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Adrenal Insufficiency and CIRCI

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory, 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 physiological actions on metabolism, cardiovascular function, and the immune system. Cortisol increases the synthesis of catecholamines and catecholamine receptors, which are 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-κB 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 are 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

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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 the cardiovascular function (hypotension).

Until recently, the exaggerated pro-inflammatory response that characterizes patients with systemic inflammation has focused on the 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 patient's 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 (hepatoadrenal syndrome). CIRCI should also be considered in patients with pancreatitis. A subset of critically ill 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 INSUFFICIENCY/CIRCI

Reversible Dysfunction of HPA Axis

- Sepsis/SIRS
- Pancreatitis
- Drugs
  - Corticosteroids (secondary AI)
  - Ketoconazole (primary AI)
  - *Etomidate* (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
  - Anti-coagulation
  - Anti-phospholipid syndrome
  - HIT
  - Trauma

Glucocorticoid Tissue Resistance

- Sepsis
- SIRS
  - ARDS
  - Trauma
  - Burns
  - Pancreatitis
  - Liver failure
  - Postcardiac surgery
  - HELLP syndrome (see Chapter 54)

■ CLINICAL FEATURES OF ADRENAL INSUFFICIENCY/CIRCI

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

- Weakness
- Weight loss

- Anorexia and lethargy
- Nausea, vomiting, and abdominal pain

Clinical signs include the following:

- Orthostatic hypotension
- Hyperpigmentation (primary adrenal insufficiency).

Laboratory testing may demonstrate the following:

- 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 the following:

- 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.
  - Postcardiac surgery.
  - HELLP syndrome (see Chapter 54).

Laboratory assessment may demonstrate the following:

- 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[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 typically 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.

■ TREATMENT OF ADRENAL INSUFFICIENCY/CIRCI

Who to Treat with Steroids?

The use of stress doses of corticosteroids (200–300 mg hydrocortisone/day) in critically ill ICU patients is controversial with little consensus in the literature. Hopefully, ongoing clinical trial will help resolve this issue. However, 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 equivalent) and patients with ARDS who show progressive disease after 48 h of supportive care. Adrenal testing is not required in these patients. Two recent meta-analyses support the use of low-dose (stress doses) corticosteroids in these patients with a very favorable risk/benefit profile.[5,6] Additional ICU patients who meet the diagnostic criteria for CIRCI (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.). Corticosteroids have also proven beneficial in patients with the HELLP syndrome (see Chapter 54) and in preventing atrial fibrillation (and limiting SIRS) in patients undergoing cardiopulmonary bypass surgery.[1]

The suggested treatment approach is outlined below. 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.[7] Since blood glucose variability has been demonstrated to have prognostic implications,[8,9] a continuous infusion of a glucocorticoid may have additional benefits.

■ MEDICATION (DRUGS) FOR ADRENAL INSUFFICIENCY/CIRCI

- Hydrocortisone 50 mg IV q 6 h or a 100 mg bolus followed by a continuous infusion at 10 mg/hr 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 h for 3–4 days.
  - Hydrocortisone 50 mg IV/PO q 12 h for 3–4 days.
  - Hydrocortisone 50 mg IV/p.o. daily for 3–4 days.
  - Reinstitution 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.

■ ADDITIONAL TREATMENT

General Measures

- Active infection surveillance is required in all patients receiving corticosteroids with a low threshold for performing blood cultures, mini-BAL, and other appropriate cultures.
- Blood glucose should be monitored closely and hyperglycemia managed by reducing the glycemic load and treating with insulin as appropriate.
- Clinicians should monitor CPKs and muscle strength and avoid neuromuscular blocking agents (at all costs).

■ CLINICAL PEARLS

- CIRCI is best defined as inadequate cellular corticosteroid activity for the severity of the patient's illness; this includes AI, glucocorticoid tissue resistance, or both.
- Consider treatment with corticosteroids in patients with septic shock, ARDS, and patients with hemodynamic instability as well as patients with pancreatitis, liver failure, and HELLP syndrome.
- Hydrocortisone in a dose of 200 mg daily (50 mg q 6 h or as a continuous infusion at 10 mg/h) is suggested.
- Monitor response to corticosteroids and taper the drug slowly.

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