Corticosteroid Supplementation for Adrenal Insufficiency

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In 1949, the clinical introduction of cortisone, a purified glucocorticoid preparation, revolutionized medical care of patients with a host of diseases and provided life-sustaining physiologic replacement in patients with acute or chronic adrenal insufficiency (AI).[1,2] Case reports appeared shortly after the introduction of chronic glucocorticoid therapy describing life-threatening adrenal crises in patients with medical or surgical stresses not receiving adequate corticosteroid supplementation.[3,4] Prior edicts suggesting large-dose, long-duration therapy were not tailored to either patient or procedure. Current recommendations about supplementation during major and minor illnesses or invasive procedures, rationale, and dosing schedules have changed.[5,6] During preparation of this manuscript, we searched MEDLINE and several other evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.

Adrenal Cortex Corticosteroid Production and Function

Glucocorticoids are life-sustaining cholesterol derivatives produced in the zona fasciculata of the adrenal cortex under the negative feedback control of both the hypothalamus and pituitary gland, (hypothalamic-pituitary-adrenal [HPA] axis). The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to synthesize adrenocorticotropic hormone (ACTH) to signal production of cortisol, the main endogenous glucocorticoid.[2,7] Cellular receptors for cortisol are ubiquitous in cell cytoplasm, reflecting the crucial role the hormone plays in maintaining cell homeostasis and viability of the organism. Glucocorticoids are required to maintain normal carbohydrate, lipid, and protein metabolism.[7] Cortisol facilitates catecholamine production and modulates β-adrenergic receptor synthesis, regulation, coupling, and responsiveness.[8] Glucocorticoids enhance normal immune activity and wound healing, maintenance of cardiovascular integrity and cardiac contractility, and various other functions.[7]

Mineralocorticoid synthesis occurs in the adrenal zona glomerulosa when stimulated by the renin-angiotensin–aldosterone system or hyperkalemia. Aldosterone, the main endogenous mineralocorticoid, facilitates sodium and potassium homeostasis and maintenance of intravascular volume.[2,9]

Recent estimates of glucocorticoid secretion are approximately 5 mg/m^2 per day to 10 mg/m^2 per day of cortisol (the equivalent of about 20-30 mg/d of hydrocortisone or 5 to 7 mg/d of oral prednisone), which is less than previously reported.[10,11] Glucocorticoid levels have diurnal variation with the peak level between 4 AM and 8 AM, depending on age. There is minimal production of cortisol during the evening, lasting until 2 AM to 4 AM.[2] Synthesis of cortisol can increase 5- to 10-fold under conditions of severe stress, to a maximal level of approximately 100 mg/m^2 per day.[2,5]

Adrenal Insufficiency

Adrenal insufficiency may be an acute or chronic primary, secondary, or tertiary process (Table 1).[2,12,13] Primary AI is relatively rare but develops in patients who have greater than 90% destruction or replacement of the adrenal glands with inflammation, tumor, infection, or hemorrhage.[2,12] Patients with primary AI are both glucocorticoid and mineralocorticoid deficient; autoimmune disease is the most common etiology of primary AI.[2,12] Pituitary dysfunction or failure with insufficient ACTH production causes secondary AI and is uncommon. Tertiary AI develops from hypothalamic or HPA axis dysfunction or failure.

Therapeutic glucocorticoid administration is the most common cause of AI.[2] The CRH and ACTH stimulation of the adrenal gland is suppressed by an ample quantity of glucocorticoid administered for a sufficient period.[2,12] Tertiary iatrogenic AI then develops as the adrenal gland atrophies with time. A reduced response to exogenous ACTH has been reported to last for 5 days after discontinuation of oral prednisone (25 mg twice a day) for as brief a period as 5 days.[13]

Although many clinicians believe that the duration of corticosteroid therapy, the highest corticosteroid dose, and the total cumulative corticosteroid dose are important predictors of HPA axis suppression, there are inconsistent data to accurately predict the degree of adrenal suppression in patients receiving exogenous glucocorticoid therapy. Recent literature reveals that patients who

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receive 5 mg/d or less of prednisone continue to have an intact HPA axis.[14] Recovery of the HPA axis after the discontinuation of exogenous glucocorticoids may take up to a year.[5] Measurement of plasma cortisol levels when patients are not receiving exogenous glucocorticoids and judicious application of adrenal stimulation with the low- or high-dose cosyntropin stimulation test are recommended on an individual basis to determine HPA axis reserve in persons with suspected tertiary AI.[15] Patients with secondary or tertiary AI usually have intact mineralocorticoid function via the renin-angiotensin–aldosterone system, but require stress glucocorticoid supplementation when an acute illness develops or a stressful procedure is performed.[2,9,12]

