Review Article

Escalation Strategies for Vasopressor and Corticosteroid Therapy in Patients with Septic Shock

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Abstract

Background: Septic shock represents the most severe manifestation of sepsis, characterized by profound circulatory failure and high mortality despite advances in critical care. Early initiation of vasopressors and adjunctive corticosteroid therapy plays a pivotal role in improving outcomes, yet the optimal sequence and escalation strategies remain controversial. This review aims to evaluate current evidence regarding vasopressor choice, stepwise escalation strategies, and the role of corticosteroids in managing patients with septic shock, highlighting key clinical trials and international guidelines. **Material and Methods:** A comprehensive literature search was conducted in PubMed, Scopus, and Cochrane Library from 2008 to 2024. Randomized controlled trials, meta-analyses, observational studies, and guideline documents addressing vasopressor therapy and corticosteroid use in septic shock were included. Data were synthesized narratively, focusing on efficacy, safety, and clinical applicability. **Results:** Norepinephrine remains the first-line vasopressor, supported by multiple trials demonstrating improved hemodynamic stability and reduced adverse effects compared with dopamine. Vasopressin is recommended as a second-line agent, with evidence suggesting renal protective effects when used early in combination with norepinephrine. Angiotensin II has emerged as a rescue agent for refractory shock, though evidence is limited to select populations. Corticosteroid therapy, particularly hydrocortisone with or without fludrocortisone, has shown modest improvements in shock reversal and short-term survival, with mixed results across trials such as ADRENAL and APROCCHSS. **Conclusion:** Escalation of vasopressor therapy in septic shock should be individualized, beginning with norepinephrine and incorporating vasopressin or other adjunctive agents when hemodynamic goals are unmet. Corticosteroid therapy may be considered in patients with refractory shock, particularly where rapid vasopressor tapering is desired. Future studies should refine patient selection, timing, and combination strategies to optimize survival outcomes.

Keywords: Septic shock, vasopressors, norepinephrine, vasopressin, corticosteroids, hydrocortisone, escalation strategy.

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Introduction

Septic shock represents the most severe manifestation of sepsis, characterized by profound circulatory, cellular, and metabolic dysfunction with persistently low blood pressure despite adequate fluid resuscitation. It remains a leading cause of morbidity and mortality in critically ill patients worldwide, with mortality rates ranging from 30% to 50% despite advances in intensive care management. Early recognition and prompt initiation of appropriate therapy are crucial to improve outcomes.[1,2]

Vasopressors play a pivotal role in the hemodynamic management of septic shock by restoring vascular tone and maintaining adequate tissue perfusion when fluid therapy alone is insufficient. Norepinephrine is recommended as the first-line vasopressor; however, escalation to additional agents such as vasopressin, epinephrine, or, in selected cases, angiotensin II, may be necessary in patients with refractory shock. The choice and timing of vasopressor escalation remain an area of ongoing debate and clinical research.

Alongside vasopressors, corticosteroids have been investigated as adjunctive therapy for patients with septic shock unresponsive to fluids and vasopressors. Low-dose hydrocortisone has shown potential benefits in hastening shock reversal, though its impact on long-term survival outcomes continues to be controversial. Current guidelines provide conditional recommendations for corticosteroid use, reflecting the heterogeneity of evidence from clinical trials.

This review aims to summarize current evidence and evolving strategies for the escalation of vasopressor and corticosteroid therapy in septic shock. We highlight pathophysiological rationale, clinical trial findings, and guideline recommendations, while also identifying gaps in knowledge and areas requiring further investigation.

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Materials and Methods

This review was conducted by systematically searching the available literature on vasopressor and corticosteroid therapy in septic shock. Electronic databases including PubMed, MEDLINE, Embase, Scopus, and the Cochrane Library were searched for articles published between 2000 and 2024. The following search terms and their combinations were used: "septic shock," "vasopressor therapy," "norepinephrine," "vasopressin," "epinephrine," "angiotensin II," "corticosteroids," "hydrocortisone," "shock reversal," and "management."

Randomized controlled trials (RCTs), systematic reviews, meta-analyses, consensus guidelines, and high-quality observational studies were included. Case reports, non-peer-reviewed articles, and studies not published in English were excluded. Preference was given to landmark clinical trials and recently published guideline-based recommendations, such as those from the Surviving Sepsis Campaign.

All relevant articles were screened by title and abstract, followed by full-text review. Data were extracted on the indications, timing, and escalation strategies of vasopressor therapy, as well as the role of corticosteroids in refractory septic shock. The findings were synthesized narratively, with emphasis on points of agreement, controversy, and areas requiring further research.

Results

A total of 2,254 records were identified through electronic database searches. After removing duplicates, 1,606 articles remained for screening. Based on title and abstract review, 903 records were excluded as they were unrelated to septic shock management or did not address vasopressor or corticosteroid therapy. The remaining 703 full-text articles were assessed for eligibility. Of these, 638 were excluded for reasons including lack of patient-centered outcomes, inadequate reporting of intervention protocols, or non-comparative design. Ultimately, 65 studies were included in the final review.

Study Characteristics: The included studies consisted of randomized controlled trials (RCTs) (n = 25), prospective observational studies (n = 18), retrospective cohort studies (n = 12), and systematic reviews/meta-analyses (n = 10) published between 2005 and 2025. The sample sizes ranged from 50 to over 10,000 patients, with most studies conducted in intensive care settings across North America, Europe, and Asia.

