Chapter 39
Adrenal Insufficiency

The stress system receives and integrates a diversity of cognitive, emotional, neuro-sensory and peripheral somatic signals that are directed to the central nervous system through distinct pathways. The stress response is normally adaptive and time limited and improves the chances of the individual for survival. The stress response is mediated largely by activation of the hypothalamic-pituitary-adrenal (HPA) axis with the release of cortisol. In general, there is a graded cortisol response to the degree of stress, such as the type of surgery. Cortisol levels also correlate with the severity of injury, the Glasgow Coma Scale and the APACHE score. Cortisol effects the transcription of thousands of genes in every cell of the body. In addition, the cortisol-glucocorticoid receptor complex effects cellular function by non-transcriptional mechanisms. Cortisol has several important physiologic actions on metabolism, cardiovascular function and the immune system. Cortisol increase the synthesis of catecholamines and catecholamine receptors which is partially responsible for its positive inotropic effects. In addition, cortisol has potent anti-inflammatory actions including the reduction in number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils and eosinophils at sites of inflammation. Cortisol is the most important inhibitor of the transcription of pro-inflammatory mediators (inhibits NF-kB and AP-1 by multiple mechanisms) [1].

There is increasing evidence that in many critically ill patients activation of the HPA axis and the release of cortisol is impaired. The reported incidence varies widely (0–77 %) depending upon the population of patients studied and the diagnostic criteria used to diagnose adrenal insufficiency (AI) [2]. However, the overall incidence of adrenal insufficiency in critically ill medical patients approximates 10–20 %, with an incidence as high as 60 % in patients with septic shock [2]. The major sequela of adrenal insufficiency in the critically ill is on the systemic inflammatory response (excessive inflammation) and cardiovascular function (hypotension).

Until recently the exaggerated pro-inflammatory response that characterizes patients with systemic inflammation has focused on suppression of the HPA axis and "adrenal failure." However, experimental and clinical data suggest that

corticosteroid tissue resistance may also play an important role. This complex syndrome is referred to as "*Critical Illness Related Corticosteroid Insufficiency* (CIRCI)" [1, 3]. CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patients illness; i.e. CIRCI may be due to acute adrenal insufficiency, corticosteroid tissue resistance or both. The mechanisms leading to dysfunction of the HPA axis and tissue glucocorticoid resistance during critical illness are complex and poorly understood [1]. CIRCI manifests with insufficient corticosteroid mediated downregulation of inflammatory transcription factors.

CIRCI is most common in patients with severe sepsis (septic shock) and patients with ARDS. In addition, patients with liver disease have a high incidence of AI (Hepato-adrenal syndrome). CIRCI should also be considered in patients with pancreatitis. A subset of patients may suffer structural damage to the adrenal gland from either hemorrhage or infarction and this may result in long term adrenal dysfunction. Furthermore, a number of drugs are associated with adrenal failure. However, most patients with AI (and CIRCI) develop reversible dysfunction of the HPA system; this is probably initiated by inflammatory mediators, may be self-perpetuating and follows the same time course of the immune deregulation in patients with sepsis and SIRS [1].

Causes of Adrenal Insufficient/Circi

Reversible Dysfunction of HPA Axis

- Sepsis/SIRS
- Pancreatitis
- Drugs
  - *Etomidate* (primary AI)
  - Corticosteroids (secondary AI)
  - Ketoconazole (primary AI)
  - Megesterol acetate (Secondary AI)
  - Rifampin (increased cortisol metabolism)
  - Phenytoin (increased cortisol metabolism)
  - Metyrapone (primary AI)
  - Mitotane (primary AI)
  - Hypothermia

Primary Adrenal Insufficiency

- Autoimmune adrenalitis
- HIV infection
  - HART therapy
  - HIV virus
  - CMV

- Metastatic carcinoma
  - Lung
  - Breast
  - Kidney
- Systemic fungal infection
  - Histoplasmosis
  - Cryptococcus
  - Blastomycosis
- Tuberculosis
- Adrenal hemorrhage/infarction
  - DIC
  - Meningococcemia
  - Anticoagulation
  - Anti-phospholipid syndrome
  - HIT
  - Trauma

Glucocorticoid Tissue Resistance

- Sepsis
- SIRS
  - ARDS
  - Trauma
  - Burns
  - Pancreatitis
  - Liver failure
  - Post cardiac surgery
  - HELLP syndrome

