Toward Increased Understanding of the Steroid Controversy in Septic Shock

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Corticosteroids have been evaluated and used in septic shock for decades but despite numerous randomized controlled trials (RCTs), they remain one of the greatest controversies in that subject. Perhaps that is due in part to the broad pleiotropic actions of corticosteroids and the differing characteristics of the RCTs (e.g., inclusion criteria, corticosteroids used, dose and duration of corticosteroid treatment, the weaning protocol, and the primary endpoint). The steroid world was awakened once again with the recent publications of Annane et al (1) and Venkatesh et al (2) RCTs of low-dose hydrocortisone that have generated more questions among clinicians who manage septic shock because the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) RCT showed a mortality benefit in patients treated with corticosteroids, while the ADjunctive coRticosteroid trEatment iN Critically IlL Patients (ADRENAL) study did not (**Table 1**). Although both studies demonstrated a shortened time on vasopressors for patients treated with corticosteroids, the trials have differences in the steroids used in the intervention arm and entry criteria. This issue contains three viewpoints that each advocate a particular message from a leading expert on steroid usage, including the principle investigators of the ADRENAL, APROCCHSS, and Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trials. Although these viewpoints may not solve the controversy, we hope that the information provided here will allow physicians to better inform their practice.

The mechanisms of glucocorticoid deficiency in sepsis are complex and incompletely understood (3). The corticosteroid axis deficiency occurs early in septic shock (4) because of increased plasma levels of cytokines that inhibit adrenocorticotropin effects on increased cortisol output (5, 6) and glucocorticoid receptor density may be decreased in septic shock resulting in glucocorticoid resistance (7). Thus, corticosteroid therapy can first reverse the sepsis-associated adrenal insufficiency using "stress" dose corticosteroids and second, can suppress the exuberant inflammatory response characteristic of septic shock.

The activated glucocorticoid-glucocorticoid receptor-alpha (GC-GRα) complex plays a central role in corticosteroid action. The corticosteroid action via the activated GC-GRα complex action on messenger RNA alters expression of thousands of genes (8) that can have many variants that later corticosteroid response or sensitivity (9). Thus once can appreciate that there is wide interindividual variation in the corticosteroid response to septic shock.

Corticosteroids also have nongenomic anti-inflammatory actions including activation of kinase pathways (mitogen-activated protein kinase), thereby altering endothelial nitric oxide synthase and nitric oxide production in septic shock (10). Corticosteroids also alter T-cell receptor signaling and decrease monocyte human leukocyte antigen-DR isotype expression (11) by nongenomic actions.

These pleiotropic actions of corticosteroids and the wide interindividual variability of gene expression via glucocorticoid response element variants all play into the interindividual responses to corticosteroids in practice and in RCTs.

Trials decades ago evaluated high-dose corticosteroids in septic shock (12–16), but high-dose corticosteroids did not improve outcomes in septic shock or acute respiratory distress syndrome, and they are not effective for preventing septic shock in patients who have sepsis but are not in shock (17).

The attention then turned to low-dose hydrocortisone to reverse sepsis-associated adrenal insufficiency. Low-dose

Dr. Russell received funding from AKPA, SIB, and Ferring, and he reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis and related to the use of vasopressin in septic shock, of which he is an inventor of these products. Dr. Russell was a founder, Director and shareholder in Cyon Therapeutics Inc; he is a shareholder in Molecular You; he has previous consulted for La Jolla Pharmaceuticals, Grifols, PAR Pharma; and he disclosed off-label product use of steroids in septic shock. Dr. Sevransky's institution received funding from Marcus Foundation, BARDA, and the Society of Critical Care Medicine.

