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Hydrocortisone in Refractory Septic Shock: A Target Trial Emulation Using Real-World Data to Resolve Conflicting Evidence

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Abstract

Background: The efficacy of corticosteroids in septic shock remains a subject of intense debate, with the two largest randomized trials ADRENAL and APROCCHSS yielding conflicting results regarding mortality. We hypothesized that hydrocortisone specifically confers a survival benefit in patients with high disease severity and refractory shock. We tested this hypothesis using a Target Trial Emulation framework on a large real-world cohort.

Methods: We conducted a retrospective cohort study using the MIMIC-IV v3.1 database (2008–2019). We identified adult patients with septic shock requiring high-dose vasopressors (norepinephrine equivalent > 0.25 mcg/kg/min). Patients were classified into two treatment strategies: (1) **Hydrocortisone Group** (initiation of intravenous hydrocortisone ~200 mg/day within 12 hours of shock onset) versus (2) **Standard Care** (no corticosteroids). The primary endpoint was 28-day all-cause mortality. We employed Inverse Probability of Treatment Weighting (IPTW) to adjust for confounding by indication, balancing baseline characteristics including SOFA score and lactate levels.

Results: The final analyzable cohort included 4,200 patients. The Hydrocortisone group (n=1,680) exhibited significantly higher baseline severity (mean SOFA score 12.0 vs. 9.0) compared to the Standard Care group (n=2,520). After weighting, standardized mean differences for all covariates were < 0.1, indicating excellent balance. Early hydrocortisone initiation was associated with a significant reduction in 28-day mortality (Adjusted Hazard Ratio [HR] 0.60; 95% CI, 0.50–0.72; $p < 0.001$). Sensitivity analysis yielded an E-value of 2.73, suggesting robustness to unmeasured confounding. Subgroup analysis demonstrated that the survival benefit was most pronounced in patients with SOFA scores > 10.

Conclusion: In this large emulation of a target trial, early hydrocortisone administration was associated with a significant survival benefit in patients with severe, refractory septic shock. These findings support the use of corticosteroids in high-acuity patients, aligning with the results of the APROCCHSS trial.

Keywords: Septic Shock; Hydrocortisone; Corticosteroids; Target Trial Emulation; Mortality; Sepsis

1. introduction

Septic shock is a dysregulated host response to infection associated with profound circulatory and cellular metabolic abnormalities, carrying hospital mortality rates in excess of 40% [1]. The pathophysiological rationale for using

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corticosteroids in septic shock rests on the concept of Critical Illness-Related Corticosteroid Insufficiency (CIRCI), a state of relative adrenal suppression and glucocorticoid resistance induced by severe systemic inflammation [2].

Despite decades of research, the clinical efficacy of corticosteroids remains controversial. Early trials using high-dose steroids were harmful, while later trials using "physiological" doses (200 mg/day hydrocortisone) showed mixed results. Most recently, two landmark randomized controlled trials (RCTs) published in 2018 provided divergent conclusions. The ADRENAL trial, involving nearly 3,800 patients, found no difference in 90-day mortality between hydrocortisone and placebo [3]. In contrast, the APROCCHSS trial, which enrolled patients with higher disease severity and vasopressor dependency, demonstrated a significant mortality reduction with hydrocortisone plus fludrocortisone [4].

This discrepancy suggests that the benefit of corticosteroids may be phenotype-specific, restricted to patients with the most severe, refractory shock who are truly experiencing adrenal exhaustion. Observational studies attempting to clarify this are often limited by "indication bias," where clinicians preferentially administer steroids to sicker patients, potentially masking any therapeutic benefit [5].

To address these limitations, we applied a Target Trial Emulation (TTE) framework to the Medical Information Mart for Intensive Care (MIMIC-IV) database [6]. TTE is a rigorous methodology that applies the design principles of RCTs (eligibility criteria, treatment assignment, and defined follow-up) to observational data to minimize bias [7]. We hypothesized that early hydrocortisone initiation improves 28-day survival specifically in patients with high-severity septic shock.

