Corticosteroids in the ICU

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Introduction

Given the severity of potential side effects, the decision to institute therapy with glucocorticoids in the intensive care unit (ICU) will always require careful consideration of the relative risks and benefits for each patient. For any disease and in any patient, the appropriate dose to achieve a given therapeutic effect must be determined by trial and error and must be reevaluated periodically as the activity of the underlying disease changes or as complications of therapy arise. A single dose of glucocorticoid, even a large one, is virtually without harmful effects, and a short course of therapy (up to 1 wk), in the absence of specific contraindications, is unlikely to be harmful. As the duration of glucocorticoid therapy is increased beyond 1 week, there are time-related and dose-related increases in the incidence of disabling and potentially lethal effects. Except in patients receiving replacement therapy, glucocorticoids are neither specific nor curative; rather, they are palliative by virtue of their anti-inflammatory and

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Table 1. *Estimates of Anti-inflammatory and Sodium-retaining Potencies of Different Steroid Preparations*

Compound	Anti-inflammatory Potency	Na^+-retaining Potency	Duration of Action	Equivalent Dose (mg)*
Cortisol	1	1	S	20
Cortisone	0.8	0.8	S	25
Fludrocortisone	10	125	I	†
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
6 α-methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75

*These dose relationships apply only to oral or intravenous administration, as glucocorticoid potencies may differ greatly after intramuscular or intra-articular administration.
†This agent is not used for glucocorticoid effects.
I indicates intermediate (ie, $t_{1/2} \approx 12$ to 36 h); L, long (ie, $t_{1/2} \approx 36$ to 72 h); S, short (ie, $t_{1/2} \approx 8$ to 12 h).
Modified from Goodman and Gilman Manual of Pharmacology and Therapeutics Copyright © 2008 by The McGraw-Hill Companies CHAPTER 59, I.

immunosuppressive actions. Finally, abrupt cessation of glucocorticoids after prolonged therapy is associated with the risk of adrenal insufficiency (AI), which may be fatal.

These principles have several implications for clinical practice. When therapy is directed at a life-threatening disease such as pemphigus or lupus cerebritis, the initial dose should be large enough to achieve rapid control of the crisis. If some benefit is not observed quickly, then the dose should be doubled or tripled. After initial control in a potentially lethal disease, dose reduction should be carried out under conditions that permit frequent, accurate observations of the patient. It is always essential to weigh carefully the relative dangers of therapy and of the disease being treated. In this review, the use of corticosteroids in the ICU setting is thoroughly addressed in patients who succumb to, sepsis, shock, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and other diseases Table 1 illustrates anti-inflammatory and sodium retaining potencies of various steroid preparations.

■ Major Indications for Corticosteroids

AI

The prevalence of AI is low, approximately 110 to 140 cases per million and autoimmune adrenal disease represent the most frequent

cause in the developed countries. AI can result from structural or functional lesions of the adrenal cortex (primary AI or Addison disease) or from structural or functional lesions of the anterior pituitary or hypothalamus (secondary AI). In developed countries, primary AI most frequently is secondary to autoimmune adrenal disease; where as tuberculous adrenalitis is the most frequent etiology in underdeveloped countries. Other causes include adrenalectomy, bilateral adrenal hemorrhage, neoplastic infiltration of the adrenal glands, and rare inherited disorders of the steroidogenic enzymes. Secondary AI resulting from pituitary or hypothalamic dysfunction generally presents in a more insidious manner than does the primary disorder, probably because mineralocorticoid biosynthesis is preserved.

Acute adrenocortical insufficiency, first recognized by Addison in 1844, is an uncommon, potentially life-threatening, readily treatable condition often misdiagnosed in the emergency department (ED). The signs and symptoms of acute AI are nonspecific, making the diagnosis difficult. The hallmark of the condition is an inadequate production of glucocorticoids, primarily cortisol, to meet the metabolic requirements of the body. The substitutive therapy with glucocorticoid and mineralocorticoid for patients with chronic AI is life saving.

