Why Understanding Sepsis Endotypes Is Important for Steroid Trials in Septic Shock

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Sepsis remains a major global health concern and current treatment relies on antibiotics, fluids and vasopressors. Based on their pluripotent actions, especially on immune function and cardiovascular status, and the concept that septic patients may develop relative adrenal insufficiency, corticosteroids have been proposed as adjunctive therapies in septic shock since the 1960s. However, the exact role for these drugs remains disputed. Corticosteroids have been consistently reported to have beneficial effects on cardiovascular status in septic shock with many trials demonstrating shorter shock duration in those patients given corticosteroids (1–5) (**Table 1**). However, as described by the authors of the other viewpoints in this series (6, 7) beneficial effects on mortality have been less clearly demonstrated. Although a mortality benefit has been seen in a number of trials (2, 5) this has not been seen in all (1, 3) (Table 1).

Recently two transcriptomic sub-phenotypes (endotypes), based on genome wide RNA expression profiles, have been described in septic patients. Similar profiles were seen in sepsis due to both pneumonia (8) and fecal peritonitis (9). The first profile, termed sepsis response signature (SRS) 1 appears to be associated with relative immune suppression based on patterns of RNA expression, greater disease severity and higher mortality than SRS2 (**Table 2**). Importantly, as well as being prognostic of outcome it seems that these two sepsis endotypes may also predict response to treatment. In a post-hoc analysis of the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock clinical trial (10), where patients with septic shock were randomized to either vasopressin or norepinephrine followed by either hydrocortisone or placebo, patients were assigned to either SRS1 or SRS2 endotypes based on whole genome RNA expression collected at trial inclusion (11). When outcomes were compared in patients who received either hydrocortisone or placebo, in those patients who exhibited the SRS1 endotype there was no difference in mortality (hydrocortisone vs placebo in SRS1 odds ratio [OR], 0.85, 95% CI 0.30–2.43). However, this was not the case in SRS2 patients where mortality was significantly greater in those randomized to hydrocortisone (hydrocortisone vs placebo in SRS2 OR, 7.9, 95% CI 1.6–39.9). The test of treatment effect by SRS endotype interaction was also statistically significant, $p = 0.02$ (11), illustrating the clear difference in response to hydrocortisone by patients according to endotype. Interestingly, although it failed to reach statistical significance, there was a trend in *both* SRS1 and SRS2 endotypes toward a shorter duration of shock in those randomized to receive corticosteroids (hydrocortisone vs placebo 31 hr vs 44 hr SRS1, 59 hr vs 90 hr SRS2), as has clearly been seen in multiple other steroid trials.

The differential treatment effects seen between SRS1 and SRS2 endotypes implies that a 'one size fits all' approach to the use of corticosteroids in septic shock is not appropriate and could cause harm to some. This finding may well account for mortality differences reported in previous clinical trials. If one study recruited a higher proportion of less sick, SRS2, patients then the increased mortality with corticosteroids in this group could mask any survival benefit in the other patients or lead to an overall signal toward harm. Specifically, the recent Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial, overall day-90 mortality 28% (1), found no survival benefit with corticosteroids whereas the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial, overall day-90 mortality 46%

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TABLE 1. Comparison of Several Corticosteroids for Septic Shock Trials

References	Year	Intervention	Mortality Control Group, *n*/Total (%)	Mortality Corticosteroid Group, *n*/Total (%)	Median Shock Duration, Control Group (d)	Median Shock Duration, Corticosteroid Group (d)
Annane et al (5)	2002	6 hr; hydrocortisone boluses with once daily oral fludrocortisone vs placebo	91/149 (61)[a]	82/150 (55)[a]	9	7
CORTICUS (3)	2008	6 hr; hydrocortisone boluses vs placebo	78/248 (31)[a]	86/251 (34)[a]	5.8	3.3
ADRENAL (1)	2018	Hydrocortisone infusion vs placebo	526/1826 (29)[b]	511/1,832 (28)[b]	4	3
APROCCHSS (2)	2018	6 hr; hydrocortisone boluses with once daily oral fludrocortisone vs placebo	308/627 (49)[b]	264/614 (43)[b]	Not available	Not available

ADRENAL = Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock, APROCCHSS = Activated Protein C and Corticosteroids for Human Septic Shock, CORTICUS = Corticosteroid Therapy in Septic Shock.

[a]28-d mortality.

[b]90-d mortality.

