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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

# Adrenal function in critically ill patients: How to test? When to treat?

## ABSTRACT

Although the true incidence of adrenal insufficiency in critically ill patients is unknown, there is evidence that even partial adrenal insufficiency in such patients is associated with increased mortality. But exactly how should adrenal insufficiency be defined and diagnosed, and who should receive treatment?

## KEY POINTS

At present, the random cortisol level and the corticotropin (ACTH) stimulation test are the best diagnostic tools. Normal values are controversial, however.

The serum free cortisol concentration is likely better than the total cortisol concentration as a measure of adrenal insufficiency, particularly in patients with albumin levels lower than 2.5 g/dL. However, since it is not widely available, the typical turn-around time is too long.

I recommend treating patients with random cortisol levels less than 15 μg/dL or stimulated cortisol levels less than 20 μg/dL. The dosage is hydrocortisone 50 mg every 6 to 8 hours, tapered after the patient has improved.

In patients with hypotension not responding to pressors and intravenous fluids but with cortisol levels higher than the above cut-off values, a short trial of a glucocorticoid in stress doses is reasonable. If the patient's hemodynamic status does not improve in 1 to 2 days, such therapy needs to be discontinued.

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AN INTACT hypothalamic-pituitary-adrenal axis is critically important for severely ill patients. For those with adrenal insufficiency, glucocorticoid replacement reduces mortality.

But unwarranted glucocorticoid therapy can lead to poor wound healing, altered immune function (making a patient more susceptible to infection), insulin resistance, and increased bone loss (exacerbated by immobility). Moreover, defining which patients have adrenal insufficiency during stress is not clear-cut.

In this article I review the hypothalamic-pituitary-adrenal axis, the clinical features of adrenal insufficiency during acute illness, and my algorithm for evaluating and managing adrenal insufficiency in critically ill patients.

## THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release corticotropin (ACTH). ACTH in turn stimulates the adrenal gland to secrete cortisol, the predominant glucocorticoid. In a negative feedback loop, increased levels of cortisol in the circulation suppress ACTH and CRH secretion.

Cortisol has a greater effect on tissues during activation of the hypothalamic-pituitary-adrenal axis than at other times, owing to several factors. Critically ill patients have lower levels of cortisol-binding globulin, so that more cortisol is present in its free (unbound) form. Metabolism of cortisol is reduced. In addition, glucocorticoid receptors increase their affinity for cortisol.

### Physiologic effects of cortisol

Cortisol has several physiologic effects:

- It suppresses the function and accumulation of most inflammatory and immune cells.[1]
- It makes more energy available for cells by stimulating hepatic gluconeogenesis, by inhibiting glucose uptake by some peripheral tissues, by promoting release of free fatty acids from adipose tissue, and by promoting release of amino acids from body proteins.[1]
- It helps maintain cardiac contractility, vascular tone, and blood pressure by mediating and enhancing the action of angiotensin II, epinephrine, and norepinephrine.[1,2]
- It may help to prevent excess retention of free water during stress by suppressing antidiuretic hormone, increasing the glomerular filtration rate, and altering vascular permeability and distribution of total body water within the vascular system.[3]

## ADRENAL INSUFFICIENCY IN CRITICALLY ILL PATIENTS

**Even partial adrenal insufficiency may increase the risk of death in ICU patients**

The incidence of adrenal insufficiency in patients in intensive care is difficult to estimate because the population is diverse, and different studies have used different criteria. Although complete adrenal insufficiency is rare in critically ill patients, there is an ongoing debate regarding the prevalence of relative or partial adrenal insufficiency.[4]

Reported incidence rates range widely (0%–77%), with most estimates in the range of 10% to 30% in critically ill patients. Some investigators have suggested rates as high as 50% in patients with septic shock.[1,5,6]

There is evidence that even partial adrenal insufficiency increases the risk of death in critically ill patients. Mortality rates in an intensive care unit at University Hospital of Glasgow in Scotland had been 22% to 29%, but rose to 44% when the short-acting hypnotic drug etomidate was introduced.[7] This drug was subsequently found to inhibit 11-beta hydroxylase, an enzyme in the final step of cortisol synthesis.[8]

### Clinical features of adrenal insufficiency

Clinical features of adrenal insufficiency include:

- Hypotension that is resistant to volume replacement
- Vasopressor dependence
- Eosinophilia (usually mild)
- Hyponatremia
- Metabolic acidosis with hyperkalemia (in primary adrenal insufficiency)
- Hypoglycemia
- Weakness, fatigue, anorexia, weight loss, nausea and vomiting, diarrhea, and unexplained fever
- Hyperpigmented skin (in primary adrenal insufficiency).