Serum corticosteroid level on body control is mediated by the hypothalamic-pituitary–adrenal (HPA) feedback mechanism (Fig. 1). A rise in glucocorticoid concentration in the blood [resulting from the action of adrenocorticotropic hormone (ACTH) on the adrenal cortex] inhibits the secretion of ACTH in the hypothalamus. Thus, glucocorticoids have a negative feedback effect on ACTH secretion, which in turn, reduces the rate of secretion of glucocorticoids by the adrenal cortex. If the blood glucocorticoid level begins to fall for some reason, this negative-feedback effect is reduced, stimulating ACTH secretion and restoring the blood glucocorticoid level. This control loop ensures that the level of glucocorticoids in the blood remains relatively stable in the resting state, although there is a diurnal variation in glucocorticoid secretion. Physical and emotional stress can alter the mechanism regulating glucocorticoid secretion.

Acute AI is probably a rare condition. It may represent either an exacerbation of long-standing disease or a new case. Chronic disease is more prevalent and probably accounts for most cases of acute AI seen in EDs. The most common cause of AI is *functional*, from HPA axis suppression from long-term exogenous glucocorticoid administration. When acute adrenal insufficiency represents a rapid worsening of chronic adrenal failure, both the cause of the underlying failure and the precipitant of abrupt decompensation should be identified. Acute precipitating stresses include surgery, anesthesia, psychologic stresses, alcohol intoxication, hypothermia, myocardial infarction, diabetes mellitus, intercurrent infection, asthma, and hypoglycemia.

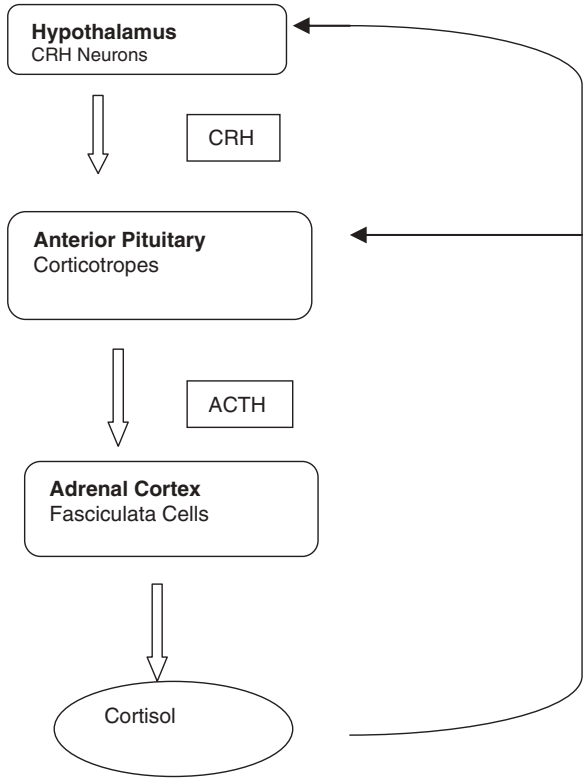

Figure 1. *Overview of the hypothalamic-pituitary–adrenal, axis and the negative feedback, of cortisol on hypothalamus and anterior pituitary. ACTH indicates adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.*

Recovery of the HPA axis after discontinuation of therapy may take up to 1 year. In addition to the oral route, glucocorticoids can produce HPA suppression when administered nasally or by inhalation.

The major cause of primary chronic AI is *idiopathic*, representing 66% to 75% of cases. Idiopathic adrenal failure encompasses 2 distinct clinical entities: autoimmune adrenal failure and true idiopathic disease. Adrenal antibodies are found in 51% to 63% of cases of idiopathic disease. Antibodies to other organs can be demonstrated in cases of autoimmune etiology as demonstrated in Hashimoto thyroiditis, Graves' disease, pernicious anemia, and hypoparathyroidsm. Metastasis from malignant carcinoma to the adrenal glands is not unusual. The usual primary malignancies are lung, gastrointestinal system, and breast. Tuberculous Addison disease, once the most common cause of AI in the United States, is now unusual. Adrenal calcifications are a possible radiographic finding.