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DOI: 10.1097/CCM.0000000000004038

TABLE 1. Comparisons and Contrasts of the Corticosteroid Trials of Annane et al (1) and Venkatesh et al (2)

	Annane et al (1)			Venkatesh et al (2)		
Variable	Placebo	Corticosteroids	*P*	Placebo	Corticosteroids	*p*
Sample size (*n*)	627	614		1,860	1,853	
Inclusion criteria	Septic shock < 24 hr Norepinephrine > 0.25 µg/kg/min for 6 hr			Ventilation Infection Vasopressor > 4 hr		
Exclusion criteria	Shock > 24 hr Risk of bleeding Pregnancy Underlying condition affecting survival Prior steroid therapy			Likely to receive steroids for other than septic shock Etomidate Underlying condition and likely to die < 90 d Treatment limitations		
Intervention	Hydrocortisone plus fludrocortisone	Placebo		Hydrocortisone	Placebo	
Primary endpoint	90-d mortality	90-d mortality		90-d mortality	90-d mortality	
Primary outcome	49.1%	43.0%	0.03	27.9%	28.8%	0.5
Key secondary endpoints				28-d mortality 22.3%	28-d mortality 24.3%	0.13
Key secondary endpoints	Vasopressor-free days	Vasopressor-free days				
Key secondary outcomes	17	15	< 0.001			
	Ventilator-free days	Ventilator-free days		Ventilator-free days	Ventilator-free days	
Key secondary outcomes	11	10	0.07	61.2	59.1	0.06
	Organ failure-free days					
Key secondary outcomes	11	12	0.003			
Adverse events						
n				21	6	
Serious adverse event by day 180	326 (53.1%)	363 (58%)	0.08			
Hyperglycemia	547 (89.1%)	520 (83.1%)	0.002	6	3	
Superinfection	191 (31.1%)	178 (28.4%)	0.3			

hydrocortisone treatment of septic shock usually shortens the duration of shock (18), and in some (19) but not all RCTs (18) decreased mortality. There was a trend to increased risk of hospital-acquired superinfections in the hydrocortisone group in one RCT (18). Older systematic reviews found that low-dose hydrocortisone decreased mortality of septic shock (19).

As a consequence of these RCTs and other literature, a review of sepsis and septic shock published in 2013 (20) and the 2017 (i.e., pre Annane et al [1] and Venkatesh et al [2]) Surviving Sepsis Campaign guidelines (21) recommend against using IV hydrocortisone to treat septic shock if adequate fluid and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, they recommend hydrocortisone 200 mg IV per day (weak recommendation, low quality of evidence).

A consensus guideline for corticosteroids (22)—published in 2017 pre Annane et al (1) and Venkatesh et al (2, 23) RCTs—recommended "using corticosteroids in patients with septic shock that is (sic) not responsive to fluid and moderate to high dose vasopressor therapy (conditional recommendation, low quality of evidence)" (19). They recommend a long course of low-dose corticosteroids (< 400 mg/d for at least 3 d) (19).

Thus, guidelines and reviews predate the recent Annane et al (1) and Venkatesh et al (2) RCTs and clinicians and readers. In an effort to better inform the debate, we have asked the

principle investigators of three recent trials to opine on the differences between the studies.

The viewpoint by Annane et al (1) addresses the topics: Why do my steroid trials in septic shock show a mortality benefit? Please provide an explanation of why the Annane et al (24) and the Annane et al (1) trials demonstrated a mortality benefit while other trials (Corticosteroid Therapy of Septic Shock [CORTICUS] [18], Venkatesh et al [2], and others [16]) did not. Venkatesh et al (2) were asked: Why did my trial Venkatesh et al (2) and some prior steroid trials in septic shock (CORTICUS [18] and others [16]) not show a mortality benefit, while? Annane et al (24) and the Annane et al (1) trials showed a mortality benefit were positive. What are the key features of trials by Annane et al (1, 24) that differ and that may explain why they showed differing results? Both Annane et al (1) and Venkatesh et al (2) were asked: What are the key features of your trials (1, 24) that differ and might explain the divergent results.

Gordon et al (25)—an expert on the steroid/vasopressin interaction based on his VANISH trial and prior studies (26)—was asked to provide further commentary especially as it relates to the steroid/vasopressin interaction in septic shock.

We doubt that these viewpoints will end the controversy about whether to use corticosteroids in patients with septic shock and which patients might be appropriate for such use. We hope that these viewpoints will raise the level of the debate, and in conjunction with recent meta-analyses on the topic (27), allow clinicians to make the best decisions for their patients based on currently available data.

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