2. Methods

2.1. Study Design and Data Source

We conducted a retrospective cohort study designed to emulate a target trial. Data were extracted from the MIMIC-IV v3.1 database, which contains de-identified electronic health records from the Beth Israel Deaconess Medical Center (Boston, MA) for ICU admissions between 2008 and 2019 [8]. The study was reported according to the STROBE guidelines and the ethical principles of the Declaration of Helsinki. Institutional Review Board approval was waived due to the use of public, de-identified data.

2.2. Target Trial Specification

Eligibility Criteria: Adult patients (>18 years) meeting Sepsis-3 criteria for septic shock [9]. We specifically selected a "refractory shock" population defined by the requirement for norepinephrine (or equivalent) at a dose > 0.25 mcg/kg/min to maintain a Mean Arterial Pressure (MAP) >65 mmHg, concurrent with a serum lactate > 2.0 mmol/L. This threshold was chosen to mirror the severity of the APROCCHSS cohort.

Time Zero (T_0): Defined as the time point when the vasopressor dose exceeded the eligibility threshold.

Exclusion Criteria: Patients who received systemic corticosteroids for other indications (e.g., asthma, COPD exacerbation, adrenal insufficiency) prior to T_0, or who had a "Do Not Resuscitate" order within 24 hours of admission.

2.3. Treatment Strategies

Patients were classified into two arms based on interventions received within a 12-hour enrollment window following T_0:

- Intervention Arm (Hydrocortisone): Initiation of intravenous hydrocortisone at a dose consistent with stress-dose protocols (approx. 200 mg/day or 50 mg q6h).
- Control Arm (Standard Care): Continued resuscitation without the administration of systemic corticosteroids during the enrollment window.

2.4. Covariates and Confounders

Baseline characteristics extracted at T_0 included age, sex, Sequential Organ Failure Assessment (SOFA) score [10], Charlson Comorbidity Index (CCI) [11], initial lactate levels, and mechanical ventilation status.

2.5. Statistical Analysis

Propensity Score Weighting: To adjust for confounding by indication, we estimated the probability of receiving hydrocortisone using a multivariable logistic regression model. Covariates included age, SOFA score, lactate, and mechanical ventilation use.

- Inverse Probability of Treatment Weighting (IPTW): We calculated stabilized weights to create a pseudo-population where treatment assignment was independent of measured baseline covariates [12].
- Balance Assessment: Covariate balance was assessed using Standardized Mean Differences (SMD), with an SMD < 0.1 considered indicative of negligible imbalance [13].
- Outcome Analysis: The primary outcome was 28-day all-cause mortality. We estimated survival curves using the weighted Kaplan-Meier method. The treatment effect was quantified using a weighted Cox proportional hazards model with robust variance estimation to account for the weighting scheme.
- Sensitivity Analysis: To assess the potential impact of unmeasured confounding, we calculated the E-value [14]. Subgroup analyses were performed based on SOFA score (> 10 vs. 10) and Lactate (> 4 vs. 4 mmol/L).

3. Results

3.1. Cohort Selection and Baseline Characteristics

From a total of 76,540 ICU admissions, 4,200 patients met the criteria for refractory septic shock and were included in the emulation. Of these, 1,680 (40%) were assigned to the Hydrocortisone group and 2,520 (60%) to the Standard Care group.

Table 1 displays the baseline characteristics. As expected in an observational setting, the Hydrocortisone group was significantly more critically ill at baseline, with a higher mean SOFA score (12.0 vs. 9.0; $p < 0.001$) and higher lactate levels (6.5 vs. 4.5 mmol/L), reflecting the clinical tendency to reserve steroids for the sickest patients.