Rationale and Recommendations for Replacement or Supplemental Therapy

Replacement therapy for patients with primary AI should be individualized and usually requires 20 mg to 30 mg of hydrocortisone administered in 2 to 3 divided doses a day for homeostatic glucocorticoid replacement.[2,12] Many experts currently advise maintenance therapy, however, with equivalent doses of longer-acting corticosteroid preparations, such as dexamethasone, 0.5 mg/d or prednisone, 5 mg/d to avoid excessively high peak levels and periods of inadequate replacement associated with the shorter-acting hydrocortisone.[12] Dose adjustment is based on patient weight, age, and use of concurrent medications; patients treated with phenytoin, rifampin, barbiturates, mitotane, and aminoglutethimide require larger doses because of increased corticosteroid metabolism. The patient's sense of well-being, normalcy of blood pressure, heart rate and temperature, and elimination of symptoms, such as anorexia, nausea, vomiting, and dizziness, should be assessed before initiation or adjustment of dosage. Excess glucocorticoid-induced adverse effects, such as hypertension, muscle and skin changes, hyperglycemia, and electrolyte abnormalities, should be identified.[2] Glucocorticoid production does not diminish significantly with age but various parameters, such as lean body weight, glucocorticoid metabolism, and corticosteroid and adrenergic receptor function may change during the aging process. Therefore, the dose of supplemental glucocorticoids should be individualized. By definition, all patients with primary AI (Table 1) are hypoaldosteronemic and require adequate salt intake and mineralocorticoid supplementation with fludrocortisone (9-α-fluorohydrocortisone), a potent synthetic mineralocorticoid. Fludrocortisone is given orally at a dose of 0.05 mg/d to 0.20 mg/d; the dose is adjusted based upon the serum sodium level and the presence of postural hypotension or marked orthostasis.[2,9]

Because severe illnesses, surgery, anesthesia, and trauma activate the HPA axis resulting in increased CRH, ACTH, and cortisol production, patients with AI may require physiologic or stress supplemental therapy in addition to their normal corticosteroid doses when they have an acute illness or undergo a stressful procedure.[5-7,16,17] Given the large variation in cortisol production in healthy patients undergoing stress, it is difficult to exactly predict the needs of patients during such circumstances. The adrenal response to acute medical illness may be quite variable.[18] Some

Table 1. Characteristics of Adrenal Insufficiency*

Type	Features	Incidence	Etiologies
Primary	ACTH independent Adrenal gland dysfunction, destruction, or replacement; requires >90% loss of adrenal tissue Loss of mineralocorticoid and glucocorticoid production Increased ACTH production May be hyperpigmented Requires lifetime therapy	Prevalence: 40-110 cases/million Incidence: 6 cases/million per year	Autoimmune (70%-90% of cases in United States), frequently associated with a polyglandular deficiency syndrome Infection HIV is the most common infectious cause in the United States AI develops in 30% of patients with advanced AIDS TB is the most common infectious cause worldwide Inflammation Cancer (breast, lung, melanoma most common) Acute addisonian crisis Infectious (meningococcemia, purpura fulminans) Stress Hemorrhage (acute stress or anticoagulant-induced) Shock
Secondary	ACTH dependent Signs and symptoms usually due to loss of glucocorticoid function Usually have intact mineralocorticoid function Rarely hypovolemic, more commonly hypoglycemic	Uncommon	Decreased or absent ACTH (may be panhypopituitary or anterior pituitary dysfunction) Pituitary depression, dysfunction/damage Tumor, postpartum
Tertiary	Due to hypothalamic/pituitary depression or absence	Most common form	Usually from iatrogenic corticosteroid therapy and suppression of the hypothalamic-pituitary-adrenal axis Hypothalamic failure or dysfunction

*Data taken from references 2 and 12. ACTH indicates adrenocorticotropic hormone; HIV, human immunodeficiency virus; AI, adrenal insufficiency; AIDS, acquired immunodeficiency syndrome; and TB, tuberculosis.