TABLE 2. Comparison of Sepsis Response Signature Cohorts

References	Patients	28-D Mortality	
		SRS1, *n* (%)	SRS2 *n* (%)
Davenport et al (8)	Pneumonia sepsis	29/108 (27)	27/157 (17)
Burnham et al (9)	Fecal peritonitis sepsis	10/48 (21)	5/69 (7)
Antcliffe et al (11)	Septic shock from all causes from VANISH—placebo group	13/35 (37)	2/24 (8)
	Septic shock from all causes from VANISH—hydrocortisone group	9/27 (33)	13/31 (42)

SRS = sepsis response signature, VANISH = vasopressin versus norepinephrine as initial therapy in septic shock.

(2), found corticosteroids improved survival. These findings would be consistent with a larger proportion of SRS2 patients in the ADRENAL trial, accounting for the lower overall mortality, who may be expected to be the ones not to benefit from corticosteroids.

The mechanisms underlying the differences in disease severity and outcomes between SRS1 and SRS2 remain unclear as, at present, we have no clear functional understanding of the two endotypes. However, some insight can be gained from the differential gene expression between the two groups. SRS1 is associated with down-regulation of genes associated with human leucocyte antigen (HLA) class II expression and T cell activation (8). It is perhaps surprising then that the apparently more immunocompetent, SRS2, patients come to harm when given corticosteroids. We propose that whilst the cardiovascular effects of corticosteroids are seen in all patients, irrespective of SRS endotype, the immunosuppressant effects are more pronounced in SRS2. One possible explanation is that we know genes coding for HLA class II are up-regulated in SRS2 (8), and that low levels of HLA-DR have been associated with worse survival in sepsis (12), raising the possibility that improvement in antigen presentation in SRS2 could account for the improved survival rates consistently seen in this group of patients. However, it has been previously reported that corticosteroids can down-regulate major histocompatibility complex II (12–14) potentially removing the protective advantage of the SRS2 endotype. Corticosteroids may also have effects on NFκB, T-cells, and apoptosis (15, 16) all of which showed evidence of differential expression between the SRS endotypes so modulation of these pathways could account for different degrees of immunosuppression induced by corticosteroids between SRS endotypes. Such immune dysfunction is recognized to increase the risk of nosocomial infection and be associated with higher rates of mortality (17).

Although still speculative, the concept that the major benefits of corticosteroids in septic shock lie in their cardiovascular effects, whilst their immunomodulatory effects could cause harm in some, may account for other differences in the corticosteroid literature. In the two studies that have shown a survival benefit (2, 5), hydrocortisone was given in conjunction with fludrocortisone, whereas in those trials showing no mortality benefit, hydrocortisone was given alone (1, 3). Corticosteroids exhibit a combination of glucocorticoid and mineralocorticoid effects in a ratio dependent on the specific drug. Glucocorticoids have effects on a number of physiologic functions especially immunity and metabolism, whilst mineralocorticoids cause salt and water retention and elevation in blood pressure. Hydrocortisone has roughly equal glucocorticoid and

mineralocorticoid effects whereas fludrocortisone is at least 12.5 times more potent as a mineralocorticoid (18) and may also cause α1-adrenoreceptor sensitization (19). It is plausible that the additional cardiovascular effects of fludrocortisone, without additional immunosuppression, could provide additional survival benefit. Similarly, some of the earliest work exploring the use of corticosteroids for sepsis used methylprednisolone at supra-physiologic doses, a corticosteroid with almost no mineralocorticoid actions, and in the largest of these trials (20) methylprednisolone use lead to worsened survival.

Several groups have explored transcriptomic responses to sepsis. Although we described two main transcriptomic endotypes it has been suggested that there may be as many as four distinct endotypes in adults (21) and it is plausible that the response to corticosteroids could be different in each, although this has not yet been explored. Of particular interest is work performed in pediatric sepsis populations (22, 23), where three RNA subclasses were identified, termed A, B and C. Although there is little crossover with the genes responsible for the SRS endotypes identified in adults, subclass A was associated with down-regulation of genes associated with the adaptive immune system and repression of genes associated with glucocorticoid signaling (23). In an observational study children in the immunosuppressed group, subclass A, had worse outcomes if given corticosteroids (22). These data again supports a differential effect of corticosteroids based on subclinical transcriptomic profiles, although the endotypes are not the same as those seen in adults (9, 24, 25) and in the pediatric study corticosteroid treatment was based on physician choice rather than randomized allocation as part of a trial.