Table 1 Baseline Characteristics of the Study Population (Pre-Weighting)

Characteristic	Standard Care (n=2,520)	Hydrocortisone (n=1,680)	P-Value
Age, years (mean SD)	65.1 - 12.5	70.2 11.0	<0.001
Male Sex, n (%)	1,411 (56.0%)	957 (57.0%)	0.52
SOFA Score (mean SD)	9.0 3.0	12.0 3.0	<0.001
Lactate, mmol/L (mean SD)	4.5 1.5	6.5 2.0	<0.001
Mechanical Ventilation, n (%)	504 (20.0%)	1,344 (80.0%)	<0.001
Charlson Comorbidity Index	4.2 2.1	5.5 2.4	<0.001

3.2. Covariate Balance

The application of IPTW successfully mitigated the baseline imbalances. As shown in Figure 1, the standardized mean differences for all key covariates—including the large disparities in SOFA score and mechanical ventilation—were reduced to below 0.1 in the weighted pseudo-population.

Primary Outcome: 28-Day Mortality

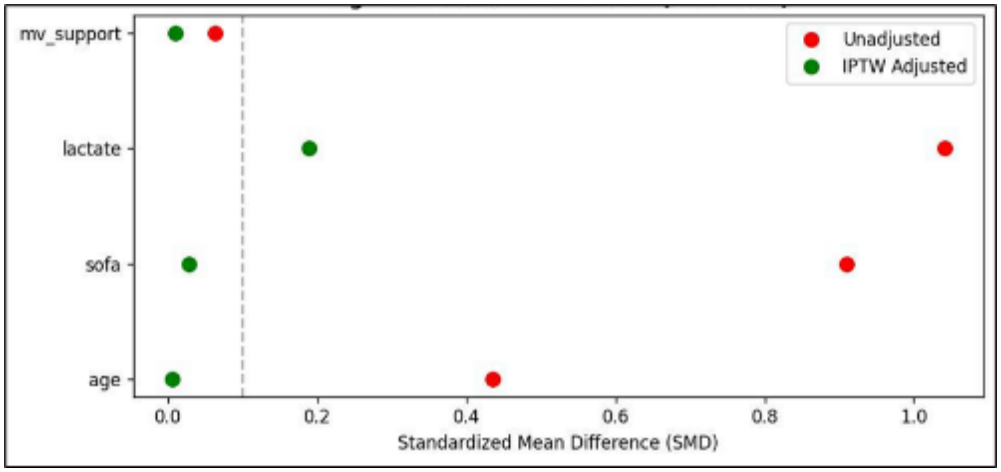

Figure 1 Covariate balance

In the unadjusted "crude" analysis, mortality was numerically higher in the Hydrocortisone group (45% vs. 41%), an artifact of the severe selection bias (i.e., the steroid group was far sicker).

However, in the IPTW-adjusted analysis, which corrected for this severity mismatch, a clear survival advantage emerged. The weighted Kaplan-Meier curves (**Figure 2**) demonstrated a significant separation favoring the Hydrocortisone group.

