utilizing adjunctive vasopressors to improve a surrogate outcome, such as kidney failure or atrial fibrillation occurrence, instead of mortality.^{14,58} Indeed, our review found moderate certainty evidence supporting adjunctive vasopressor administration was associated with reduced kidney replacement therapy receipt. However, these outcomes have not been validated as important to patients and may be inadequate surrogates for mortality.^{32,59,60} To address shortcomings of the current literature, additional trials of sufficient size and quality evaluating the effect of adjunctive vasopressors on mortality and other patient-important outcomes are greatly needed to inform clinical practice. These trials should consider sepsis subclasses and other methods to enhance predictive enrichment for a treatment response.⁶¹⁻⁶⁴

Our review has several strengths. We overcame limitations of previous reviews by examining the direct evidence for adjunctive vasopressor administration in adults with septic shock. We closely adhered to established standards including reporting the evidence certainty for our findings and incorporating a minimum clinically important difference threshold in our assessment. We further performed a priori-planned sensitivity and subgroup analyses to ensure the robustness of our findings.

Limitations

This study has several limitations. First, we included all adjunctive vasopressors in our main analysis instead of focusing on a particular drug or mechanism of action. This approach heavily

weighs the considerations put forth in the Cochrane Handbook on developing a broad versus a narrow review and informs the administration of an additional vasopressor beyond norepinephrine monotherapy, but does not isolate the effect of a particular adjunctive vasopressor of interest.²⁴ Because our grouping of adjunctive vasopressors can be perceived as a heterogeneous collection of trials we proactively sought to overcome this limitation by exploring reasons for heterogeneity with a subgroup analysis by drug class/mechanism of action, which did not detect a substantial subgroup or treatment effect. Second, we did not seek to evaluate actions taken with standard care vasopressors after initiation of the intervention adjunctive vasopressor. While standard care vasopressors may have been titrated off first, leaving the intervention adjunctive vasopressor as the sole agent, at the time of trial enrollment the intervention was initiated as an adjunctive therapy. As such we included trials utilizing this approach and did not separately evaluate trials where the standard care vasopressor regimen was concomitantly administered throughout the intervention time period. Third, in some trials the comparison standard care vasopressor regimen included an open-label intervention vasopressor of interest.^{45,47,48,54} This could bias our findings in an unpredictable direction. However, results from a sensitivity analysis excluding these trials were similar to our primary analysis. Fourth, in the single study included in the analysis of intermediate-term mortality,⁹ the outcome was assessed at hospital discharge. However, the median hospital length of stay in both groups in the study was 16 days; a follow-up duration shorter than the follow-up time point we used to assess short-term mortality (28 days) for the study. Although our assessment and reporting approach for this outcome followed our pre-specified protocol and recommendations from the literature,^{23,31} this finding from the single study leads to unclear interpretation of our intermediate mortality result. Fifth, we did not evaluate the intermediate outcome atrial fibrillation or other catecholamine-specific adverse effects because their presence on the causal pathway for mortality in septic shock is indeterminant, but associations have been observed and these outcomes have the potential to drive administration of adjunctive vasopressors in practice.⁶⁵⁻⁶⁷ Sixth, our subgroup analysis based on shock severity stratified studies based on reported baseline norepinephrine dosage. However, the norepinephrine formulation utilized in the studies is unclear, which may have impacted the finding.⁶⁸ Further, utilization of a norepinephrine dosage threshold based on the overall median baseline value from all studies does not account for the number of patients included in each study. Therefore, this threshold may not reflect the true weighted value for an average patient; rather it reflects the value from an average study. Lastly,

limiting trials to English language publication could have led to language bias.

