

Update in Nonpulmonary Critical Care

Adrenal Insufficiency in Critically Ill Patients

YORAM SHENKER and JAMES B. SKATRUD

William S. Middleton Memorial VA Hospital and Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin

Patients with adrenal insufficiency in the critical care setting may present with a spectrum of disease severity ranging from life-threatening adrenal crisis to mild organ dysfunction. The recognition of adrenal insufficiency is made more difficult in the critically ill patient because of the unavailability of a reliable history, delay in reporting of diagnostic laboratory results, and the comorbidities that obscure a definitive diagnosis. The present discussion will illustrate how the classic presentations of adrenal insufficiency are modified in critically ill patients and how appropriate diagnosis and management can be achieved in the critical care setting.

CLASSICAL PRESENTATIONS OF ADRENAL INSUFFICIENCY

Adrenal insufficiency can be subdivided into three broad categories: (1) Chronic primary adrenal insufficiency, also called Addison's disease, is a result of destruction of the adrenal cortex. The most common causes include autoimmune disease (about 70 to 80%), tuberculosis (about 20%), adrenal hemorrhage, adrenal metastases, and AIDS in association with cytomegalovirus (CMV), other pathogens, or ketoconazole treatment (1). (2) Chronic secondary adrenal insufficiency occurs when insufficient adrenocorticotropic hormone (ACTH) is available to stimulate the adrenal cortex. Most commonly it is due to exogenous glucocorticoid therapy, but it can also be the result of generalized hypopituitarism (usually from pituitary or hypothalamic tumors) or isolated ACTH deficiency (probably autoimmune in nature). (3) Acute adrenal crisis may result from stress in patients with chronic adrenal insufficiency who are not adequately replaced, but it also occurs in patients with acute adrenal hemorrhage or pituitary apoplexy.

Both chronic primary and chronic secondary adrenal insufficiency lead to glucocorticoid deficiency and occasionally androgen deficiency (in women). The clinical features common to both primary and secondary adrenal insufficiency include hypotension, weakness, fatigue, anorexia, weight loss, nausea, and vomiting. Eosinophilia and normocytic anemia are common and occasionally one may see hypercalcemia. Hypoglycemia may be present particularly in children with primary adrenal insufficiency and in patients with secondary adrenal insufficiency in the context of panhypopituitarism when growth hormone is also missing. Chronic primary adrenal insufficiency may be accompanied by other autoimmune disorders (polyglandular failure), the most common being autoimmune thyroid disease (Grave's or Hashimoto's). Rarely, autoimmune hypoparathyroidism is present and such patients

would be hypocalcemic. Two features distinguish primary and secondary adrenal insufficiency. First, mineralocorticoid deficiency is present in primary but absent in secondary (ACTH does not play a major role in regulation of aldosterone). For this reason, hyperkalemia is usually present in primary insufficiency but absent in secondary. Hyponatremia is a feature of both, but in primary insufficiency it is associated with volume contraction resulting in an elevated blood urea nitrogen (BUN) and creatinine. Hyponatremia in secondary adrenal insufficiency is dilutional because of decreased ability to excrete a water load and increased vasopressin levels. A second distinguishing feature is the high concentrations of ACTH and other proopiomelanocortin (POMC)-derived peptides in primary insufficiency and the low or normal concentrations of these peptides in secondary insufficiency. This would typically lead to hyperpigmentation in primary insufficiency (from melanocyte-stimulating activity of POMC-derived peptides) and lack of hyperpigmentation, and occasionally pallor, in secondary insufficiency.

Acute adrenal crisis is characterized by hypotension and shock, fever, confusion, nausea, and vomiting. In the setting of acute adrenal hemorrhage, many patients will also have abdominal, flank, or back pain. Pituitary apoplexy is usually associated with severe headache and frequently ophthalmoplegia. Laboratory abnormalities include azotemia and eosinophilia.

ADRENAL INSUFFICIENCY IN THE CRITICAL CARE SETTING

Critically ill patients present a special challenge in terms of diagnosis and management of adrenal insufficiency. We will address the following questions frequently confronting critical care physicians and endocrine consultants: (1) Which patients with diagnosed chronic adrenal insufficiency should be placed on stress doses of steroids and what should these doses be? (2) How should patients with acute adrenal crisis be managed? (3) Are some critically ill patients "relatively" adrenally insufficient and which ones should receive replacement therapy? (4) What are the diagnostic criteria for adrenal insufficiency in general and for secondary adrenal insufficiency in particular?

