

## REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

## Adrenal Crisis

R. Louise Rushworth, M.B., B.S., Ph.D., David J. Torpy, M.B., B.S., Ph.D.,  
and Henrik Falhammar, M.D., Ph.D.

From the School of Medicine, Sydney (R.L.R.), the University of Notre Dame Australia, Darlinghurst, NSW (R.L.R.), the Endocrine and Metabolic Unit, Royal Adelaide Hospital and University of Adelaide, North Terrace, Adelaide, SA (D.J.T.), and the Menzies School of Health Research and Royal Darwin Hospital, Tiwi, NT (H.F.) — all in Australia; and the Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, and the Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm (H.F.). Address reprint requests to Dr. Falhammar at the Department of Molecular Medicine and Surgery, D2:04, Karolinska Institutet, SE-171 76 Stockholm, Sweden, or at [henrik.falhammar@ki.se](mailto:henrik.falhammar@ki.se).

N Engl J Med 2019;381:852-61.

DOI: 10.1056/NEJMra1807486

Copyright © 2019 Massachusetts Medical Society.

GLUCOCORTICOID REPLACEMENT THERAPY, AVAILABLE SINCE THE 1950S, has prolonged the survival of patients with adrenal insufficiency.<sup>1</sup> However, adrenal crises, which are life-threatening medical emergencies, still develop in many affected patients. Adrenal crisis appears to be increasing in frequency, despite the availability of effective preventive strategies.<sup>2-4</sup> This review examines the definitions, pathophysiology, epidemiology, and treatment of adrenal crises.

## DEFINITIONS OF ADRENAL CRISIS

There is no universally accepted definition of an adrenal crisis, also called acute adrenal insufficiency or Addisonian crisis.<sup>5</sup> Generally, acute physiological disturbances in patients with known hypoadrenalism are labeled as adrenal crises on the basis of clinical assessment.<sup>2,5,6</sup> Diagnostic misclassification may not alter immediate management but, at the epidemiologic level, can impede an understanding of the nature of adrenal crises.

Given the lack of a research-based classification and in recognition of the physiological changes that distinguish an adrenal crisis from a milder episode of hypoadrenalism,<sup>5-11</sup> pragmatic definitions of adrenal crisis have generally been adopted.<sup>2,5,8,9</sup> An adrenal crisis in an adult is defined as an acute deterioration in health status associated with absolute hypotension (systolic blood pressure <100 mm Hg) or relative hypotension (systolic blood pressure  $\geq$ 20 mm Hg lower than usual), with features that resolve within 1 to 2 hours after parenteral glucocorticoid administration (i.e., a marked resolution of hypotension within 1 hour and improvement in clinical symptoms over a period of 2 hours).

Since identification of hypotension in infants and young children during an emergency may be difficult, an adrenal crisis in this age group is defined as an acute deterioration in health status associated with an acute hemodynamic disturbance (hypotension or sinus tachycardia relative to age-related normative data) or a marked electrolyte abnormality (e.g., hyponatremia, hyperkalemia, or hypoglycemia not attributable to another illness). After parenteral glucocorticoid administration, the features ascribed to adrenal crisis resolve substantially.<sup>12-16</sup>

Concomitant features in patients of all ages include acute abdominal symptoms; delirium, obtundation, or both; and hyponatremia, hyperkalemia, hypoglycemia, and pyrexia.<sup>5-11</sup> When hypotension ascribed to an adrenal crisis does not respond or responds poorly to glucocorticoid administration, the coexistence of other illnesses associated with hypotension, such as sepsis, should be considered.

Adrenal crises are the most severe manifestation of adrenal insufficiency, but they share symptoms with milder hypoadrenal states. These symptoms include anorexia, nausea, vomiting, fatigue, postural dizziness, abdominal pain, limb and back pain, and impaired consciousness. Shared biochemical perturbations include

hyponatremia, hyperkalemia (in primary adrenal insufficiency [Addison's disease and congenital adrenal hyperplasia]), and hypoglycemia (more common in children than in adults) (Table 1).<sup>5-8,11</sup> However, an acute illness in a patient who has previously received a diagnosis of primary adrenal insufficiency without evidence of hemodynamic compromise or hypotension (or in young children, delayed capillary refill or tachycardia as alternative physical manifestations) should be considered physiologically distinct from an adrenal crisis and instead classified as symptomatic adrenal insufficiency, a precursor of adrenal crisis, or an incipient adrenal crisis.<sup>2,5,7,8</sup> Marked symptoms in the absence of hypotension probably signal an incipient adrenal crisis, and treatment with hydrocortisone and intravenous fluids may avert the development of an actual adrenal crisis.

#### PATHOPHYSIOLOGICAL FEATURES

Adrenal crises arise from an absolute or a relative deficiency of cortisol, an endogenous glucocorticoid; in that circumstance, there is insufficient tissue glucocorticoid activity to maintain homeostasis. The contributing pathophysiological processes are depicted in Figure 1.

