CHAPTER 8.

Critical illness related corticosteroid insufficiency

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Critical illness related corticosteroid insufficiency (CIRCI)

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Introduction

Relative adrenal insufficiency (RAI) or critical illness related corticosteroid insufficiency (CIRCI) is a common phenomenon in the critically ill patient, predominantly in the course of septic shock. Critical illness is often accompanied by hypercortisolemia, due to alternative activators of cortisol production such as proinflammatory cytokines and perhaps as well due to reduced cortisol breakdown caused by suppressed expression and activity of cortisol metabolizing enzymes1. However, sometimes this stress response is not enough in patients with adrenal insufficiency. Twenty to 70% of critically ill patients may have RAI/CIRCI, depending on studies and definitions. It is thought to contribute to fluid- and vasopressor-insensitive hypotension and to require adjuvant therapy by 'stress' doses of hydrocortisone. The mechanisms leading to dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis during septic shock are poorly understood and the benefit of corticosteroid treatment is not beyond controversy either[2-5]. Hydrocortisone treatment may increase (or speed) shock reversal by improving vessel wall sensitivity to circulating or exogenously administered vasoactive drugs and thereby promote survival, in high risk patients[2,4]. A substudy from the otherwise negative CORTICUS study points into the same direction (preliminary data). Moreover, too wide application of corticosteroids may be associated with adverse effects, outweighing potential benefits. Therefore tests are sought for that help to identify those patients most likely to benefit.

Definition

Currently, the standard test to evaluate the adrenocortical function is the short adrenocorticotrophic hormone (ACTH) stimulation test: 250 μg of ACTH is given intravenously and serum (total) cortisol is assessed basally and at 30 and 60 minutes after injection.

There may be relatively wide variation among assays and laboratories. The 1 μg ACTH test has not yet been fully validated in the critically ill.

Although criteria vary among studies, RAI/CIRCI is highly likely when the increment in circulating (total) cortisol after ACTH is <100-250 nmol/L (18 μg/dL = 500 nmol/L), regardless of baseline levels, or when baseline cortisol values are relatively low, for the stress involved

(<280-694 nmol/L), both independently of cortisol binding capacity in blood[3-5,7]. According to the literature, these values are most likely to be associated with a haemodynamic and even survival benefits from treatment by 'stress' doses of hydrocortisone. Also, salivary cortisol concentrations, which are simple to obtain and easy to measure, can serve as a surrogate marker for the free cortisol in the circulation[8]. Nevertheless, ACTH testing has not received a high recommendation in the most recent Surviving Sepsis Campaign guidelines[9].

Indications

The criteria to test (by ACTH) and treat patients for RAI/CIRCI (in septic shock) are:

- **Fluid- and vasopressor-insensitive shock of 3-6 hours duration.** RAI/CIRCI may also be associated with non-specific signs and symptoms, including metabolic acidosis, coagulation disturbances, mental disturbances, relative eosinophilia, and fever. Intubation with help of etomidate is also an important risk factor. Etomidate suppresses adrenal cortisol synthesis for 24-72 h, even after a single dose. Awaiting the ACTH test results, hydrocortisone therapy should be started. The hemodynamic responses (or lack of it) to the therapy is noted.

There are some comorbid conditions or causes of septic shock that may particularly benefit from treatment by (non-'stress' dosed) corticosteroids, so that concomitant 'stress' doses of hydrocortisone are unnecessary:

- **Chronic obstructive lung disease (COPD)**, where pharmacological doses may have to be administered to alleviate bronchospasms.
- **Typhoid fever and bacterial meningitis in children and adults.**

Precautions/adverse effects

Corticosteroid therapy may carry adverse effects as hyperglycaemia and immunosuppression. They may increase the risk for infections, including new episodes of sepsis or septic shock and may contribute in inducing or aggravating critical illness polyneuromyopathy.