The main clinical manifestations of this disease are usually gastrointestinal symptoms (nausea, vomiting, and abdominal pain), dehydration, hyponatremia, hyperkalemia, weakness, lethargy, anorexia, weight loss, low blood pressure, cutaneous and mucosal hyperpigmentation, and salt craving. These clinical symptoms do not appear until approximately 90% of the adrenal cortex has been destroyed or when stress events occur, which require an increase in adrenocortical function. Chronic AI patients present with many of the same manifestations seen in adrenal crisis, but with a lesser severity. Frequently, the diagnosis and treatment of AI must proceed simultaneously. There is little risk of giving a single dose of steroids when the diagnosis of AI is suspected but not confirmed.

Assessment of Adrenal Function in the Critically Ill Patients As there are no clinically useful tests to assess the cellular actions of cortisol (ie, end-organ effects), the diagnosis of AI is based on measurement of serum cortisol levels; this has resulted in much confusion and misunderstanding.[1–4] Traditionally, the "integrity" of the HPA axis has been assessed by the short corticotropin stimulation test (also known as the *Cosyntropin stimulation test*).

This test is usually performed by administering 250 μg of synthetic corticotropin intravenously (IV) and obtaining a serum cortisol determination before, at 30 and 60 minutes after administration. A 30 and 60-minute serum cortisol level below 18 μg/dL or an increase in the cortisol concentration of less than 9 μg/dL has been regarded by many as diagnostic of AI.[2] However, these criteria were developed to assess adrenal reserve in patients with destructive diseases of the adrenal glands and are based on responses in normal, nonstressed, healthy controls. It is believed that the standard corticotropin stimulation test lacks sensitivity for the diagnosis of AI.[2,5] Endogenous stresses such as hypotension, hypoxemia, fever, and hypoglycemia are superior stimuli for testing the integrity of the HPA axis than is ACTH testing. These endogenous stressors test the function of the entire HPA axis and therefore should be regarded as the "gold standard" for adrenal testing. In other words, the HPA axis evolved to respond to stress and is best-evaluated using stress that tests all components of the axis.

High doses of corticotropin (eg, 250 μg) are supraphysiologic (over 1000-fold higher than normal maximal stress ACTH levels).[1] The very high levels of corticotropin obtained with 250 μg can override adrenal resistance to ACTH and result in a normal cortisol response. Patients with normal responses to high-dose corticotropin may fail to respond normally to stress.[4] Owing to the decreased sensitivity of the high-dose ACTH stimulation test for the diagnosis of AI, many investigators evaluated the use of lower doses of ACTH (ie, 1 to 2 μg) for the diagnosis

of AI. A number of studies have showed that a 1-μg dose [low-dose (LD)-ACTH] of corticotropin is more sensitive and specific for diagnosing primary and secondary AI than the 250-μg dose.

Many inappropriately assume that the ACTH stimulation test is capable of detecting the presence of AI because they assume that significant adrenal atrophy has occurred and results in diminished ACTH responsiveness. This concept is flawed for a variety of reasons. First, it takes 1 to 2 weeks for the adrenal gland to atrophy after pituitary removal when all ACTH secretion from the pituitary is lost. Thus the ACTH stimulation test may easily miss acute AI. Second, the duration for complete atrophy may be prolonged in patients with partial AI. Third, the response to ACTH may be normal in patients with partial secondary AI. ACTH testing is not required to diagnose AI in severely stressed patients because the central nervous system-HPA axis already should be maximally activated. In such patients, a random stress cortisol level provides adequate information on the integrity of the entire HPA axis.

There is much controversy regarding levels of circulating cortisol that are considered to be an adequate response to stress.[2] Many textbooks and published manuscripts state that the normal circulating cortisol response to stress is a level greater than 15 to 20 μg/dL. However, the choice of 15 to 20 μg/dL is based primarily on the response to exogenous high-dose ACTH (250 μg) and the response to insulin-induced hypoglycemia in nonstressed, noncritically ill patients. During surgical procedures such as laparotomy, serum corticotropin, and cortisol concentrations rise rapidly, peaking in the immediate post-operative period, and then decline to baseline levels over the next 72 hours.[6] The magnitude of the postoperative increase in serum cortisol concentration is correlated with the extent of the surgery, with a peak between 30 and 45 μg/dL in patients undergoing major surgery.[7] During severe illness, serum cortisol concentrations tend to be higher than those of patients undergoing major surgery.[6] In patients with multiple trauma, the serum cortisol level remains greater than 30 μg/dL for at least a week, with peak values between 40 and 50 μg/dL. Cortisol levels are increased in critically ill ICU patients, with the highest values being reported in patients with the highest illness severity scores and those with the highest mortality. Studies have found cortisol levels to be elevated in all forms of shock, however, cortisol levels are significantly lower in patients with septic shock compared with patients with hypovolemic and cardiogenic shock, suggesting the presence of mediators that impair HPA axis function.