Cortisol has a circulating half-life of 90 minutes; hence, tissues become deficient within several hours after cortisol deprivation. Cortisol has highly pleiotropic effects that are due to transcriptional modulation of genes bearing a glucocorticoid response element (29% of all genes).<sup>17</sup> The physiological consequences of cortisol deficiency are extensive and start with loss of the normal suppressive action of endogenous glucocorticoids on inflammatory cytokines, resulting in rapid increases in cytokine levels, which cause fever, malaise, anorexia, and bodily pain. Consequently, cortisol deficiency leads to altered immune-cell populations (neutropenia, eosinophilia, and lymphocytosis); loss of the synergistic action of cortisol with catecholamines on vascular reactivity, leading to vasodilatation and hypotension; hepatic effects on intermediary metabolism, with reduced gluconeogenesis, hypoglycemia, or both; and reduced circulating free fatty acids and amino acids.<sup>18-21</sup>

At the cellular level, loss of cortisol depresses the action of activator protein 1 (AP-1) and nuclear factor  $\kappa$ B (NF- $\kappa$ B), leading to the unfettered acti-

**Table 1. Symptoms, Signs, and Biochemical Characteristics of Adrenal Crisis.\***

#### Symptoms

Gastrointestinal: anorexia, nausea, vomiting

Pain: abdominal, limb, back

Severe fatigue

Severe weakness

Postural dizziness, syncope

Confusion

#### Signs

Abdominal tenderness or guarding

Hyperpigmentation (only in primary adrenal insufficiency)†

Pyrexia

Hypotension: systolic pressure <100 mm Hg in adults or  $\geq 20$  mm Hg lower than usual in adults, acute hemodynamic disturbance according to age-related normative levels in children, delayed capillary refill or tachycardia in young children, circulatory collapse

Impaired consciousness: delirium, obtundation, coma

#### Biochemical abnormalities on routine blood tests

Hyponatremia

Hyperkalemia

Hypercalcemia

Hypoglycemia (more common in children than in adults)

Altered immune-cell populations: neutropenia, eosinophilia, lymphocytosis

Mild normocytic anemia

\* An adrenal crisis is defined as an acute deterioration in health status associated with hypotension (absolute or relative), with features that resolve within 1 to 2 hours after parenteral glucocorticoid administration (i.e., a marked resolution of hypotension within 1 hour and improvement in clinical symptoms over a period of 2 hours). Since hypotension may be more difficult to identify in infants and young children than in adults, an acute hemodynamic disturbance, a marked abnormality in one or more electrolytes, or hypoglycemia not attributable to another illness can be used for identification.

† Hyperpigmentation develops slowly and can be a specific sign of undiagnosed primary adrenal insufficiency (Addison's disease or congenital adrenal hyperplasia) or of an insufficient dose of glucocorticoid replacement over a long period in a patient with primary adrenal insufficiency.

vation of genes that produce inflammatory proteins, since the normal cortisol inhibition of the binding of NF- $\kappa$ B to the glucocorticoid receptor is lost.<sup>17,18</sup> Furthermore, mineralocorticoid deficiency, which is prominent in primary but not secondary adrenal insufficiency,<sup>3,22,23</sup> is likely to exacerbate adrenal crises through sodium and water loss and potassium retention.

## EPIDEMIOLOGIC FEATURES

Each year, approximately 6 to 8% of patients with adrenal insufficiency have an incident adrenal crisis.<sup>2,3</sup> Adrenal crises are slightly more frequent in patients with primary hypoadrenalism than in those with secondary adrenal insufficiency, probably because of partial preservation of cortisol secretion in some patients with secondary adrenal insufficiency,<sup>3</sup> as well as the absence of mineralocorticoid secretion in those with primary hypoadrenalism.<sup>22-24</sup> Adrenal crises are uncommon in patients with hypoadrenalism due to long-term glucocorticoid therapy, despite a variable degree of consequent adrenal suppression.<sup>25</sup>

Susceptibility to adrenal crises varies among patients with hypoadrenalism. Risk factors include older age, a history of prior adrenal crises, the presence of autoimmune polyglandular syndromes, type 1 diabetes mellitus, and nonendocrine coexisting conditions such as asthma and cardiac disease. However, the mechanism of action of these various factors in adrenal crisis is unclear and may be specific to coexisting conditions.<sup>22,23,26,27</sup> In addition, unknown factors may potentiate the risk of adrenal crisis, since some patients have numerous episodes, whereas others have few, if any, episodes.<sup>28</sup> An association between the occurrence of an adrenal crisis and the chronic asthenia that is characteristic of hypoadrenalism is plausible but not established. However, a recent prospective, multicenter study using questionnaires to obtain data from 110 patients with primary adrenal insufficiency showed a positive association between episodes of incipient adrenal crisis and a poor quality of life.<sup>29</sup>

It has been suggested, on the basis of epidemiologic data, that rising rates of adrenal crisis may be due to current use of lower-dose, short-acting glucocorticoid regimens (hydrocortisone or cortisone acetate) in patients with hypoadrenalism.<sup>2,4,30,31</sup> This hypothesis is supported by evidence from a longitudinal analysis involving 156 patients with congenital adrenal hyperplasia who received care at a referral center. The study showed that a low baseline hydrocortisone replacement dose was associated with more frequent episodes of various illnesses, requiring supplemental doses (“stress doses”) of glucocorticoids.<sup>30</sup>

