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Systematic review

Norepinephrine Versus Vasopressin as First-Line Vasopressor Therapy in Septic Shock: Implications for Patients Presenting to the Emergency Department

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Abstract

Background: Septic shock requires rapid restoration of perfusion with infection treatment. Norepinephrine is the recommended initial vasopressor, while vasopressin offers an alternative mechanism of vascular support. This review examines comparative clinical outcomes and their relevance to emergency department treatment. **Methods:** A systematic review was reported according to PRISMA 2020 guidelines. PubMed, Scopus, Web of Science Core Collection, and Cochrane CENTRAL were searched from inception to May 2026. Two authors independently screened studies, extracted data, and assessed risk of bias, resolving disagreements through consensus. We include comparative studies of adults with septic shock, renal outcomes, hemodynamic responses, and adverse events. Initial and adjunctive treatment comparisons were distinguished, and overlapping trial reports were linked. **Results:** Ten original articles represented seven independent study populations, including three secondary analyses of VASST. In VASST, involving 778 treated patients, mortality at 28 days was 35.4% with vasopressin and 39.3% with norepinephrine. VANISH enrolled 409 patients and

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demonstrated no improvement in its primary kidney outcome, despite lower renal replacement therapy use with vasopressin. VANCS II enrolled 250 patients with cancer and found no significant mortality difference. Smaller investigations documented blood pressure responses and selected renal physiological improvements. Differences in treatment timing, concomitant vasopressors, and patient selection restricted direct comparison across studies. **Conclusion:** Renal and catecholamine-sparing findings support further investigation of selected treatment strategies. Emergency department recommendations remain largely extrapolated from intensive care evidence, with a need for trials specifically evaluating initial vasopressor selection during early emergency resuscitation.

Keywords: Septic shock; norepinephrine; vasopressin; emergency department; vasopressors; mortality; acute kidney injury.

Introduction

Sepsis involves infection-associated organ dysfunction arising from a dysregulated host response, while septic shock identifies a subgroup with severe circulatory and metabolic abnormalities (1). Operational criteria combine vasopressor dependence to maintain mean arterial pressure of at least 65 mmHg with lactate exceeding 2 mmol/L after adequate volume resuscitation (2). This distinction matters when comparing vasopressor studies because historical definitions, enrollment thresholds, and baseline organ dysfunction differ in research populations (1,2). Emergency management addresses perfusion failure and its infectious cause, with vasopressor selection forming one component of coordinated resuscitation (3).

The 2021 Surviving Sepsis Campaign recommends norepinephrine as the first-line vasopressor and add vasopressin when arterial pressure remains inadequate during norepinephrine treatment. This treatment sequence distinguishes initial drug selection from subsequent escalation, which addresses persistent hypotension despite an established catecholamine infusion. The guideline also supports an initial mean arterial pressure target of 65 mmHg and emphasizes repeated assessment of perfusion during treatment (3).

The physiology for vasopressin treatment emerged from observations of unexpectedly low circulating concentrations in patients with vasodilatory septic shock. Landry and colleagues demonstrated substantial pressor responsiveness to exogenous vasopressin, supporting a contribution of relative hormone deficiency to persistent vasodilation (4). Subsequent work by Sharshar and colleagues established that circulating concentrations vary over time, with early elevation followed by declining levels and relative deficiency in a subset of patients (5).

Evidence addressing early resuscitation also separates treatment timing from drug identity, as illustrated by the CENSER trial of early norepinephrine administration (6). CENSER demonstrated improved six-hour shock control, while its mortality comparison did not reach statistical significance (6). Similarly, CLOVERS compared restrictive and liberal fluid strategies incorporating different vasopressor exposure, rather than randomizing patients between norepinephrine and vasopressin (7). These studies establish the importance of distinguishing initial

resuscitation strategies from direct pharmacological comparisons when interpreting outcomes relevant to emergency care. The present review addresses that distinction by examining comparative vasopressor evidence and its applicability to the initial treatment decision.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review examined norepinephrine versus vasopressin in adults with septic shock, focusing on initial vasopressor selection and applicability to emergency department management. Studies evaluating initial treatment were distinguished from investigations of adjunctive vasopressin in patients already receiving catecholamine.

A literature search was conducted in PubMed, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 2026. Search strategies combined controlled vocabulary and free-text terms for “septic shock,” “sepsis,” “vasopressin,” “arginine vasopressin,” “norepinephrine,” and “noradrenaline,” using Boolean operators. Emergency department terminology was evaluated in supplementary searches without restricting the principal search by treatment setting. Reference lists of eligible publications and relevant reviews were examined to identify additional studies (Fig 1).