Clearly, there is no absolute serum cortisol level that distinguishes an adequate from an insufficient adrenal response. On the basis of the current evidence, we believe that a random cortisol level should be interpreted in conjunction with the severity of illness, and 25 μg/dL is a

useful threshold value for an appropriate response to severe stress. We believe that a random cortisol level should be above 25 μg/dL in severely stressed ICU patients with normal adrenal function.

It is not necessary to obtain cortisol levels at a specific time of the day because critically ill patients lose the diurnal variation in their cortisol levels.[7] In nonhypotensive critically ill patients, the normal cortisol response (30 to 60 min) after 1 to 2 μg corticotropin (LD-ACTH) should be a level greater than 20 μg/dL. It is not recommended to perform the nonphysiologic high-dose corticotropin stimulation test. Importantly, a random cortisol level of less than 15 μg/dL or a level less than 20 μg/dL after LD-ACTH test in a nonhypotensive critically ill patient with unexplained fever, eosinophilia or, metal status changes may warrant a trial of replacement doses of corticosteroids.

In glucocorticoid replacement dexamethasone is preferred because it does not interfere with the ACTH stimulation test. Recommended dose: dexamethasone 4 to 10 mg IV q 6 to 8 hours. If the diagnosis of AI is clear (ie, previously diagnosed or history of abrupt withdrawal of steroids), hydrocortisone is preferred as it has a greater mineralocorticoid (salt-retaining) effect. Recommended dose: hydrocortisone 100 mg IV q 6 to 8 hours.

In replacing mineralocorticoids a single daily dose of 0.05 to 0.1 mg of fludrocortisone is usually required for the purposes of mineralocorticoid replacement to prevent salt loss.

A 24-hour urinary-free cortisol test is considered a good marker for deciding a correct dosage of cortisone, whereas measurement of the ACTH level may be incorrect. Standard doses of glucocorticoids are often adjusted in patients taking drugs that increase metabolic clearance (eg, phenytoin, barbiturates, or rifampin) and in severe illness.

Based largely on empirical data, glucocorticoid doses also are adjusted when patients with AI undergo either elective or emergency surgery. In this setting, the doses are designed to approximate or exceed the maximal cortisol secretory rate of 200 mg/d; a standard regimen is hydrocortisone, 80 to 100 mg parenterally every 8 hours. After surgery, the dose is halved each day until it is reduced to routine maintenance levels.

In conclusion, patients with AI who encounter emergency situations such as febrile illnesses, injury, vomiting, surgical interventions, dental extractions, minor illness, or pregnancies should contact their physician or seek emergency attention, because these situations require glucocorticoids use that may be needed to be doubled or tripled in dosage or be administered parenterally by the patient or family member (4 mg subcutaneously or intramuscularly). The international task force by the American College of Critical Care Medicine has recently published recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill patients.[8]

Septic Shock and Sepsis

Severe stress, associated with critical illness, activates the HPA axis and stimulates the release of cortisol from the adrenal cortex. Corticosteroid therapy in septic patients has improved survival in patients with septic shock and relative AI treated with a 50-mg IV bolus of hydrocortisone every 6 hours and fludrocortisone (50 mg tablet once daily).[9]

Despite earlier negative trials, recent studies have indicated that low-dose corticosteroids may reduce morbidity and mortality in septic shock patients. Corticosteroids may improve hemodynamics and facilitate weaning from catecholamines in septic shock. According to some authors, such effects are only accomplished in the presence of absolute or relative AI. Consequently, corticosteroids are usually given only to patients who present low blood cortisol values or show an inadequate response to cosyntropin (Synacthen test).

