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Fludrocortisone in septic shock: revisiting the potential role of mineralocorticoid supplementation

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Corticosteroids have been one of the most debated adjunctive therapies in septic shock. Despite decades of trials and meta-analyses, their impact on survival remains inconsistent. Guidelines have therefore adopted a cautious position, recommending low-dose hydrocortisone mainly for patients with vasopressor-refractory shock.[1] However, recent data have revived an old hypothesis that supplementing hydrocortisone with fludrocortisone, thereby restoring both glucocorticoid and mineralocorticoid activity, may confer additional benefit. In APROCCHSS, hydrocortisone plus fludrocortisone was associated with lower 90-day mortality than placebo. Because the trial compared the combination with placebo, it did not isolate the independent contribution of fludrocortisone.[2] And subsequent real-world analyses and meta-analyses have reinforced this signal.[3, 4] Mechanistic studies suggest that mineralocorticoid receptor (MR) activation complements glucocorticoid receptor (GR) effects, influencing vascular tone, endothelial integrity, and immune balance.[5] This Viewpoint argues that the benefit of combining hydrocortisone and fludrocortisone reflects not merely pharmacologic synergy, but restoration of the adrenal stress axis. Reintegrating the mineralocorticoid pathway may help address the limitations of glucocorticoid-only therapy.

The missing mineralocorticoid axis in septic shock

During severe infection, the hypothalamic–pituitary–adrenal axis is profoundly dysregulated. Cytokine-driven inhibition of steroidogenesis, tissue resistance to cortisol, and impaired adrenal blood flow all contribute to critical illness-related corticosteroid insufficiency.[6] In this state, both cortisol and aldosterone synthesis may be inadequate.

Hydrocortisone, the most commonly used glucocorticoid in sepsis, has only weak mineralocorticoid potency, approximately 1/40 that of fludrocortisone. As a result, hydrocortisone has both glucocorticoid and mineralocorticoid activity, although its mineralocorticoid potency is substantially lower than that of fludrocortisone. Whether supplemental fludrocortisone provides an independent clinical benefit remains uncertain. Several studies have described a "relative aldosterone deficiency" phenotype in septic patients, characterized by low aldosterone, high plasma renin activity, hyponatremia, and vasopressor dependence.[5, 6] This dysregulated aldosterone response may reflect impaired adrenal steroidogenesis or receptor downregulation secondary to inflammatory cytokines.[6] This deficiency matters because mineralocorticoid signaling through MR is essential for vascular responsiveness, sodium-water homeostasis, and immune regulation. Without it, patients may remain hypotensive despite adequate glucocorticoid exposure. Therefore, supplementing with fludrocortisone may physiologically restore the dual stress response mediated by GR and MR.

Mechanistic rationale for adding fludrocortisone

Fludrocortisone exerts its effects through MR activation across multiple physiological systems, integrating hemodynamic, endothelial, and immune responses. In the kidney, MR activation enhances sodium reabsorption through upregulation of epithelial sodium channels and sodium–potassium adenosine triphosphatase, leading to expansion of intravascular volume and improved preload and mean arterial pressure.[5] At the doses used in septic shock, this effect is generally self-limited and rarely associated with clinically significant edema.[2, 7, 8] Consistent with this mechanism, the addition of fludrocortisone in the APROCCHSS trial was associated with earlier vasopressor independence without an increase in adverse events.[2]

MR signaling contributes to vascular responsiveness, alongside its role in volume regulation. Activation of MR in vascular smooth muscle and endothelial cells increases sensitivity to catecholamines and angiotensin II, while reducing the production of vasodilatory mediators such as inducible nitric oxide synthase and cyclooxygenase-2.[5, 9] These effects may facilitate faster shock reversal and reduce vasopressor requirements, as suggested by observational data,[3] and can occur independently of sodium retention through nongenomic pathways.

At the microvascular level, MR activation supports endothelial integrity. By stabilizing junctional proteins such as VE-cadherin and occludin, it enhances barrier function and limits capillary leak, thereby preserving microcirculatory flow and organ perfusion.[9, 10] Experimental data further suggest that MR activation can mitigate inflammation-induced endothelial permeability and glycocalyx disruption.[10] In contrast, hydrocortisone alone primarily exerts anti-inflammatory effects and may have a limited impact on structural endothelial stability.

In addition to these hemodynamic and endothelial effects, MR activation also modulates immune responses. It influences

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macrophage polarization and cytokine production, attenuating excessive proinflammatory signaling while preserving anti-inflammatory pathways.[5, 9] This contrasts with the predominantly immunosuppressive effects of high-dose glucocorticoids, which may contribute to immune dysfunction and heterogeneous treatment responses in sepsis.[11]

At the transcriptional level, glucocorticoid and MRs exhibit distinct but partially overlapping genomic programs. GR signaling predominantly suppresses cytokine and chemokine pathways, whereas MR activation regulates genes involved in vascular tone, endothelial stability, and tissue homeostasis.[5, 9] When both receptors are engaged, their effects appear complementary, integrating anti-inflammatory and pro-homeostatic responses. This dual-axis framework provides a biologically plausible explanation for the observed benefit of combination therapy, in which GR attenuates the inflammatory response while MR supports vascular integrity and perfusion.