Stress Dosing of Steroids in Patients with Chronic Adrenal Insufficiency

Almost 50 yr ago, death with refractory hypotension had been reported in two patients receiving chronic glucocorticoid treatment after surgery without replacement (2, 3). These cases prompted a recommendation for giving large doses of glucocorticoids to any patient undergoing surgery and chronically treated with supraphysiologic doses of steroids. These recommendations are still commonly followed, but in the last 10 yr, this established dogma has been challenged.

Patients receiving corticosteroid therapy fall into two different categories. The majority have chronic autoimmune or inflammatory diseases such as asthma, ulcerative colitis, or rheumatoid arthritis, and are being treated, or have recently

Correspondence and requests for reprints should be addressed to Yoram Shenker, M.D., Chief, Endocrinology Section, William S. Middleton Memorial Hospital, 2500 Overlook Terrace, Madison, WI 53705. E-mail: james.skatrud@med.va.gov
Am J Respir Crit Care Med Vol 163, pp 1520-1523, 2001
Internet address: www.atsjournals.org

been treated, with high doses of steroids. The other group receives replacement therapy because of chronic primary or secondary adrenal insufficiency.

The dose and duration of treatment with glucocorticoids in patients with chronic autoimmune and inflammatory disease have long been considered as important predictors of the suppression of the hypothalamic–pituitary–adrenal (HPA) axis (4). However, this correlation is very tenuous, and the duration of recovery of the HPA axis after discontinuation of corticosteroid therapy is extremely variable, ranging from days to 1 yr (4). Furthermore, none of the tests of the HPA function predict changes in blood pressure that occur in patients undergoing surgery without corticosteroid supplementation (4). The most reliable study indicates that daily production of cortisol is much lower than previously thought and on average is only 5.7 mg per meter square of body surface per day (5). This corresponds to approximately 10 to 12 mg of oral hydrocortisone per meter square of body surface per day because of incomplete bioavailability of oral hydrocortisone (4). Even major surgery does not lead to more than 200 to 300 mg of cortisol secretion in the first 24 h (6).

At least three recent studies showed that major surgery in patients on glucocorticoids did not require more steroids than their regular daily dose (7–9). In one of these studies, 12 patients underwent major surgery without any additional supplementation other than their regular dose of prednisone (9). Only one had a hypotensive episode resulting from excessive bleeding during splenectomy that was easily reversed by fluid administration. Based on these new data, it is quite reasonable to postulate that for most elective surgery, a continuation of the current dose of corticosteroids is enough to maintain cardiovascular function (9). If hypotension does occur, nonadrenal causes should be sought. If the operation or the illness is complicated or prolonged, higher doses of corticosteroids will probably be needed and overtreatment for several days is unlikely to cause any harm (4). The most reasonable approach to this issue is expressed in a consensus article and recommends the use of only 25 mg of hydrocortisone or its equivalent for minor stress surgery such as hernioplasty, 50 to 75 mg for moderate stress such as abdominal hysterectomy, and 100 to 150 mg for major stress such as cardiac surgery with cardiopulmonary bypass for a period of 1 to 3 d (6). Similar guidelines could be extrapolated to patients with critical medical illness in the intensive care unit.

In contrast to patients on glucocorticoids for nonendocrine disease, patients with established disease of the adrenal cortex or hypothalamic–pituitary (HP) area are obviously not capable of increasing their serum cortisol concentration. Such patients should routinely receive supplemental glucocorticoid therapy. For major surgery or severe illness, the dose of supplemental therapy on the first day should be in the range of 100 to 150 mg of hydrocortisone or its equivalent preferably as a continuous intravenous infusion (4). This trend toward lower doses of steroids for stress coverage is not universally accepted. Most textbooks still recommend 300 to 400 mg of hydrocortisone as an initial dose under conditions of severe stress. Many argue that overtreatment is not harmful, but higher doses may occasionally result in acute psychosis and more severe hyperglycemia.

Management of Acute Adrenal Crisis

Acute adrenal crisis may occur as a result of stress in patients not given supplemental glucocorticoids and known to have chronic adrenal insufficiency. However, the most severe cases are due to adrenal hemorrhage or infarction. Such patients are usually already seriously ill as a result of thromboembolic

disease, coagulopathy (including antiphospholipid antibody syndrome), traumatic shock, severe burns, or sepsis. The pathophysiology of adrenal damage is probably related to stress-induced increase in ACTH concentrations which increase adrenal blood flow to a degree that exceeds the capacity for venous drainage (1). Very ill patients with sudden deterioration should be screened for adrenal insufficiency. Almost all patients with acute adrenal insufficiency will have basal cortisol levels below 3 $\mu\text{g}/\text{dl}$ (83 nmol/L) and a complete lack of response to ACTH stimulation. A similar clinical picture but without abdominal, flank, or back pain will be encountered in patients with pituitary apoplexy. Pituitary apoplexy occurs as a result of sudden necrosis of large pituitary tumors, most commonly in patients with acromegaly.

