REVIEW ARTICLE

CURRENT CONCEPTS

Corticosteroid Insufficiency in Acutely Ill Patients

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A N INCREASE IN TISSUE CORTICOSTEROID LEVELS DURING ACUTE ILL-ness is an important protective response. Many diseases and their treatments interfere with the normal corticosteroid response to illness and thus induce tissue corticosteroid insufficiency. In this article, we review the physiology of the corticosteroid response to acute illness, describe the clinical features of hypoadrenalism in patients with acute illness, and discuss practical issues relating to diagnosis and treatment of corticosteroid insufficiency in acutely ill patients.

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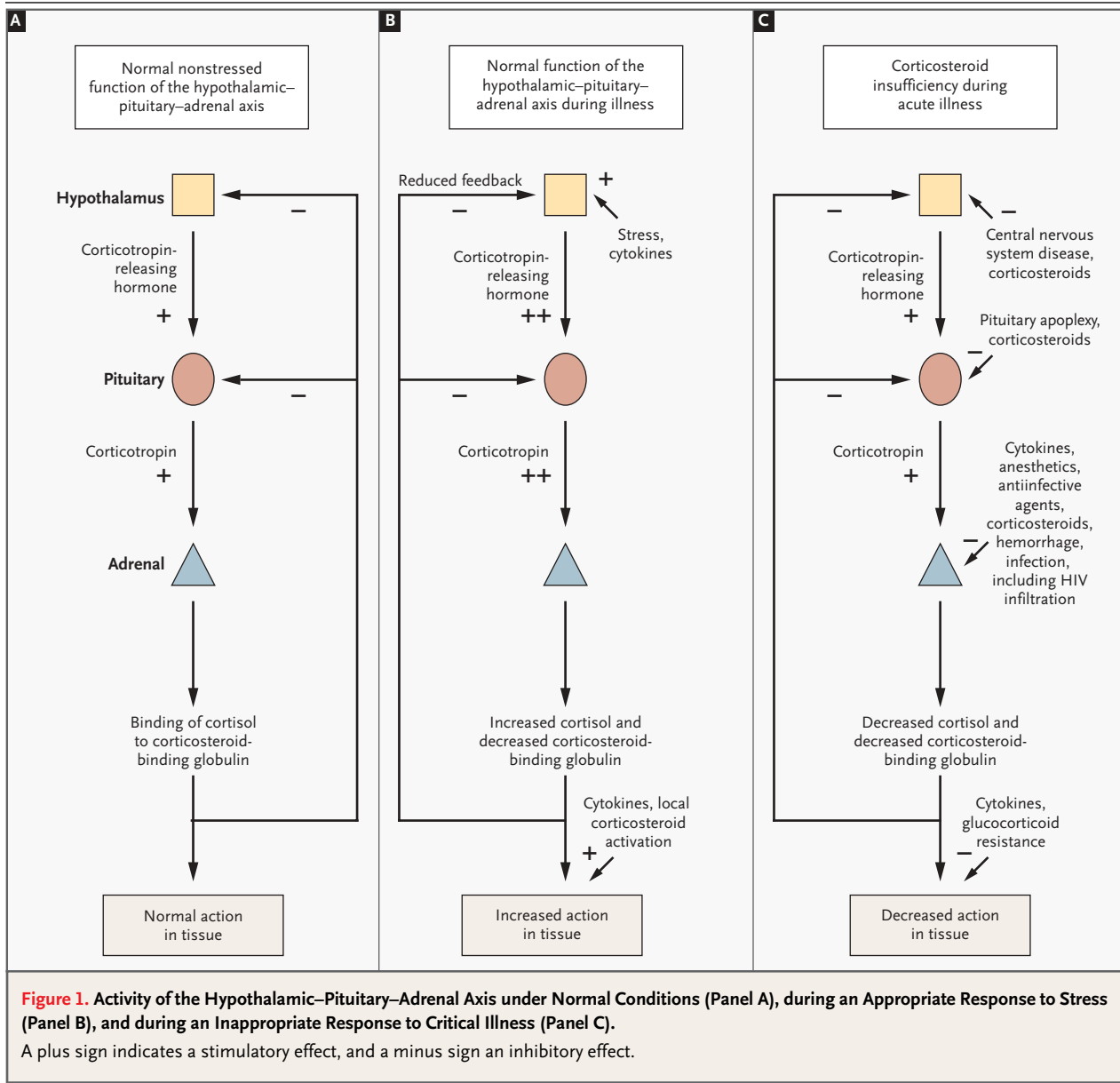
THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN ACUTE ILLNESS