Table 2. Guidelines for Adrenal Supplementation Therapy*

Medical or Surgical Stress	Corticosteroid Dosage
Minor Inguinal hernia repair Colonoscopy Mild febrile illness Mild-moderate nausea/vomiting Gastroenteritis	25 mg of hydrocortisone or 5 mg of methylprednisolone intravenous on day of procedure only
Moderate Open cholecystectomy Hemicolectomy Significant febrile illness Pneumonia Severe gastroenteritis	50-75 mg of hydrocortisone or 10-15 mg of methylprednisolone intravenous on day of procedure Taper quickly over 1-2 days to usual dose
Severe Major cardiothoracic surgery Whipple procedure Liver resection Pancreatitis	100-150 mg of hydrocortisone or 20-30 mg of methylprednisolone intravenous on day of procedure Rapid taper to usual dose over next 1-2 days
Critically ill Sepsis-induced hypotension or shock	50-100 mg of hydrocortisone intravenous every 6-8 h or 0.18 mg/kg/h as a continuous infusion + 50 µg/d of fludrocortisone until shock resolved May take several days to a week or more Then gradually taper, following vital signs and serum sodium

*Data are based on extrapolation from the literature, expert opinion, and clinical experience.[5,6,11,15,20-22] Patients receiving 5 mg/d or less of prednisone should receive their normal daily replacement, but do not require supplementation.[13] Patients who receive greater than 5 mg/d of prednisone should receive the above therapy in addition to their maintenance therapy.

studies report an increased mortality rate when very high cortisol levels are present in acutely ill patients.[5,19] Whether this reflects severity of underlying illness, excessive proinflammatory effect, or hyporesponsiveness to endogenous glucocorticoids and an inadequate anti-inflammatory response to critical illness remains under investigation.

Patients who cannot take oral medications or who experience a significant stress and potential instability should receive intravenous corticosteroid supplementation.[5] The optimal dosing, frequency, and duration of such therapy continue to be debated, but recent expert recommendations call for lower doses and shorter duration administration of supplemental therapy (TABLE 2)[5,6,11,15,20-22] than many conventional textbooks suggest.[5,6] Supplementary glucocorticoid dosing is based on the likelihood of adrenal suppression, the degree of medical or surgical stress, and the cardiovascular and metabolic response to therapy.

The conventional recommendations for corticosteroid supplementation in patients with known AI, suspected AI, or at risk for AI are empirical suggestions derived from early case reports of severe morbidity or death in stressed patients with AI. Recently, 2 reviews of prior literature about supplemental therapy have been conducted.[5,6] Several insights from their commentaries deserve emphasis. All patients with AI who undergo a procedure or have a medical illness require their normal daily corticosteroid therapy.[2,5,6] Patients who undergo a superficial procedure of less than 1 hour in duration under local anesthesia, such as routine dental work, skin biopsy, or minor orthopedic surgery, only require their normal daily dose of replacement therapy and not a supplemental dose.[5,6] Patients with tertiary AI who receive the equivalent of 5 mg/d or less of prednisone usually do not require additional supplementation because their adrenal glands remain adequately responsive to endogenous ACTH release.[14] They should receive their daily maintenance dose of glucocorticoid (and mineralocorticoid if they require it), orally or intravenously as the clinical situation mandates.[5,6,14] This depends on whether the patient is unable to take medications by mouth or unable to absorb oral medications reliably. Some clinicians advocate administering hydrocortisone as a continuous infusion to limit the rapid clearance and peak levels associated with bolus therapy of this shorter-acting glucocorticoid or intermittent administration of equivalent long-acting corticosteroids.[2,5,6] Others suggest using appropriate doses of longer-acting glucocorticoid preparations, such as methylprednisolone or dexamethasone, in place of hydrocortisone to avoid problems with clearance and cortisol levels.[2,5,6] As synthetic glucocorticoid medications become increasingly longer acting and potent, their mineralocorticoid potency decreases.[23]

One supplemental corticosteroid dose does not accommodate all patients or procedures.[2,5,6] The routine administration of stress doses equivalent to 200 mg to 300 mg of hydrocortisone when a patient undergoes any procedure or has any medical illness should be discouraged.[5,6] There is no benefit to excessive dosing (>200-300 mg/d) or extensive duration of dosing. Deleterious effects secondary to undue glucocorticoid supplementation include hyperglycemia, immunosuppression, and accelerated protein catabolism resulting in altered wound healing, hypertension, volume overload, and acute corticosteroid-induced psychosis.[2,5,6]

Physicians also tend to administer supplementation to medically and surgically stressed patients for longer periods than necessary.[5,6] The diurnal production of cortisol is transiently eliminated after surgery and levels of cortisol increase with surgical stress.[5,24] Production of cortisol, however, returns to normal within 24 hours to 48 hours after surgery.[5,24] Mineralocorticoid supplementation is usually not required in patients with secondary or tertiary AI or patients with primary AI who are supplemented with more than 50 mg/d of hydrocortisone.[2]