During sepsis or ARDS, the HPA axis is rapidly activated through a systemic pathway, that is, by circulating proinflammatory cytokines and through the vagus nerve. Subsequently, the adrenal glands release cortisol, a hormone which will likely counteract the inflammatory process and restore cardiovascular homeostasis. Cortisol is essential for general adaptation to stress and plays a crucial role in cardiovascular, metabolic, and immunologic homeostasis.

There are several potential mechanisms of action that suggest that glucocorticoid therapy might be beneficial in patients with severe sepsis: (1) correction of a state of relative AI, (2) inhibition of the synthesis of inducible nitric oxide synthase, (3) improved hemodynamics secondary to restoration of the sensitivity of vascular catecholamine receptors, and (4) liberation of bound nuclear factor-κ B with decreased transcription of inflammatory cytokines and increased synthesis and release of the receptor antagonist for interleukin-1 (IL-1).[10]

Sepsis involves uncontrolled host defense responses that lead to inflammation, endothelial damage, enhanced coagulation, diminished fibrinolysis and fibroproliferation to produce microthrombi, and relative AI. Corticosteroids inhibit the host defense response and may offer an inexpensive therapeutic option. Critically ill patients at some stage may develop AI. Factors that may contribute to the adrenal dysfunction in critically ill patients include loss of the normal diurnal secretory pattern, increased levels of free cortisol resulting from a combination of a decrease in the levels of cortisol-binding globulin and cleavage of cortisol-binding globulin by neutrophil elastase, inflammatory cytokine-mediated alterations in peripheral cortisol metabolism and changes in the affinity of cellular glucocorticoid receptors for their ligand. Glucocorticoid insufficiency may also be related to a decrease in glucocorticoid synthesis (ie, AI) or to a reduced delivery of glucocorticoid to target tissues and cells. Diagnosis relies on clinical suspicion and ACTH.

Both experimental models and studies in humans suggest that inadequate HPA axis response to stress accounts, at least partly, for the genesis of shock and organ dysfunction in sepsis and ARDS. Relative AI and peripheral glucocorticoid resistance syndrome are the 2 main features of the inappropriate hormonal response and provide the grounds for cortisol replacement in these diseases.

There is increasing evidence of reversible HPA insufficiency in critically ill septic patients.[1] Untreated AI is associated with a high mortality in critically ill patients.

In patients with severe sepsis at high risk of death, it is reasonable to administer combination glucocorticoid/mineralocorticoid therapy with the 7-day protocol described by Annane et al.[9] Therapy should begin immediately after a short ACTH stimulation test [ACTH 250 μg (1 vial of cosyntropin) IV or intramuscularly with a serum cortisol level 45 to 60 minutes later]. Once the results become available, steroids can be discontinued in patients whose baseline serum cortisol is increased by 10 μg/dL or greater (ie, responders). Nonresponders, patients with a change in their serum cortisol levels of 9 μg/dL or less, can continue to receive low-dose steroids for the full 7-day period.

Sprung et al and Annane et al concluded that there is no role for high-dose corticosteroids or steroids in patients who are not vasopressor dependent. Early randomized controlled trials that evaluated the early use of high-dose corticosteroids did not show a survival benefit in severe sepsis.[11] A large study in the mid-1980s conducted by the Veterans Administration Systemic Sepsis Cooperative Study Group found no reduction in mortality among patients receiving early methylprednisolone (MP) therapy.[12]

One multicenter, randomized, controlled trial of patients with septic shock showed a reduction in the mortality rate and number of days on vasoactive medications in nonresponders to a corticotropin stimulation test (defined as an increase of serum cortisol ≤ 9 pg/dL after stimulation) who received low-dose hydrocortisone (50 mg every 6 h for 7 d) versus placebo.[9] Briegel and associates showed decreased time of vasopressor therapy with stress doses of hydrocortisone but no reduction in mortality.[13]