Conclusions

Among adults with septic shock, adjunctive vasopressor treatment versus standard care may lower short-term death risk and likely lowers kidney replacement therapy receipt risk but may increase risk of intermediate-term death and adverse effects. The evidence certainty for adjunctive vasopressors reducing short-term mortality was low due to concerns for risk of bias and imprecision with the evidence. Current adjunctive vasopressor use prevalence in septic shock in the United States is disconnected from the low evidence certainty for a favorable mortality-to-risk profile.

References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211.
2. Liu V, Escobar GJ, Greene JD, et al. Hospital Deaths in Patients With Sepsis From 2 Independent Cohorts. *JAMA*. 2014;312(1):90-92.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
4. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143.
5. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of Vasopressin Use for Adults with Septic Shock. *Ann Am Thorac Soc*. 2016;13(10):1760-1767.
6. Bosch NA, Teja B, Wunsch H, Walkey AJ. Practice Patterns in the Initiation of Secondary Vasopressors and Adjunctive Corticosteroids during Septic Shock in the United States. *Ann Am Thorac Soc*. 2021;18(12):2049-2057.
7. Sacha GL, Kiser TH, Wright GC, et al. Association Between Vasopressin Rebranding and Utilization in Patients With Septic Shock. *Crit Care Med*. 2022;50(4):644-654.
8. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.
9. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA*. 2016;316(5):509-518.
10. Laterre PF, Berry SM, Blemings A, et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. *JAMA*. 2019;322(15):1476-1485.
11. Abril MK, Khanna AK, Kroll S, McNamara C, Handisides D, Busse LW. Regional differences in the treatment of refractory vasodilatory shock using Angiotensin II in High Output Shock (ATHOS-3) data. *J Crit Care*. 2019;50:188-194.
12. Pasin L, Umbrello M, Greco T, et al. Methylene blue as a vasopressor: a meta-analysis of randomised trials. *Crit Care Resusc*. 2013;15(1):42-48.

13. Belletti A, Benedetto U, Biondi-Zoccai G, et al. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. *J Crit Care*. 2017;37:91-98.
14. McIntyre WF, Um KJ, Alhazzani W, et al. Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. *JAMA*. 2018;319(18):1889-1900.
15. Nagendran M, Russell JA, Walley KR, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med*. 2019;45(6):844-855.
16. Honarmand K, Um KJ, Belley-Cote EP, et al. Canadian Critical Care Society clinical practice guideline: The use of vasopressin and vasopressin analogues in critically ill adults with distributive shock. *Can J Anaesth*. 2020;67(3):369-376.
17. Zhong L, Ji X-W, Wang H-L, Zhao G-M, Zhou Q, Xie B. Non-catecholamine vasopressors in the treatment of adult patients with septic shock—evidence from meta-analysis and trial sequential analysis of randomized clinical trials. *J Intensive Care*. 2020;8(1):83.
18. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. *Res Synth Methods*. 2013;4(1):26-35.
19. Sarri G, Paterno E, Yuan H, et al. Framework for the synthesis of non-randomised studies and randomised controlled trials: a guidance on conducting a systematic review and meta-analysis for healthcare decision making. *BMJ Evid Based Med*. 2022;27(2):109-119.
20. Geri G, Vignon P, Aubry A, et al. Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis. *Intensive Care Med*. 2019;45(5):657-667.
21. Lambden S, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. *Crit Care*. 2018;22(1):174.
22. Levy B, Fritz C, Tahon E, Jacquot A, Auchet T, Kimmoun A. Vasoplegia treatments: the past, the present, and the future. *Crit Care*. 2018;22(1):52.
23. Bauer SR, Wieruszewski PM, Bissell BD, et al. Adjunctive Vasopressors in Patients with Septic Shock: Protocol for a Systematic Review and Meta-Analysis. *medRxiv*. 2023.

