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The Hypothalamic-Pituitary-Adrenal Axis in Critical Illness

Philipp Schuetz, MD, Beat Müller, MD*

Clinic of Endocrinology, Diabetes and Clinical Nutrition, Department of Internal Medicine, University Hospital Basel, Petersgraben 4, Basel CH-4031, Switzerland

Life-threatening disease induces acute adaptive responses specific to the stimulus and generalized responses when the disturbances are more extensive and sustained [1]. An appropriate adaptation of the hypothalamic-pitu itary-adrenal (HPA) axis to stress is essential for survival [2,3]. Increasing circulating levels of adrenal steroids (eg, cortisol) are the consequence of an acutely and markedly activated anterior pituitary (ie, adrenocorticotropin hormone [ACTH]) and hypothalamic (eg, corticotropin-releasing hormone [CRH] and vasopressin, also termed *antidiuretic hormone* [ADH]) response [4]. This response happens under the influence of higher cortical functions, spinal and peripheral baroreceptors, among others. The acute stress response adapts throughout the course of critical illness [5]. In addition, disease-related variations in the binding capacities of circulating proteins (ie, cortisol-binding globulin and albumin) result in even more fluctuating levels of free stress hormones during critical illness [6–10]. The tissue and cellular responses to free circulating hormone levels vary substantially based on the receptor and postreceptor levels (eg, by modulation of the number and activity of cellular receptors or the activity of downstream responses, respectively) [11–15]. The half-life of cortisol in the blood is increased during stress owing to a decreased rate of hepatic extraction and renal enzymatic inactivation of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase [16]. The immuno-neuro-endocrine interactions are bidirectional, mutually potentiating and attenuating, and not fortuitous. Several gluco- and mineralocorticoids modulate the immune response distinctively [17]. On the other hand, cytokines (eg, tumor necrosis factor, interleukins, and macrophage-migration inhibitory factor) and bacterial products (eg, endotoxin) are able to modulate the response of the HPA axis at each level [1].

* Corresponding author.
E-mail address: happy.mueller@unibas.ch (B. Müller).

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Of course, "critical illness" is not a simple disease entity, and, when scanning the literature, one cannot evade the impression that this fact is sometimes neglected. Inducers of life-threatening critical stress include trauma, burns, surgery, infections, and multiple other diseases typically associated with variable levels of inflammation [18]. The mediator profile during these distinct diseases varies substantially [19]. For didactic purposes, any attempt to summarize hormonal changes during so-called "critical illness" is oversimplistic and inherently problematic. These caveats need to born in mind before drawing heroic therapeutic implications from allegedly promising hypotheses for a disease syndrome in the absence of unequivocal scientific evidence.

Timing and profile of steroids during critical illness are essential

Cortisol (also called hydrocortisone or compound F) is considered the primary active glucocorticoid and is essential for the adaptation and maintenance of stress homeostasis during critical illness. It is a pluripotent hormone acting on all tissues to regulate pleiotropic and numerous aspects of metabolism, growth, and physiologic functioning, being in this way essential for survival in critical illness [20–22]. Characteristically, any acute insult will result in an augmented release of cortisol and other adrenal steroids, among other factors mediated by a sharp rise of circulating short-lived ACTH, which, in turn, is driven by CRH, vasopressin, cytokines, and an upregulated noradrenergic system, and other factors [5]. The production of cortisol in the adrenocortical cells in response to ACTH occurs within minutes and begins with the enzymatic cleavage of the side chain of cholesterol to generate pregnenolone and, by additional enzyme systems, cortisol (Fig. 1) [23,24]. The normal feedback system might be altered because hypercortisolism is less suppressible by dexamethasone infusion in septic shock [25]. Moreover, the normal circadian rhythm of cortisol secretion, especially the nadir during night time, is disturbed [26,27]. Reported plasma hormone levels vary widely among studies. The persistence of pulsatile secretion may explain the observed variability, and, accordingly, the accuracy of single samples is potentially inadequate, as is true for all hormones [28]. Furthermore, the interindividual and interassay variability of cortisol and other steroid assays measuring free or total hormone concentrations at different sites and centers can be substantial [6,29,30].