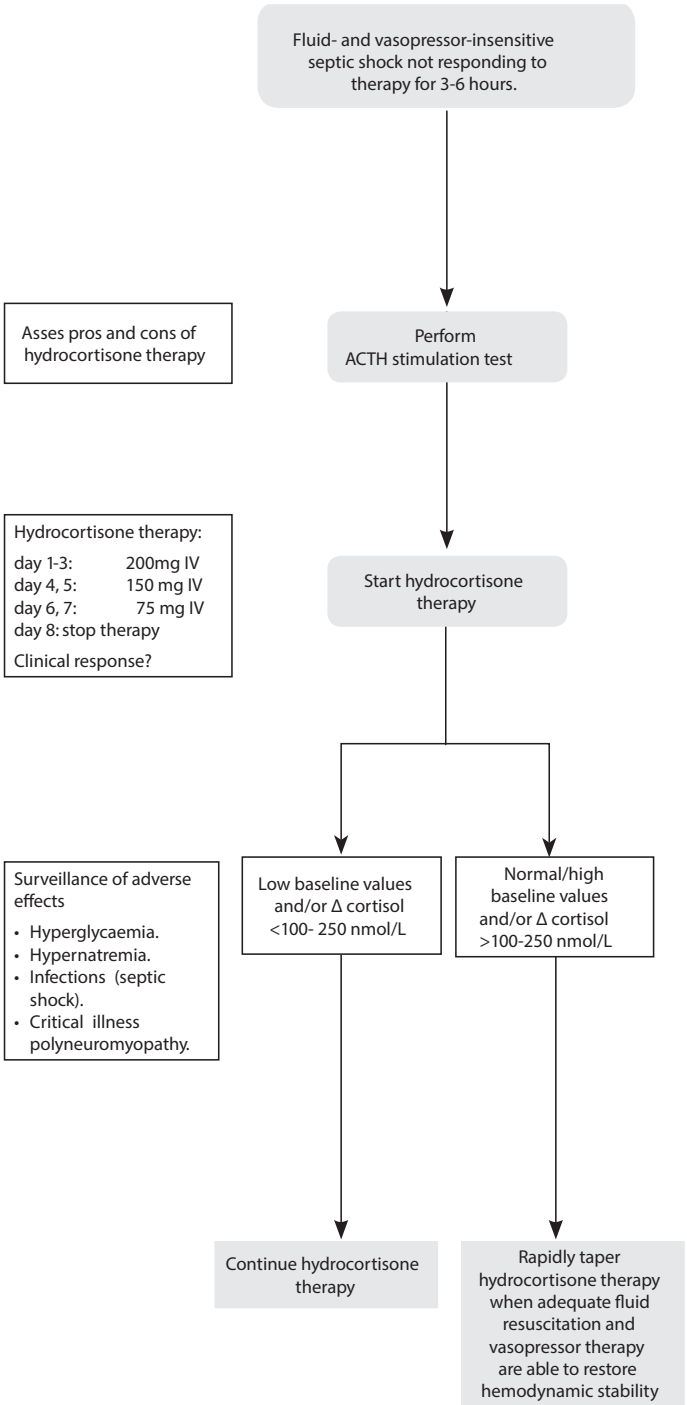
Pros and cons thus include:

PROS	CONS
• More rapid/frequent shock reversal • Mortality benefit in some studies in high risk patients • Effect most pronounced in patients with low cortisol increase upon ACTH, suggesting RAI/CIRCI • Pharmacological doses useful in specific infections • Useful when septic shock is associated with communityacquired pneumonia or acute respiratory distress syndrome • May facilitate weaning from mechanical ventilation	• Diagnostic criteria for RAI/ CIRCI non-uniform and controversial ACTH test results do not always predict effect of corticosteroids • Mortality benefit controversial • Elevated risk for hyperglycemia, new infection and critical illness Polyneuromyopathy

Method/procedure/administration

Hydrocortisone is given intravenously in divided doses thrice daily as a bolus injection, at daily cumulative doses of 200(-300 mg). There is probably no need to add fludrocortisone. Continuous hydrocortisone infusion may help to reduce potential hyperglycemia resulting from the therapy.

When ACTH test results likely point to RAI/CIRCI, therapy is continued for 5-7 days and tapered within days, guided by clinical signs and symptoms. When RAI/CIRCI is unlikely, therapy started can be tapered relatively rapidly, again guided by clinical signs and symptoms (haemodynamics). As a guide for RAI/CIRCI:
day 1-3: 200 mg IV daily
day 4, 5: 150 mg IV daily
day 6, 7: 75 mg IV daily
day 8 discontinue hydrocortisone therapy



ACTH stimulation test = Adrenocorticotropic hormone.

Monitoring

Surveillance of potential adverse effects of corticosteroid therapy is mandatory. These include hyperglycemia, new infections and sepsis, and development (or aggravation) of critical illness polyneuromyopathy. Vasopressor needs and relative eosinophilia typically decrease within hours after start of treatment, particularly in the presence of RAI/ CIRCI.

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