24. Cochrane Handbook for Systematic Reviews of Interventions. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
26. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
27. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
28. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
29. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017;45(3):486-552.
30. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
31. Friedrich JO, Harhay MO, Angus DC, et al. Mortality As a Measure of Treatment Effect in Clinical Trials Recruiting Critically Ill Patients. *Crit Care Med*. 2023;51(2):222-230.
32. Gaudry S, Messika J, Ricard J-D, et al. Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. *Ann Intensive Care*. 2017;7(1):28.
33. Marshall JC, Vincent JL, Guyatt G, et al. Outcome measures for clinical research in sepsis: a report of the 2nd Cambridge Colloquium of the International Sepsis Forum. *Crit Care Med*. 2005;33(8):1708-1716.
34. Zarbock A, Nadim MK, Pickkers P, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. *Nature Rev Nephrol*. 2023;19(6):401-417.
35. Bauer SR, Sacha GL, Lam SW. Safe Use of Vasopressin and Angiotensin II for Patients with Circulatory Shock. *Pharmacotherapy*. 2018;38(8):851-861.

36. Deeks JJ, Higgins JPT, Altman DJ. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol 6.3 (updated February 2022): Cochrane; 2022.
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
38. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. *J Clin Epidemiol*. 2021;137:163-175.
39. Abrams D, Montesi SB, Moore SKL, et al. Powering Bias and Clinically Important Treatment Effects in Randomized Trials of Critical Illness. *Crit Care Med*. 2020;48(12):1710-1719.
40. Young P, Arabi Y, Bagshaw S, et al. Protocol and statistical analysis plan for the mega randomised registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). *Crit Care Resusc*. 2022;24(2):137-149.
41. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. *Critical Care*. 2020;24(1):239.
42. Peters E, Antonelli M, Wittebole X, et al. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. *Critical Care*. 2018;22(1):188.
43. Kaplan D, Casper TC, Elliott CG, et al. VTE Incidence and Risk Factors in Patients With Severe Sepsis and Septic Shock. *Chest*. 2015;148(5):1224-1230.
44. Barzegar E, Ahmadi A, Mousavi S, Nouri M, Mojtahedzadeh M. The Therapeutic Role of Vasopressin on Improving Lactate Clearance During and After Vasogenic Shock: Microcirculation, Is It The Black Box? *Acta Med Iran*. 2016;54(1):15-23.
45. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. *Crit Care*. 2014;18(5):534.
46. Dünser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory

- shock: a prospective, randomized, controlled study. *Circulation*. 2003;107(18):2313-2319.
47. Ibarra-Estrada M, Kattan E, Aguilera-González P, et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. *Crit Care*. 2023;27(1):110.
 48. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017;377(5):419-430.
 49. Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med*. 2001;29(10):1860-1867.
 50. Lauzier F, Lévy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med*. 2006;32(11):1782-1789.
 51. Liu ZM, Chen J, Kou Q, et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. *Intensive Care Med*. 2018;44(11):1816-1825.
 52. Morelli A, Ertmer C, Lange M, et al. Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. *Br J Anaesth*. 2008;100(4):494-503.
 53. Oliveira S, Dessa F, Rocha C, Oliveira F. Early Vasopressin Application in Shock study. *Crit Care*. 2014;18(Suppl 1):P158.
 54. Patel JJ, Willoughby R, Peterson J, et al. High-Dose IV Hydroxocobalamin (Vitamin B12) in Septic Shock: A Double-Blind, Allocation-Concealed, Placebo-Controlled Single-Center Pilot Randomized Controlled Trial (The Intravenous Hydroxocobalamin in Septic Shock Trial). *Chest*. 2023;163(2):303-312.
 55. Russell JA, Vincent JL, Kjølbye AL, et al. Selepressin, a novel selective vasopressin V(1A) agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. *Crit Care*. 2017;21(1):213.
 56. Svoboda P, Scheer P, Kantorová I, et al. Terlipressin in the treatment of late phase catecholamine-resistant septic shock. *Hepatology*. 2012;59(116):1043-1047.
 57. Wang J, Shi M, Huang L, et al. Addition of terlipressin to norepinephrine in septic shock and effect of renal perfusion: a pilot study. *Ren Fail*. 2022;44(1):1207-1215.
 58. Nedel WL, Rech TH, Ribeiro RA, Pellegrini JAS, Moraes RB. Renal Outcomes of Vasopressin and Its Analogs in Distributive Shock: A Systematic Review and Meta-