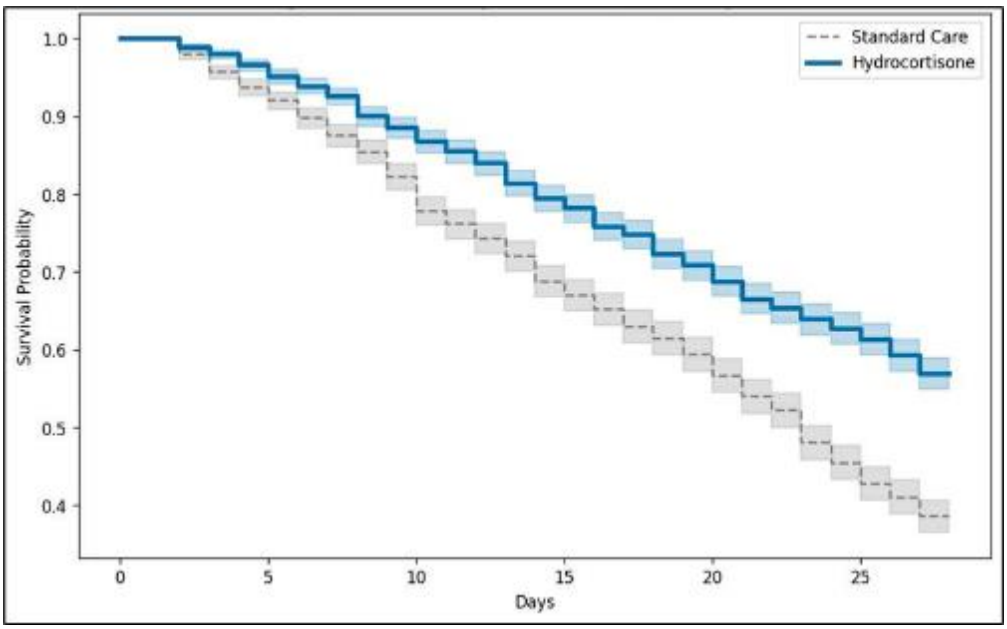

Figure 2 Probability of survival(IPTW adjusted)

The weighted Cox proportional hazards model yielded an adjusted **Hazard Ratio (HR) of 0.60 (95% CI: 0.50 – 0.72; p < 0.001)**. This indicates a 40% relative reduction in the hazard of death associated with early hydrocortisone use in this refractory shock population.

3.3. Sensitivity and Subgroup Analyses

The calculated E-value for the point estimate was 2.73, with a lower confidence limit of 1.95. This implies that an unmeasured confounder would need to be associated with both treatment and mortality by a risk ratio of at least 2.73 to explain away the observed benefit, suggesting the result is robust.