**Shock.** Acute adrenal insufficiency can be seen in patients with either hypovolemic shock (decreased preload and myocardial contractility, increased systemic vascular resistance) or hypervolemic shock (high cardiac output, decreased systemic vascular resistance). For this reason it is important to consider adrenal insufficiency in the differential diagnosis of patients presenting with either type of shock.[2] Chronic adrenal insufficiency is associated with decreased systemic vascular resistance and reduced cardiac contractility.

**Eosinophilia** occurs in about 17% of patients with Addison disease and may suggest that a critically ill patient has adrenal insufficiency. The eosinophilia is usually mild. Rivers et al[9] found that postoperative patients with adrenal insufficiency had mean eosinophil counts of 3.5% ± 6.4%, vs 0.9% ± 1.4% in patients with normal adrenal function ($P < 0.05$).

**Lymphocytosis and neutropenia are not good indicators** of adrenal function. Although low glucocorticoid levels lead to sequestering of neutrophils, which may result in neutropenia, there is little evidence to suggest that either lymphocytosis or neutropenia helps in evaluating adrenal function in critically ill patients.

## TESTS OF ADRENAL FUNCTION

Several tests are used to evaluate adrenal function, but not all are appropriate for critically ill patients.

### Random cortisol level

Cortisol's normal diurnal variation is often lost in critically ill patients, so cortisol can be measured at any time during stress.[10] Various

minimum values have been proposed for the diagnosis of adrenal insufficiency, with some evidence to support them; these range from 10 to 34 μg/dL.[1,9,11–13] Many clinicians consider a cortisol level above 18 to 20 μg/dL to be an adequate response to stress.[14]

## The ACTH stimulation test

The ACTH stimulation test has been used for evaluation of adrenal function for the past 40 years. During the standard ACTH stimulation test, cortisol is measured before and then 30 and 60 minutes after cosyntropin (Cortrosyn; ACTH 1-24) 250 μg is given intravenously or intramuscularly. The test can be performed at any time of day with similar maximum cortisol levels.

The test is limited in that it may not detect partial adrenal insufficiency in patients with hypothalamic or pituitary disorders, especially during the first 2 to 4 weeks after an acute event.[15,16] The reason is that the adrenal gland does not atrophy enough in the early weeks after an acute event to affect the test result.

**Low-dose or standard-dose test?** It has long been known that the dose of cosyntropin used in the standard ACTH stimulation test—250 μg—is a large overdose. For this reason and to improve the test's sensitivity in detecting partial secondary or tertiary adrenal insufficiency, Dickstein et al[17] introduced the low-dose ACTH stimulation test, which uses cosyntropin 1 μg intravenously.[17]

Some authors report that the low-dose test is more sensitive in detecting partial adrenal insufficiency in critically ill patients,[1] but others disagree and feel that more research is needed.[11] Some clinicians have raised a concern about the possibility of error in administration in the low-dose test, since a 1-μg cosyntropin vial is not commercially available.

Studies show that the cortisol level at 30 minutes during the standard ACTH stimulation test is similar to the result during the low-dose test.[18] For this reason, I recommend the standard test be used, with a cortisol threshold of 20 μg/dL at 30 minutes.

**"Delta 9" as a cutoff value?** The "delta" value during the ACTH stimulation test is the difference between the baseline and the maximum cortisol value at either 30 or 60 minutes. Annane et al,[19] in a randomized multicenter study, demonstrated that patients with septic shock and a delta value less than 9 μg/dL had a significantly lower mortality rate at 28 days if they received glucocorticoids (hydrocortisone 50 mg every 6 hours and fludrocortisone 50 μg once daily) for 7 days than if they received placebo ($P = .02$).

After this study, many physicians have regarded delta 9 as the cutoff for diagnosing relative or functional adrenal insufficiency in patients with septic shock in an intensive care unit. Many patients are now treated on this basis.