- Analysis of Randomized Trials. *Crit Care Med*. 2019;47(1):e44-e51.
59. Young P, Hodgson C, Dulhunty J, et al. End points for phase II trials in intensive care: recommendations from the Australian and New Zealand Clinical Trials Group consensus panel meeting. *Crit Care Resusc*. 2012;14(3):211-215.
 60. Turnbull AE, Sepulveda KA, Dinglas VD, Chessare CM, Bingham CO, 3rd, Needham DM. Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. *Crit Care Med*. 2017;45(6):1001-1010.
 61. DeMerle KM, Angus DC, Baillie JK, et al. Sepsis Subclasses: A Framework for Development and Interpretation. *Crit Care Med*. 2021;49(5):748-759.
 62. Seymour CW, Gomez H, Chang CH, et al. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. *Crit Care*. 2017;21(1):257.
 63. Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. *Nat Rev Nephrol*. 2020;16(1):20-31.
 64. Bauer SR, Gellatly RM, Erstad BL. Precision fluid and vasoactive drug therapy for critically ill patients. *Pharmacotherapy*. 2023;43(11):1182-1193.
 65. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306(20):2248-2254.
 66. Wieruszewski PM, Khanna AK. Vasopressor Choice and Timing in Vasodilatory Shock. *Crit Care*. 2022;26(1):76.
 67. Teja B, Bosch NA, Walkey AJ. How We Escalate Vasopressor and Corticosteroid Therapy in Patients With Septic Shock. *Chest*. 2023;163(3):567-574.
 68. Wieruszewski PM, Leone M, Kaas-Hansen BS, et al. Position Paper on the Reporting of Norepinephrine Formulations in Critical Care from the Society of Critical Care Medicine and European Society of Intensive Care Medicine Joint Task Force. *Crit Care Med*. 2024;52(4):521-530.

Tables

Table 1. Characteristics of All Included Trials Comparing Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Table 2. Evidence Profile for the Comparison of Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Table 3. Sensitivity and Subgroup Analyses for Short-Term Mortality for the Comparison of Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Figures

Figure 1. Flow Diagram of Search Strategy and Included Studies

Figure 2. Relative Risks of Short-Term Mortality in All Included Trials Comparing Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Relative risks, represented as risk ratios, were calculated using a random-effects model with DerSimonian and Laird weighting. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. Green circles with a plus indicate low risk of bias. Yellow circles with a question mark indicate some concerns for bias. Red circles with a minus indicate high risk of bias.

CI = confidence interval; IV = inverse variance.