Cortisol is the predominant corticosteroid secreted from the adrenal cortex in humans. In a healthy, unstressed person, cortisol is secreted according to a diurnal pattern under the influence of corticotropin released from the pituitary gland. Corticotropin secretion, in turn, is under the influence of hypothalamic corticotropin-releasing hormone (Fig. 1A), and both hormones are subject to negative feedback control by cortisol itself. Circulating cortisol is bound to corticosteroid-binding globulin, with less than 10 percent in the free, bioavailable form. With severe infection, trauma, burns, illness, or surgery, there is an increase in cortisol production by as much as a factor of six that is roughly proportional to the severity of the illness (Fig. 1B).[1-3] Diurnal variation in cortisol secretion is also lost. These effects are due to increased production of corticotropin-releasing hormone and corticotropin and a reduction in negative feedback from cortisol.[4] Stimulation of the hypothalamic–pituitary–adrenal axis in this context is caused by elevated levels of circulating cytokines, among other factors.[5]

Adrenal responsiveness to exogenous corticotropin is normally maintained during acute illness.[6,7] In addition, during critical illness, levels of corticosteroid-binding globulin decrease rapidly,[8] leading to increased levels of circulating free corticosteroids. Levels of free cortisol may also increase at sites of inflammation owing to the cleavage of corticosteroid-binding globulin by neutrophil elastase, an effect that liberates cortisol.[9] In addition to having systemic actions, inflammatory cytokines can increase tissue cortisol levels through changes in peripheral cortisol metabolism[10] and can increase the affinity of glucocorticoid receptors for cortisol.[11] These changes in cortisol action appear to be important adaptive mechanisms regulating the inflammatory response.[5]

During severe illness, many factors can impair the normal corticosteroid response (Fig. 1C). These factors include preexisting conditions affecting the hypothalamic–pituitary–adrenal axis,[12] but corticosteroid insufficiency can also occur during the course of acute illness. Responses involving corticotropin-releasing hormone and corticotropin can be impaired by head injury, central nervous system depressants, or pituitary infarction.[13] Adrenal cortisol synthesis can be impaired by multiple mechanisms.[6,12] The anesthetic agent etomidate and the antifungal agent ketoconazole inhibit the activity of enzymes involved in cortisol synthesis.[14] Adrenal hemorrhage can occur in sick

Figure 1. Activity of the Hypothalamic–Pituitary–Adrenal Axis under Normal Conditions (Panel A), during an Appropriate Response to Stress (Panel B), and during an Inappropriate Response to Critical Illness (Panel C).

A plus sign indicates a stimulatory effect, and a minus sign an inhibitory effect.

patients, especially those with septicemia and underlying coagulopathy, and adrenal insufficiency can occur when there is extensive destruction of adrenal tissue caused by tumors or infection. The high levels of inflammatory cytokines in patients with sepsis can also directly inhibit adrenal cortisol synthesis.[15]

Exogenous corticosteroid therapy suppresses the production of corticotropin-releasing hormone and corticotropin and can induce adrenal atrophy that may persist for months after the cessation of corticosteroid treatment.[16] This effect depends on the dose and duration of treatment and varies greatly from person to person but should be anticipated in any patient who has been receiving more than 30 mg of hydrocortisone per day (or 7.5 mg of prednisolone or 0.75 mg of dexamethasone per day) for more than three weeks. Similar suppression of the hypothalamic–pituitary–adrenal axis has been reported with medroxyprogesterone and megestrol acetate treatment.[17,18] The hepatic metabolism of cortisol might be enhanced by drugs such as rifampin or phenytoin. In contrast to the tissue-sensitizing effect of low levels of cytokines, excessive produc-

tion of inflammatory cytokines during sepsis can induce systemic or tissue-specific corticosteroid resistance[19,20] so that normal adrenal responses may be insufficient to control inflammation.

