Adjunctive Steroid Therapy for Treatment of Pediatric Septic Shock

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KEYWORDS

• Septic shock • Adjunctive sepsis therapy • Glucocorticoids/corticosteroids
• Aldosterone • Oxandrolone • 17β-estradiol • Cortisol • Hydrocortisone

KEY POINTS

- Mineralocorticoids, glucocorticoids, and gonadocorticoids are subject to individual synthetic regulation within the adrenal cortex and remote sites of steroid synthesis.
- In addition to governing sodium and potassium homeostasis, aldosterone mediates multiple aspects of hemodynamics that may be disrupted by endogenous and exogenous dopamine.
- Oxandrolone, an anabolic steroid, has been used to improve nitrogen balance and lean body mass among children with thermal burn injury, and this effect may be beneficial among children with sepsis.
- Estrogen analogs facilitate mitochondrial function and aspects of aerobic metabolism that logically might abrogate widespread energy failure as an antecedent to multiple organ dysfunction syndrome associated with severe sepsis.
- Corticosteroids have favorable hemodynamic and anti-inflammatory properties that may be invaluable among septic patients with recalcitrant septic shock, but immunosuppression and promotion of lean body catabolism associated with gluconeogenesis and hyperglycemia may ultimately mitigate any clinical benefit. A high-quality, prospective, double-blinded, randomized controlled interventional trial examining the potential benefits and risks of hydrocortisone as adjunctive therapy for pediatric sepsis is warranted.

ADRENAL STEROIDOGENESIS

With major involvement of cytochrome P450 isoforms, 3 classes of steroids are produced from cholesterol in the adrenal cortex. Generally mineralocorticoids are synthesized in the zona glomerulosa, glucocorticoids in the zona fasciculata, and

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gonadocorticoids in the zona reticularis.[1] Synthesis of mineralocorticoids depends primarily on the renin-angiotensin-aldosterone (RAA) axis; synthesis of glucocorticoids is governed by activity of the hypothalamic-pituitary-adrenal (HPA) axis; and synthesis of gonadocorticoids is regulated by hypothalamic-derived gonadotropin-releasing hormone and pituitary-derived follicle stimulating hormone and luteinizing hormone with critical involvement of steroidogenic acute regulatory protein.[2] Steroid hormones are not stored at their sites of biosynthesis; rather, release of steroid hormones is controlled almost entirely through regulation of their synthesis. Although critical care medicine practitioners frequently prescribe glucocorticoids for their favorable hemodynamic as well as immunosuppression properties to patients with septic shock, the purpose of this review is to suggest that mineralocorticoids as well as gonadocorticoids may also represent potentially useful adjuncts for treatment of sepsis.

MINERALOCORTICOIDS

A schematic summary of aldosterone synthesis and regulation is provided in **Fig. 1**.

As an aspect of the RAA axis activation, angiotensin II production is enhanced by endothelial angiotensin-converting enzyme, particularly within the pulmonary vasculature.[3] Angiotensin II (a peptide not steroid hormone) mediates multiple activities also essential to the (sepsis) stress response:

- Increases systemic vascular resistance and blood pressure
- Stimulates aldosterone release
- Increases plasminogen activator inhibitor-1, facilitating a prothrombotic state
- Enhances thirst and salt craving
- Increases antidiuretic hormone, adrenocorticotropic hormone, and norepinephrine release
- Facilitates sodium reabsorption at proximal convoluted tubule
- Stimulates renal afferent/efferent vasoconstriction
- Increases nuclear factor κB (NF-κB), resulting in increased proinflammatory cytokine release

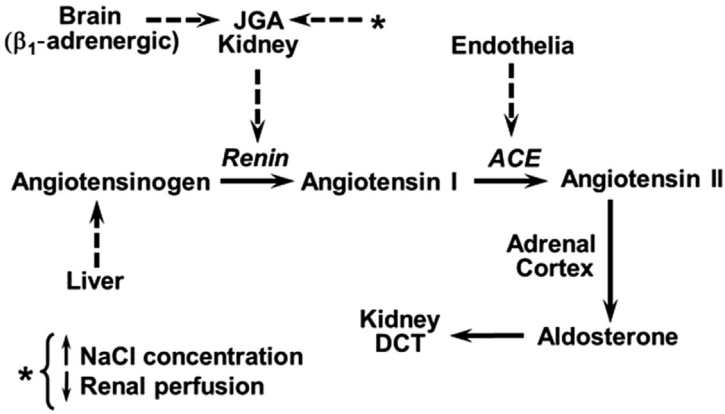

Fig. 1. RAA axis. ACE, angiotensin-converting enzyme; DCT, renal distal convoluted tubule; JGA, renal juxtaglomerular apparatus. In addition to monitoring local perfusion pressure and environmental Na^+ and Cl concentrations, the JGA receives β_1-adrenergic neural input from the brain.