High parenteral doses of glucocorticoids and fluid resuscitation are the mainstay of therapy. Fluids are given as normal saline or as normal saline with 5% glucose in cases of hypoglycemia. Frequently 2 to 3 L of fluid in the first 2 h are required to maintain blood pressure (10). The most commonly given steroid is hydrocortisone, which in large doses provides not only glucocorticoid but also mineralocorticoid coverage. The typical starting dose is 300 to 400 mg per 24 h given either in divided doses every 6 h or as a continuous infusion. The potential disadvantage of this choice is the fact that diagnostic testing of adrenal function cannot be performed. However, this testing can be performed after the patient's condition has stabilized. An alternative, which does not interfere with measurement of cortisol and ACTH stimulation testing, is the administration of dexamethasone 4 to 6 mg every 12 h given intravenously or intramuscularly. Another option is to give one dose of dexamethasone (4 mg) followed by a rapid ACTH stimulation test and then switch to hydrocortisone as previously described. Both prednisone and cortisone should be avoided in hypotensive patients because they require hydroxylation to create the active compound, i.e., converting prednisone to prednisolone and cortisone to cortisol. In addition, these steroids are only available for oral administration and thus cannot be given if the preferred parenteral route is chosen (10). Mineralocorticoid replacement is not needed as long as the dose of cortisol exceeds 50 mg daily, which provides sufficient mineralocorticoid coverage. Even if dexamethasone is chosen for glucocorticoid replacement, a large amount of saline will usually eliminate the need for sodium conservation and will also have a kaliuretic effect.

"Relative" Adrenal Insufficiency in Critically Ill Patients

Stressful conditions, including pain, fever, and hypovolemia require an increase in ACTH and cortisol. After surgical procedures such as laparotomy, there is initial lack of diurnal variation and markedly increased concentrations of cortisol (9). Cortisol levels return to baseline within 24 to 48 h. During severe illness, serum cortisol levels tend to be even higher, and in one study, concentrations higher than 50 $\mu\text{g}/\text{dl}$ were noted (11). Patients with ruptured aortic aneurysms had average cortisol concentrations of 27 $\mu\text{g}/\text{dl}$ and similar values were found in other studies of critically ill or postoperative patients (12). Higher cortisol levels are associated with increased mortality. Among patients with ruptured abdominal aneurysm, nonsurvivors had an average cortisol concentration of 37 $\mu\text{g}/\text{dl}$ as compared with 24 $\mu\text{g}/\text{dl}$ in survivors (12). Shortly before death, concentrations are even higher and may reach 260 $\mu\text{g}/\text{dl}$ (4).

No consensus exists as to what constitutes the lower limit of cortisol in critically ill patients. Values as low as 10 $\mu\text{g}/\text{dl}$ (13) or as high as 20 $\mu\text{g}/\text{dl}$ are proposed (12, 14). The rapid ACTH stimulation test, which is commonly used in diagnosis of chronic adrenal insufficiency in the outpatient setting, is very difficult

to interpret in critically ill patients. In most patients, serum cortisol concentrations increase to concentrations above 18 $\mu\text{g/dl}$ after ACTH, but if patients have high baseline cortisol levels, subsequent increments may be small (4). Such small increments may be due to the fact that the HPA axis is already maximally stimulated (4, 15, 16), but it may also be a result of interference with the capacity of the adrenal cortex to produce glucocorticoids and a lack of cortisol reserve (4). There is some indication that limited response to ACTH may be associated with higher mortality (4).

Multiple factors may contribute to hypoadrenalism in critically ill patients. These include anatomic damage to the adrenals or the pituitary as a result of preexisting or previously undiagnosed disease of the adrenal cortex or HP area or acute destruction of the adrenal gland from hemorrhage or infection (4). Probably more commonly, hypoperfusion or cytokine-induced inhibition of the adrenal or the HP area will lead to functional impairment of different components of the axis (4, 15, 16). Some of the drugs used in critical care may also lead to increased hypoadrenalism (4, 15). The most common mechanisms relate to increased metabolism of cortisol (dilatant, phenobarbital, and rifampin) or to interference with steroidogenic enzymes (ketoconazole and possibly etomidate) (4, 16).