However, the delta value is a measure of adrenal reserve; it does not assess the integrity of the hypothalamic-pituitary-adrenal axis and does not measure adrenal function. To some extent, the delta is directly proportional to the basal cortisol level, and a patient under maximum stress may already be secreting all the cortisol that his or her adrenals can synthesize and therefore will have a small delta value on the ACTH stimulation test.[20]

Nevertheless, until further studies measuring free cortisol are available (see below), a low delta value in some patients with septic shock may indicate that the patient would benefit from glucocorticoid therapy.[19,21,22] The benefit may be due to the effect of glucocorticoids on inflammatory cytokines, which are elevated during septic shock. Some of these cytokines have a direct or indirect effect on the hypothalamic-pituitary-adrenal axis.[23–25] Evidence in support of this comes from some studies that showed benefit from glucocorticoids in physiologic ("stress") doses in patients with septic shock, regardless of their delta value.[26]

**Most cortisol is protein-bound, but only the free form is active**

## Is free cortisol a better test?

More than 90% of circulating cortisol is bound to proteins: about 70% is tightly bound to cortisol-binding globulin (CBG), and about 10% to 20% is loosely bound to albumin. Most experts agree that only free cortisol is biologically active.

We recently compared basal and ACTH-stimulated total cortisol and free cortisol levels in healthy subjects and two groups of critically ill patients who were divided according to

their serum albumin level. Patients with hypoalbuminemia (albumin levels ≤ 2.5 g/dL) had significantly lower basal and stimulated total cortisol levels during the ACTH stimulation test, and nearly 40% of them failed the test (ie, had a stimulated total cortisol level ≤ 18.5 µg/dL). However, the baseline and stimulated *free* cortisol levels were similar in both groups of intensive care unit patients and three to four times higher than in healthy subjects.[27]

The study suggests that, at least in critically ill patients with hypoalbuminemia, total serum cortisol may be a poor indicator of glucocorticoid activity. The clinical utility of free cortisol in evaluation of adrenal function in different subgroups of critically ill patients needs to be studied further.

Serum free cortisol measurement is commercially available, but the typical turnaround time is about 7 to 10 days—too long for a critically ill patient. When it is integrated into clinical practice, measurement of serum free cortisol will likely prevent the treatment of many ill patients with normal adrenal function who meet the criteria for adrenal insufficiency because of hypoalbuminemia. At the same time, it will likely help us to redefine the concept of adrenal insufficiency in critically ill patients.

**A short trial of steroids is reasonable if hypotension does not respond to pressors and IV fluids**

### Other tests

**The metyrapone test and the insulin tolerance test should not be used** to evaluate adrenal function in critically ill patients: the metyrapone test may actually precipitate an adrenal crisis, and the insulin tolerance test is not safe in an intensive care unit setting.

**The CRH stimulation test** bypasses the hypothalamus but requires intact pituitary and adrenal glands for a response. The test has not been adequately studied in critically ill patients and at this point should be used only as part of a research protocol.

## GLUCOCORTICOID TREATMENT IN SEPTIC SHOCK

Glucocorticoid therapy in patients with septic shock continues to be an unresolved subject. Earlier studies using supraphysiologic doses of glucocorticoids (ie, one or two doses of methylprednisolone 30 mg/kg) did not show any benefit in septic shock.[28]

In contrast, in some of the more recent studies, physiologic stress-dose glucocorticoid therapy (ie, hydrocortisone 150–200 mg daily for 5–7 days) has been associated with fewer days of vasopressor support, earlier resolution of organ dysfunction, shorter ventilator time, shorter stay in the intensive care unit, and decreased mortality at 28 days.[19,26,29]

In my opinion, the routine use of glucocorticoids in septic shock has not yet been proven to be effective and safe in all patients. Some of the shortcomings may be related to limitations of serum total cortisol in defining adrenal insufficiency in critically ill patients.

Other critical illnesses in which glucocorticoid treatment has shown to be beneficial include bacterial meningitis and nonresolving acute respiratory distress syndrome.[11]

## AN ALGORITHM FOR EVALUATING ADRENAL FUNCTION

For a patient in the intensive care unit whom I suspect may have adrenal insufficiency, I recommend the following steps (FIGURE 1):

**Perform a standard ACTH stimulation test.** This provides a baseline (random) cortisol level, a 30-minute stimulated cortisol level, and, for those with septic shock, a delta value. If an ACTH stimulation test cannot be done in a reasonable time, then I recommend measuring random cortisol and giving hydrocortisone 100 mg intravenously while waiting for the results.

**If the random cortisol level is 15 µg/dL or greater and the stimulated cortisol is 20 µg/dL or greater,** the patient is unlikely to have adrenal insufficiency. In patients with hypotension not responding to pressors and intravenous fluids but cortisol levels above these cutoff values or those with septic shock and a delta less than 9 µg/dL, a short trial of a glucocorticoid in stress doses is reasonable. If the hemodynamic status does not significantly improve in 1 to 2 days, the therapy should be discontinued.