## MORTALITY

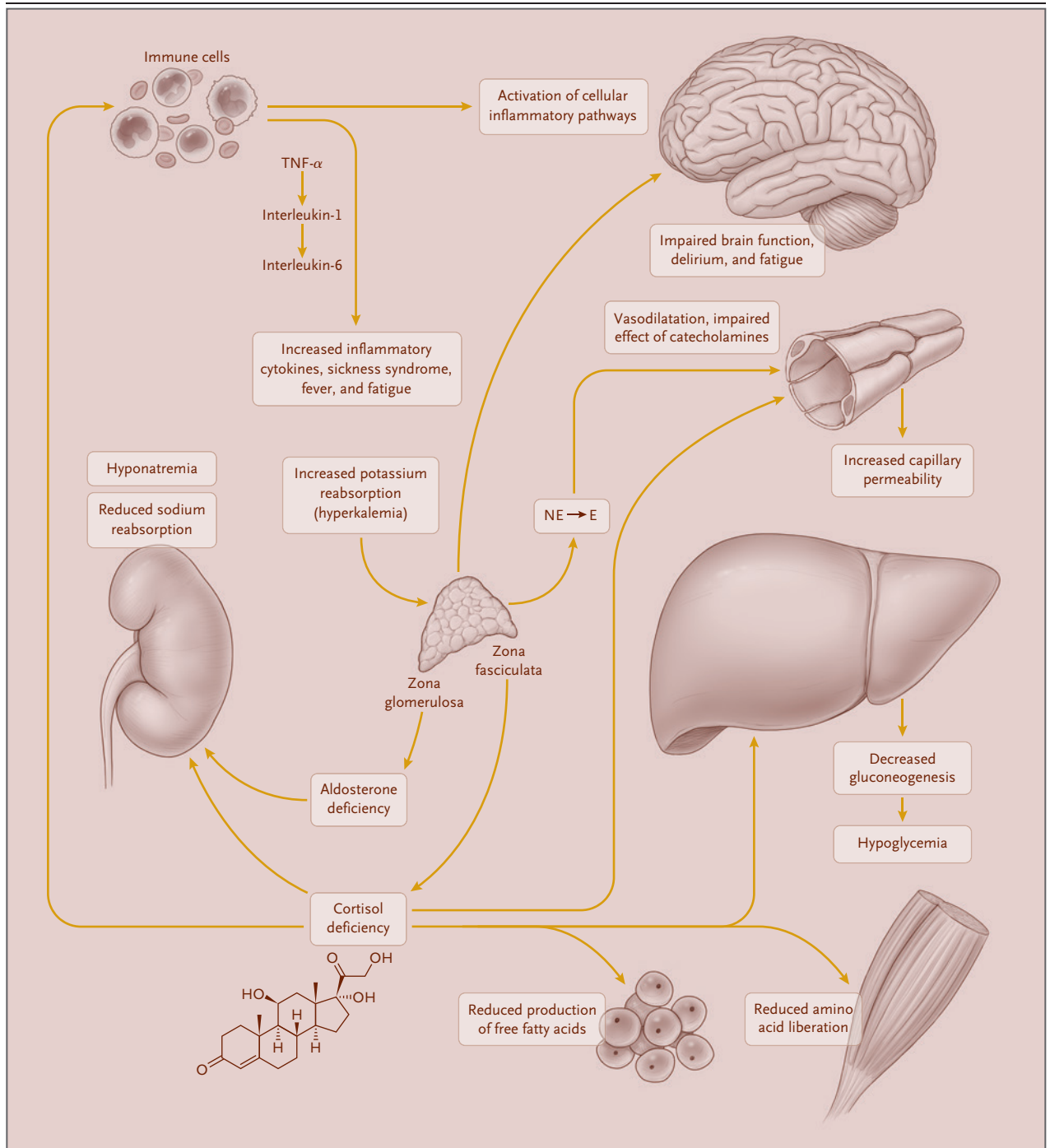
Adrenal crises contribute to mortality among patients with hypoadrenalism<sup>23,28,32-36</sup>; the adrenal crisis–associated rate of death may reach 6% of crisis events.<sup>28</sup> Adrenal crises may contribute to the increased mortality attributed to infectious disease among patients with hypoadrenalism.<sup>33</sup> Fatal adrenal crises have occurred in patients without a preceding diagnosis of hypoadrenalism, although symptoms may have been overlooked before the fatal episode.<sup>1,37-40</sup>

## EVENTS THAT PRECIPITATE ADRENAL CRISIS

Infections, which act as inflammatory stressors, commonly precipitate adrenal crises.<sup>2,3,22,26-28</sup> Gastroenteritis is frequently cited as a precipitant and can be particularly hazardous, since vomiting and diarrhea impair the absorption of oral medication and may also exacerbate dehydration. However, the abdominal symptoms of adrenal crisis may lead to an erroneous diagnosis of gastroenteritis.<sup>2,5,22</sup> Bacterial infections predominate among infection-related precipitating events in older patients, whereas viral infections are more common precipitating events in children.<sup>12,22,27,28,41,42</sup>

Other pathophysiological states may precipitate an adrenal crisis if the body cannot mount an increase in endogenous cortisol and if the amount of replacement therapy is not increased. Such conditions include serious injury and major surgery, but situations that generally are associated with the need for milder cortisol increases (exercise and emotional upset) have been reported as crisis precipitants in up to 10% of episodes, according to the results of patient surveys in which no specific precipitant was identified.<sup>3,22,24,27,28</sup> Adrenal crises have been reported in association with the release of acute-phase cytokines and other substances after certain relatively minor medical procedures such as vaccinations and zoledronic acid infusion.<sup>43,44</sup>

Some types of immunotherapy or chemotherapy may precipitate adrenal crises. For example, immune-checkpoint inhibitor therapy, typically used in the treatment of melanoma and certain other cancers, may cause adrenal insufficiency



**Figure 1. Pathophysiology of Adrenal Crisis.**

Cortisol and aldosterone deficiency leads to an adrenal insufficiency syndrome as a result of effects on most of the body's organs and tissues. Severe adrenal insufficiency, with hypotension (i.e., adrenal crisis), often develops at times of an increased cortisol requirement or physiological stress, leading to derangements of the physiological processes depicted. E denotes epinephrine, NE norepinephrine, and TNF- $\alpha$  tumor necrosis factor  $\alpha$ .