Although the renin-angiotensin-aldosterone system is also activated [31], the acute adaptive adrenal response to stress is typically seen as a shift from mineralocorticoid production to a marked increase in glucocorticoid production. In addition, in acute illness, the biologic effects of cortisol increase owing to a decrease in cortisol binding globulin and an increase in receptor sensitivity and number [1,10].

Metabolically, hypercortisolism acutely induces glycogen, fat, and protein breakdown so that energy becomes abundantly available to critical

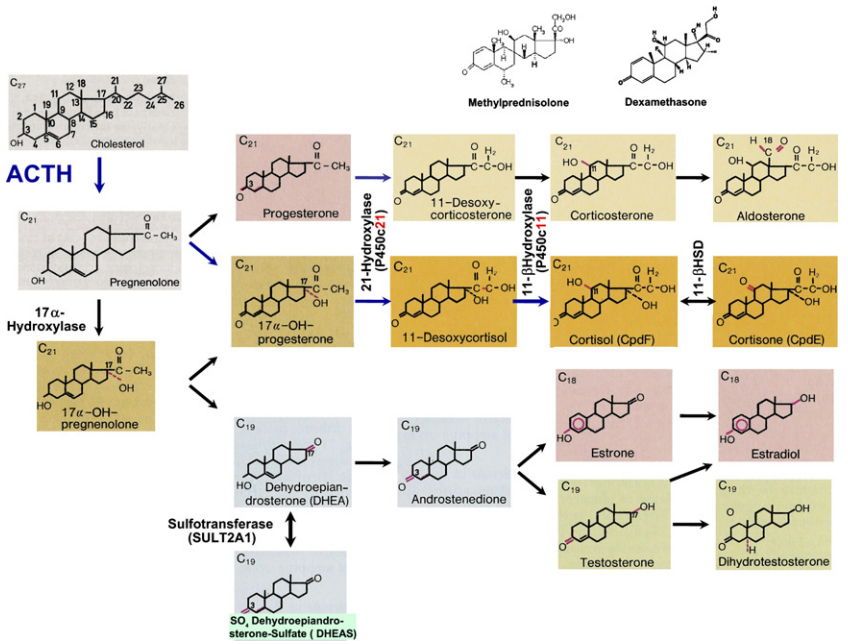

Fig. 1. Adrenal steroidogenesis and commonly used generic steroid drugs. 11-βHSD, 11 beta hydroxysteroid dehydrogenase.

organs. Cortisol-mediated retention of intravascular fluid and an enhanced ionotropic and vasopressor response to catecholamines and angiotensin II offer hemodynamic advantages in the ''fight or flight'' reflex. The acute steroid excess can be interpreted as an attempt of the organism to mute its own inflammatory cascade to protect against an overresponse of the endogenous ''fire brigade'' [5].

This acute phase typically lasts for a few hours or days. If death or recovery does not occur within a few days of intensive medical care, the critical illness becomes protracted. Arguably, a protracted severe illness with intensive care has not been critical during the evolution of mankind. Contemporary medical technology through its artificial life support systems has created conditions never before experienced by complex life forms [1]. Accordingly, the neuroendocrine response in this subsequent chronic phase of illness may be considered to be insufficient rather than beneficial for the adaptation to chronic disease.

Hormonally during the prolonged phase of critical illness of weeks to months there is a dissociation between high plasma cortisol and low ACTH levels, suggesting non-ACTH mediated mechanisms for regulation of the adrenal cortex [32]. Cytokines and other circulating factors might suppress ACTH synthesis and secretion. For example, endothelin 1 [33], atrial natriuretic peptides [33,34], and pro-adrenomedullin [35] are elevated at

stages when ACTH is suppressed. Moreover, despite an increase in plasma renin activity, paradoxically, a decreased concentration of aldosterone is found in protracted critical illness [36,37]. Upon recovery, normal responses are seen, indicating the reversibility of this phenomenon.