Clinical evidence: from trials to meta-analyses

Early randomized trials, including Ger-Inf-05 and APROCCHSS, suggested a potential benefit of combining hydrocortisone with fludrocortisone in septic shock.[2, 7] In the APROCCHSS trial, the combination reduced 90-day mortality (43.0% vs. 49.1%, P = 0.03), along with shorter vasopressor duration and more ventilator-free days, without an increase in adverse events.[2] In contrast, the Corticosteroid and Intensive Insulin Therapy for Septic Shock trial, which compared hydrocortisone alone with hydrocortisone plus fludrocortisone in 509 patients, did not demonstrate a significant mortality benefit, although the trial was not powered for this endpoint.[12] However, interpretation of this finding is limited by methodological considerations, including crossover and variability in corticosteroid exposure.

In a target-trial emulation of more than 88,000 intensive care unit admissions, hydrocortisone plus fludrocortisone was associated with a 3.7-percentage-point lower absolute mortality than hydrocortisone alone.[3] Despite extensive adjustment and sensitivity analyses, residual and unmeasured confounding cannot be excluded. This association was consistent across multiple sensitivity analyses and clinically relevant subgroups. Findings from observational analyses are complemented by evidence from recent meta-analyses. In a comprehensive pairwise and dose–response meta-analysis of 45 randomized trials (9563 patients), Pitre et al.[13] reported that mortality reduction with corticosteroids was more apparent in regimens that included fludrocortisone.

Taken together, these data suggest a consistent signal favoring the addition of fludrocortisone, although differences in study design, patient populations, and analytical approaches should be considered when interpreting these findings.

Biological plausibility and patient heterogeneity

The rationale for fludrocortisone use in septic shock is supported by converging clinical and translational evidence. Although the optimal dosing strategy remains uncertain, a recent phase II trial demonstrated a dose-dependent increase in plasma levels without additional hemodynamic benefit beyond 0.1 mg/d, supporting the conventional 50–100 µg dosing used in prior trials.[8] Oral absorption of fludrocortisone may be altered in patients with shock because of gastrointestinal hypoperfusion and delayed gastric emptying; however, direct pharmacokinetic evidence for fludrocortisone in this setting is limited. These limitations highlight the need for alternative delivery strategies, such as intravenous or sublingual formulations.

MR activation regulates endothelial and vascular gene expression in a manner distinct from GR signaling, supporting its role in hemodynamic stability and inflammatory modulation.[5, 9] These mechanistic effects align with emerging evidence that treatment response in sepsis is not uniform but depends on underlying biological phenotypes. Transcriptomic studies have identified reproducible immune endotypes, including Sepsis Response Signature (SRS)1 and SRS2, which differ in their response to corticosteroid therapy.[11] Patients with immunosuppressed profiles appear more likely to benefit, whereas those with more inflammatory phenotypes may not. This heterogeneity may help explain the variable effects of corticosteroids observed across clinical trials. In particular, MR activation by fludrocortisone may be most relevant in patients with immunosuppression and concurrent endothelial dysfunction, where restoration of vascular integrity and immune balance is critical. Conversely, in hyperinflammatory states, additional corticosteroid exposure may exacerbate immune dysfunction and increase susceptibility to secondary infections.[14]

Integrating immune phenotyping with hormonal profiling, including assessment of the renin–aldosterone axis, may therefore provide a path toward more targeted and effective use of mineralocorticoid therapy in septic shock.

Challenges and research priorities

Despite encouraging signals from both clinical and mechanistic studies, several uncertainties remain regarding the optimal use of fludrocortisone in septic shock. First, pharmacokinetic factors may limit the reliability of current regimens. Oral absorption during shock is often unpredictable due to gut hypoperfusion and delayed gastric emptying, which supports the need for studies evaluating alternative routes of administration such as intravenous or sublingual delivery. Second, appropriate patient selection remains a major challenge. Identifying a mineralocorticoid deficiency phenotype, potentially defined by low aldosterone levels, elevated renin activity, or suppression of MR-related pathways, may allow a more targeted use of therapy. This is consistent with growing evidence that treatment response in sepsis is influenced by underlying biological heterogeneity. Finally, several key clinical questions remain unresolved. It is unclear whether earlier initiation improves outcomes, how fludrocortisone should be integrated with vasopressors or angiotensin II, and how it should be incorporated into corticosteroid strategies. Future trials should extend beyond mortality endpoints and include mechanistic measures such as vascular responsiveness, endothelial function, and immune profiling to better define treatment effects and identify responsive subgroups.

In conclusion, available evidence suggests that the benefit of combining hydrocortisone with fludrocortisone in septic shock may reflect restoration of both glucocorticoid and mineralocorticoid pathways. By complementing anti-inflammatory effects with improvements in vascular function and endothelial stability, dual-axis activation provides a coherent mechanistic framework for the observed clinical signals. Future research should focus on identifying patients most likely to benefit from mineralocorticoid supplementation and on integrating immune and hormonal profiling to guide a more personalized approach to corticosteroid therapy in sepsis.

Conflict of interest statement

The author declares no conflict of interest.

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