(risk <1%) due to induction of hypophysitis (and pituitary hormone deficits) or adrenalitis.<sup>45</sup> If these serious adverse events occur, prompt glucocorticoid replacement is required.<sup>45,46</sup>

Nonadherence to glucocorticoid replacement therapy may also precipitate an adrenal crisis.<sup>22,28</sup> Patients need to be educated about the dangers of dose omission or cessation, particularly during a perioperative period and during long-term glucocorticoid therapy for other illnesses in which the daily dose is higher than the replacement dose (3 to 5 mg of prednisone or the equivalent per day), since sudden discontinuation can act as a precipitant.<sup>22,47</sup> Clinician-initiated abrupt cessation of glucocorticoid therapy has also been reported as a cause of adrenal crisis.<sup>48</sup>

Undiagnosed coexisting thyrotoxicosis, or the initiation of thyroxine therapy in a patient with undiagnosed hypoadrenalism, may precipitate an adrenal crisis.<sup>2,49,50</sup> Furthermore, cytochrome P-450 3A4 (CYP3A4) inducers such as avasimibe, carbamazepine, rifampicin, phenytoin, and St. John's wort extract may increase hydrocortisone metabolism, necessitating an increase in the glucocorticoid dose in patients being treated for adrenal insufficiency, or may induce an adrenal crisis in patients with undiagnosed adrenal insufficiency.<sup>51</sup> In contrast, CYP3A4 inhibitors such as voriconazole, grapefruit juice, itraconazole, ketoconazole, clarithromycin, lopinavir, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and conivaptan may inhibit the metabolism of hydrocortisone, increasing cortisol levels and thereby enhancing the adrenal suppressive effect of ongoing glucocorticoid therapy,<sup>51,52</sup> but the risk of adrenal crisis may be increased once the agent has been discontinued.

## TREATMENT

Treatment of an adrenal crisis is effective if administered promptly, before prolonged hypotension leads to irremediable effects.<sup>6,27,41</sup> Treatment includes prompt administration of intravenous hydrocortisone, given as a 100-mg bolus, followed by 200 mg every 24 hours, administered as a continuous infusion or as frequent intravenous (or intramuscular) boluses (50 mg) every 6 hours, with subsequent doses tailored to the clinical response (Table 2). If hydrocortisone is unavailable, another parenteral glucocorticoid,<sup>7</sup> such as dexamethasone (4 mg every 24 hours), methylprednisolone (40 mg every 24 hours), or pred-

nisolone (25 mg as a bolus, followed by two 25-mg doses, for a total of 75 mg in the first 24 hours; thereafter, 50 mg every 24 hours), may be used. In children, hydrocortisone should be administered as a parenteral bolus of 50 mg per square meter of body-surface area, followed by 50 to 100 mg per square meter every 24 hours (administered as a continuous intravenous infusion or as intravenous or intramuscular boluses every 6 hours). Hydrocortisone (cortisol) is the preferred drug for treatment of an adrenal crisis because of its physiological glucocorticoid pharmacokinetics, plasma protein binding, tissue distribution, and balanced glucocorticoid–mineralocorticoid effects.

The doses suggested for prednisolone and dexamethasone are based on their glucocorticoid potency relative to hydrocortisone, in agreement with current treatment guidelines for primary adrenal insufficiency.<sup>7</sup> Fludrocortisone is not required if hydrocortisone doses exceed 50 mg given every 24 hours. As a practical matter, in patients with primary adrenal insufficiency, fludrocortisone therapy is usually resumed once the adrenal crisis has resolved and oral hydrocortisone replacement is feasible.

During an ongoing adrenal crisis in an adult, intravenous normal saline should be administered (1000 ml within the first hour), with crystalloid fluids (e.g., 0.9% isotonic sodium chloride) given according to standard resuscitation guidelines and with adjustment for the patient's circulatory status, body weight, and relevant coexisting conditions.<sup>2,5,6</sup> Intravenous dextrose 5% in normal saline is given for hypoglycemia (i.e., when the glucose values are less than 3.9 mmol per liter [70 mg per deciliter]). In children, a bolus of normal saline is given at a dose of 20 ml per kilogram of body weight, with repeated doses at up to 60 ml per kilogram the first hour. If there is hypoglycemia, dextrose at a dose of 0.5 to 1 g per kilogram is administered.

On rare occasions, patients have both adrenal insufficiency and diabetes insipidus, most often in those with lymphocytic hypophysitis. Fluids should be administered with caution in patients with diabetes insipidus, whether or not they are receiving treatment for it, since excessive free water may cause hyponatremia and too little may cause hypernatremia. Careful matching of urine output and normal saline infusion generally maintains isonatremia.<sup>2</sup>

Concomitant investigation and treatment of



**Table 2. Management of Adrenal Crisis.**

Treatment	Dose and Procedure
<b>Adults</b>	
Hydrocortisone*	Provide prompt administration at a dose of 100 mg intravenously (or intramuscularly if intravenous access is not feasible), followed by 200 mg every 24 hr, given as a continuous infusion or as intravenous (or intramuscular) boluses (50 mg) every 6 hr; if initial treatment is successful (usually after 24 hr), oral hydrocortisone at 2 to 3 times the usual dose can be given, with tapering down to the usual dose over the next 2 to 3 days†
Fluids	Provide intravenous administration of 1000 ml of normal saline (0.9% isotonic sodium chloride) in the first hour, with intravenous dextrose to 5% concentration in normal saline added if the patient has hypoglycemia; subsequently, administer crystalloid fluids according to standard resuscitation guidelines‡
<b>Children</b>	
Hydrocortisone	Provide prompt administration at a dose of 50 mg per square meter of body-surface area intravenously (or intramuscularly if intravenous access is not feasible), followed by 50–100 mg per square meter every 24 hr, given as a continuous infusion or as intravenous (or intramuscular) boluses (12.5–25 mg per square meter) every 6 hr; if initial treatment is successful (usually after 24 hr), oral hydrocortisone at 2 to 3 times the usual dose can be given, with tapering down to the usual dose over the next 2 to 3 days†
Fluids	Give a bolus of normal saline at a dose of 20 ml per kilogram of body weight, with repeated doses up to a maximum of 60 ml per kilogram in the first hour, along with intravenous dextrose, 0.5–1 g per kilogram, if the patient has hypoglycemia; provide subsequent administration of crystalloid fluids according to standard resuscitation guidelines‡
<b>Adults and children</b>	
Possible additional measures	Antibiotic therapy, admission to intensive care or high-dependency unit, administration of low-dose heparin Prompt investigation of other causes when hypotension persists despite adequate initial treatment Consideration of precipitating events (e.g., sepsis, gastroenteritis)

