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Clinical Review

CONTROVERSIES IN CORTICOSTEROID USE FOR SEPSIS

Brit Long, MD* and Alex Koyfman, MD†

*Department of Emergency Medicine, San Antonio Military Medical Center, Fort Sam Houston, Texas and †Department of Emergency Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas
Reprint Address: Brit Long, MD, 506 Dakota St., Apt. 1, San Antonio, TX 78203

□ **Abstract—Background: Severe sepsis and septic shock are potentially deadly conditions managed in the emergency department (ED). Management centers on source control, fluid resuscitation, broad-spectrum antimicrobials, and vasopressors as needed. The use of corticosteroids is controversial. Objective: To evaluate the evidence behind corticosteroid therapy in patients with septic shock. Discussion: Septic shock is associated with severe mortality and morbidity. Cytokine release produces a systemic inflammatory state. Vasopressor-resistant septic shock warrants consideration of the disease state and other pathologies such as adrenal insufficiency. Many studies and meta-analyses have been conducted evaluating corticosteroid therapy for this population. High-dose corticosteroid therapy is associated with increased harm, but physiologic-dose corticosteroids may decrease the need for vasopressors. Mortality benefit is controversial, with much of the literature demonstrating no effect. The risk of superinfection is not suggested by the majority of studies. The Surviving Sepsis Campaign advises consideration of corticosteroids in patients with vasopressor and fluid-resistant septic shock. Patients with vasopressor-resistant septic shock with no contraindications to corticosteroids may benefit from hydrocortisone 100 mg intravenously (i.v.) every 8 h or 50 mg i.v. every 6 h. Fludrocortisone is not recommended at this time. Conclusions: Septic shock is associated with higher mortality, specifically for patients with vasopressor and fluid-refractory shock. The use of physiologic-dose steroids can reduce vasopressor requirements and improve time of shock resolution. Current literature suggests corticosteroids do not improve mortality, but further studies are required. Published by Elsevier Inc.**

□ **Keywords—corticosteroids; septic shock; severe sepsis; hydrocortisone; HPA axis; cosyntropin**

INTRODUCTION

Sepsis Epidemiology

Sepsis is a condition emergency providers manage daily. The reported annual incidence is 50 to 300 cases per 100,000 persons, with over 750,000 patients evaluated and managed in the emergency department (ED) per year in the United States (1–4). Morbidity and mortality can be severe, particularly for septic shock, with mortality ranging from 20% to 70% (1–4).

Emergency physicians are masters of resuscitation, and sepsis is no different. Management requires rapid diagnosis and early administration of intravenous (i.v.) fluids with broad-spectrum antimicrobials and source control. Early diagnosis and treatment can significantly reduce mortality and morbidity in affected patients. Early goal-directed therapy first brought these elements to the forefront of emergency medicine, with modifications since the revolutionary study in the ProCESS, ARISE, and ProMISe trials (5–9). Specific components of sepsis management remain essential, including fluid resuscitation, broad-spectrum antimicrobials, and vasopressors (2,6–9).

Steroid Controversy

Systemic corticosteroids are one component of sepsis management that has undergone significant modification

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in sepsis management. The systemic response of sepsis results in the release of pro-inflammatory pathways centered on cytokines. Corticosteroids can act to attenuate these inflammatory molecules, suggesting a possible role for corticosteroid use in sepsis management (2,3,10). Vasomotor tone may decrease in septic shock, and corticosteroids can improve vascular function and effective blood volume, improving organ perfusion and preload (3,10).

Septic shock is associated with relative adrenal insufficiency, in which a patient's own cortisol levels are not sufficient to maintain hemodynamic and electrolyte status. However, studies demonstrate conflicting results with steroid use in these patients. The role of corticosteroid therapy in patients with vasopressor-resistant septic shock remains controversial and uncertain, specifically, whether corticosteroids reduce mortality, reduce time of shock and vasopressor need, and contribute to adverse events such as superinfection. Despite recent meta-analyses, there is no clear guidance on when corticosteroids should be provided, as well as what patient class would benefit (11–17).

This review evaluates the current literature behind the use of corticosteroids in sepsis, evaluates the utility of cosyntropin testing, and offers an approach with recommendations for when these medications may benefit patients.

METHODS

Authors conducted a literature search pertaining to "steroids," "corticosteroids," "glucocorticoids," "sepsis," "septic shock," "severe sepsis," "hydrocortisone," "HPA axis," "ACTH," and "cosyntropin" of MEDLINE, Google Scholar, Cochrane Reviews, CENTRAL, and Google FOAM from 1960 to 2016. Studies were included based on agreement by the two authors.

Effect of Sepsis on the Hypothalamic–Pituitary–Adrenal (HPA) Axis

Sepsis has many effects on the body, and one organ system in particular includes the HPA axis. Several endocrine organs including the thyroid, pancreas, and adrenal glands comprise this system. The hypothalamus is responsible for stimuli integration and secretion of corticotropin-releasing hormone during times of stress (10,11,16,17). This secretion of corticotropin-releasing hormone results in initiation of adrenal corticotropin hormone (ACTH) synthesis and release from the anterior pituitary. ACTH results in adrenal production of cortisol. This intricate feedback system allows regulation. Vasopressin is a neurohormone associated with maintaining vasomotor tone and cortisol regulation. Severe sepsis and septic shock result in decreased albumin and corticosteroid binding proteins, affecting cortisol tissue distribution (16,17).

Normal serum cortisol levels range from 5 to 24 μg/dL, depending on time of day and stress. Levels may reach 50 μg/dL during periods of peak stress (16–21). Cortisol function is affected by several aspects of illness including reduced cortisol breakdown (resulting in increased levels), increased free cortisol, steroid receptor affinity modifications, decreased steroid inactivation, and increased peripheral production of cortisol. However, septic shock can drastically affect cortisol levels, including increased cortisol inactivation through 11β-hydroxysteroid dehydrogenase activity, increased clearance of cortisol, changes in ACTH synthesis and release, decreased cortisol binding globulin and albumin (resulting in less delivery of cortisol to tissues), and cytokine effect (potentially reducing tissue response to steroids) (17,20–23).

Adrenal insufficiency can be challenging in sepsis, and the incidence of relative adrenal malfunction may approach 50% in severe sepsis and septic shock (11–17). The concept of relative adrenal insufficiency is based on several physiological factors. The first is that physiologic stress results in cortisol increase, and the greater stress, the greater rise in cortisol. Sepsis functions as a stressor, triggering increase in cortisol. Adrenal insufficiency is due to impaired glucocorticoid and vasopressin production or dysregulated cortisol response (11–17). Medications can also result in HPA axis dysregulation and dysfunction, such as etomidate, antifungals, and chronic steroid use. These often act to decrease intrinsic corticosteroid production and intrinsic effects (24,25).

DISCUSSION

Steroids in Septic Shock

Steroids have been utilized in the treatment of septic shock for over 50 years, with initial literature based on animal data supporting improved survival when provided with antibiotics (26–33). From the 1950s to the 1980s, high-dose steroids, methylprednisolone 30 mg/kg or dexamethasone 3-6 mg/kg for several days, were used to treat patients in severe sepsis or septic shock (30–33). Schumer utilized high-dose methylprednisolone vs. dexamethasone vs. normal saline, finding that patients in the normal saline group experienced higher mortality (28). However, the mid-1980s ushered in several prospective, randomized, placebo-controlled trials that did not demonstrate improved mortality in high-dose steroids (34–36). Bone et al. in 1987 randomized 382 patients with sepsis and organ dysfunction to methylprednisolone 30 mg/kg i.v. vs. placebo, finding