Human immunodeficiency virus (HIV) infection has complex effects on the hypothalamic–pituitary–adrenal axis. Adrenal infections and increased use of drugs such as rifampin, ketoconazole, and megestrol acetate increase the risk of hypoadrenalism, and in some patients there is acquired tissue-specific corticosteroid resistance.[21] Adrenal insufficiency in critically ill HIV-infected patients is thus common.[22] The threshold for testing of the hypothalamic–pituitary–adrenal axis in critically ill patients with HIV infection should be low. Care is also required in the interpretation of cortisol measurements in women taking oral contraceptives, since synthetic estrogens increase the level of corticosteroid-binding globulin. Total cortisol levels may thus be elevated to the normal range even when adrenal insufficiency is present.

Subnormal adrenal corticosteroid production during acute severe illness has been termed "functional adrenal insufficiency," to reflect the notion that hypoadrenalism can occur without obvious structural defects in the hypothalamic–pituitary–adrenal axis.[7] Functional adrenal insufficiency has proved difficult to define biochemically, but some guidance is given below. It can develop during the course of an illness and is usually transient. A related concept is that of "relative adrenal insufficiency," in which cortisol levels, although high in absolute terms, are insufficient to control the inflammatory response. Inability to mount an adequate cortisol response, as seen in patients with structural disease of the hypothalamic–pituitary–adrenal axis, adrenal suppression by corticosteroids, or prolonged treatment with offending drugs, increases the risk of death during acute illness.[16,23] Thus, if functional adrenal insufficiency can be identified, treatment with supplemental corticosteroids may be of benefit.

DIAGNOSIS OF CORTICOSTEROID INSUFFICIENCY DURING ACUTE ILLNESS

CLINICAL FEATURES

Corticosteroid insufficiency associated with acute illness can be difficult to discern clinically, but there are some features that suggest the diagnosis (Table 1). In patients with preexisting but unrecognized hypoadrenalism, symptoms before the onset of illness have included fatigue, weight loss, nausea, abdominal pain, arthralgia, and postural syncope. Increased skin pigmentation, reflecting high concentrations of circulating corticotropin, may be present in patients with long-standing adrenal disease, and vitiligo could indicate the presence of autoimmune Addison's disease. A history of oligomenorrhea or amenorrhea, decreased libido, intolerance to cold, or weight gain may reflect hypopituitarism with an associated deficiency of gonadotropins or thyrotropin.

When the classic features of an addisonian crisis are present, the diagnosis may be obvious, but features such as anorexia, nausea, vomiting, diarrhea, abdominal pain, and delirium are common in patients with acute severe illness. Similarly, fever and hypotension are common features in critically ill patients and may be attributed to sepsis and hypovolemia. Characteristic biochemical findings

Table 1. Features Suggesting Corticosteroid Insufficiency.

Symptoms
Weakness and fatigue
Anorexia, nausea, vomiting
Abdominal pain
Myalgia or arthralgia
Postural dizziness
Craving for salt
Headaches
Memory impairment
Depression

Findings on physical examination
Increased pigmentation
Hypotension (postural)
Tachycardia
Fever
Decreased body hair
Vitiligo
Features of hypopituitarism
 Amenorrhea
 Intolerance of cold

Clinical problems
Hemodynamic instability
 Hyperdynamic (common)
 Hypodynamic (rare)
Ongoing inflammation with no obvious source
Multiple-organ dysfunction
Hypoglycemia

Laboratory findings
Hyponatremia
Hyperkalemia
Hypoglycemia
Eosinophilia
Elevated thyrotropin levels

such as hyponatremia and hyperkalemia may occur, but in an intensive care setting these features are often masked by changes in fluid-replacement regimens. Furthermore, hyperkalemia is uncommon in patients with secondary adrenal failure, because mineralocorticoid secretion remains intact thanks to the renin–angiotensin–aldosterone axis. Hypoglycemia and eosinophilia are relatively uncommon in critically ill patients, however, and should alert the clinician to the possibility of hypoadrenalism.[24]

In the majority of cases, it remains extremely difficult to recognize adrenal insufficiency in a patient in the intensive care unit. Important diagnostic clues are hemodynamic instability despite adequate fluid resuscitation (most often associated with a hyperdynamic circulation and decreased systemic vascular resistance) and ongoing evidence of inflammation without an obvious source that does not respond to empirical treatment.[6,7] Limitations of the physical examination suggest that the threshold for investigation should be low, especially in patients with septic shock (as discussed below).