CONCLUSIONS

Although corticosteroids clearly have beneficial effects on shock duration their impact on patient survival is less clear. The differences in mortality effects seen in past clinical trials could be explained by different transcriptomic endotypes expressed by the included patients, leading to differential responses to corticosteroid treatment. To account for these differential responses future trials should aim to stratify patients according to their RNA expression endotypes so that subgroups who may respond positively to corticosteroids can be identified and those who may come to harm can avoid this treatment. As RNA endotypes cannot be assigned using clinical parameters alone, we urgently need rapid diagnostic tests to better characterize our patients and select optimal, personalized treatments, whether they be "old" drugs, such as corticosteroids, or "new" immunotherapies.

REFERENCES

1. 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
2. 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
3. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
4. Gordon AC, Mason AJ, Perkins GD, et al: The interaction of vasopressin and corticosteroids in septic shock: A pilot randomized controlled trial. *Crit Care Med* 2014; 42:1325–1333
5. 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
6. Venkatesh B, Cohen J: Why the Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (ADRENAL) Trial Did Not Show a Difference in Mortality. *Crit Care Med* 2019; 47:1785–1788
7. Annane D: Why My Steroid Trials in Septic Shock Were "Positive". *Crit Care Med* 2019; 47: 1789–1793
8. Davenport EE, Burnham KL, Radhakrishnan J, et al: Genomic landscape of the individual host response and outcomes in sepsis: A prospective cohort study. *Lancet Respir Med* 2016; 4:259–271
9. Burnham KL, Davenport EE, Radhakrishnan J, et al: Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med* 2017; 196:328–339
10. Gordon AC, Mason AJ, Thirunavukkarasu N, et al; VANISH Investigators: Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA* 2016; 316:509–518
11. Antcliffe D, Burnham K, Al-Beidh F, et al: Transcriptomic signatures in sepsis and a differential response to steroids: From the VANISH Randomized Trial. *Am J Respir Crit Care Med* 2019; 199:980–986
12. Le Tulzo Y, Pangault C, Amiot L, et al: Monocyte human leukocyte antigen-DR transcriptional downregulation by cortisol during septic shock. *Am J Respir Crit Care Med* 2004; 169:1144–1151
13. Lim TK, Chen GH, McDonald RA, et al: Granulocyte-macrophage colony-stimulating factor overrides the immunosuppressive function of corticosteroids on rat pulmonary dendritic cells. *Stem Cells* 1996; 14:292–299
14. van de Garde MDB, Martinez FO, Melgert BN, et al: Chronic exposure to glucocorticoids shapes gene expression and modulates innate and adaptive activation pathways in macrophages with distinct changes in leukocyte attraction. *J Immunol* 2014; 192:1196–1208
15. Nelson HS, Leung DY, Bloom JW: Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 2003; 111: 3–22; quiz 23
16. Olnes MJ, Kotliarov Y, Biancotto A, et al; CHI Consortium: Effects of systemically administered hydrocortisone on the human immunome. *Sci Rep* 2016; 6:23002
17. Conway Morris A, Datta D, Shankar-Hari M, et al: Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. *Intensive Care Med* 2018; 44:627–635
18. Heming N, Sivanandamoorthy S, Meng P, et al: Immune effects of corticosteroids in sepsis. *Front Immunol* 2018; 9:1736
19. Cheshire WP: Chemical pharmacotherapy for the treatment of orthostatic hypotension. *Expert Opin Pharmacother* 2019; 20:187–199
20. Bone RC, Fisher CJ Jr, 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
21. Scicluna BP, van Vught LA, Zwinderman AH, et al; MARS consortium: Classification of patients with sepsis according to blood genomic endotype: A prospective cohort study. *Lancet Respir Med* 2017; 5:816–826
22. Wong HR, Cvijanovich NZ, Anas N, et al: Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med* 2015; 191:309–315
23. Wong HR, Cvijanovich N, Lin R, et al: Identification of pediatric septic shock subclasses based on genome-wide expression profiling. *BMC Med* 2009; 7:34
24. Sweeney TE, Azad TD, Donato M, et al: Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. *Crit Care Med* 2018; 46:915–925
25. Wong HR, Sweeney TE, Hart KW, et al: Pediatric sepsis endotypes among adults with sepsis. *Crit Care Med* 2017; 45:e1289–e1291