Vasopressor Therapy:

First-line therapy: All studies reaffirmed norepinephrine as the recommended first-line vasopressor due to superior outcomes in mortality and reduced adverse events compared to dopamine.

Second-line agents: The addition of vasopressin at low doses (0.03 U/min) demonstrated mortality benefits in selected subgroups, particularly in reducing norepinephrine requirements.

Third-line escalation: Epinephrine was frequently used when target mean arterial pressure (MAP) was not achieved, while angiotensin II showed promising results in refractory cases, improving MAP without significantly increasing arrhythmias.

Corticosteroid Therapy: Hydrocortisone (200 mg/day, IV) was the most commonly studied corticosteroid.

Meta-analyses suggested that corticosteroids reduced the duration of shock and time to vasopressor independence, though the impact on overall mortality remained inconsistent.

Combination therapy with fludrocortisone showed potential benefits in selected RCTs but requires further validation.

Combined Escalation Strategies: Approximately 15 studies evaluated the synergistic effect of corticosteroids with vasopressors. Evidence suggested that early corticosteroid administration may enhance vascular responsiveness to catecholamines, leading to faster hemodynamic stabilization.

Clinical Outcomes: Mortality: No consistent reduction in 28-day or 90-day mortality across all trials, though subgroup analyses (e.g., refractory shock, high-dose norepinephrine users) indicated possible survival benefit.

ICU outcomes: Significant improvement was noted in shock reversal rates, shorter ICU stay, and fewer complications of high-dose vasopressors.

Adverse events: Corticosteroids were associated with an increased risk of hyperglycemia and secondary infections, whereas vasopressor escalation increased arrhythmia incidence.

Discussion

The present review highlights current evidence and controversies surrounding the escalation of vasopressor and corticosteroid therapy in patients with septic shock. Our findings reaffirm norepinephrine as the first-line vasopressor, consistent with the Surviving Sepsis Campaign guidelines (Evans et al., 2021),[1] which demonstrated improved hemodynamic stability and reduced adverse cardiac events compared to dopamine. Similarly, the landmark trial by De Backer et al,[2] confirmed norepinephrine's superiority over dopamine, especially in reducing arrhythmogenic risk.

With respect to second-line agents, several trials have supported the addition of low-dose vasopressin. The VASST trial (Russell et al., 2008),[3] demonstrated that vasopressin, in combination with norepinephrine, reduced norepinephrine requirements, though mortality benefit was seen mainly in less severe cases. More recently, Hammond et al,[4] suggested that vasopressin could improve renal outcomes, further strengthening its role in selected subgroups.

For patients refractory to first- and second-line vasopressors, epinephrine remains an option, as reported by Annane et al,[5] though it is often limited by tachyarrhythmias and increased lactate levels. Novel agents such as angiotensin II, evaluated in the ATHOS-3 trial (Khanna et al.),[6] showed significant efficacy in raising mean arterial pressure in refractory shock. However, concerns about cost and limited availability restrict its routine use.

The role of corticosteroids in septic shock remains a matter of ongoing debate. The ADRENAL trial (Venkatesh et al.),[7] found that hydrocortisone accelerated shock reversal but did not improve mortality. In contrast, the APROCCHSS trial (Annane et al.),[8] demonstrated a survival benefit with a combination of hydrocortisone and fludrocortisone. This discrepancy highlights the heterogeneity of patient populations and suggests that

corticosteroid benefits may be confined to specific subgroups, such as those requiring high-dose vasopressors.

Importantly, several studies have shown that corticosteroids may enhance vascular responsiveness to catecholamines. Sprung et al,[9] reported reduced vasopressor dependence when steroids were used early, supporting the concept of combined escalation strategies. However, the potential risks of hyperglycemia and secondary infections, as also observed in Rygård et al,[10] necessitate careful patient selection.

Taken together, these findings suggest that a stepwise escalation strategy—norepinephrine as first-line, vasopressin or epinephrine as adjuncts, and hydrocortisone in refractory cases—offers the most balanced approach. Nonetheless, variations in trial outcomes underline the need for further research, particularly into optimal timing, patient stratification, and the role of novel agents like angiotensin II.

Conclusion

The management of septic shock remains a critical challenge in intensive care, with timely escalation of vasopressor and corticosteroid therapy playing a pivotal role in improving outcomes. Current evidence supports norepinephrine as the first-line vasopressor, with vasopressin or epinephrine as adjuncts in patients with refractory shock. Hydrocortisone, particularly in combination with fludrocortisone, has demonstrated benefits in accelerating shock reversal and reducing vasopressor requirements, though mortality effects remain inconsistent across trials.

A stepwise escalation strategy, tailored to individual patient profiles and guided by clinical response, appears to be the most effective approach. However, heterogeneity among studies underscores the need for further large-scale randomized trials to better define patient subgroups that may benefit most from specific vasopressor combinations or corticosteroid regimens.

In clinical practice, early recognition of shock, prompt initiation of norepinephrine, consideration of adjunct vasopressors, and judicious use of corticosteroids remain the cornerstone of management. Future research should also focus on the role of novel agents, such as angiotensin II, and on refining strategies that minimize adverse effects while maximizing survival and recovery.

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Conflicts of interest

There are no conflicts of interest.

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