Metabolically, there is a delay and suppression of anabolic processes, resulting in typical features of prolonged critical care cachexia, including breakdown of muscle tissue, loss of lean body mass, polyneuropathy, generalized tissue wasting, and dystrophy [38–41]. These changes resemble the features of Cushing's syndrome, in which a subtle (ie, average cortisol production rate of 36 mg/d) and prolonged (ie, months to years) corticoid excess leads to severe morbidity and, if left untreated, to a mortality rate of more than 50% within 5 years [42].

Dehydroepiandrosterone sulfate (DHEAS) is the most abundant adrenal steroid in the human circulation. The adrenals secrete DHEA and DHEAS, but only DHEA is considered biologically active, mediating its action mainly indirectly via downstream conversion to sex steroids and intermediate steroids with potentially distinct properties (Fig. 1) [43]. The conversion of DHEA sulfotransferase (SULT2A1) is the rate-limiting step regulating the equilibrium between DHEA and DHEAS [44]. SULT2A1 is downregulated in sepsis [45], which suggests that circulating DHEAS levels may not appropriately reflect the biologically active DHEA pool. DHEA administration showed beneficial effects on experimental induced sepsis in rodents [46–51]. Serum cortisol is increased while DHEAS is decreased in septic shock and trauma patients, especially if moribund [52,53]; however, when compared with the level in healthy controls, DHEA is significantly increased in sepsis but decreased after trauma. Most severely ill patients have higher cortisol and lower DHEA and a significantly higher cortisol to DHEA ratio. Similarly, the cortisol to DHEA ratio is significantly increased in nonsurvivors of septic shock whereas the ratio in survivors does not differ from that in controls [52]. In another study [54], lowered DHEAS and androstenedione levels could be measured in chronically ill males but not in ill females. 17α-OH-progesterone and 17α-OH-pregnenolone levels in subgroups of the patients suggested a probable enzymatic block in the δ-5-pathway of androgen biosynthesis in severe illness.

These findings have been interpreted as a shift from adrenal androgen toward glucocorticoid biosynthesis. Accordingly, acute and sustained hypogonadism in both sexes is virtually always observed during any critical illness [55,56]. This constellation suggests a stress-induced intra-adrenal shift of pregnenolone metabolism away from the mineralocorticoid and adrenal androgen pathway toward the glucocorticoid pathway, indicating a resetting between the immunostimulatory (DHEA) and immunosuppressive (cortisol) adrenocortical hormones [1,53,57,58]. This mechanism may ultimately also fail, as indicated by the 20-fold higher incidence of adrenal insufficiency seen in critically ill patients over the age of 50 years who had been treated in the intensive care unit for more than 14 days [59].

The question of a normal or abnormal response

Increased circulating cortisol levels seem to reflect an increasing severity of illness (Fig. 2) [60,61], and mortality associated with untreated adrenal insufficiency increases with the severity of the acute stress [62]. Similarly, peri- and postoperative basal cortisol concentrations reflect the degree of surgical stress [63,64]. Peak cortisol levels are achieved in the immediate postoperative period, around the time of extubation [65,66]. Cortisol levels after major surgery resemble the levels during the acute phase of septic shock [60,67,68]. Although in the acute phase of critical illness, the secretory activity of the HPA axis is essentially maintained or augmented, it starts to diminish during the chronic phase, that is, after a few weeks of protracted critical illness [60,69]. Nonsurvivors of sepsis and patients with relative adrenal insufficiency had the lowest DHEAS values, suggesting that DHEAS might be a prognostic marker and a sign of exhausted adrenal reserve in critical illness [53]. During severe illness, co-morbidities such as head injury or adrenal hemorrhage, pharmacologic agents (eg, etomidate, opioids, ketokonazole), or inflammatory mediators (eg, tumor necrosis factor-α, interleukins) can impair the proper stress response of the HPA axis [70]. The interindividual range of measured serum cortisol in a given stress situation is wide [71,72]. The characteristics and extent of the HPA response also vary in different age