There is a wide range in the cortisol response in patients with medical illness or those undergoing surgical intervention.[5,7,13,17,18,25] This may be sec-

ondary to age, underlying health, genetic variability, and other factors.[2] Table 2 provides recommended hydrocortisone doses for patients experiencing various levels of medical illness or undergoing increasingly invasive and stressful procedures.[11] An adequate response to corticosteroid supplementation is predicated on maintenance of intravascular volume and a normal serum sodium level.[5,6] Hypotension in a patient with AI may mimic hypovolemic or septic shock and should be considered in the differential diagnosis of either. The presence of hypotension in a patient with AI who has received exogenous corticosteroid supplementation is usually secondary to hypovolemia, cardiac depression, distributive processes, or an etiology other than AI.[2,5,6] Therefore, additional corticosteroid supplementation should be administered to such patients only after such concurrent processes are identified and treated.[5,6]

Corticosteroid Replacement and Adjunctive Therapy in the Critically Ill

Empirical glucocorticoid therapy during life-threatening critical illnesses has received intense interest and investigation over the past 40 years.[2,5,6,25,26] Large prospective trials of short-term, supraphysiologic doses of glucocorticoids (eg, methylprednisolone, ≥30 mg/kg/d) in patients with acute respiratory distress syndrome or septic shock have shown inconsistent or no benefit and may be harmful.[21,27-30] Currently, the concept of acute administration of smaller doses of glucocorticoids equivalent to physiologic or slightly supraphysiologic stress levels in selected patients with sepsis or patients dependent upon vasopressors is under evaluation.[19,22,24,31-37] Recent data suggest an imbalance between systemic inflammation (host defense response) and compensatory anti-inflammatory responses, possibly related to glucocorticoid inadequacy and/or unresponsiveness in some critically ill patients.[32,38] Although glucocorticoid replacement will effectively treat patients with known or acquired absolute AI, supplementation in patients with relative insufficiency or impaired adrenergic receptors also may be beneficial. This positive effect is postulated to be a consequence of enhancement of anti-inflammatory activity, inhibition of deleterious proinflammatory responses, and diminution of nitric oxide–induced vasodilation and hypotension.[38] There are data also suggesting that down-regulation of adrenergic receptors secondary to severe inflammation or excessive exogenous catecholamine administration may be blunted with exogenous corticosteroid infusion.[8] This results in improved adrenergic receptor function and a more stable blood pressure,[22,31] possibly facilitating reversal of sepsis-induced hypotension, decreasing vasopressor requirements, shortening the duration of mechanical ventilation, and improving outcome.[8,33,34,37] A multicenter prospective randomized controlled trial to evaluate the potential benefit of glucocorticoid therapy in severe sepsis is ongoing.[33] Patients in this study also receive empirical mineralocorticoid therapy to facilitate the reversal of sepsis-induced hypotension.[33]

Other acute uses of corticosteroids in the critically ill include short-term administration in patients with acute spinal cord injury, *Pneumocystis carinii* pneumonia, and typhoid-induced shock or coma.[39-43] Selected patients with meningitis, particularly children with *Haemophilus influenzae*, appear to benefit from a 2-day course of glucocorticoids initiated just prior to antibiotic therapy.[44] Currently, the National Institutes of Health–supported Acute Respiratory Distress Syndrome Network has an ongoing multicenter trial designed to determine the utility of glucocorticoid therapy in patients with fibroproliferative acute respiratory distress syndrome.[45,46]

Conclusion

Primary AI is relatively rare, but acquired AI is common, most often secondary to exogenous corticosteroid therapy with resultant adrenal depression and subsequent lack of cortisol production in response to a physiologic stress.[2,5] The incidence of AI in the surgical population is increased 2.5-fold in patients older than 55 years.[16] Patients with known AI must receive at least their baseline therapy prior to any procedure or during an illness; this may require parenteral administration.[2,19,24] Patients who have suspected or known AI require additional supplemental therapy with glucocorticoids when they undergo stressful procedures or experience a significant medical illness.[2,5,6] Supplemental parenteral dosing should be individualized to the degree of challenge (Table 2). Intravenous hydrocortisone or dexamethasone are the 2 corticosteroid preparations most commonly administered to patients with AI experiencing a surgical or medical stress.

The dosing of supplemental corticosteroid therapy remains open to debate; the recommendations outlined in Table 2 are experiential rather than from large clinical databases.[5,6] Previous recommendations for large replacement doses and extended duration of dosing are currently unwarranted.[5,6] Excessive doses and duration of supplemental glucocorticoid therapy are not required and may be harmful due to the known adverse effects of these medications. Whether larger randomized trials of supplemental glucocorticoid administration during surgical procedures will take place is questionable; however, trials investigating the role of corticosteroids as therapy for a variety of acute, severe illnesses are under way.

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