\* If hydrocortisone is unavailable, another parenteral glucocorticoid, such as dexamethasone (4 mg every 24 hours), methylprednisolone (40 mg every 24 hours), or prednisolone (25 mg bolus followed by two 25-mg doses, for a total of 75 mg in the first 24 hours; thereafter, 50 mg every 24 hours), may be used.

† Fludrocortisone replacement is not required if hydrocortisone doses exceed 50 mg every 24 hours but is typically administered in adults and children with primary adrenal insufficiency when oral hydrocortisone is started.

‡ Circulatory status, body weight, and relevant coexisting conditions should be taken into account.

the precipitating illness are required in all patients with adrenal crisis. Persistent shock despite specific treatment for adrenal crisis suggests another cause of hypotension.

After successful management of an adrenal crisis, hydrocortisone doses should be tapered, typically over a period of 3 days, to the patient's usual maintenance dose. An assessment for preventable precipitating events should be made, and preventive strategies should be explained to the patient, including self-administration of parenteral hydrocortisone.<sup>2,6</sup>

## MANAGEMENT ISSUES

### HEALTH CARE MILIEU

Adrenal crisis prevention relies on responsive and informed health care professionals (ambulance, nursing, and medical staff) and on effective

patient education, so that the patient can initiate glucocorticoid dose escalation if needed. However, case reports (see the illustrative case in the Supplementary Appendix, available with the full text of this article at NEJM.org) and, more recently, systematic studies of the timeliness of the assistance provided by health care professionals have exposed a range of potential delays and difficulties that may affect the incidence and outcome of adrenal crisis.<sup>5,48,53</sup> Some environmental factors, such as the slow arrival of an ambulance, may be unavoidable but are nevertheless important to address.<sup>54</sup> For example, ensuring that ambulances have hydrocortisone available for injection, a policy adopted by emergency services in some regions, may be very useful in the management of an adrenal crisis.

Of great concern are published reports of refusal by medical staff to administer hydrocorti-

sone because of the mistaken belief that the adverse effects of glucocorticoids are greater than the risk of withholding hydrocortisone from an ill patient with hypoadrenalism.<sup>2,5,48,53,54</sup> Indeed, recent evidence of unsatisfactory levels of knowledge about adrenal insufficiency and adrenal crisis among various types of clinicians highlights the importance of continuing education.<sup>55-58</sup>

Hospital reviews of time-critical events in the treatment of patients with adrenal insufficiency, particularly the time to intravenous hydrocortisone administration, can be used for quality-assurance purposes and benchmarking.<sup>54,59</sup> Audits of hospital treatment (inpatient admissions, admissions to the intensive care unit [use of mechanical ventilation], adverse sequelae, and mortality) may help ensure adequate outcomes. In the hospital, use of a “red flag” system to indicate hypoadrenalism should encourage the administration of glucocorticoid replacement therapy and of appropriate doses of glucocorticoids for surgical procedures.<sup>25,58</sup> On a national basis, regular evaluation of hospital admissions and data on pharmaceutical prescriptions can identify other problems, such as variations in the incidence of adrenal crises<sup>4,31,60</sup> due to, among other issues, interruption in the supply of glucocorticoid tablets.<sup>60</sup>

#### PATIENT FACTORS

Patients with hypoadrenalism often report dissatisfaction with medical care; reasons for their dissatisfaction include demanding glucocorticoid replacement schedules, a delay in the initial diagnosis, post-treatment impairment of well-being (in up to 40% of patients), and adrenal crisis–related anxiety.<sup>26,54,61-67</sup> Functional impairment in patients with adrenal insufficiency, manifested by fatigue and by reduced participation in work owing to sick leave and disability,<sup>68</sup> may be related to noncircadian<sup>69</sup> or nonindividualized glucocorticoid replacement. Moreover, there is a marked interindividual variation in hydrocortisone pharmacokinetics,<sup>70</sup> and hydrocortisone treatment affects mental and physical health through altered tryptophan metabolism.<sup>71</sup> Furthermore, reduced quality of life may lead to an elevated risk of adrenal crisis among those most severely affected.<sup>29</sup>

#### PREVENTION

Key strategies that can prevent adrenal crisis include an individualized prescription and plan

for the use of supplementary glucocorticoid administration for physiological stress; use of parenteral hydrocortisone, preferably at home, when oral glucocorticoids cannot be taken; and the provision of devices, such as a MedicAlert bracelet or necklace (discussed below), that can warn caregivers of the risk of adrenal crisis when patients cannot communicate verbally.

