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EDITORIAL

Editorial to: Adrenocortical function during prolonged critical illness and beyond: a prospective observational study

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Pitfalls in the assessment of adrenocortical activity during prolonged critical illness

A patient with septic shock is still in the ICU on day 14. The clinician is considering prescription of glucocorticoid treatment. He performs a corticotropin stimulation test and finds a low incremental total cortisol. Does this patient have critical illness associated adrenal insufficiency (CIRCI) or not? The Leuven group recently investigated hypothalamus–pituitary–adrenal (HPA) axis alterations during *prolonged* critical illness and beyond. The group found that despite a low incremental total cortisol, calculated incremental free cortisol could be normal as a result of low cortisol binding proteins and increased distribution volume [1, 2], and concludes that the corticotropin stimulation test cannot provide reliable information on adrenocortical integrity or functional reserve in this setting.

This Leuven study included patients still in ICU on day 7. Long-stay ICU patients always demonstrated low incremental total cortisol, but normal incremental free cortisol responses to weekly corticotropin stimulation testing. Between day 7 and 28, plasma ACTH remained low/normal and free cortisol remained high with evidence of decreased breakdown, which could be adaptive. Beyond ICU-day 28, plasma (free) cortisol was no longer elevated and binding proteins increased. One week after ICU discharge, plasma ACTH and (free) cortisol always increased to supranormal levels. These adrenal parameters were not different among patients with sepsis/septic shock or patients subsequently receiving glucocorticoids. Non-survivors had higher (free) cortisol [1] as was previously demonstrated [3–5]. Among other interesting results, the study confirmed the questionable interpretation of corticotropin stimulation testing during prolonged stay in the ICU, a finding previously ascertained during the acute phase of sepsis [5].

Do the combined measurements in this study answer the question whether these long-stay ICU patients had CIRCI? An international task force of the American College of Critical Medicine defined CIRCI as inadequate cellular corticosteroid *activity* for the *severity of the patient's critical illness* [6]. Of note, this definition refers to cellular activity, not to plasma cortisol concentrations, and incorporates the knowledge that optimal activity relates to the state of illness. Furthermore, an expert panel recently formulated three major pathophysiologic events constituting CIRCI: dysregulation of the HPA axis, altered cortisol metabolism, and tissue resistance to glucocorticoids [7].

The Leuven study explored two of the three criteria in patients during prolonged critical illness, but did not examine potential tissue resistance to glucocorticoids. Tissue corticosteroid resistance is seen in chronic inflammatory diseases such as COPD and autoimmune diseases, but also in acute inflammatory illnesses such as sepsis [8]. Glucocorticoids bind to cytosolic glucocorticoid receptors, which are ligand-dependent transcription factors that alter the immune response at the gene level [9]. Glucocorticoid resistance may be due to reduced receptor-density and transcription, to receptor oxidation, and to β-receptor isoform overexpression. The β-isoform does not bind known ligands and does not alter gene

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expression [10]. Pro-inflammatory cytokines decrease the expression of the glucocorticoid α-receptor and increase its oxidation. Oxidation of the receptor hampers both ligand and DNA binding, reducing glucocorticoid activity (summarized in [11]). Adjuvant administration of vitamin C may counteract this damage [11]. In addition, TNF-α has been shown to increases the expression of the β-isoform over the α-isoform. After binding of glucocorticoids to the α-receptor and subsequent translocation of this receptor complex to the nucleus, modulation of gene expression occurs [12]. Responders to corticosteroids showed a high nuclear-to-cytoplasmatic density of the glucocorticosteroid receptor ex vivo [13]. Real-time measurement of nuclear and cytoplasmic glucocorticoid receptor levels by flow cytometry is feasible and could identify individuals exhibiting glucocorticoid resistance. Unfortunately, this methodology is still not available in clinical practice [12].

Still more difficult is the answer to the question of what cortisol concentration is adequate during different phases of critical illness. The results of the Leuven study are confusing in this regard: non-survivors demonstrated higher (free) cortisol, but (free) cortisol also rose to supranormal levels 1 week after discharge to the hospital ward. Furthermore, in a matched comparison between patients who subsequently receive corticosteroids and patients who did not, measured adrenal markers were not different. Thus, higher concentrations of cortisol are seen in both non-survivors and in patients recovering from prolonged critical illness, and measured adrenal markers were not predictive of need for subsequent glucocorticoid treatment. Unmeasured glucocorticoid tissue resistance may have been operative or glucocorticoids may have been administered for other reasons than supposed CIRCI.

The rationale for the use of glucocorticoids in sepsis is that glucocorticoids modulate the immunologic response to stress from pro- to anti-inflammation without inducing overt immunosuppression [11]. In addition, this intervention is associated with improved hemodynamics and reduced nitric oxide formation in patients with septic shock [14]. The effect of glucocorticoids seems dose-dependent. Low concentrations of endogenous glucocorticoids sensitize the innate immune system while high concentrations may suppress excessive and/or prolonged immune responses [9]. Thus, optimal concentrations seem to depend on the stage of disease and the degree of inflammation. However, in case of glucocorticoid insufficiency, exogenous corticosteroids may not be effective [13].

Despite these uncertainties, the Leuven study provides important information on the HPA axis during prolonged critical illness. Interpretation of the study findings, however, remains difficult. Cortisol concentrations were generally high in the setting of decreased breakdown, while ACTH was consistently low. A biphasic ACTH pattern was previously reported, with low ACTH and persistently high cortisol concentrations in the second phase of critical illness (beyond day 6) [15]. Whether low ACTH reflects feedback downregulation or suppressed ACTH release is not known. Suppressed ACTH release is suggested by the finding that plasma ACTH and (free) cortisol consistently rose to supranormal levels following discharge from the ICU.

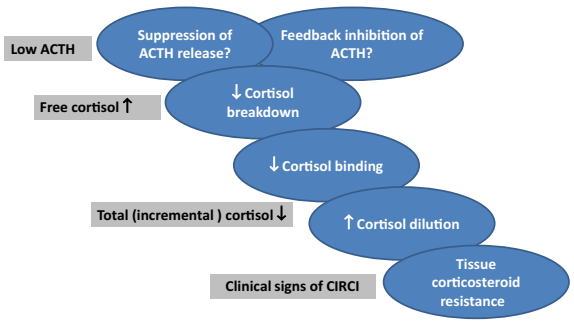

Fig. 1 Pitfalls in the assessment of adrenocortical activity during prolonged critical illness

Complete understanding of the HPA axis and criteria for optimal adrenal activity during critical illness remain elusive (Fig. 1). The Leuven study confirms that the corticotropin stimulation test cannot exclude CIRCI during prolonged critical illness. Despite a low incremental total cortisol, free cortisol can be normal because of low cortisol binding proteins and increased distribution volume. Furthermore, the test is not appropriate to diagnose central adrenocortical suppression, which plays a role during prolonged critical illness. In addition, optimal cortisol concentrations for the specific stage of disease are unknown. Finally, tissue glucocorticoid resistance may be present. For this reason, exogenous corticosteroid administration could also be ineffective. Further research is needed to diagnose and manage this condition.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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