LABORATORY INVESTIGATIONS

Several factors complicate investigation of the hypothalamic–pituitary–adrenal axis in patients with critical illness. Expected cortisol levels vary with the type and severity of disease, making it difficult to define normal ranges. Since the highest levels of cortisol are found in patients with the severest illness, both high and low cortisol levels have been shown to be associated with a poor prognosis.[25,26] Changes in levels of corticosteroid-binding globulin further complicate the estimation of free cortisol levels. Even if levels of free circulating cortisol could be measured accurately, the fact that tissue-specific resistance to corticosteroids varies implies that the optimal levels of circulating corticosteroids are likely to vary according to the patient's condition. In addition, tests that assess the whole of the hypothalamic–pituitary–adrenal axis, such as the insulin-tolerance test, are unsuitable for use in patients with critical illness. With these caveats, assessment of corticosteroid sufficiency has been made on the basis of randomly measured cortisol levels or the corticotropin stimulation test.

Despite the correlation between cortisol levels and the severity of illness, it is difficult to estimate usefully what an appropriate response should be in a critically ill patient. More useful would be the identification of a minimal threshold level below which

adrenal insufficiency is likely and a maximal threshold level above which insufficiency is unlikely. Many threshold levels have been proposed for the definition of an insufficient cortisol level (measured at any time of day) during acute illness,[7] but none is entirely satisfactory.[27] Proposed minimal levels have ranged from 10 μg per deciliter (276 nmol per liter)[28] to 34 μg per deciliter (938 nmol per liter), but several studies suggest that a threshold of 15 μg per deciliter (414 nmol per liter) best identifies persons with clinical features of corticosteroid insufficiency or who would benefit from corticosteroid replacement.[29-32]

The corticotropin stimulation test has also been evaluated in patients with critical illness (with the intramuscular or intravenous administration of 250 μg of cosyntropin [a synthetic peptide consisting of the first 24 amino acids of corticotropin], with plasma cortisol levels measured 0, 30, and sometimes 60 minutes after administration). The use of the test in this setting remains controversial, but the incremental response after the administration of corticotropin (in contrast to the response found in patients who are not critically ill) may have prognostic implications, with a small increase (less than 9 μg per deciliter [250 nmol per liter]) from the base-line cortisol level to the highest cortisol level (measured at 30 or 60 minutes) associated with an increased risk of death.[26,33] Our belief is that adrenal insufficiency appears to be unlikely when a random cortisol measurement is greater than 34 μg per deciliter. Conversely, adrenal insufficiency is likely if the serum cortisol level is below 15 μg per deciliter during acute severe illness (Fig. 2). For persons with cortisol levels between these two values, a poor response on a corticotropin test would indicate the possibility of adrenal insufficiency and a need for supplemental corticosteroids. At least among patients in septic shock, these criteria appear to identify many patients who will benefit from supplemental corticosteroid treatment (as discussed below).[33] However, such cutoffs are somewhat arbitrary, since levels of circulating cortisol only partly mediate corticosteroid action at the tissue level.
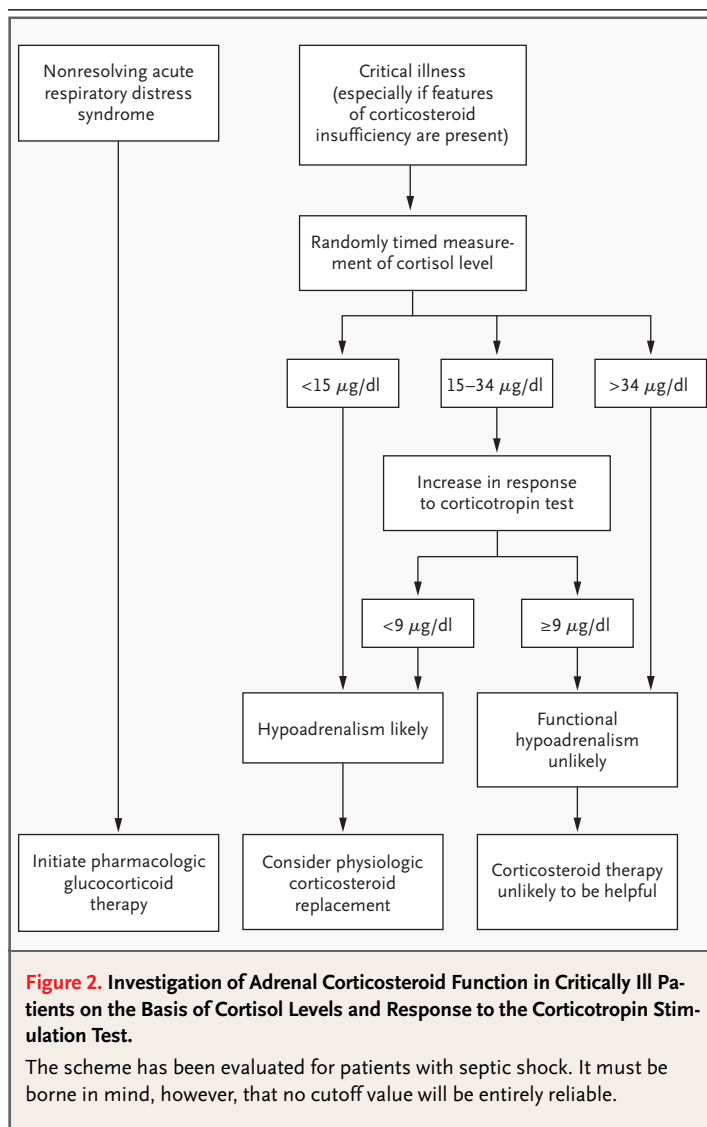
Ideally, physicians should perform a corticotropin test at the outset, rather than wait for the results of random measurements of cortisol. The corticotropin test, however, has clear limitations when hypoadrenalism occurs secondary to recent hypothalamic or pituitary insults, and caution is necessary. A low-dose (1-μg) corticotropin stimulation test has been proposed, with the suggestion that it may be