Figure 1

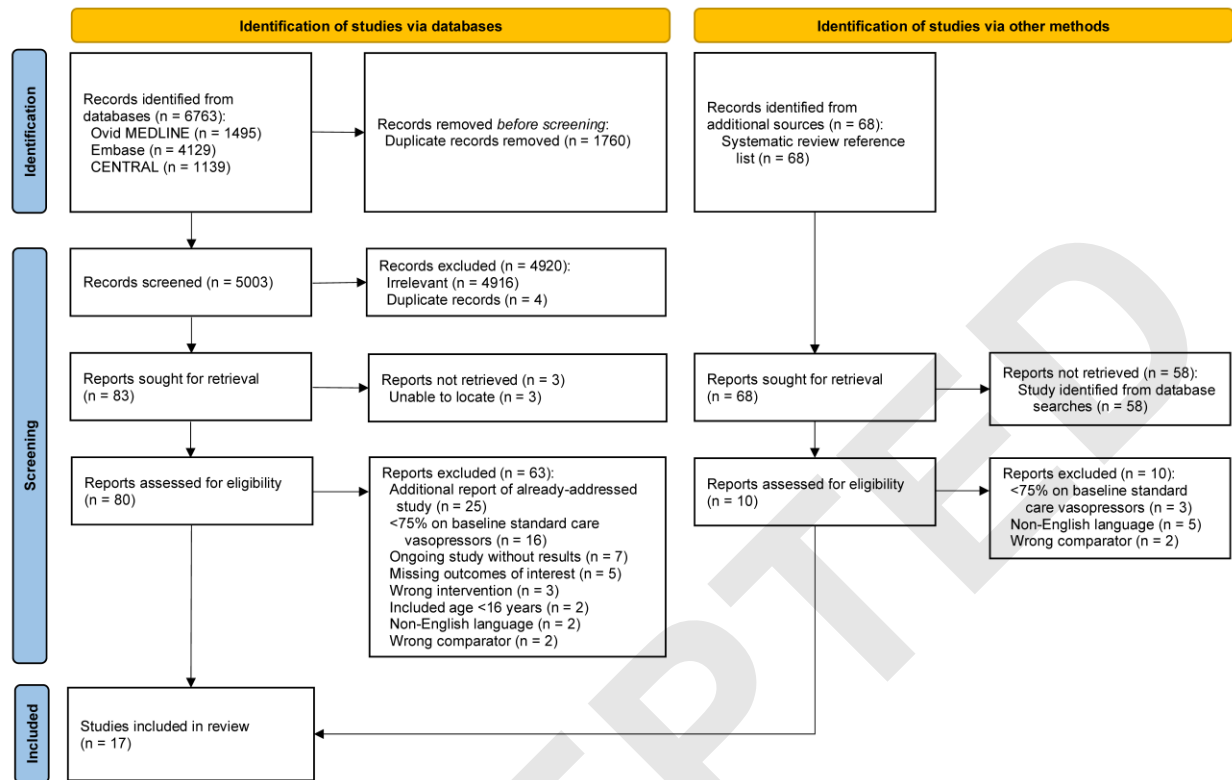
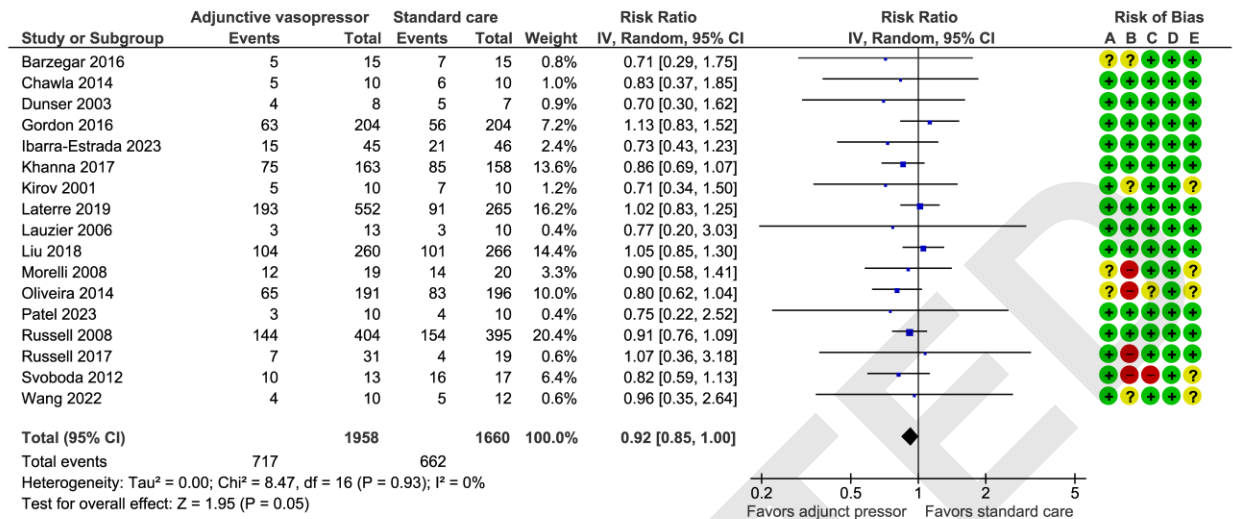


