COMMENTARY

OPEN

Alternatives to Hydrocortisone for Hemodynamic Support in Septic Shock Management Due to Medication Shortage

Mohammed Aldhaeefi, PharmD[1]
Abdulrahman Alshaya, PharmD[2,3,4]
Sanaa Belrhiti, PharmD[5]
Dhakrit Rungkitwattanakul, PharmD[1]

ABSTRACT: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection. Septic shock is when initial fluid resuscitation fails to increase the mean atrial pressure to greater than or equal to 65 mm Hg. The 2021 Surviving Sepsis Campaign guidelines recommend corticosteroids for vasopressor and fluid-refractory septic shock patients. Medication shortages can arise, and their etiologies include natural disasters, quality control issues, and manufacturing discontinuation. The U.S. Food and Drug Administration and the American Society of Health-System Pharmacists announced a shortage of IV hydrocortisone. Methylprednisolone and dexamethasone are considered therapeutic alternatives to hydrocortisone. This commentary aims to guide clinicians on the alternative to hydrocortisone among septic shock patients due to medication shortage.

KEY WORDS: critical care; drug shortage; hydrocortisone; sepsis; septic shock

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection (1). The mainstay of sepsis and septic shock management includes fluid resuscitation, antibiotics, and vasopressors, followed by inotropes (1). The use of corticosteroids is recommended among vasopressor and fluid-refractory septic shock patients. Medication shortages create challenges across health systems and a lack of access to standard-of-care therapies when caring for septic shock patients (2). The increased demand for healthcare utilization due to the global pandemic can lead to medication shortages (2). Recently, the U.S. Food and Drug Administration and the American Society of Health-System Pharmacists announced current limitations in the supply of several medications commonly used in the ICU (i.e., hydrocortisone sodium succinate injection, hydromorphone hydrochloride injection, fentanyl citrate injection, epinephrine injection, 0.1 mg/mL, and mannitol injection) (3, 4). Hydrocortisone sodium succinate injection is commonly used in the ICU for hemodynamic support (1, 5, 6). This commentary aims to guide clinicians on the alternative to hydrocortisone among septic shock patients because of medication shortage.

The effect of corticosteroids can be classified into two general categories, glucocorticoid (metabolism, inflammation, immunity, wound healing, myocardial, and muscle contractility) and mineralocorticoid (salt and water reabsorption and retention, and mineral metabolism) effects (5, 7). Animal models and clinical data suggested that septic shock results in a dysregulated response of the hypothalamic–pituitary–adrenal (HPA) axis (8). Based on sodium-retaining potency, hydrocortisone has potentially adequate mineralocorticoid effects among septic shock patients (9, 10). One of the many consequences of HPA axis dysregulation is the inhibition of cortisol production (8). Corticosteroids

DOI: 10.1097/CCE.0000000000000940

support hemodynamics by reducing the natural production of nitric oxide, increasing catecholamine's effect on smooth muscles, enhancing vasopressin production, and increasing myocardial contractility (5–7). Furthermore, reinstating effective blood volume through the mineralocorticoid activity and increased systemic vascular resistance were noted after the administration of corticosteroids (5, 7).

Although conflicting mortality reduction outcomes were reported, the early administration of steroids was associated with improved survival (9, 11–14). The 2021 International Surviving Sepsis Campaign guidelines suggest the use of IV hydrocortisone 200 mg/day given as a continuous infusion or 50 mg IV every 6 hours for vasopressor and fluid-refractory septic shock patients (1). Ideal corticosteroid therapy, proper dose, time of initiation, and treatment duration among septic shock patients remain uncertain (1, 6). IV alternatives to hydrocortisone sodium succinate in the ICU are methylprednisolone and dexamethasone (5, 7). When converting corticosteroids, 50 mg of hydrocortisone is equivalent to 40 mg and approximately 7.5 mg of methylprednisolone and dexamethasone, respectively (5, 7). Methylprednisolone and dexamethasone have a major disadvantage of possessing a lower mineralocorticoid activity than hydrocortisone sodium succinate (5, 7).

Clinical pharmacists should collaborate with providers and work diligently to select and identify the subpopulation of patients who should receive corticosteroids during the hydrocortisone shortage. Patients who might benefit the most from corticosteroid therapy are those receiving norepinephrine or epinephrine greater than or equal to 0.25 μg/kg/min for at least 4 hours after initiation and patients who are on oral corticosteroid therapy for other indications, patients with documented adrenal insufficiency (1, 5, 7, 9). However, corticosteroid therapy should be initiated cautiously in patients with diabetes and those with hypernatremia at baseline (1, 5, 7, 9). Various strategies could be implemented to avoid hydrocortisone overuse during the current shortage. Continuous patient reassessment using perfusion and hemodynamic parameters, electronic medical records (EMR) 7-day duration of therapy stop alerts, and EMR pop-up suggested alternative therapy are recommended to avoid hydrocortisone overuse.