more sensitive than the 250-μg test.[34,35] Further validation is required to support this theory, and we believe that a low-dose test should not be used at present. It is important to be aware that even in patients who have normal test results, adrenal insufficiency may develop later in the illness. It is unclear how often one should perform such tests, but the development of new clinical features suggesting corticosteroid insufficiency or a deterioration in clinical condition should prompt further testing.

DURATION OF INSUFFICIENCY

In practice, it is often unclear whether adrenal insufficiency is functional and transient during acute illness or whether it is due to established structural disease of the hypothalamic–pituitary–adrenal axis. Lifelong corticosteroid-replacement therapy should not be sanctioned on the basis of equivocal biochemical tests in an acutely ill patient. When there is doubt, testing the hypothalamic–pituitary–adrenal axis with the use of the corticotropin stimulation test or an insulin-tolerance test after resolution of the illness will determine whether long-term corticosteroid replacement will be required.

The diagnosis of adrenal insufficiency is less problematic in the absence of acute illness. In patients with primary adrenal insufficiency, corticotropin levels are disproportionately elevated relative to plasma cortisol levels. Plasma cortisol levels are measured 0 and 30 minutes after the administration of corticotropin, and a normal response is defined by a peak of more than 19 μg per deciliter (525 nmol per liter) — a response that would be at the 5th percentile among normal subjects.[36] Incremental responses are of no value outside the context of critical illness and should not be used. The corticotropin test should not be used after a recent pituitary insult (such as surgery or pituitary apoplexy), since it may take two to three weeks for the adrenal cortex to readjust to the reduced level of corticotropin secretion. The insulin-tolerance test assesses the integrity of the whole hypothalamic–pituitary–adrenal axis and should be considered the gold standard.[37] However, it cannot be performed in patients with ischemic heart disease, epilepsy, or severe cortisol deficiency (a cortisol level at 9 a.m. of less than 7 μg per deciliter [193 nmol per liter]). In normal subjects, the peak plasma cortisol level exceeds 18 μg per deciliter (497 nmol per liter). However, the cortisol response to hypoglycemia can be reliably predicted by the corticotropin stimulation test — a safer, cheaper, and quicker test.

Figure 2. Investigation of Adrenal Corticosteroid Function in Critically Ill Patients on the Basis of Cortisol Levels and Response to the Corticotropin Stimulation Test.