Figure 2



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result

Table 1. Characteristics of All Included Trials Comparing Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Study	No. of Trial sites	No. of Participants	Septic shock (%)	Baseline standard care vasopressors (%, NE dose)	MAP goal (mm Hg)	Intervention ^a	Comparison ^a
Barzegar et al, ⁴⁴ 2016	1	30	100	100%, NE 12.5 mcg/min	≥ 65	Vasopressin 0.03 units/min without titration	NE titrated to goal MAP
Chawla et al, ⁴⁵ 2014	1	20	100	100%, NE 25.1 mcg/min	≥ 65	Angiotensin II 20 ng/kg/min, titrated to goal MAP between 5-40 ng/kg/min	Placebo with titration to match intervention process
Dünser et al, ⁴⁶ 2003 ^b	1	15	100	100%, NR	≥ 70	Vasopressin 0.067 units/min without titration	NE titrated to goal MAP
Gordon et al, ⁹ 2016	18	409	100	76%, NE 0.16 mcg/kg/min	65-75	Vasopressin 0.013 units/min, titrated to goal MAP up to 0.06 units/min	NE 2.66 mcg/min titrated to goal MAP up to 12 mcg/min
Ibarra-Estrada et al, ⁴⁷ 2023	1	91	100	100%, NE 0.45 mcg/kg/min	65-75	Methylene blue 100 mg intermittent infusion over 6 hours once daily	Placebo intermittent infusion to match intervention process
Khanna et al, ⁴⁸ 2017	75	344	81	98%, NE-equivalent 0.34 mcg/kg/min	≥ 75 initial 3 hours, then 65-75	Angiotensin II 20 ng/kg/min titrated to goal MAP between 1.25-200 ng/kg/min	Placebo with titration to match intervention process
Kirov et al, ⁴⁹ 2001	1	20	100	100%, NE 0.35 mcg/kg/min	70-90	Methylene blue 2 mg/kg bolus, then 0.25 mg/kg/hr increased stepwise to 2 mg/kg/hr	Sodium chloride bolus, then increased stepwise to match intervention process
Laterre et al, ¹⁰ 2019	63	868	100	100%, NE 0.25 mcg/kg/min	≥ 65	Selepressin 1.7, 2.5, or 3.5 ng/kg/min, titrated (by up to 50%) to goal MAP	Placebo with titration to match intervention process

Lauzier et al, ⁵⁰ 2006	2	23	100	78%, NE 0.16 mcg/kg/min	≥ 70	Vasopressin 0.04 units/min, titrated to goal MAP up to 0.20 units/min	NE 0.1 mcg/kg/min titrated to goal MAP up to 2.8 mcg/kg/min
Liu et al, ⁵¹ 2018	21	617	100	88%, NE 0.46 mcg/kg/min	65-75	Terlipressin 20 mcg/hr titrated to goal MAP up to 160 mcg/hr	NE 4 mcg/min titrated to goal MAP up to 30 mcg/min
Morelli et al, ⁵² 2008	1	40	100	100%, NE 0.9 mcg/kg/min	65-75	Terlipressin 1 mg bolus times 1 dose only	NE titrated to goal MAP
Oliveira et al, ⁵³ 2014	NR	407	100	100%, NR	65-75	Vasopressin 0.01 units/min, titrated to goal MAP up to 0.03 units/min	NE 0.05 mcg/kg/min, titrated to goal MAP up to 2 mcg/kg/min
Patel et al, ⁵⁴ 2023	1	20	100	100%, NE 0.29 mcg/kg/min	65	Hydroxocobalamin 5 g bolus times 1 dose only	Placebo bolus times 1 dose only
Russell et al, ⁸ 2008	27	802	100	86%, NE 20.7 mcg/min	65-75	Vasopressin 0.01 units/min, titrated to goal MAP up to 0.03 units/min	NE 5 mcg/min, titrated to goal MAP up to 15 mcg/min
Russell et al, ⁵⁵ 2017	NR (≥3) ^c	53	100	100%, NE 0.28 mcg/kg/min	≥ 65	Selepressin 1.25, 2.5, or 3.75 ng/kg/min without titration	Placebo without titration
Svoboda et al, ⁵⁶ 2012	1	32	100	100%, NE 1.4 mcg/kg/min	65-75	Terlipressin 167 mcg/hr without titration	NE titrated to goal MAP
Wang et al, ⁵⁷ 2022	1	22	100	100%, NE 20 mcg/min	≥ 65	Terlipressin 1.3 mcg/kg/hr without titration	NE titrated to goal MAP