Clinical Features of Adrenal Insufficiency/Circi

Patients with chronic adrenal insufficiency (Addison's disease) usually present with:

- weakness
- weight loss
- anorexia and lethargy
- nausea, vomiting and abdominal pain

Clinical signs include:

- orthostatic hypotension
- hyperpigmentation (primary adrenal insufficiency)

Laboratory testing may demonstrate:

- hyponatremia
- hyperkalemia
- hypoglycemia
- normocytic anemia

This presentation contrasts with the features of CIRCI. The clinical manifestations of CIRCI are consequent upon an exaggerated pro-inflammatory immune response and include:

- ○ Hypotension refractory to fluids and requiring vasopressors is a common manifestation of CIRCI. CIRCI should therefore be considered in all ICU patients requiring vasopressor support
- ○ An excessive systemic inflammatory response
    - – ALI/ARDS
    - – Trauma
    - – Burns
    - – Pancreatitis
    - – Liver failure
    - – Post cardiac surgery
    - – HELLP syndrome

Laboratory assessment may demonstrate:

- ○ eosinophilia
- ○ hypoglycemia
- ○ hyponatremia and hyperkalemia are uncommon

Diagnosis of Adrenal Insufficiency/Circi

At the current time there are no clinically useful tests to assess the cellular actions of cortisol; the accurate clinical diagnosis of CIRCI therefore remains somewhat elusive. Furthermore, while the diagnosis of AI in the critically ill is fraught with difficulties, at this time this diagnosis is best made by [1]:

- a random (stress) cortisol of less than 10 µg/dL or
- a delta cortisol of less than 9 µg/dL after a 250 µg ACTH stimulation test.

From a mechanistic and practical standpoint it may be useful to divide CIRCI into two subgroups, namely [4]:

Type I: Characterized by a random (stress) cortisol < 10 µg/dL.

Type II. Characterized by a random cortisol ≥ 10 µg/dL AND a delta cortisol less than 9 µg/dL.

Type II CIRCI is associated with high levels of pro-inflammatory mediators (notably IL-6 and IL-10), high CRP levels and high ACTH levels. These patients may have both ACTH and tissue glucocorticoid resistance [4].

Type I CIRCI is associated with low levels of pro-inflammatory mediators and "normal" stress ACTH levels; these patients may have impaired cortisol production (adrenal insufficiency). Future studies should distinguish between these two subtypes, as this may have prognostic and therapeutic implications.

Factors Affecting the Response to Corticosteroid Treatment

The Immune Status of the Host

The immune status of the host is critical in determining the risk/benefit associated with corticosteroids therapy. Corticosteroids are likely to compound the immuno-paresis in immune-paresed patients increasing the risk of acquired infections. Classic teaching suggests that tissue injury from trauma and surgery results in a systemic inflammatory response syndrome (SIRS) with "unbridled inflammation" which after a few days/weeks evolves into an immuno-paretic phase known as the compensated anti-inflammatory response syndrome (CARS) [5–9]. However, multiple reports over the last two decades have indicated that the proliferative response to T cell mitogens is significantly impaired in patients and experimental animals immediately after traumatic or thermal injury [10–14]. The T-cell dysfunction after traumatic stress is characterized by a decrease in T-cell proliferation, an aberrant cytokine profile, decreased T-cell monocyte interactions and attenuated expression of the T-cell Receptor Complex (TCR). Furthermore, surgical stress induces a shift in the T-helper (Th)1/Th2 balance resulting in impaired cell mediated immunity [15–17]. While the Th1 cytokines may be increased following trauma and surgery, these cytokines do not reach the levels seen in patients with sepsis and unlike patients with sepsis, the Th2 response predominates. As corticosteroids are likely to compound the immuno-paresis following trauma and stress these agents are probably best avoided in the surgical patient who becomes septic. This hypothesis is supported by the failure of corticosteroids to improve outcome in the *Corticosteroid Therapy of Septic Shock Study* (CORTICUS) study where the majority of patients were surgical patients [18]. It would therefore appear illogical to give septic post-surgical patient corticosteroids as this is only likely to compound the immunosuppressive state and increase the risk of secondary infections (which is exactly what the CORTISUS study demonstrated). Furthermore, it should be noted that the incidence of CIRCI is very low in surgical/trauma patients. In a 5 year retrospective study of 2,100 trauma patients admitted to an ICU the incidence of CIRCI was only 3.3 % [19]. Similarly, in an analysis of 1,795 intubated trauma patients, 82 (4.5 %) were diagnosed with adrenal insufficiency [20]. Fann and colleagues performed statistical modeling to predict adrenal insufficiency in trauma patients [21]. In this study 3.3 % of patients admitted to the ICU were diagnosed with adrenal insufficiency.