Three recent studies support the use of physiologic replacement doses of corticosteroids in patients with severe sepsis. Bollaert et al[14] randomized 41 patients with septic shock to hydrocortisone (100 mg IV every 8 h) or placebo. Glucocorticoid-treated patients had a significantly greater reversal of shock at 7 and 28 days and reduced 28-day mortality compared to the placebo group. Briegel and colleagues[13] randomized 40 critically ill septic shock patients to IV hydrocortisone or placebo. Hydrocortisone treatment was associated with improved shock reversal and decreased days of vasopressor support. There was also earlier resolution of organ dysfunction, shorter ventilator time, and shorter

ICU stay. In a multicenter, randomized, controlled trial, Annane and colleagues showed a 30% reduction in mortality in septic shock patients treated with stress doses of hydrocortisone.

Steroid therapy consisted of 200 mg of hydrocortisone (50 mg at 6-h intervals) and a single 50-μg dose of fludrocortisones daily for 7 days. In patients characterized on the basis of the short ACTH stimulation test as having relative AI (ie, nonresponders), steroid therapy significantly decreased mortality rate and the duration of vasopressor therapy. Steroid treatment of the nonresponder population produced 16% and 10% relative and absolute reductions, respectively, in the risk of 28-day mortality ($P = 0.04$). Furthermore, steroid treatment of this subpopulation improved hemodynamics and enabled the investigators to wean patients from vasopressors 3 days earlier than placebo-treated controls.

A high dose of corticosteroids (ie, 1 to 4 boluses of 30 mg/kg of MP or equivalent) had no effects on survival in severe sepsis or ARDS. There are at least 7 randomized controlled trials reporting the benefits and risks of low-dose corticosteroids (ie, 200 to 300 mg daily of hydrocortisone or equivalent) given for a prolonged period in severe sepsis or in the late phase of ARDS.[15]

High glucocorticoid doses were harmful to the patients. Recently, the subject has been raised again as some studies showed that AI may happen in sepsis and that low-dose/long-term regimen with cortisol may be beneficial to sepsis and septic shock.

Relative AI is very frequent in patients with septic shock. Hydrocortisone administration in these patients is associated with a high frequency of shock resolution and high survival rate. A 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative AI without increasing adverse events.[9]

ALI, ARDS

During sepsis or ARDS, the HPA axis is rapidly activated through a systemic pathway, that is, by circulating proinflammatory cytokines and through the vagus nerve. Subsequently, the adrenal glands release cortisol, a hormone which will likely counteract the inflammatory process and restore cardiovascular homeostasis. Relative AI and peripheral glucocorticoid resistance syndrome are the 2 main features of the inappropriate hormonal response and provide the grounds for cortisol replacement in these diseases.

Both experimental models and studies in humans suggest that inadequate HPA axis response to stress accounts, at least partly, for the genesis of shock and organ dysfunction in sepsis and ARDS.

Several prospective multicenter placebo-controlled studies showed that patients with ARDS do not benefit from high-dose corticosteroids

administered early in the disease. Hudson[16] concluded that there was no difference in 60-day mortality, or ICU or hospital length of stay between those treated with high-dose MP and those treated with placebo. In addition, investigators reported more adverse events related to weakness in the steroid-treated group than in the placebo-treated group.

A few patients with ARDS have high numbers of eosinophils in their blood and lungs (as assayed by bronchoalveolar lavage). These patients may have a form of eosinophilic pneumonia. Some of these patients seem to respond to the use of early corticosteroids. Despite this lack of proved efficacy in early ARDS, Meduri et al,[17] in a randomized controlled crossover trial using prolonged corticosteroid treatment in ARDS at more modest doses than previously used, found a significant improvement in mortality in patients who received parenteral corticosteroids, presumably the result of suppressing ongoing inflammation during the fibroproliferative phase of ARDS. This study is supplemented by other studies that have reported improved survival and outcomes compared with those of historical controls.[18] Meduri et al[19] concluded that prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables, and has a distinct survival benefit when initiated before day 14 of ARDS.