The scheme has been evaluated for patients with septic shock. It must be borne in mind, however, that no cutoff value will be entirely reliable.

TREATMENT OF ACUTE ADRENAL INSUFFICIENCY

Critically ill patients with established hypoadrenalism (known structural or functional defects in the hypothalamic–pituitary–adrenal axis) should be treated with intravenous or intramuscular hydrocortisone at a dose of 50 mg every six hours (Fig. 3). For patients who are in shock, 5 percent dextrose in normal saline should be given intravenously initially. Subsequent saline-and-dextrose therapy will depend on the results of clinical and biochemical monitoring.

SEPTIC SHOCK

There is now preliminary evidence to support the use of supplemental corticosteroids in patients with established septic shock who are in an intensive care unit, especially in those with biochemical evidence of functional hypoadrenalism.[33,38,39] Three randomized, controlled trials of hydrocortisone replacement in patients with septic shock have shown improvements in hemodynamics and a reduction in the need for vasopressor therapy. In the largest randomized, placebo-controlled trial, treatment of 300 medical and surgical patients with 200 mg of hydrocortisone per day and 50 µg of fludrocortisone once daily for seven days significantly reduced mortality and the duration of vasopressor therapy.[33] Patients were receiving mechanical ventilation, had hypotension that was unresponsive to fluids, and had other organ dysfunction. The benefits that were seen were restricted to patients who had a small increase in the cortisol level in response to the corticotropin test (an increase of less than 9 µg per deciliter from base line to the highest measurement at 30 or 60 minutes). Such patients should be treated with 50 mg of hydrocortisone intravenously every six hours or with similar amounts by continuous infusion. These treatments lead to moderately supraphysiologic cortisol levels, which may be important in overcoming an element of tissue-specific corticosteroid resistance.

Since adrenal insufficiency appears to be common in patients with septic shock, treatment should be initiated at the time of diagnostic testing and can be stopped if results do not indicate the presence of adrenal insufficiency. In the largest trial of corticosteroid replacement in patients with septic shock, fludrocortisone (50 µg once daily through a nasogastric tube) was given to replace mineralocorticoids. Whether mineralocorticoid replacement accounted for any of the beneficial effects is unclear, but at these doses, adverse effects are unlikely to occur.

OTHER CRITICAL ILLNESSES

In addition to having a role in septic shock, physiologic corticosteroid replacement may be beneficial in patients with other critical illnesses such as trauma, burns, and medical and surgical conditions in which there is evidence of adrenal insufficiency,[7] although no data from randomized trials are available. Until further studies have been conducted, treatment with supplemental corticosteroids is indicated for patients who have adrenal insufficiency on biochemical testing. There are few data to suggest that corticosteroids at the doses mentioned above are detrimental,[33] but given the possibility of decreased resistance to infection, this treatment should not be used for prolonged periods in the absence of evidence of corticosteroid insufficiency.

The role of pharmacologic glucocorticoid treatment in patients with critical illnesses is controversial, but short-term treatment of heterogeneous groups of patients with supraphysiologic doses of glucocorticoids (e.g., 30 mg of methylprednisolone
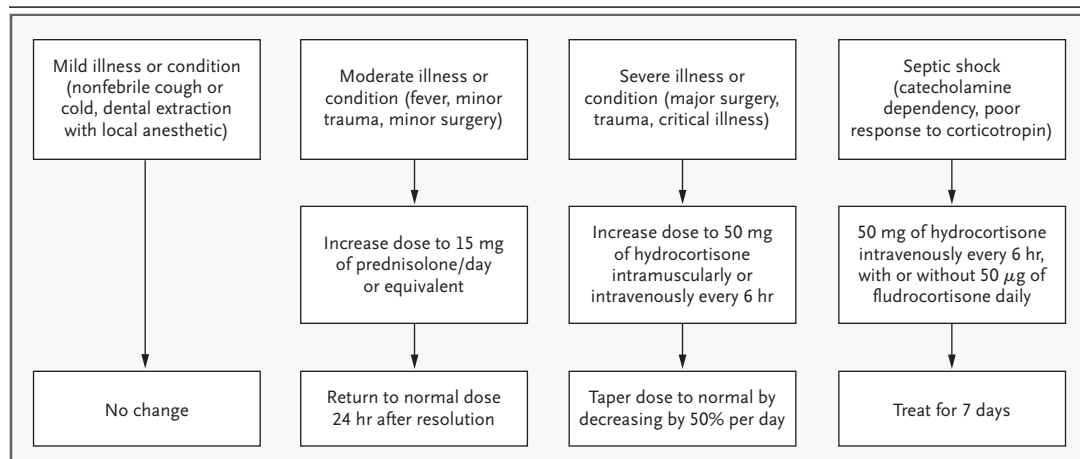
Figure 3. Suggested Corticosteroid-Replacement Doses during Intercurrent and Acute Illness in Patients with Proven or Suspected Adrenal Insufficiency, Including Those Receiving Corticosteroid Therapy.