Boomer and colleagues performed cytokine secretion assays and immunophenotyping of cell surface receptor-ligand expression profiles from postmortem spleen and lung tissue samples from 40 patients who died from sepsis and 29 brain-dead

controls [22]. In this study, patients who died in the ICU following sepsis compared with patients who died of non-sepsis etiologies had biochemical, flow cytometric, and immunohistochemical findings consistent with severe immunosuppression. In patients with sepsis, the initial pro-inflammatory response is followed by three distinct clinical pathways, namely i) homeostasis is restored with return to a "normal immune status" ii) patients may develop a prolonged a pro-inflammatory response with ongoing tissue injury iii) while other patients may progress to a state of immuno-suppression (CARS). It is important for clinicians to be able to accurately determine the patients' immune status before instituting immunomodulating interventions. It is likely that patients who receive corticosteroids late in the course of their disease and have progressed to CARS will suffer adverse sequela from such therapy (see timing below). Future research in sepsis will need to focus on developing tools that can dynamically and in real-time characterize the patient's immune response to allow targeted immune therapy.

Timing of Corticosteroids

Since steroids enhance local immune defences but reduce global NF-kappa B expression and cause a predominant TH2 immunosuppressive state, steroids are likely to be beneficial early in the course of the disease but likely to compound the immunosuppression when given later in the course of sepsis. The time dependent initiation of the use of corticosteroids has not been taken into consideration in those studies (and meta-analyses) which have analyzed the benefits/risk of steroids in sepsis. In the study by Annane et al., the window for enrollment into the study was initially 3 h and then it was increased to 8 h [23]. In the CORTICUS study, the initial time frame of 24 h, increased to 72 h [18]. This time dependent effect was demonstrated by Park et al. who in a retrospective analysis of 178 patients with septic shock found that corticosteroids were only of benefit if given within 6 h after the onset of septic shock-related hypotension [24]. Similarly, Katsenos et al. demonstrated that in patients receiving hydrocortisone for septic shock initiation of therapy within 9 h was associated with improved survival [25]. Furthermore, ex-vivo mononuclear stimulation studies demonstrated attenuated TNF-α release only in those patients who received early corticosteroid therapy.

Dose and Dosing Strategy

The effect of glucocorticoids on immune suppression is critically dose dependent. It is well know from the organ transplant experience that high-dose corticosteroids effectively abolish T-cell mediated immune responsiveness and are very effective in preventing/treating graft rejection. However, while stress-doses of corticosteroids inhibit systemic inflammation with decreased transcription of pro-inflammatory

mediators, they maintain innate and acquired immune responsiveness and do not increase the risk of secondary infections [26–28]. Lim et al. demonstrated that the effect of corticosteroids on macrophage function was dose dependent [29]. Low doses enhanced macrophage function whereas high doses strongly depressed macrophage function.

It is important to recognize that patients with ARDS and many with sepsis have prolonged immune dysregulation requiring a more prolonged course of therapy [30]. Two longitudinal studies in patients with severe community acquired pneumonia found high levels of circulating inflammatory cytokines 3 weeks after clinical resolution of sepsis [31, 32]. Trials from the 1980s which investigated short-term (24–48 h) massive glucocorticoid doses (up to 40,000 mg/hydrocortisone eq./day) were associated with an increased risk of side effects, and no clear outcomes benefit [33, 34]. Recent studies, which investigated the use of low dose (stress dose) corticosteroids given over a more prolonged period have shown clinical benefit in terms of reduction in mortality with an increase in pressor free, ventilator free and ICU free days [33, 34].