^aAll routes of administration for intervention and comparison medications were intravenous and given via continuous infusion unless otherwise specified. Patients received open-label standard care vasopressors (norepinephrine or dopamine) titrated to goal MAP in addition to intervention

and placebo comparison, except in the five trials noted with baseline standard care vasopressor percentage below 100. In three of the five trials with baseline vasopressor percentage below 100, a minority of patients (range 12-24%) solely received the intervention or comparison vasopressor titrated to goal MAP,^{9,50,51} and in the other two trials all patients were receiving a baseline vasopressor titrated to goal MAP but some patients (range 2-14%) were solely receiving a vasopressor other than norepinephrine or dopamine.^{8,48}

^bTotal trial sample size n = 48. Data for subset of patients with septic shock (n = 15) used in this study was obtained from the individual patient data systematic review and meta-analysis by Nagendran, et al. *Intensive Care Med* 2019;45:844-55.¹⁵

^cReported as multicenter trial of patients in 3 countries, but the number of centers enrolling patients was not reported.

MAP = mean arterial pressure; NE = norepinephrine; NR = not reported.

Table 2. Evidence Profile for the Comparison of Adjunctive Vasopressors to Standard Care Vasopressors in Adults With Septic Shock

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjunctive vasopressors	Standard care vasopressors	Relative (95% CI)	Absolute (95% CI)		

Short-term mortality (follow-up: 28 days, 30 days, and ICU discharge)

17 ^{8-10,44-57}	randomized trials	serious ^a	not serious	not serious	serious ^b	none	717/1958 (36.6%)	662/1660 (39.9%)	RR 0.92 (0.85 to 1.00)	32 fewer per 1,000 (from 60 fewer to 0 fewer)	⊕⊕○ ○ Low	CRITICAL
--------------------------	-------------------	----------------------	-------------	-------------	----------------------	------	------------------	------------------	-------------------------------	--	-----------------	----------

Intermediate-term mortality (follow-up: hospital discharge)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjunctive vasopressors	Standard care vasopressors	Relative (95% CI)	Absolute (95% CI)		
1 ⁹	randomized trials	not serious	not serious	not serious	very serious ^c	none	68/204 (33.3%)	60/204 (29.4%)	RR 1.13 (0.85 to 1.51)	38 more per 1,000 (from 44 fewer to 150 more)	⊕⊕○ ○ Low	CRITICAL

Kidney replacement therapy (follow-up: range 28 to 30 days)

8 ^{8-10,44,46,48,50,54}	randomized trials	not serious	not serious	not serious	serious ^b	none	553/1361 (40.6%)	448/1047 (42.8%)	RR 0.92 (0.84 to 1.01)	34 fewer per 1,000 (from 68 fewer to 4 more)	⊕⊕⊕ ○ Moderate	CRITICAL
----------------------------------	-------------------	-------------	-------------	-------------	----------------------	------	------------------	------------------	----------------------------------	--	----------------------	----------