One milligram of prednisolone has corticosteroid potency equivalent to that of 4 mg of hydrocortisone.

per kilogram of body weight per day) conveys no benefit and may be harmful.[6] Pharmacologic glucocorticoid treatment (2 mg of methylprednisolone per kilogram per day) does, however, reduce mortality among patients with nonresolving acute respiratory distress syndrome,[40] and early treatment with dexamethasone may improve the outcome in bacterial meningitis.[41,42] In patients in whom improved outcomes are seen, high doses of corticosteroids may be required to overcome tissue-specific resistance to corticosteroids.[43] Supraphysiologic doses of glucocorticoids in patients with critical illness outside the situations in which benefit has been proved are not indicated.

LONGER-TERM TREATMENT

Continued corticosteroid replacement is indicated if there is a persistent abnormality of the hypothalamic–pituitary–adrenal axis. Cortisone must be converted to cortisol in the liver by 11β-hydroxysteroid dehydrogenase type I[44]; because the activity of this enzyme varies markedly from person to person, hydrocortisone, rather than cortisone acetate, should be used for replacement therapy. (Since 11β-hydroxysteroid dehydrogenase type I also converts inactive prednisone to active prednisolone,[45] the widespread use of prednisone, particularly in the United States, should be reviewed.) The normal rate of endogenous cortisol production was previously thought to be 25 to 30 mg per day, but studies of stable isotopes have demonstrated rates of 8 to 15 mg per day.[1] Increasingly, most patients with hypoadrenalism manage with doses of hydrocortisone of less than 30 mg per day (15 to 25 mg per day). Doses are usually given on wakening, with a smaller dose in the early evening to mimic the normal diurnal pattern of secretion, but some patients may feel better when receiving three doses daily. Patients with adrenal disease usually also require mineralocorticoid replacement with 0.05 to 0.2 mg of fludrocortisone per day.

Patients receiving corticosteroid-replacement therapy should be advised to double the daily dose during febrile illnesses, after accidents, or when they have mental stress caused by such events as an important academic examination.[46] If the patient is vomiting, parenteral hydrocortisone must be given urgently, as mentioned above. For minor surgery, 50 to 100 mg of hydrocortisone is given along with any other medication administered before the operation. For major surgery, this dose is followed by the same regimen used for acute adrenal insufficiency (Fig. 3). Patients receiving corticosteroid therapy should register for a Medic Alert bracelet or necklace and carry a medical identification card, stating the need for corticosteroid replacement. In addition to corticosteroid and mineralocorticoid replacement, adrenal androgens (25 to 50 mg of dehydroepiandrosterone per day) have been reported to have beneficial effects on well-being in both patients with primary adrenal failure and patients with secondary adrenal failure.[47,48] Further studies are required before such treatment can be recommended routinely.

CONCLUSIONS

It continues to be difficult to diagnose corticosteroid insufficiency in patients with critical illnesses. Recent trials exploring corticosteroid replacement during established septic shock have reported substantial benefits. Treatment with physiologic levels of corticosteroids appears to carry few risks, and we recommend a low threshold for testing of the hypothalamic–pituitary–adrenal axis and prescription of corticosteroid-replacement therapy in acutely ill patients. Short-term treatment with low-dose corticosteroids is unlikely to cause harm and should be initiated while the patient awaits the results of diagnostic tests. Further studies are needed to clarify specific situations in which corticosteroid replacement is beneficial and to determine the optimal dose of corticosteroids and the optimal duration of therapy.

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