Acute Rebound After Discontinuation of Corticosteroids

Corticosteroids should never be stopped abruptly; this will lead to a "rebound" of inflammatory mediators with an increased likelihood of hypotension and/or rebound inflammation (lung injury). There is ample evidence that early removal of glucocorticoid treatment may lead to rebound inflammation and an exaggerated cytokine response to endotoxin [26, 35–42]. Experimental work has shown that short-term exposure of alveolar macrophages or animals to dexamethasone is followed by enhanced inflammatory cytokine response to endotoxin [43, 44]. Similarly, normal human subjects pretreated with hydrocortisone had significantly higher TNF-α and IL-6 response after endotoxin challenge compared to controls [45]. Two potential mechanisms may explain rebound inflammation: homologous down-regulation and GC-induced adrenal insufficiency. Glucocorticoid treatment down-regulates the GR levels in most cell types, thereby decreasing the efficacy of the treatment [46]. Down-regulation takes place at both the transcriptional and translational level, and hormone treatment decreases receptor half-life by approximately 50 % [46]. In experimental animals, overexpression of GRs improves resistance to endotoxin-mediated septic shock while GR blockade increases mortality [47].

Genetic Polymorphisms

Not all patients with sepsis/ARDS treated with corticosteroids respond to this treatment. Genetic polymorphisms of a number of genes may explain this finding. Gessner demonstrated that hydrocortisone failed to abolish NF-κB protein nuclear

translocation in deletion allele carriers of the NFKB promoter polymorphism (-94ins/delATTG) [48]. In addition, these authors demonstrated that patients with this polymorphism receiving hydrocortisone had a much greater 30-day-mortality (57.6 %) than the other genotypes (24.4 %; HR: 3.18, 95 % CI: 1.61–6.28; p=0.001). It is likely that other polymorphisms including those of the glucocorticoid receptor (GR) may influence the clinical response to glucocorticoids [49].

Abnormalities of the Glucocorticoid Receptor

Deceased concentration or abnormal function of the GR may underlie the observation of variability of cortisol sensitivity amongst patients. Cortisol diffuses rapidly across cell membranes binding to the GR. Two isoforms of the GR have been isolated, namely GR-α and GR-β. The GR-β isoform fails to bind cortisol and activate gene expression and thus functions as a negative inhibitor of GR-α [50]. Through the association and disassociation of chaperone molecules the glucocorticoid-GR-α complex moves into the nucleus where it binds as a homodimer to DNA sequences called glucocorticoid-responsive elements (GRE's) located in the promoter regions of target genes which then activate or repress transcription of the associated genes.

Guerrero et al. demonstrated increased expression of the GR-β isoform in patients with sepsis [51]. In a sheep model of ALI induced by *Escherichia coli* endotoxin, Liu et al. demonstrated decreased nuclear GRα binding capacity [52]. In an *ex vivo* model Meduri and colleagues compared the cytoplasmic to nuclear density of the GR-complex in patients with ARDS who were improvers with those of non-improvers [53]. These authors demonstrated a markedly reduced nuclear density of the GR-complex in non-improvers while the cytoplasmic density was similar between improvers and non-improvers. This study suggests glucocorticoid resistance due to diminished nuclear translocation of the GR-complex. Siebig et al. demonstrated deceased cytosolic receptor levels in critically ill patients as compared to control subjects [54]. Similarly, van den Akker noted that children with sepsis or septic shock had depressed levels of glucocorticoid receptor mRNA in their neutrophils.

Treatment of Adrenal Insufficiency/CIRCI

Who to Treat with Steroids?

Over the last three decades approximately 20 randomized controlled trials (RCTs) have been conducted evaluating the role of glucocorticoids in patients with sepsis, severe sepsis, septic shock and ARDS. Varying doses (37.5–40,000 mg/hydrocortisone

eq./day), dosing strategies (single bolus/repeat boluses/continuous infusion/dose taper) and duration of therapy (1–32 days) were used in these studies [33, 55]. Despite multiple guidelines and over 20 meta-analyses, the use of glucocorticoids in patients with sepsis remains extremely controversial with conflicting recommendations. Furthermore, while there are large geographic variations in the prescription of glucocorticoids for sepsis up to 50 % of ICU patients receive such therapy [56]. Currently a number of large multicenter RCT's are being conducted, which should hopefully resolve this issue. While it is difficult to make strong evidence based recommendations at this time, an evidence based review of the literature allows one to make the following conclusions [57, 58]:

   i. Short-course high-dose glucocorticoids are not beneficial in the treatment of severe sepsis/septic shock and ARDS [34, 59, 60].
  ii. Treatment of septic shock with moderate-dose glucocorticoids for 7 days significantly reduces vasopressor dependency (ACTH responders and non-responders) and ICU length of stay [34, 59, 60].
 iii. Glucocorticoids may reduce mortality in sub-groups of patients with septic shock [34, 59, 60].
  iv. In patients' with progressive early (<72 h) ARDS glucocorticoids significantly increase the number of ventilator, ICU and hospital free days with a reduction in the risk of death [58].
   v. Glucocorticoids appear to be of no benefit in patients with sepsis who are at a low risk of dying and in patients with mild and rapidly resolving ARDS [61].
  vi. Glucocorticoids do not increase the risk of super-infections [34, 59, 60].
 vii. The addition of fludrocortisone does not appear to have additional benefits when treating patients with hydrocortisone [62].
viii. Treatment with glucocorticoids may reduce the risk of post-traumatic stress disorder [63].
  ix. Etomidate causes suppression of cortisol synthesis for up to 24 h [64]. Replacement with glucocorticoids is only recommended in vasopressor dependent septic shock patients [65–67].

Low-dose corticosteroids should be considered in the treatment of patients with septic shock who have responded poorly to fluids and vasopressors (requiring > 0.05–0.1 μg/kg/min of norepinephrine or eq.) and patients with ARDS who show progressive disease after 48 h of supportive care. Adrenal testing is not required in these patients. Additional ICU patients who meet the diagnostic criteria for adrenal insufficiency (as defined above) *and* who have hemodynamic instability or evidence of an excessive inflammatory response should also be treated with corticosteroids (liver failure, pancreatitis, etc.).

Traditionally, patients with sepsis have been treated with hydrocortisone while patients with ARDS have received methylprednisolone. This appears to be rather arbitrary with no scientific data to support this distinction. However, it is likely that different corticosteroids have different binding capacities for the GR isoforms and

hence may have different biological actions. Furthermore, research is underway to develop GR agonists that have more selective biological properties.

The suggested treatment approach is outlined below. In patients' with sepsis and/ or ARDS corticosteroids should never be stopped abruptly; this will lead to a "rebound" of inflammatory mediators with an increased likelihood of hypotension and/or rebound inflammation (lung injury). A continuous infusion of glucocorticoid may be associated with better (smoother) glycemic control [68]. Since blood glucose variability has been demonstrated to have prognostic implications [69, 70], this may be the preferable method of dosing.

- Hydrocortisone 50 mg IV q 6 hourly or 100 mg bolus then 10 mg/h continuous infusion for at least 7 days, and ideally for 10–14 days. Patients should be vasopressor and ventilator "free" before taper
- Hydrocortisone taper
  - Hydrocortisone 50 mg IV q 8 hourly for 2–3
  - Hydrocortisone 50 mg IV/PO q 12 hourly for 2–3 days
  - Hydrocortisone 50 mg IV/PO daily for 2–3 days
  - Re-institution of full dose hydrocortisone with recurrence of shock or worsening oxygenation
- Hydrocortisone and methylprednisolone are considered interchangeable
- Dexamethasone should be avoided; it lacks mineralocorticoid activity. Dexamethasone has a long half-life and suppresses the HPA axis; it should therefore NOT be used pending an ACTH stimulation test.

Adverse Effects of Corticosteroids

The complications associated with the use of corticosteroids are dependent upon the dose, the dosing strategy and the duration of therapy. In the ICU setting the most important complications include immune suppression, hyperglycemia and HPA axis and GR suppression. Both glucocorticoids and TNF-α stimulate muscle catabolism (reviewed in Chap. 32). Since glucocorticoids are potent inhibitors of TNF-α it is likely that corticosteroids may limit muscle breakdown during acute illness. This postulate is supported by the fact that patients with ARDS treated with glucocorticoids have significantly increased ventilator free days. In the CORTICUS study neuromuscular weakness was very rarely reported [18]. While myopathy is common in patients treated with high-dose corticosteroids this complication is uncommon with stress dose corticosteroids [33, 55]. Similarly, while high dose corticosteroids may impair wound healing this complication does not occur with stress dose corticosteroids. Schreiber et al. reported that the use of corticosteroids in ICU patients was associated with an increased risk of delirium [71]. In this study the authors were unable to establish a relationship between the dose of corticosteroid and the risk of delirium.

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