Comparative Effectiveness of Fludrocortisone and Hydrocortisone vs hydrocortisone Alone Among Patients with Septic Shock

Key Article

- *Bosch NA, Teja B, Law AC, et al. Comparative Effectiveness of Fludrocortisone and Hydrocortisone vs Hydrocortisone Alone Among Patients with Septic Shock. JAMA Intern Med. Published online March 27, 2023.*

Background

- Sepsis occurs in 1.7 million US hospitalizations, of which one-third of hospitalizations result in death. Septic shock is associated with fatality rates greater than 30%.
- Septic shock is a form of distributive shock involving vasoplegia and end organ dysfunction requiring vasopressor use in addition to fluid resuscitation.
- Steroids act on glucocorticoid and mineralocorticoid receptors to varying degrees. They increase vascular tone/permeability, promote volume retention, and suppress the hyperinflammatory state.
- Steroids in septic shock have historically been controversial. In the 1950s-1980s, high dose steroids were used. In the 1990s, meta-analyses demonstrated possible harm, higher mortality, secondary infections and hepatic/renal dysfunction. Over the past 20 years there has been reintroduction of steroids for septic shock.
- The 2021 Surviving Sepsis Campaign guidelines recommend adding corticosteroids, specifically hydrocortisone at 200 mg/d for septic shock requiring vasopressors. These guidelines were born out of multiple RCTs and subsequent meta-analyses that found steroids correlated with shortened shock duration and possible reduced mortality.
    - COIITSS (JAMA 2010) – 2.9% absolute reduction in mortality hydrocort + fludrocort vs hydrocort alone, not statistically significant but underpowered.
    - APROCCHSS Trial (NEJM 2018) – multicenter, double-blinded RCT evaluated hydrocortisone-fludrocortisone vs placebo in septic shock. Experimental group with lower mortality, higher vasopressor free days and organ failure free days.

Objective

- To compare the effectiveness of hydrocortisone-fludrocortisone versus hydrocortisone alone in patients admitted with septic shock.

Methods

- Large multicenter observational cohort study using the Premier Healthcare Database from 2016-2020. ~20% US inpatient hospitalizations are included in database.
- Patients
    - Included:
        - Admitted to ICU or step-down unit with septic shock
        - Received norepinephrine
        - Began hydrocortisone within 3 days of admission

    - Excluded
        - Age < 18 years
        - Alternative indications for hydrocortisone (1^0 adrenal insufficiency, orthostatic hypotension, congenital adrenal hyperplasia)
- Trial procedures
    - Accessed Premier Healthcare Database and searched for ICD-10 septic shock.
    - Used hospital billing data to find treatment assignments hydrocortisone-fludrocortisone vs hydrocortisone alone
    - Study day 0 was initiation of hydrocortisone treatment
- Primary outcome
    - Composite of hospital death and discharge to hospice
- Secondary outcomes
    - Hospital death
    - Vasopressor-free days by day 28
    - Hospital-free days by day 28
- Safety outcomes
    - Hypernatremia
    - Healthcare-associated infections

Results

- 384394 patients with septic shock received norepinephrine
    - 88275 met inclusion criteria
        - 85995 hydrocortisone alone
        - 2280 hydrocortisone-fludrocortisone
- Primary Outcomes
    - **Death or discharge to hospice**
        - Hydrocortisone-fludrocortisone: 47.2%
        - Hydrocortisone only: 50.8%
        - Adjusted risk difference -3.7% (95% CI, -4.2 to -3.1 % CI, P < .001) favoring hydrocortisone-fludrocortisone group
        - Risk reduction with added fludrocortisone held true even in subgroup analyses (age, sex, hx CHF, time to corticosteroid initiation)

Median (IQR)	**Hydrocortisone – fludrocortisone**	**Hydrocortisone**
# Days of follow up	6	5
Duration of tx	3	3
Hydrocortisone dose (mg)	225	200
Fludrocortisone dose (mg)	0.1	N/A

- Secondary Outcomes
    - Hospital death
        - Hydrocortisone – fludrocortisone: 39.3%
        - Hydrocortisone only: 42.7%
        - Adjusted risk difference -3.7% (95% CI, -4.2% to -3.3%, P < .001)
    - Vasopressor-free days:
        - Hydrocortisone – fludrocortisone: 13.8 days

        - Hydrocortisone only: 12.9 days
        - Adjusted risk difference 0.9 days (95% CI, 0.8-1.1), P < .001)
    - Hospital-free days: 0.7d (95% CI, 0.6-0.8)
        - Hydrocortisone – fludrocortisone: 8.7 days
        - Hydrocortisone only: 8.4 days
        - Adjusted risk difference 0.7 days (95% CI, 0.6-0.8), P < .001)
- Safety Outcomes
    - Hypernatremia
        - Hydrocortisone – fludrocortisone: 11.4%
        - Hydrocortisone only: 11.3%
    - Health care associated infections
        - Hydrocortisone – fludrocortisone: 1.4%
        - Hydrocortisone only: 1%
- Difference- in- Differences Analysis
    - "Adopter" hospitals are hospitals that increased hydrocortisone -fludrocortisone use after APROCCHSS trial in 2018
    - Compared primary outcome (death/discharge to hospice) in "adopter" hospitals vs control hospitals
    - Adjusted difference-in-difference estimator of -2 % meaning LOWER probability of death/discharge to hospice in "adopter" hospitals

Limitations Identified by Authors

- Observational study at risk for unmeasured confounders
- Premier Healthcare database lacks physiologic data and vasopressor doses. Risk for unmeasured confounders.
- Database only provided data by calendar day and not within the day.

Take Home Points

- Current guidelines recommend only hydrocortisone for septic shock requiring vasopressors.
- The trial results show that fludrocortisone may decrease mortality, increase vasopressor and hospital free days, and have no measurable impact on patient safety.
- The hydrocortisone and fludrocortisone combination therapy may be considered in this high-risk demographic of patients with septic shock requiring vasopressors.