Randomized controlled trials and comparative observational studies were eligible if they evaluated vasopressin against norepinephrine in adults with septic shock and reported relevant clinical outcomes. Intensive care studies were retained as indirect evidence for emergency department practice. Pediatric studies, animal experiments, noncomparative reports, and studies of nonseptic shock without separately extractable septic shock data were excluded. Vasopressin analogues were treated as distinct interventions, with only relevant vasopressin and norepinephrine groups extracted from multiarm trials.

Two authors independently screened titles and abstracts after duplicate removal. Potentially eligible articles underwent independent full-text assessment, and reasons for exclusion were documented. Disagreements were resolved through discussion and consensus. Multiple publications arising from the same trial were linked and treated as reports of one underlying study to prevent duplicate participant counting.

Two authors independently extracted data using a standardized form. Extracted variables included study design, setting, sample size, participant characteristics, shock severity, vasopressor sequence, intervention doses, treatment timing, concomitant therapies, follow-up, and clinical outcomes. The primary outcome was 28-day all-cause mortality. Secondary outcomes included mortality at other time points, renal replacement therapy, kidney failure, hemodynamic responses, vasopressor requirements, length of stay, arrhythmias, and ischemic complications.

Assessments were reconciled through consensus and considered when interpreting the findings. Results were analyzed narratively according to treatment sequence, study design, setting, and outcome. Initial-treatment comparisons were

presented separately from adjunctive-treatment evidence. Secondary trial analyses informed interpretation without being counted as independent treatment comparisons. No pooled effect estimate was calculated because the synthesis addressed clinically heterogeneous treatment strategies and populations.