Oral stress dosing of glucocorticoids, designed to replicate the cortisol stress response, involves doubling or tripling the replacement dose, depending on the intensity of the stress (e.g., a double dose for a lower fever [temperature <38.5°C] and a triple dose for a higher fever [temperature ≥38.5°C]), until the illness has abated. Stress dosing is based on mimicking the physiological response to illness, but oral hydrocortisone pharmacokinetics are highly variable, and patients with rapid metabolism may have a less marked response to modest dose manipulations than patients with slower metabolism.<sup>70</sup> Higher doses, administered parenterally, may be needed in cases of severe stress such as major surgery and may perhaps reach maximal adrenal secretory output (approximately 200 mg of hydrocortisone every 24 hours [8.5 times the normal output], as used in intervention studies of septic shock).<sup>72-74</sup>

In patients with vomiting or diarrhea, parenteral hydrocortisone (100 mg in adults) is recommended.<sup>2,5,6</sup> Patients and their family members should be taught how to perform intramuscular injection of hydrocortisone and should be provided with vials, needles, and syringes.<sup>2,5,12</sup> Omission of stress dosing may result in progression to adrenal crisis and may contribute to the observed lack of efficacy of current preventive measures.<sup>41,48</sup> Parenteral administration of hydrocortisone at home may prevent progression of an early adrenal crisis.<sup>3,5</sup>

However, injectable hydrocortisone is not offered to, or may not be obtained by, all patients.<sup>54,57</sup> Barriers to hydrocortisone use by patients include reluctance to inject the drug intramuscularly,<sup>26,41</sup> impaired dexterity,<sup>48</sup> and advanced age.<sup>26</sup> Subcutaneous administration of hydrocortisone is an alternative to the intramuscular route, and although this is an off-label method of administration, it may be more acceptable to patients.<sup>2,75</sup> Pharmacokinetic data indicate that subcutaneous and intramuscular injections in nonobese patients with adrenal

insufficiency, albeit without shock, have similar effects.<sup>75</sup> Rectal hydrocortisone suppositories may be an alternative in some circumstances.

Measures that enhance communication may be simple but are important. For example a “steroid card,” MedicAlert card, or the equivalent (Fig. S1 in the Supplementary Appendix) and a subscription service that uses medical jewelry inscribed with a patient’s diagnosis and linked by an identification number to a call center for further information are recommended.<sup>76,77</sup> Non-use of these measures is common,<sup>57,77</sup> but use may be improved through patient education.<sup>77</sup>

Despite efforts directed at encouraging patients to manage their glucocorticoid treatment in order to prevent adrenal crises, only some patients initiate dose escalation effectively.<sup>41,48,57,78</sup> Outcomes from intensive patient education programs are disappointing and contribute to the persistent or increasing rates of adrenal crises.<sup>4,31,79</sup>

#### REDUCING THE INCIDENCE OF ADRENAL CRISES

##### AVAILABLE APPROACHES

Broader application of preventive strategies may decrease the incidence of adrenal crises, and prompt domiciliary and health service–based treatment may lessen their severity and sequelae. Pre-emergency injection of intramuscular or off-label subcutaneous hydrocortisone may avert many episodes of adrenal crisis. Formal regulatory approval for subcutaneous hydrocortisone may increase its home use.

##### FUTURE APPROACHES

A preloaded hydrocortisone syringe, similar to the epinephrine autoinjector, has been recommended<sup>2</sup> but is not yet generally available. It may be possible to devise other products or routes for hydrocortisone administration that are simpler for patients to use in emergencies, such as an intranasal or inhaled spray or powder. Ultimately, alternative delivery systems for adrenal hormone replacement such as a “bioartificial adrenal cortex,” as a cell-based solution, are appealing. Such constructs may use adrenal allogeneic or xenogeneic cells in an implanted container such as an alginate capsule; alternatively, a method in which the cells can evade the patient’s immune system may become feasible. If successful, these approaches will improve the quality of life for patients with adrenal insufficiency and eliminate adrenal crises.<sup>80,81</sup>

#### SUMMARY

Adrenal crises are life-threatening episodes of adrenal insufficiency, which continue to occur despite preventive interventions. Patient education in the use of oral stress dosing, parenteral hydrocortisone administration when required, and communication devices to inform health care workers of the risk of adrenal crisis and required treatment are the current approaches to preventing adrenal crises. New solutions to this persistent problem are needed.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

##### REFERENCES

- Gidlöf S, Falhammar H, Thilén A, et al. One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. *Lancet Diabetes Endocrinol* 2013;1:35-42.
- Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. *Endocrine* 2017;55:336-45.
- Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol* 2010;162:597-602.
- Rushworth RL, Torpy DJ. Adrenal insufficiency in Australia: is it possible that the use of lower dose, short-acting glucocorticoids has increased the risk of adrenal crises? *Horm Metab Res* 2015;47:427-32.
- Allolio B. Extensive expertise in endocrinology: adrenal crisis. *Eur J Endocrinol* 2015;172:R115-24.
- Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal crisis: still a deadly event in the 21st century. *Am J Med* 2016;129(3):339.e1-339.e9.
- Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016;101:364-89.
- Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet* 2014;383:2152-67.
- Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996;335:1206-12.
- Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol* 2015;3:216-26.
- Arlt W, Allolio B. Adrenal insufficiency. *Lancet* 2003;361:1881-93.
- Rushworth RL, Torpy DJ, Stratakis CA, Falhammar H. Adrenal crises in children: perspectives and research directions. *Horm Res Paediatr* 2018;89:341-51.
- Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. *J Clin Endocrinol Metab* 2011;96(6):E925-E928.
- Cortet C, Barat P, Zenaty D, Guignat L, Chanson P. Group 5: acute adrenal insufficiency in adults and pediatric patients. *Ann Endocrinol (Paris)* 2017;78:535-43.
- Odenwald B, Nennstiel-Ratzel U, Dörr HG, Schmidt H, Wildner M, Bonfig W. Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises dur-