When steroids are deemed necessary, we suggest using steroid combination therapy of methylprednisolone or dexamethasone with enteral fludrocortisone to overcome their low mineralocorticoid activity (5, 7, 9). Suggested alternatives are summarized in **Table 1**. Limited evidence supports their role as monotherapy among septic shock patients because of their low mineralocorticoid activity. Based only on one historical study, dexamethasone resulted in a mortality reduction when used among septic shock patients (15). However, methylprednisolone had no effect on septic shock patients' mortality rate (16).

Multiple previously published studies examined the effect of steroid combination therapy among septic shock patients (5, 7, 9, 10, 17). In 2002, Annane et al (9) demonstrated that the combination therapy of hydrocortisone (50 mg IV push every 6 hr) plus fludrocortisone (50 μg oral tablet once daily) significantly reduced 28-day mortality among patients with septic shock and relative adrenal insufficiency without increasing the risk of adverse event rates. Furthermore, the Activated Protein C and Low Dose of Hydrocortisone and

TABLE 1.
Suggested Alternatives to the 2021 Surviving Sepsis Campaign Guidelines Corticosteroids Recommendations Due to Hydrocortisone Shortage

The 2021 Surviving Sepsis Campaign Guidelines Recommendation	Suggested Alternative
IV hydrocortisone 200 mg continuous infusion	IV methylprednisolone 40 mg continuous infusion plus fludrocortisone 50 μg oral tablet once daily OR IV dexamethasone 8 mg continuous infusion plus fludrocortisone 50 μg oral tablet once daily
Hydrocortisone 50 mg IV every 6 hr	Methylprednisolone 10 mg IV every 6 hr plus fludrocortisone 50 μg oral tablet once daily OR Dexamethasone 2 mg IV every 6 hr plus fludrocortisone 50 μg oral tablet once daily

Fludrocortisone in Adult Septic Shock (APROCCHSS) trial, published in 2018, reported a significantly lower 90-day all-cause mortality when fludrocortisone 50 µg oral tablet once daily was added to hydrocortisone 50 mg IV push every 6 hours compared with placebo (49.1% vs 43.0%) (17). Lastly, an observational study demonstrated a significantly lower in-hospital death or discharge to hospice when fludrocortisone 100 µg was used in combination with hydrocortisone among septic shock patients (10).

Several limitations of enteral medication administration during septic shock must be considered. Blood flow is remarkably redistributed at the splanchnic circulatory level and in peripheral tissues to increase the perfusion of vital organs during shock (5, 7, 9). Additionally, the use of vasopressors results in splanchnic vasoconstriction (5, 7, 9). This could reduce enteral medication absorption (5, 7, 9). Finally, corticosteroids may improve the rate of septic shock reversal in the ICU, and using therapeutic alternatives to IV hydrocortisone, such as methylprednisolone or dexamethasone with enteral fludrocortisone is necessary to mitigate drug shortage and overcome possible low mineralocorticoid activity.

1 *Department of Clinical and Administrative Pharmacy Sciences, College of Pharmacy, Howard University, Washington, DC, USA.*

2 *Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia*

3 *Department of Pharmaceutical Care, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, KSA*

4 *King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.*

5 *Department of Pharmacy Services, Howard University Hospital, Washington, DC 20060, USA*

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: mohammed.aldhaeefi@howard.edu

REFERENCES

1. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143
2. Fox ER, McLaughlin MM: ASHP guidelines on managing drug product shortages. *Am J Health Syst Pharm* 2018; 75:1742–1750
3. Hydrocortisone sodium succinate injection. https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=920&loginreturnUrl=SSOCheckOnly. Accessed 04/22/2023.
4. Current and resolved drug shortages and discontinuations reported to FDA. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm. Accessed April 22, 2023.
5. Williams DM: Clinical pharmacology of corticosteroids. *Respir Care* 2018; 63:655–670
6. Prescott HC, Sussman JB: Smarter use of corticosteroids in treating patients with septic shock. *JAMA Netw Open* 2020; 3:e2029323
7. Samuel S, Nguyen T, Choi HA: Pharmacologic characteristics of corticosteroids. *J Neurocrit Care* 2017; 10:53–59
8. Annane D: The role of ACTH and corticosteroids for sepsis and septic shock: An update. *Front Endocrinol (Lausanne)* 2016; 7:70
9. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
10. 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* 2023; 5:451–459
11. Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378:797–808
12. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of hydrocortisone on development of shock among patients with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016; 316:1775–1785
13. Sprung CL, Singer M, Kalenka A, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 2:111–124
14. Katsenos CS, Antonopoulou AN, Apostolidou EN, et al; Hellenic Sepsis Study Group: Early administration of hydrocortisone replacement after the advent of septic shock: Impact on survival and immune response*. *Crit Care Med* 2014; 42:1651–1657
15. Cicarelli DD, Vieira JE, Benseñor FEM: Early dexamethasone treatment for septic shock patients: A prospective randomized clinical trial. *Sao Paulo Med J* 2007; 125:237–241
16. Bone RC, Fisher CJ, Clemmer TP, et al: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653–658
17. Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378:809–818