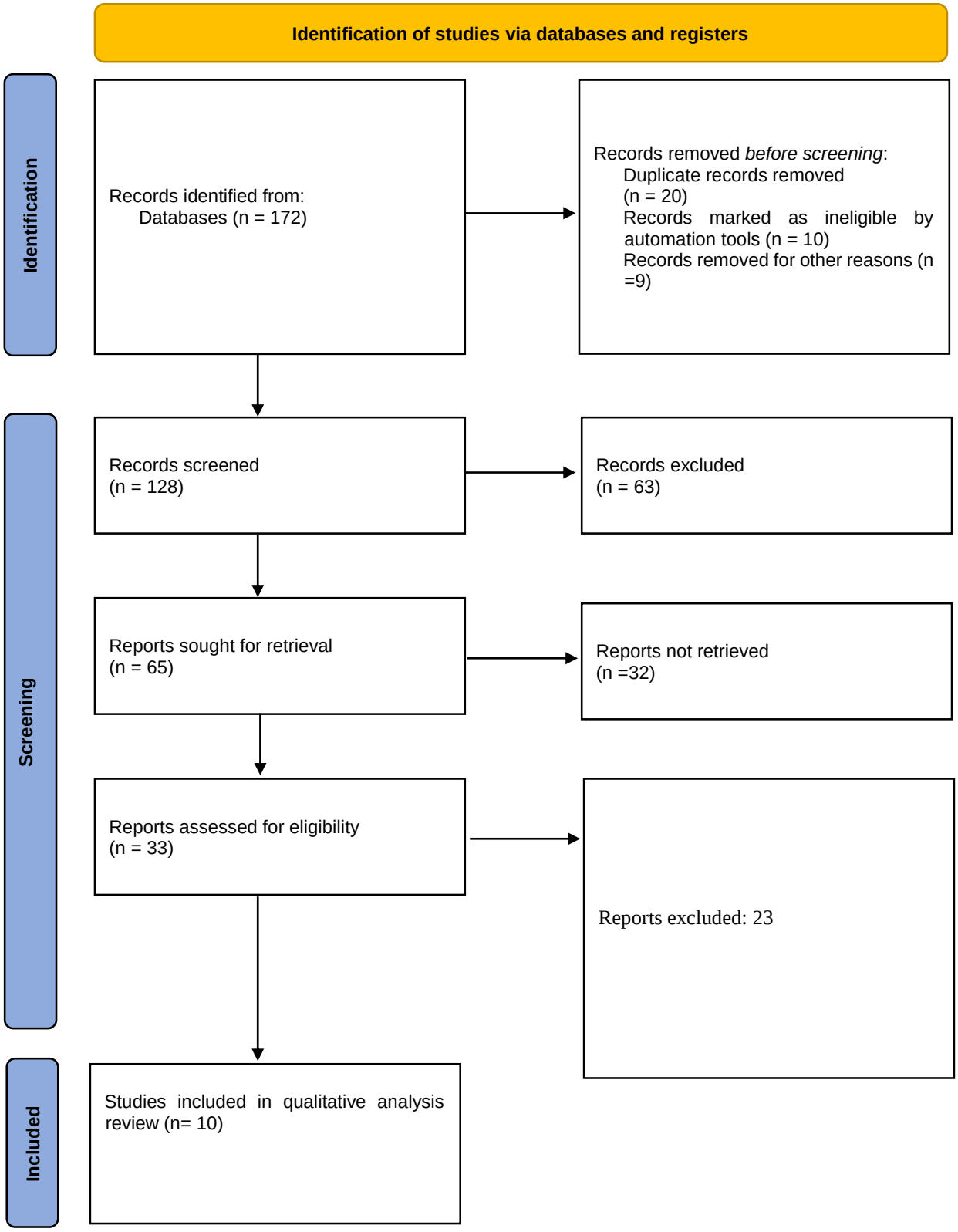

Fig 1: PRISMA flow chart

Results

VASST provided the largest randomized comparison, with 778 patients receiving study treatment in addition to existing vasopressor support (8). Its adjunctive design differs from the early-treatment strategy evaluated in VANISH, which enrolled 409 patients (9). VANCS II directly evaluated first-line treatment in 250 patients with cancer and septic shock, adding evidence from a selected intensive care population (10). These differences in treatment sequence and case mix limit interpretation of the trials as interchangeable evaluations of emergency department prescribing (8–10) (Table 1).

Mortality findings did not establish an overall advantage for vasopressin: VASST reported 28-day mortality of 35.4% versus 39.3%, with P=0.26 (8). The lower mortality observed in its less severe shock stratum was accompanied by a nonsignificant test for heterogeneity between severity strata, restricting claims of a confirmed subgroup effect (8). VANISH reported no significant mortality difference and no improvement in its primary kidney failure–free outcome, despite reduced renal replacement therapy use (9). VANCS II similarly found no significant difference in 28-day mortality, with rates of 56.8% and 52.8%, respectively, or in its reported secondary clinical outcomes (10).

Smaller trials concentrated on physiological responses, including Patel and colleagues' randomized four-hour study of 24 patients requiring substantial vasopressor support (11). Vasopressin reduced norepinephrine requirements while maintaining arterial pressure and cardiac index, alongside increases in urine output and creatinine clearance (11). Lauzier and colleagues studied 23 patients with early hyperdynamic septic shock and documented reduced catecholamine exposure and improved selected organ-function measures during vasopressin treatment (12). Additional norepinephrine remained necessary in some vasopressin recipients, demonstrating incomplete hemodynamic support with monotherapy (12) (Table 2).

TERLIVAP randomized 45 patients across terlipressin, vasopressin, and norepinephrine groups, leaving 30 participants in the comparison relevant to this review (13). No significant overall differences in systemic or regional hemodynamics were reported across the three groups, and rescue norepinephrine formed part of the treatment protocol (13). Hall and colleagues retrospectively evaluated initial vasopressor therapy in 150 patients, including 50 receiving vasopressin and 49 receiving norepinephrine (14). Both treatments increased arterial pressure, while baseline differences and nonrandom treatment allocation restricted causal interpretation of the mortality comparison (14).

Three additional original reports examined overlapping VASST participants rather than independent cohorts, beginning with a renal analysis that identified favorable associations in patients initially classified as being at risk of kidney injury (15). A corticosteroid analysis reported an interaction between vasopressor allocation and corticosteroid exposure, with lower mortality among steroid-treated patients assigned vasopressin (16). A cardiopulmonary analysis documented reduced heart rate without an accompanying improvement in cardiac output (17). These publications extend outcome characterization without increasing the number of

independent treatment comparisons (15–17). Collectively, the ten reports represent seven study populations, with substantial variation in treatment timing, intervention intensity, and clinical setting (8–17).

Table 1. Characteristics and relevance of the original research reports

Study	Design and population	Treatment comparison
Russell, 2008: (8)	Multicentre randomized trial; 778 treated patients	Low-dose vasopressin versus additional norepinephrine
Gordon, 2016: (9)	Multicentre randomized trial; 409 patients	Early vasopressin versus norepinephrine; hydrocortisone versus placebo
Hajjar, 2019(10)	Single-centre randomized trial; 250 patients with cancer	First-line vasopressin versus norepinephrine
Patel, 2002 (11)	Randomized double-blind trial; 24 patients	Four-hour vasopressin versus norepinephrine infusion
Lauzier, 2006 (12)	Randomized open-label trial; 23 patients	Vasopressin versus norepinephrine over 48 hours
Morelli, 2009 (13)	Three-arm randomized pilot; 45 patients	Terlipressin, vasopressin, or norepinephrine
Hall, 2004 (14)	Retrospective cohort; 150 patients	Initial vasopressin, norepinephrine, or dopamine
Gordon, 2010 (15)	Secondary VASST analysis	Renal outcomes by randomized treatment
Russell, 2009 (16)	Secondary VASST analysis	Treatment effects according to corticosteroid exposure
Gordon, 2012 (17)	Secondary VASST analysis	Cardiopulmonary responses