Kallet et al concluded that although most pharmacologic ALI/ARDS therapies have been ineffective, high-dose MP is indicated in the subgroups of ALI/ARDS patients who have pneumonia or are at risk of ARDS due to fat embolization.[20] Hooper and Kearl[18] concluded that high-dose corticosteroids may be of some benefit during the proliferative phase of ARDS. Meduri et al[19] in their study of steroid treatment in ARDS concluded that prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables, and has a distinct survival benefit when initiated before day 14 of ARDS.

In later phases of ARDS high-dose corticosteroids may be of some benefit during the proliferative phase of ARDS. The rationale behind this therapy is that much of the scarring that occurs during this phase of the illness is a consequence of unattenuated inflammation that can cause severe damage to the affected alveoli.[21]

The initial dosing regimen used by Meduri et al[17] is reasonable until further information is available: 2 mg/kg IV MP/d in divided doses. A clinical response (improved oxygenation, clearing of chest radiographic infiltrates), if one is to occur, is usually evident in 3 to 5 days. If a favorable response is evident, the steroids should be reduced gradually over the next 1 to 2 weeks to approximately 0.5 to 1.0 mg/kg/d and maintained at least until extubation is possible. If no initial response is evident, the steroids can simply be discontinued in most cases.

Parenteral steroids should not be used in patients who are only "at risk" for ARDS or during the first few days of ARDS (unless blood or bronchoalveolar lavage eosinophilia is documented). If a prolonged course of corticosteroids is to be administered during the fibroproliferative stage, it is important to exclude systemic infection first or ensure that it has been adequately treated.

■ Other Systemic Uses

Pulmonary—Chronic Obstructive Pulmonary Disease, Asthma

Status asthmaticus is a life-threatening condition where systemic corticosteroids early use is an effective treatment against the inflammatory component. Steroids main action in the airways is inhibition of recruitment of inflammatory cells and inhibition of release of proinflammatory mediators and cytokines from activated inflammatory and epithelial cells. Corticosteroids increase the number of B_2-adrenergic receptors and improve receptor responsiveness to B_2-adrenergic stimulation.

A systematic review of 12 studies for the Cochrane Review showed that corticosteroids within 1 hour of arrival in the ED reduced admissions.[22] MP 125 mg IV on arrival to the ED showed decreased admission rates compared to placebo and Lin and colleagues[23] showed improved peak flows after 1 and 2 hours of solumedrol. Use of early systemic steroids also reduces the number of relapses in the first 7 to 10 days and the risk of death.

Inhaled corticosteroids are the most effective long-term control therapy for persistent asthma, regardless of severity, and the only therapy shown to reduce the risk of death from asthma even in relatively low doses. Use of these agents in acute asthma has the potential benefits of reduced systemic side effects, direct delivery to the airway, and greater efficacy in reducing airway reactivity and edema alone or in addition to systemic steroids. Patients treated with inhaled steroids are less likely to be admitted whether they received systemic steroids or not, and no increased cough or bronchospasm is seen with their use. Inhaled corticosteroid therapy should be considered for symptomatic patients with stage III or IV disease ($FEV_1 < 50\%$) who experience repeated exacerbations.

In mild exacerbations, it is often appropriate to start with oral prednisone at a dose of 60 mg/d. This can either be dosed as a rapid pulse of 60 mg daily for 3 days, or tapered slowly over the course of 10 to 14 days. In more severe cases, the use of IV MP sodium succinate at a dose of 0.5 to 1.0 mg/kg every 6 hours is preferred. This is then transitioned to an oral formulation, often prednisone, as the patient's clinical status improves.

Multiple daily dosing appears warranted for initial therapy of acute exacerbations. It may take 6 to 8 hours for improvement in pulmonary function to occur after initiation of systemic therapy. Most patients achieve 70% of predicted FEV_1 within 48 hours and 80% by 6 days. Full doses should be continued until the patient's peak flow reaches 80% of predicted normal or personal best. Many patients require only 3 to 5-day courses of systemic corticosteroids. Tapering the steroid dosage after short courses is unnecessary.

Side effects of short-term (hours or days) steroid use include reversible increases in glucose (important in diabetics) and decreases in potassium, fluid retention with weight gain, mood alterations including rare psychosis, hypertension, peptic ulcers, aseptic necrosis of the femur, and rare allergic reactions to these agents.