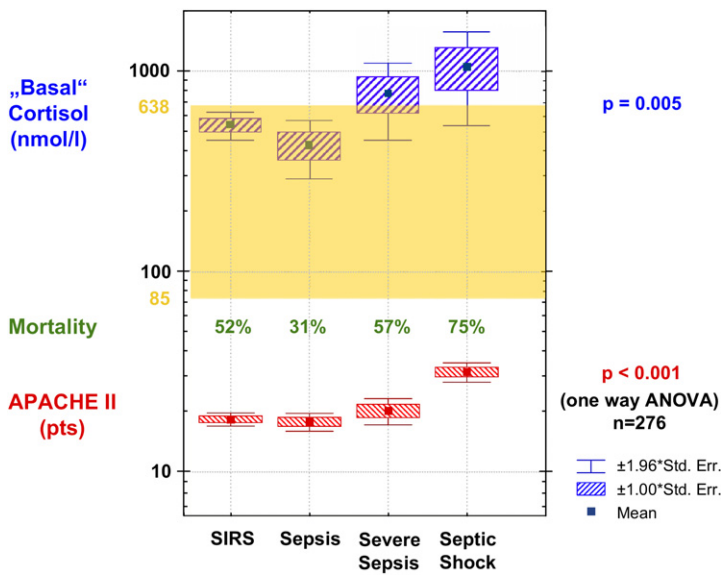

Fig. 2. Circulating cortisol levels in different severities of disease and infection. ANOVA, analysis of variance; APACHE II, acute physiologic and chronic health evaluation II score; SIRS, systemic inflammatory response syndrome. (*Data from* Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 2000;28(4):977–83.)

groups, namely, in children [73]. This dispersion of results complicates the differentiation of a normal from an abnormal adrenal response in the course of acute illness. In addition, critical illness can alter and impair the proper stress response of the HPA axis [70].

The terms *relative* or *functional* adrenal insufficiency have been proposed for hypotensive septic critically ill patients who show hemodynamic improvement upon cortisol administration. In these patients, the cortisol levels, despite being within the normal reference range or even elevated, are still considered inadequate for the severity of stress, and the patient may be unable to respond to any additional or protracted stress [70].

Corticosteroid insufficiency is difficult to discern clinically and must be actively sought by the treating physician. There are no clinical indicators (eg, eosinophilia, vasopressor dependence, or hemodynamic response) with proven diagnostic accuracy, partly because of a lack of a reference standard [74,75]. The life-threatening dangers of stress in untreated absolute adrenal insufficiency are undisputable. In contrast, there is a debate concerning the definition of relative adrenal insufficiency, its treatment, and the identification of patients at risk [1,70,74,76,77].

A simple and widely used test is the stimulation of cortisol with injection of synthetic ACTH (Synacthen) in hypotensive critically ill patients. A basal level of cortisol of greater than 935 nmol/L combined with an increase (Δ) of cortisol less than 250 nmol/L (9 μg/dL) after stimulation with 250 μg of ACTH has been associated with a mortality rate of 80%, arguably pointing to a relative adrenal insufficiency [60]. Nevertheless, circulating ACTH levels after a standard injection of 250 μg of ACTH are extremely high (10,00–60,000 pg/mL) and much higher than the 100 to 300 pg/mL found after stimulation with 1 μg of synthetic ACTH [68,74,78]. Because the 250-μg ACTH stimulation test induces supraphysiologic ACTH concentrations, the 1-μg synthetic ACTH test has been suggested to be more sensitive to diagnose adrenocortical insufficiency [79]. In healthy individuals, 1 μg is the lowest ACTH dose to cause a maximal cortisol response, and there is no diurnal variation of cortisol response to submaximal ACTH stimulation [79]. There is a stress-dependent dissociation of the cortisol response to increasing doses of synthetic ACTH in situations of stress, as shown during strong surgical stress (Fig. 3) [61]. Accordingly, in stressed patients without HPA disease, cortisol concentrations are higher after stimulation with 250 μg as compared with 1 μg of ACTH. The adrenal reserve is not completely used and is not the limiting organ in this model of strong surgical stress.