**If the random cortisol level is less than 15 µg/dL or the stimulated cortisol level is less than 20 µg/dL,** the patient should be started on hydrocortisone 50 mg every 6 to 8

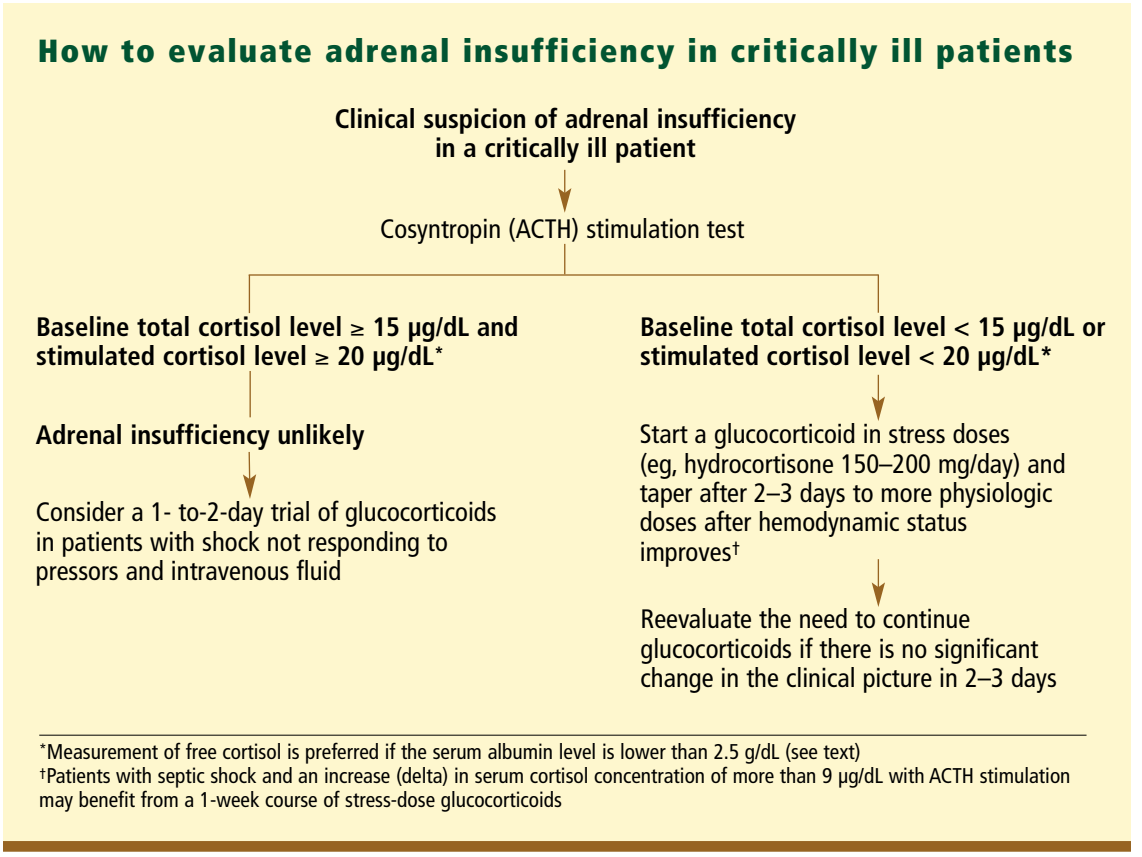


**FIGURE 1**

hours and continued on this as long as his or her hemodynamic status is unstable. The dose of hydrocortisone can be tapered to 25 mg every 8 hours 2 to 3 days after the patient has hemodynamically improved and is off pressors.

Based on our study and while we await future studies, critically ill patients with random free cortisol levels lower than 2.0 µg/dL or stimulated free cortisol levels lower than 3.1 µg/dL should receive glucocorticoid therapy in stress doses.

The need for lifelong glucocorticoid replacement therapy should not be determined on the basis of equivocal biochemical evaluation during critical illness. Such patients should have their adrenal function reevaluated once they are in stable condition and discharged from the intensive care unit.

## FUTURE STUDIES

More study is needed to improve the diagnostic tools for adrenocortical function. There is a need to establish normal ranges for free cortisol during different levels of stress using the Acute Physiology and Chronic Health Evaluation (APACHE) score. It is also necessary to look into controversial issues such as the delta value of the free cortisol level during the ACTH stimulation test in patients with septic shock.

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