Digital/peripheral ischemia (follow-up: range 48 hours after study drug completion to 30 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjunctive vasopressors	Standard care vasopressors	Relative (95% CI)	Absolute (95% CI)		
9 ⁸ -10,44,46,48,51,55,57	randomized trials	not serious	serious ^d	not serious	serious ^e	none	77/1650 (4.7%)	19/1331 (1.4%)	RR 2.44 (1.17 to 5.10)	21 more per 1,000 (from 2 more to 59 more)	⊕⊕⊖ ○ Low	CRITICAL

Venous thromboembolism (follow-up: 28 days)

1 ⁴⁸	randomized trials	not serious	not serious	not serious	very serious ^c	none	8/163 (4.9%)	0/158 (0.0%)	RR 16.48 (0.96 to 283.17)	5 more per 1,000 (from 2 more to 8 more)	⊕⊕⊖ ○ Low	CRITICAL
-----------------	-------------------	-------------	-------------	-------------	---------------------------	------	--------------	--------------	----------------------------------	---	-----------------	----------

^aSee risk of bias figure and sensitivity analysis based on risk of bias. Some evidence for heterogeneity of outcome by risk of bias subgroup ($P = 0.13$) with $I^2 = 56\%$. Interpretation of effect differs by subgroup; no detected mortality effect of adjunctive vasopressors in low bias risk subgroup, and lower mortality risk of adjunctive vasopressors in some concerns or high bias risk subgroup.

^bWide confidence intervals, defined as the ends of the confidence intervals leading to different courses of action. Confidence interval range includes no effect.

^cWide confidence intervals, defined as the ends of the confidence intervals leading to different courses of action. Confidence interval range includes no effect. Total sample size does not meet optimal information size.

^dLarge heterogeneity ($P = 0.10$). $I^2 = 40\%$.

^eTotal sample size does not meet optimal information size. Confidence interval range includes no clinically important difference.

CI = confidence interval; ICU = intensive care unit; RR = risk ratio.

Table 3. Sensitivity and Subgroup Analyses for Short-Term Mortality for the Comparison of Adjunctive Vasopressors to Standard Care

Vasopressors in Adults With Septic Shock

Group	No. of Trials	No. With Events/Total No. of Participants		Relative Effect		Absolute Effect, Events per 1,000 (95% CI) ^a
		Adjunctive Vasopressors	Standard Care Vasopressors	Risk Ratio (95% CI) ^a	Interaction <i>P</i> value ^b	
Sensitivity analysis						
Risk of bias					0.13	
Low risk	10	609/1669	526/1371	0.95 (0.87 to 1.03)		19 fewer (50 fewer to 12 more)
Some concerns or high risk	7	108/289	136/289	0.82 (0.69 to 0.97)		85 fewer (146 fewer to 14 fewer)
Subgroup analysis						
Drug class/mechanism of action					0.34	
Vasopressin analogues	12	614/1720	539/1426	0.95 (0.87 to 1.04)		19 fewer (49 fewer to 15 more)
Angiotensin II	2	80/173	91/168	0.85 (0.69 to 1.06)		81 fewer (168 fewer to 33 more)
Methylene blue or hydroxocobalamin	3	23/65	32/66	0.73 (0.49 to 1.09)		131 fewer (247 fewer to 44 more)
Shock severity						
Baseline NE dosage below median	8	422/1239	324/930	0.98 (0.87 to 1.10)		7 fewer (45 fewer to 35 more)
Baseline NE dosage above median	7	226/520	250/527	0.90 (0.80 to 1.02)		47 fewer (95 fewer to 9 more)

^aRisk ratio <1.0 and absolute effect with fewer events favors adjunctive vasopressors.

^b*P* value for the between-subgroup interaction test.

NE = norepinephrine

ACCEPTED