What is really measured with adrenal stimulation tests [74,80]? Is an additional rise in cortisol upon ACTH stimulation of any clinical significance, namely, the arguably decisive increment (Δ) in serum cortisol concentration of 250 nM (9 μg/dL) from baseline [81]? In the study by Widmer and coworkers, approximately 40% of surgical patients did not achieve this target change in cortisol, yet none of them sustained any adverse clinical consequences from severe surgical stress without glucocorticoid substitution

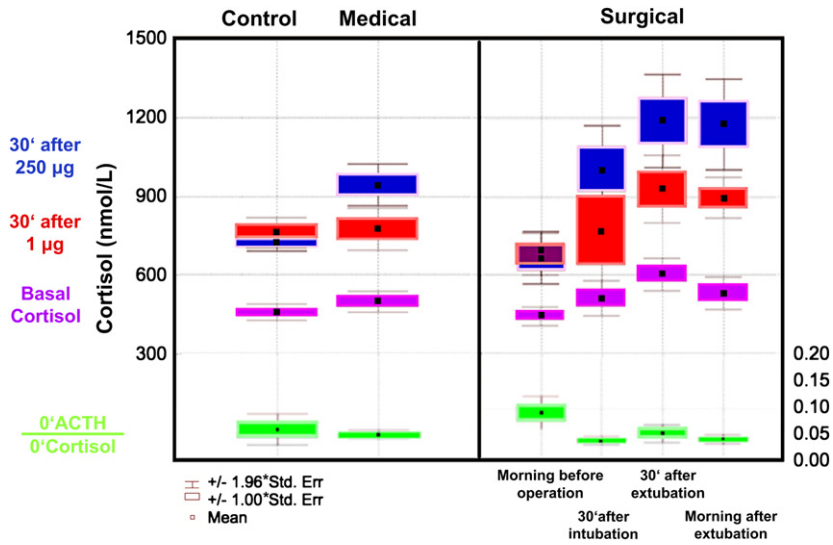

Fig. 3. Variable cortisol response to ACTH. Squares denote mean; boxes denote ± standard error of the mean; and whiskers denote ± 1.96 × standard error of the mean. For subjects in Group A and B, the mean values of each subject over all 4 days is shown. In Group C, basal and peak cortisol concentrations increased, whereas the basal ACTH levels and basal ACTH/basal cortisol ratio decreased during the operation (all $P \leq .001$). Overview shows the basal (purple) and peak cortisol concentrations after stimulation with 1 µg (red) and 250 µg (blue) of ACTH in subjects in Group A, B, and C. Basal ($P < .00001$ for trend) and peak cortisol (after 1 µg ACTH: $P = .07$; after 250 µg ACTH: $P = .02$) concentrations increased in the three stress groups (A, B, C3). To convert cortisol from nmol/L into µg/dL, divide by 27.7. (*Adapted from* Widmer IE, Puder JJ, Konig C, et al. Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab 2005;90(8):4582.)

[61]. Indeed, in the setting of severe illness and stress, the use of the low-dose (1-µg) ACTH stimulation test may increase the number of overdiagnosed patients [82,83]. Because of the circadian rhythm in healthy individuals, basal cortisol levels are lower in the evening than in the morning, yet the stimulated cortisol levels will be similar. This observation is true regardless of whether the stimulation is performed by using ACTH [84], insulin hypoglycemia [85], metyrapone [86], or CRH [87]; therefore, the incremental rise (Δ) of cortisol is inherently negatively correlated with basal cortisol levels and not a useful parameter. Furthermore, the interindividual variability of different cortisol and other steroid hormone assays performed at different sites can be substantial [29]. This variability calls for a complete rethinking of the term *relative adrenal insufficiency* [80].