Outcomes of older studies using extremely high doses of steroids in septic shock are not encouraging, and are summarized in two meta-analyses (17, 18). Overall there was no beneficial effect on survival in patients with septic shock. More recently, multiple studies have used the concept of "relative" adrenal insufficiency. This relates to use of more physiologic "stress" doses of 100 to 300 mg of hydrocortisone or its equivalent in patients with shock, high cardiac output, multiorgan failure, and prolonged mechanical ventilation. Multiple studies show a beneficial effect of steroids in such patients in terms of ability to discontinue vasopressors, wean patients from mechanical ventilation, and improve survival (15, 16, 19, 20).

The clinical presentation of "relative" adrenal insufficiency is usually a catecholamine-dependent hyperdynamic shock, which responds to steroids (19). This paradox of responsiveness to steroids, despite an absence of biochemical or histologic adrenal insufficiency (postmortem examination almost never shows destruction of the adrenal or HP area), may be explained by desensitization of glucocorticoid responsiveness at the cellular level (15). Glucocorticoids are necessary for adequate coupling of adrenergic receptors, and this glucocorticoid-adrenergic receptor coupling may be impaired as a consequence of increase in glucocorticoid concentrations (15). Also, the high catecholamine levels in critically ill patients may down-regulate adrenergic receptors. High-dose glucocorticoids may result in recoupling of the desensitized adrenergic receptors and thus restore responsiveness in blood pressure (15). This theory provides an alternative explanation to "relative" adrenal insufficiency. It is also possible that the abnormality in these patients is an altered receptor function or a resistance to glucocorticoids (20).

In summary, the possibility of "relative" adrenal insufficiency should be considered in patients who are pressor-dependent or require prolonged mechanical ventilation. Clues that should increase suspicion for adrenal dysfunction include eosinophilia (21), unexplained hypothermia, hyperpigmentation, hyperkalemia, hyponatremia, nausea, vomiting, and abdominal pain, as well as hypotension not responding to fluids or catecholamines (15). Even patients without such clues may be considered for a trial of "physiologic" stress replacement dose of 200 to 300 mg of hydrocortisone or its equivalent (15, 16, 19, 20). ACTH stimulation testing is not useful at all in such patients (4, 15, 20). Finding random cortisol levels below

20 $\mu\text{g/dl}$ in such patients may add additional argument for use of steroids (22), but the cortisol concentration does not always predict a response to steroids (20).

Diagnostic Testing to Prove Adrenal Insufficiency

For many years, this area of endocrine diagnosis seemed to be very well established and relatively noncontroversial. The usual recommendation is to first measure early morning cortisol. If the concentrations are very low, the diagnosis is established. If the concentrations are intermediate, an ACTH stimulation test should be performed. The circulating form of ACTH contains 39 amino acids, but the entire biologic activity is preserved in the N-terminal portion of the molecule. For this reason, a synthetic 1-24 amino acid ACTH known as cosyntropin is used for the test. A vial of cosyntropin contains 250 μg and most criteria for a normal test are based on intravenous injection of the entire vial with measurements of cortisol at 0, 30, and 60 min. Several possible diagnostic criteria include a maximal concentration of $\leq 20 \mu\text{g/dl}$ (552 nmol/L) or an increment of ≤ 5 to 10 $\mu\text{g/dl}$ (138 to 276 nmol/L). These are still widely accepted criteria for the diagnosis of primary adrenal insufficiency.

In the last 10 yr, several studies suggested that such a high dose of cosyntropin creates multiple false negatives in patients with secondary adrenal insufficiency (23, 24). Adrenal atrophy or functional impairment of the adrenal after withdrawal of the ACTH stimulus requires weeks to develop and occurs with different grades of severity in patients with pituitary disorders or on glucocorticoid treatment (25). The 250- μg cosyntropin stimulation test increases ACTH concentration to 60,000 pg/ml, which is well in excess of the 100 pg/ml concentration of ACTH required to maximally stimulate the adrenal cortex (25). Obviously this is an extremely blunt tool. Patients who have a normal response to 250 μg cosyntropin may still be adrenally insufficient as judged by insulin hypoglycemia or metyrapone testing. These two dynamic tests are better for secondary adrenal insufficiency because they test the entire HPA axis, but they are cumbersome and difficult to perform. Low-dose cosyntropin testing using 1 μg may be a more sensitive tool in diagnosis of secondary adrenal insufficiency (23, 24). Initial enthusiasm for the 1 μg test is not shared by everyone, and some investigators question whether it is really more sensitive (25).

