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The adrenal gland and corticosteroid therapy in sepsis: I certainly remain uncertain

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Adrenal dysfunction in sepsis, described for over a century and previously termed *relative adrenal insufficiency*, now is labeled *critical illness-related corticosteroid insufficiency* (CIRCI) [1]. The history of the investigation, data, and practice patterns revolving around the adrenal gland and corticosteroid supplementation in septic shock is a tour de force in evidence-based uncertainty. Corticosteroid replacement in sepsis has seen an evolution in dose (high vs. low), dosing strategies (bolus dosing vs. infusion, taper vs. no taper), duration of therapy, and guideline recommendations [2].

High dose steroids were commonly given until the mid-1990s when data revealed not only a lack of benefit, but harm associated with this strategy [3]. On the heels of smaller studies showing earlier shock reversal and potential mortality benefit with low-dose steroids, a multicenter randomized controlled trial (RCT) showed a 10% absolute risk reduction in mortality for septic shock patients with relative adrenal insufficiency [4]. These results were not duplicated by another multicenter RCT, which differed significantly from the Annane trial [5]. Accordingly, as these data have evolved, the “official” recommendations have changed from “...are recommended...” (2004) to “We suggest not using.....” (2012) [6, 7].

Data suggests that CIRCI increases mortality, yet it is difficult to say who even has it, given the testing limitations to diagnose it [8]. So at least two questions still remain: 1) Does this patient have CIRCI?; and 2) “Should I dose this particular patient with steroids?”.

The present study is an attempt to tackle the first question [9]. Using a *post-hoc* analysis, the authors aimed to use computer-assisted modeling to examine free cortisol appearance and elimination rates [maximal cortisol secretion rate (CSR_{max})] and free cortisol half-life]. Subjects included septic shock (n=45), sepsis (n= 25), and healthy controls (n= 10), and were given a cosyntropin stimulation test within 24 hours of sepsis diagnosis. Survivors also

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Conflicts of Interest

There are no conflicts of interest.

received cosyntropin testing at hospital discharge and as outpatients. Contrary to the primary hypothesis, CSR_{max} was higher in septic shock than in sepsis and healthy controls, and this decreased between the first and second cosyntropin test. The free cortisol half-life was also longer in septic shock and sepsis vs. controls.

The strengths of the study are its accuracy when compared to isotope dilution, as well as its attempt at better refining this topic by assessing the kinetics of cortisol parameters. It also has weaknesses. The small numbers and lack of patient-level details make extrapolation of this data beyond this manuscript impossible. We do know that the original study from which this *post-hoc* data was obtained excluded patients with hepatic and liver disease, a fact that further limits generalizability. The use of healthy subjects as a comparator group can also be debated as well. Furthermore, there was a significant age difference between the healthy controls and the sepsis patients, raising further questions about an accurate comparator. There was also no difference in the CSR_{max} between sepsis patients and healthy volunteers. Given the abundance of data regarding sepsis, inflammation, and the adrenal axis, this makes little intuitive sense. Finally, while this study is an attempt at better diagnosing CIRCI, the variance in CSR_{max} in the septic shock group, shows some rather high between-subject variability. This suggests that this approach will either be inaccurate in a significant percentage of patients, and/or needs further refinement.

What do we do with these results? While they add to our knowledge base regarding the possible diagnosis of CIRCI, practice cannot be changed based on these data. At the end of the day, even if we can accurately diagnoses CIRCI, it still doesn't mean that patients will benefit from exogenous steroid replacement. Anemia is easily diagnosed and associated with worse outcome in critically ill patients, yet transfusion does not improve outcome. I believe the decision to treat septic shock patients for possible CIRCI should revolve around the question: "Is my patient more similar to the Annane trial (early septic shock with 60% mortality risk) or the CORTICUS trial?" If the former (an absolute minority of sepsis patients), then dosing with steroids can be considered. Until our specialty is better at tailoring therapy to an individual, it will be difficult to answer these questions. In the meantime, I thank the authors of this work for advancing the science and inching us closer.

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