- ing the first 6 years of life. *Eur J Endocrinol* 2016;174:177-86.
16. Bowden SA, Henry R. Pediatric adrenal insufficiency: diagnosis, management, and new therapies. *Int J Pediatr* 2018; 2018:1739831.
  17. Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. *Rheum Dis Clin North Am* 2016;42:15-31.
  18. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol* 2011;335:2-13.
  19. Annane D, Bellissant E, Sebillé V, et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. *Br J Clin Pharmacol* 1998;46:589-97.
  20. Dinneen S, Alzaid A, Miles J, Rizza R. Metabolic effects of the nocturnal rise in cortisol on carbohydrate metabolism in normal humans. *J Clin Invest* 1993;92: 2283-90.
  21. Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. *J Endocrinol* 2008;197:189-204.
  22. Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 2016;84:17-22.
  23. Falhammar H, Frisé L, Norrby C, et al. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2014;99(12):E2715-E2721.
  24. Iwasaku M, Shinzawa M, Tanaka S, Kimachi K, Kawakami K. Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study. *BMC Endocr Disord* 2017;17:58.
  25. Rushworth RL, Chrisp GL, Torpy DJ. Glucocorticoid-induced adrenal insufficiency: a study of the incidence in hospital patients and a review of peri-operative management. *Endocr Pract* 2018;24:437-45.
  26. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *Eur J Endocrinol* 2010;162:115-20.
  27. Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. *BMC Endocr Disord* 2014;14:79.
  28. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab* 2015;100:407-16.
  29. Meyer G, Koch M, Herrmann E, Bojunga J, Badenhop K. Longitudinal AddiQoL scores may identify higher risk for adrenal crises in Addison's disease. *Endocrine* 2018;60:355-61.
  30. El-Maouche D, Hargreaves CJ, Sinaii N, Mallappa A, Veeraraghavan P, Merke DP. Longitudinal assessment of illnesses, stress dosing, and illness sequelae in patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2018;103: 2336-45.
  31. Rushworth RL, Torpy DJ. Modern hydrocortisone replacement regimens in adrenal insufficiency patients and the risk of adrenal crisis. *Horm Metab Res* 2015;47: 637-42.
  32. Tomlinson JW, Holden N, Hills RK, et al. Association between premature mortality and hypopituitarism. *Lancet* 2001; 357:425-31.
  33. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab* 2006;91:4849-53.
  34. Bensing S, Brandt L, Tabaroj F, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. *Clin Endocrinol (Oxf)* 2008;69:697-704.
  35. Erichsen MM, Løvås K, Fougner KJ, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. *Eur J Endocrinol* 2009;160:233-7.
  36. Burman P, Mattsson AF, Johannsson G, et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *J Clin Endocrinol Metab* 2013;98: 1466-75.
  37. Molander N. Sudden natural death in later childhood and adolescence. *Arch Dis Child* 1982;57:572-6.
  38. Hajsheikholslami F, Yazdani S. Sudden cardiac death as a result of neglected hypopituitarism. *Int J Endocrinol Metab* 2013;11:117-9.
  39. Saevik AB, Åkerman AK, Grønning K, et al. Clues for early detection of autoimmune Addison's disease — myths and realities. *J Intern Med* 2018;283:190-9.
  40. Bird S. Failure to diagnose: Addison disease. *Aust Fam Physician* 2007;36:859-61.
  41. Chrisp GL, Maguire AM, Quartararo M, et al. Variations in the management of acute illness in children with congenital adrenal hyperplasia: an audit of three paediatric hospitals. *Clin Endocrinol (Oxf)* 2018;89:577-85.
  42. Rushworth RL, Falhammar H, Munns CF, Maguire AM, Torpy DJ. Hospital admission patterns in children with CAH: admission rates and adrenal crises decline with age. *Int J Endocrinol* 2016; 2016:5748264.
  43. Major A, Chacko K. Routine vaccinations as a precipitant of adrenal crisis in adrenal insufficiency. *Intern Med J* 2018; 48:360-1.
  44. Smrecnik M, Kavcic Trsinar Z, Kocjan T. Adrenal crisis after first infusion of zoledronic acid: a case report. *Osteoporos Int* 2018;29:1675-8.
  45. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol* 2018;4:173-82.
  46. Akarca FK, Can O, Yalcinli S, Altuncu YA. Nivolumab, a new immunomodulatory drug, a new adverse effect; adrenal crisis. *Turk J Emerg Med* 2017;17:157-9.
  47. Falhammar H, Nordenström A. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome. *Endocrine* 2015;50:32-50.
  48. Burger-Stritt S, Kardonski P, Pulzer A, Meyer G, Quinkler M, Hahner S. Management of adrenal emergencies in educated patients with adrenal insufficiency — a prospective study. *Clin Endocrinol (Oxf)* 2018;89:22-9.
  49. Lewandowski KC, Marcinkowska M, Skowrońska-Józwiak E, Makarewicz J, Lewiński A. New onset Graves' disease as a cause of an adrenal crisis in an individual with panhypopituitarism: brief report. *Thyroid Res* 2008;1:7.
  50. Roque C, Fonseca R, Bello CT, Vasconcelos C, Galzerano A, Ramos S. Thyrotoxicosis leading to adrenal crises reveals primary bilateral adrenal lymphoma. *Endocrinol Diabetes Metab Case Rep* 2017;2017: 17-0002.
  51. Syche DA, Ashraf GM, Svistunov AA, et al. The cytochrome P450 isoenzyme and some new opportunities for the prediction of negative drug interaction in vivo. *Drug Des Devel Ther* 2018;12:1147-56.
  52. Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009; 360:2328-39.
  53. Gargya A, Chua E, Hetherington J, Sommer K, Cooper M. Acute adrenal insufficiency: an aide-memoire of the critical importance of its recognition and prevention. *Intern Med J* 2016;46:356-9.
  54. Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the management of adrenal crisis — targets, limits and reality. *Clin Endocrinol (Oxf)* 2015;82:497-502.
  55. Kampmeyer D, Lehnert H, Moenig H, Haas CS, Harbeck B. A strong need for improving the education of physicians on glucocorticoid replacement treatment in adrenal insufficiency: an interdisciplinary and multicentre evaluation. *Eur J Intern Med* 2016;33:e13-e15.
  56. Kampmeyer D, Lehnert H, Moenig H, Haas CS, Harbeck B. Experience pays off! Endocrine centres are essential in the care