Table 2. Selected verified comparative outcomes

Study and outcome	Vasopressin	Norepinephrine
VASST: 28-day mortality	35.4%	39.3%
VANISH: renal replacement therapy	25.4%	35.3%
VANCS II: 28-day mortality	56.8%	52.8%
Patel: median urine output, baseline to four hours	32.5→65 mL/hour	25→15 mL/hour
Hall: 28-day mortality	52%	65%
VASST corticosteroid analysis: mortality among corticosteroid recipients	35.9%	44.7%

Discussion

The interpretation is that available articles does not establish vasopressin as a superior initial vasopressor for septic shock, although individual physiological outcomes favor its use in selected circumstances. An individual participant data meta-analysis by Nagendran and colleagues reinforced the absence of a demonstrated mortality benefit, reporting a relative risk of 0.98 with a 95% confidence interval of 0.86–1.12 (18). That interval also demonstrates residual uncertainty rather than proof that the treatments produce identical outcomes (18). Accordingly, treatment decisions require consideration of the intervention sequence and outcome priorities rather than interpretation of nonsignificant mortality results as established equivalence (8,10,18).

The renal findings deserve particular attention because several investigations reported favorable physiological or treatment-related signals despite neutral primary clinical outcomes (11,12,15). Increased urine output and creatinine clearance during short infusions demonstrate an acute functional response, without establishing durable prevention of kidney injury or improved long-term recovery (11,12). The individual participant data meta-analysis identified reduced renal replacement therapy use, although this association was not robust across sensitivity analyses (18). Differences between acute physiological measurements, initiation of dialysis, and sustained kidney recovery therefore restrict conclusions that vasopressin consistently provides clinically meaningful renal protection across septic shock populations (11,12,15,18).

Safety also involves competing effects rather than a single overall advantage, as the individual participant data analysis identified more digital ischemia and fewer arrhythmias with vasopressin (18). McIntyre and colleagues reported a lower risk of atrial fibrillation when vasopressin was added to catecholamine vasopressors across randomized distributive shock studies (19). Their broader population included shock settings beyond sepsis, limiting direct transfer of the pooled estimate to emergency department septic shock (19). The Cochrane review of vasopressors likewise highlighted uncertainty in comparative patient-important outcomes across heterogeneous shock populations and treatment comparisons (20).

Resuscitation targets provide another source of clinical heterogeneity, illustrated by the SEPSISPAM comparison of higher and lower arterial pressure targets (21). Higher targets did not improve overall survival and were associated with more newly diagnosed atrial fibrillation, demonstrating that the intensity of hemodynamic treatment influences the balance of outcomes (21). For emergency care, CENSER supplies evidence about earlier norepinephrine administration, while CLOVERS addresses fluid and vasopressor prioritization rather than direct vasopressor selection (6,7). These distinctions prevent the use of successful shock-control strategies as evidence that vasopressin outperforms norepinephrine as the first drug administered (6,7,21).

The evidence base has additional limitations, including small physiological trials, selected oncology patients, observational confounding, and repeated analyses of the same randomized population. A review that counts secondary publications as independent trials would overstate

both sample size and replication, making explicit linkage of reports essential for interpretation. The next decisive comparison requires emergency department enrollment, clearly documented first vasopressor exposure, standardized rescue treatment, and clinically meaningful renal and survival outcomes addressing the gaps identified here.

Conclusion

Norepinephrine remains the reference initial treatment, while vasopressin provides an additional mechanism of hemodynamic support. Selected studies report reduced catecholamine exposure and favorable renal signals, without consistent improvement in survival or primary kidney outcomes. Most comparative evidence originates from intensive care populations, restricting direct application to emergency department initiation. Future randomized investigations require explicit first-line treatment definitions, standardized rescue therapy, and emergency department enrollment.

Abbreviations

CI: Confidence interval.

CENSER: Early Use of Norepinephrine in Septic Shock Resuscitation.

CLOVERS: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

ICU: Intensive care unit.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RoB 2: Revised Cochrane risk-of-bias tool for randomized trials.

ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions.

SEPSISPAM: Sepsis and Mean Arterial Pressure.

TERLIVAP: Terlipressin versus Vasopressin.

VANCS II: Vasopressin versus Norepinephrine in Patients with Septic Shock and Cancer.

VANISH: Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock.

VASST: Vasopressin and Septic Shock Trial.

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