Treatment

Whether "iatrogenic" hypercortisolism during critical illness is truly needed and beneficial remains uncertain. Even a continuous, intended-to-be-physiologic

"low-dose" infusion of hydrocortisone results in several fold higher levels (up to 3000–5000 nM) as compared with maximal endogenous hypercortisolism reached during the severest near-death stress in patients with intact adrenal reserve [88,89]. Concerning the treatment of relative adrenal insufficiency in patients with septic shock, one single large trial found a reduction of mortality; however, this change occurred only post hoc in the subgroup of patients with an impaired rise (Δ) of cortisol less than 250 nM (<9 μg/dL) 30 minutes after the injection of 250 μg of synthetic ACTH [81]. Previously published criteria for the prognostic characterization of critical illness from the same group were not considered [60]. The large confidence interval of pre- and poststimulation cortisol levels in this study reveals that the patients were heterogeneous and clearly included a sizable number of patients with true "absolute" adrenal insufficiency, potentially skewing the results [90]. Furthermore, in contrast to all other studies, in this trial, oral fludrocortisone was added to the intravenous administration of hydrocortisone [81]. The administration of tablets in critically ill patients may be cumbersome; therefore, fludrocortisone is often omitted in routine intensive care. Unfortunately, as the researchers in this study state, there was "no interest in formally demonstrating a deleterious effect of corticosteroids" [81]. Suggesting thereafter that corticosteroids do not have potential for harm in critically ill septic patients is untenable [91]. Despite these limitations, this study had a landslide impact on the management of critically ill patients by affecting not only patients who had vasopressor-refractory septic shock but also and, albeit, unproven, other "therapy-refractory" intensive care unit patients with milder or even without infections. Possibly, the administration of steroids was so welcomed and became fashionable because the time had come to resurrect past rites (Fig. 4). In the context of such controversy, the premature publication of preliminary data from small underpowered studies in high-impact journals is of little help [92]. Some intensivists argued that a hemodynamic improvement can be observed after the administration of "stress doses" (ie, 50 to 200 mg) of hydrocortisone, justifying its administration to reduce the harmful doses of catecholamines needed to maintain blood pressure. In this context, the question was raised whether one should use hydrocortisone as a therapy to improve the charts or the outcome of patients [93].

Multiple studies were performed by opinion leaders from both sides, not surprisingly yielding opposite conclusions, especially with regard to dosing of the steroids and the interpretations of the change in cortisol after ACTH stimulation [71,74,94–98]. The comparison of different studies in systematic reviews and meta-analyses is inherently problematic, because the patient groups included differ widely in terms of underlying diagnosis (eg, patients sustaining infections, acute lung injury, acute respiratory distress syndrome, burns, malaria, and other entities), inclusion criteria (eg, all consecutive patients versus subgroups of selected patients, different severities of infection ranging from sepsis to severe sepsis to refractory septic shock), and

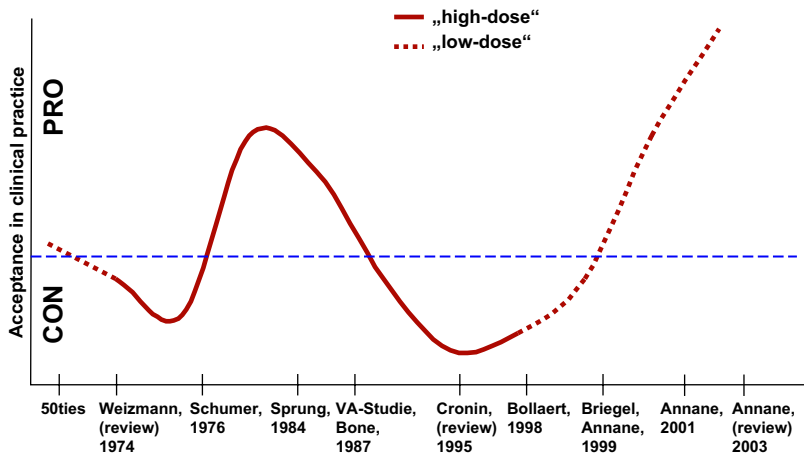

Fig. 4. A historical view of the use of steroids in the treatment of sepsis showing ''ups and downs.'' (*Adapted from* F.M. Brunkhorst, MD, personal communication, 2006.)