Systemic toxicity is minimal with low to moderate inhaled doses, but the risk of systemic effects increases with high doses. Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, severe side effects such as adrenal suppression, osteoporosis, and cataract formation are reported less frequently than with systemic corticosteroids, but clinicians should monitor patients receiving high-dose chronic inhaled therapy.

Transplant

Corticosteroids have been used for immunosuppression since the 1960s. Glucocorticoids have a wide range of effects on the immune system, specifically the T lymphocytes. They were found to reverse and prevent rejection in the early transplant successes. In organ transplantation, most patients are kept on a regimen that includes glucocorticoids in conjunction with other immunosuppressive agents.

The pharmacologic effect steroids have on the immune system include inhibition of T-cell proliferation, T-cell–dependent immunity, and the expression of various cytokines, especially IL-2, IL-6, interferon-γ, and tumor necrosis factor-α.[6] They also suppress antibody formation and the delayed hypersensitivity response found in allograft rejection.

Every effort is made to minimize the dosage of glucocorticoids. *Combination therapy*, in which 2 or more immunosuppressants are administered simultaneously, has decreased the reliance on long-term, high-dose glucocorticoid administration for allograft survival.

For use in standard immunosuppression, recipients typically begin on a high initial dose (anywhere from 1 mg/kg to 500 mg IV of MP) the day of the transplant, and then taper over weeks to months to their final maintenance dose. Most centers maintain recipients on 5 to 10 mg daily or every other day. Prednisone is the oral drug of choice in most programs; however, if IV dosing is required, MP is the drug of choice.

Endocrine

Thyroid Storm Corticosteroids are uniformly used (in stress dosages of 300 mg/d of hydrocortisone equivalent administered IV) for potential relative AI. Glucocorticoid use in thyroid storm is associated with improved survival rates.[24] Dexamethasone inhibits thyroid hormone release by preventing the peripheral conversion of T_4 to T_3, which is responsible for perhaps 85% of T_3 present in the circulation. Dexamethasone has shown to be effective and should be given as 2 mg IV every 6 hours. Hydrocortisone may be substituted in place of dexamethasone.

Myxedema Coma Myxedema coma is a rare, exaggerated and life-threatening form of hypothyroidism. Steroids are given because myxedema may be either a manifestation of panhypopituitarism or a coexisting condition with primary adrenal failure. There is a 5% to 10% incidence of concurrent hypoadrenalism, so a cosyntropin stimulation test should be administered if possible, and then empiric stress doses of corticosteroids should be given until adrenal status is known. Glucocorticoids should be given before levothyroxine because of the risk of precipitating adrenal crisis if T_4 is given to a patient with hypoadrenalism, so a full stimulation test may not be always be possible. Stress dosages of corticosteroids, such as 300 mg of hydrocortisone IV followed by 100 mg IV every 6 to 8 hours, are routinely given to patients in myxedema coma.

Malignancies

Dexamethasone is used in conjunction with radiotherapy to reduce edema related to tumors in critical areas such as the superior mediastinum, brain, and spinal cord. Doses of 4 to 6 mg every 6 hours have dramatic effects in restoring neurologic function in patients with cerebral metastases, but these effects are temporary. As acute changes in dosage can lead to a rapid recrudescence of symptoms, dexamethasone should not be discontinued abruptly in patients receiving radiotherapy or chemotherapy for brain metastases. Gradual tapering of the dosage may be undertaken if a clinical response to definitive antitumor therapy has been achieved.

■ Adverse Effects of Corticosteroid Therapy

Systemic side effects of steroids include hypertension, hyperlipidemia, and steroid-induced diabetes that may be partly responsible for increasing the risk of cardiovascular death. The complications from long-term corticosteroid therapy are osteoporosis, cataracts, gastrointestinal bleeding, glucose intolerance, steroid skeletal myopathy, bone disease, and adrenal suppression. Acute administration may lead to

glucose and electrolyte abnormalities and altered mental status. Acute withdraw may lead to an Addisonian crisis. Most of these problems are magnified with higher doses and are reduced or eliminated once the dosage is reduced.

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