- of patients with adrenal insufficiency. *Eur J Intern Med* 2016;35:e27-e28.
57. Shepherd LM, Tahrani AA, Inman C, Arlt W, Carrick-Sen DM. Exploration of knowledge and understanding in patients with primary adrenal insufficiency: a mixed methods study. *BMC Endocr Disord* 2017;17:47.
58. Nour MA, Gill H, Mondal P, Inman M, Urmson K. Perioperative care of congenital adrenal hyperplasia — a disparity of physician practices in Canada. *Int J Pediatr Endocrinol* 2018;2018:8.
59. Leblieq C, Rottembourg D, Deladoëy J, Van Vliet G, Deal C. Are guidelines for glucocorticoid coverage in adrenal insufficiency currently followed? *J Pediatr* 2011;158(3):492.e1-498.e1.
60. Rushworth RL, Slobodian P, Torpy DJ. Interruptions to supply of high-dose hydrocortisone tablets and the incidence of adrenal crises. *Clin Endocrinol (Oxf)* 2015;83:999-1000.
61. Forss M, Batcheller G, Skrtic S, Johansson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency — a worldwide patient survey. *BMC Endocr Disord* 2012;12:8.
62. Chapman SC, Llahana S, Carroll P, Horne R. Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. *Clin Endocrinol (Oxf)* 2016;84:664-71.
63. Burger-Stritt S, Pulzer A, Hahner S. Quality of life and life expectancy in patients with adrenal insufficiency: what is true and what is urban myth? *Front Horm Res* 2016;46:171-83.
64. Løvås K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. *Clin Endocrinol (Oxf)* 2002;56:581-8.
65. Hahner S, Loeffler M, Fassnacht M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. *J Clin Endocrinol Metab* 2007;92:3912-22.
66. Bleicken B, Hahner S, Loeffler M, Ventz M, Allolio B, Quinkler M. Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. *Eur J Endocrinol* 2008;159:811-7.
67. Daae E, Feragen KB, Neramoen I, Falhammar H. Psychological adjustment, quality of life, and self-perceptions of reproductive health in males with congenital adrenal hyperplasia: a systematic review. *Endocrine* 2018;62:3-13.
68. Strandqvist A, Falhammar H, Lichtenstein P, et al. Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a nonbiased national cohort in Sweden. *J Clin Endocrinol Metab* 2014;99:1425-32.
69. Mallappa A, Debono M. Recent advances in hydrocortisone replacement treatment. *Endocr Dev* 2016;30:42-53.
70. Werumeus Buning J, Touw DJ, Brummelman P, et al. Pharmacokinetics of oral hydrocortisone — results and implications from a randomized controlled trial. *Metabolism* 2017;71:7-16.
71. Sorgdrager FJH, Werumeus Buning J, Bos EH, Van Beek AP, Kema IP. Hydrocortisone affects fatigue and physical functioning through metabolism of tryptophan: a randomized controlled trial. *J Clin Endocrinol Metab* 2018;103:3411-9.
72. Keenan DM, Roelfsema F, Carroll BJ, Iranmanesh A, Veldhuis JD. Sex defines the age dependence of endogenous ACTH-cortisol dose responsiveness. *Am J Physiol Regul Integr Comp Physiol* 2009;297:R515-R523.
73. Remmelts HH, Meijvis SC, Kovaleva A, Biesma DH, Rijkers GT, Heijligenberg R. Changes in serum cortisol levels during community-acquired pneumonia: the influence of dexamethasone. *Respir Med* 2012;106:905-8.
74. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797-808.
75. Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. *Eur J Endocrinol* 2013;169:147-54.
76. Quinkler M, Dahlqvist P, Husebye ES, Kämpe O. A European Emergency Card for adrenal insufficiency can save lives. *Eur J Intern Med* 2015;26:75-6.
77. Vidmar AP, Weber JF, Monzavi R, Koppin CM, Kim MS. Improved medical-alert ID ownership and utilization in youth with congenital adrenal hyperplasia following a parent educational intervention. *J Pediatr Endocrinol Metab* 2018;31:213-9.
78. Repping-Wuts HJ, Stikkelbroeck NM, Noordzij A, Kerstens M, Hermus AR. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. *Eur J Endocrinol* 2013;169:17-22.
79. Hahner S. Acute adrenal crisis and mortality in adrenal insufficiency: still a concern in 2018! *Ann Endocrinol (Paris)* 2018;79:164-6.
80. Balyura M, Gelfgat E, Ehrhart-Bornstein M, et al. Transplantation of bovine adrenocortical cells encapsulated in alginate. *Proc Natl Acad Sci U S A* 2015;112:2527-32.
81. Balyura M, Gelfgat E, Steenblock C, et al. Expression of progenitor markers is associated with the functionality of a bio-artificial adrenal cortex. *PLoS One* 2018;13(3):e0194643.

Copyright © 2019 Massachusetts Medical Society.

#### IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.