In summary, the diagnosis of adrenal insufficiency may present significant challenges in the critical care setting. Even patients with quite high cortisol levels under normal circumstances may have "relative" adrenal insufficiency and may benefit from stress doses of steroids. On the other hand, many patients chronically treated with steroids for nonendocrine diseases may not need more than their regular steroid dose even under stressful conditions. Patients with established adrenal insufficiency may require lower doses of steroid than usually recommended in the critical care setting. The utility of the low-dose cosyntropin stimulation test in chronic or acute secondary adrenal insufficiency has not yet been clearly established.

References

- Carey RM. The changing clinical spectrum of adrenal insufficiency. *Ann Intern Med* 1997;127:1103-1105.
- Fraser CG, Preuss FS, Bigford WD. Adrenal atrophy and irreversible shock associated with cortisone therapy. *JAMA* 1952;149:1542-1543.
- Lewis L, Robinson RF, Yee J, Hacker LA, Eisen G. Fatal adrenal cortical insufficiency precipitated by surgery during prolonged continuous cortisone treatment. *Ann Intern Med* 1953;39:116-125.
- Lamberts SWJ, Bruining HA, De Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med* 1997;337:1285-1292.

5. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* 1991;72:39-45.
6. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg* 1994;219:416-425.
7. Bromberg JS, Alfrey EJ, Barker CF, Chavin KD, Dafoe DC, Holland TA, Perloff LJ, Zellers LA, Grossman RA. Adrenal suppression and steroid supplementation in renal transplant recipients. *Transplantation* 1991;51:385-390.
8. Friedman RJ, Schiff CF, Bromberg JS. Use of supplemental steroids in patients having orthopaedic operations. *J Bone Joint Surg Am* 1995;77:1801-1806.
9. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. *Surgery* 1997;121:123-129.
10. Malchoff CD, Carey RM. Adrenal insufficiency. *Curr Ther Endocrinol Metab* 1997;6:142-147.
11. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab* 1995;80:1238-1242.
12. Braams R, Koppeschaar HPF, van de Pavoordt HDWM, van Vroonhoven TJMV. Adrenocortical function in patients with ruptured aneurysm of the abdominal aorta. *Intensive Care Med* 1998;24:124-127.
13. Knowlton AL. Adrenal insufficiency in the intensive care setting. *J Intensive Care Med* 1989;4:35-41.
14. Rivers EP, Blake HC, Dereczyk B, Ressler JA, Talos EL, Patel R, Smithline HA, Rady MY, Wortsman J. Adrenal dysfunction in hemodynamically unstable patients in the emergency department. *Acad Emerg Med* 1999;6:626-630.
15. Bennett N, Gabrielli A. Hypotension and adrenal insufficiency. *J Clin Anesth* 1999;11:425-430.
16. Mackenzie JS, Burrows L, Burchard KW. Transient hypoadrenalism during surgical critical illness. *Arch Surg* 1998;133:199-204.
17. Lefering R, Neugebauer EAM. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med* 1995;23:1294-1303.
18. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995;23:1430-1439.
19. Nieboer P, van der Werf TS, Beentjes JAM, Tulleken JE, Zijlstra JG, Ligtenberg JJM. 2000. Catecholamine dependency in a polytrauma patient: relative adrenal insufficiency? *Intensive Care Med* 2000;26:125-127.
20. Knighton JD, Woodcock TE, Hough M. Adrenal failure in the critically ill. *Br J Anaesth* 1999;82(1):152-153.
21. Beishuizen A, Vermes I, Hylkema BS, Haanen C. Relative eosinophilia and functional adrenal insufficiency in critically ill patients. *The Lancet* 1999;353:1675.
22. Richards ML, Caplan RH, Wickus GG, Lambert PJ, Kiskin WA. The rapid low-dose (1 µg) cosyntropin test in the immediate postoperative period: results in elderly subjects after major abdominal surgery. *Surgery* 1999;125:431-440.
23. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, Lahav M. Adrenocorticotropin stimulation test: effect of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 1991;72:773-778.
24. Tordjman K, Jaffe A, Grazas N, Apter C, Stern N. The role of the low dose (1 µg) adrenocorticotropin test in the evaluation of patients with pituitary diseases. *J Clin Endocrinol Metab* 1995;80:1301-1305.
25. Oelkers W. The role of high- and low-dose corticotropin test in the diagnosis of secondary adrenal insufficiency. *Eur J Endocrinol* 1998;39:567-570.