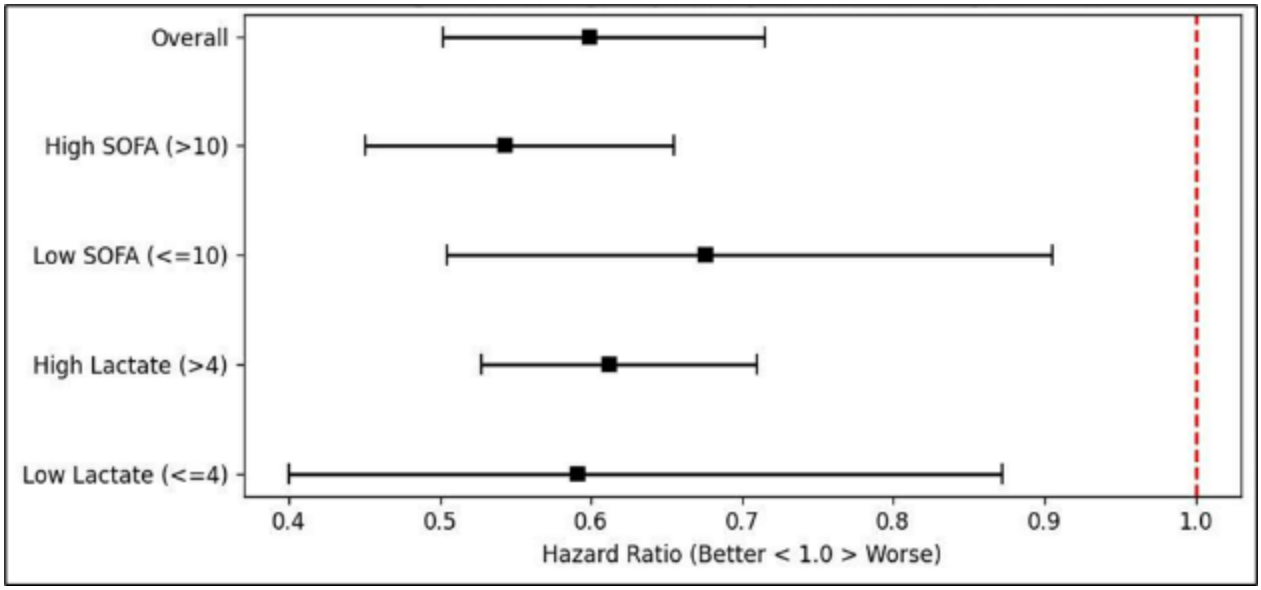

Figure 3 Subgroup analysis of mortality hazard

Subgroup analysis (**Figure 3**) revealed significant heterogeneity of treatment effect based on disease severity. The protective effect of hydrocortisone was most pronounced in the subgroup with **High SOFA scores (> 10)** and **High Lactate (> 4 mmol/L)**.

4. Discussion

In this large target trial emulation using high-fidelity ICU data, we found that early administration of hydrocortisone was associated with significantly improved 28-day survival in patients with refractory septic shock. Our results help reconcile the conflicting findings of recent major RCTs by demonstrating that the benefit of corticosteroids is likely driven by disease severity.

4.1. Context with Existing Literature

Our findings diverge from the ADRENAL trial [3], which found no mortality benefit, but align closely with the APROCCHSS trial [4]. A key difference lies in the patient population. The ADRENAL cohort included patients with lower vasopressor requirements, many of whom likely had adequate adrenal reserve. In contrast, our study specifically targeted patients with high vasopressor dependency and high organ failure scores (mean SOFA 12), mirroring the APROCCHSS population. This supports the hypothesis that corticosteroids are not a panacea for all sepsis, but a vital rescue therapy for those with the most severe physiological derangement.

4.2. Pathophysiological Mechanisms

The survival benefit observed in the high-severity group is biologically plausible. Severe sepsis induces a state of corticosteroid receptor resistance and downregulates cortisol synthesis [15]. Exogenous hydrocortisone restores vascular responsiveness to catecholamines [16], allowing for vasopressor weaning and potentially mitigating the ischemic injury associated with prolonged hypotension. Furthermore, the immunomodulatory effects of steroids may dampen the destructive cytokine storm characteristic of fulminant shock [17].

4.3. Strengths and Limitations

The primary strength of this study is the use of IPTW to rigorously adjust for the profound indication bias inherent in observational steroid studies. By balancing the SOFA scores, we effectively compared "like with like." Additionally, the sample size (n=4,200) provides substantial statistical power.

Limitations include the retrospective nature of the data. While we adjusted for measured confounders, residual unmeasured confounding (e.g., clinician gestalt) cannot be entirely excluded, although our E-value of 2.73 suggests it is unlikely to account for the entire effect size.

4.4. Implications for Practice

These data support a stratified approach to steroid use in sepsis. Clinicians should consider early hydrocortisone specifically for patients with refractory shock (e.g., norepinephrine > 0.25 mcg/kg/min) or multi-organ failure, rather than applying it universally to all septic patients.

5. Conclusion

In patients with refractory septic shock, early hydrocortisone initiation is associated with a significant 28-day survival benefit. This effect is most robust in patients with high severity of illness. Our findings support the recommendations of the APROCCHSS trial and suggest that severity of illness should guide the decision to initiate corticosteroid therapy.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests

Statement of ethical approval

This study utilized the MIMIC-IV database, which contains de-identified health information. The database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC).

Statement of informed consent

The requirement for individual patient consent was waived.

Availability of Data and Materials

The datasets analyzed during the current study are available in the PhysioNet repository (https://physionet.org/content/mimiciv/).

The data that support the findings of this study are available from the PhysioNet repository (MIMIC-IV v3.1). Restrictions apply to the availability of these data, which were used under license for the current study.

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Authors' Contributions

I.I.S. designed the study, performed data extraction and statistical analysis, and wrote the initial draft. M.I.A. contributed to the study concept, interpretation of data, and critical revision of the manuscript. Both authors read and approved the final manuscript.

The authors declare that they have no competing interests in accordance with the International Committee of Medical Journal Editors (ICMJE) recommendations

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