the timing of inclusion (on admission, during the early phase of critical illness, and during the course of disease after failing to respond to other supportive interventions such as the administration of fluids and catecholamines). In part, patients were post hoc dichotomized based on an allegedly inadequate response in the ACTH stimulation test [81] or ''basal'' cortisol levels [90]. The remedies tested were diverse and included hydrocortisone [97], methylprednisolone [99], dexamethasone [100], fludrocortisone [81], and even DHEA [101–103] in part combined and among others. The circulating half-life ($T_{1/2}$), biologic effects, and potency of these drugs vary widely. Similarly, the correlation between a given circulating $T_{1/2}$ of a glucocorticoid and its duration of action is poor [21]. Dosages applied in critically ill patients ranged from so-called ''supraphysiological'' [97] to ''low-dose'' [81] to ''high dose'' [99,100]. The use of these terms is not validated given the fact that one is unable to determine and monitor the true needs for a given individual with a specific critical disease at a certain time point. All of the different steroids administered have markedly distinct biologic effects, which is self-evident based on their variable structure (see Fig. 1). Subtle differences in the biochemistry of steroid hormones can alter the biologic response dramatically. For example, the only difference between the ''male'' hormone testosterone and the ''female'' hormone estradiol (see Fig. 1) is the interchangeable oxidation of a hydroxyl side group. Nevertheless, phenotypic differences between both sexes can be impressive. In this context, the differences between the steroids used therapeutically in critical illness, including but not limited to glucocorticoids and mineralocorticoids, are even more important and should not be neglected.

Upon cessation, any short or long-term exposure to ''supraphysiological'' glucocorticoid dosages will expose the patient subsequently to the risk of

"absolute" insufficiency of the HPA axis, that is, Addison's syndrome. This iatrogenic complication can be life threatening in stress situations (eg, recurrence of the critical illness). Rapid restoration of ACTH release with CRH infusion suggests that the suppression of the HPA axis after iatrogenic hypercortisolism is predominantly due to reduced CRH secretion [104]. The extent and duration of this functional deficiency is unpredictable, may last from weeks to years, and is largely independent of the dose and duration of steroid therapy [105,106]. This observation has led to the conservative practice of replacing glucocorticoid before an anticipated stress in any patient who has received supraphysiologic dosages of glucocorticoids within the past year [22,107].

There is little definitive advice to offer concerning the use of pharmacologic doses of glucocorticoids in critical illness in general, especially in critically ill patients who do not meet the criteria for "relative adrenal insufficiency." The alleged benefits should be weighed against the proven dangers of therapy, such as hyperglycemia [108,109] and a suppression of the immune response [96,99,110–112]. In comatose patients with cerebral malaria, high-dose dexamethasone treatment has been proven deleterious [113]. The ebb and flow of attitudes regarding the usefulness of large-dose steroid treatment in spinal cord injured patients, also referred to as "CRASH-landing of steroids" based on the acronym of a seminal study, is a case in point [114–116]. The clinical frustrations of dealing with severe sepsis and its high mortality rate may tempt many clinicians to use corticosteroids; however, our urge to do something should not tempt us to do anything. Adhering to the results of current randomized controlled trials is the best guide to clinical practice. More rigorously controlled multicenter studies are required to further clarify this complex clinical enigma. The results of one such trial, the ongoing CORTICUS study, are anxiously awaited by intensivists [117].

Summary

The interindividual differences in the extent, timing, and modulators of the HPA response during distinct critical illnesses are not trivial. The correct assessment of the adequate individual stress response in severe disease is unresolved. The accurate substitution of the subtle and varying needs of an allegedly disturbed HPA axis is problematic. If we do not learn from previous mistakes regarding the characterization, interpretation, substitution, and suppression of allegedly abnormal endocrine responses in severe and acute diseases, we will continue to repeat them [118,119]. Inappropriate assumptions will lead to inappropriate administrations of potentially life-saving steroids and, ultimately, contradict our principal aim in medicine of "primum non nocere." Further randomized controlled trials are needed to unravel this complex and important clinical problem before widespread therapy can be advocated.

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