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Adrenal Crisis: Still a Deadly Event in the 21st Century

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ABSTRACT

Adrenal crisis is a life-threatening medical emergency, associated with a high mortality unless it is appropriately recognized and early treatment is rendered. Despite it being a treatable condition for almost 70 years, failure of adequate preventive measures or delayed treatment has often led to unnecessary deaths. Gastrointestinal illness is the most common precipitant for an adrenal crisis. Although most patients are educated about "sick day rules," patients, and physicians too, are often reluctant to increase their glucocorticoid doses or switch to parenteral injections, and thereby fail to avert the rapid deterioration of the patients' condition. Therefore, more can be done to prevent an adrenal crisis, as well as to ensure that adequate acute medical care is instituted after a crisis has occurred. There is generally a paucity of studies on adrenal crisis. Hence, we will review the current literature, while also focusing on the incidence, presentation, treatment, prevention strategies, and latest recommendations in terms of steroid dosing in stress situations.

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KEYWORDS: Adrenal crisis; Adrenal insufficiency; Crisis; Emergency

DEFINITION AND EPIDEMIOLOGY

In 1855, Thomas Addison first described patients with chronic adrenal insufficiency.[1] Most of those patients had primary adrenal failure due to tuberculosis, although autoimmune adrenal disease has superseded it as the most frequent cause for primary adrenal insufficiency in the developed world. Causes of adrenal insufficiency can be classified as primary, secondary, or glucocorticoid-induced adrenal insufficiency (from chronic exogenous glucocorticoid exposure) (**Table 1**).[2,3] Of note, metastasis to the adrenal glands rarely causes adrenal insufficiency, and occurs only if metastatic disease is bilateral, with extensive damage to the adrenal glands.[4]

Without adequate steroid replacement therapy, this was an invariably fatal condition in the time of Addison, with almost all patients dying within the initial 5 years of diagnosis. The discovery of cortisone by Hench, Kendall, and Reichstein in the late 1940s improved the outlook on patients with adrenal insufficiency dramatically, and initial data suggested that life expectancy was normalized.[5,6] However, during an acute stress event, these patients are unable to mount a normal physiological response with increased endogenous cortisol production. Failure to increase their dose of exogenous glucocorticoids adequately can lead to acute adrenal insufficiency, or adrenal crisis.

Adrenal crisis may be defined as an acute deterioration in a patient with adrenal insufficiency. The principal manifestation of adrenal crisis is hypotension or hypovolemic shock, but other symptoms and signs such as weakness, anorexia, nausea, abdominal pain, fever, vomiting, fatigue, electrolyte abnormalities, confusion, coma, and marked laboratory abnormalities can also occur, which necessitates immediate treatment.[2,7] However, use of variable definitions

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in different studies has led to difficulty in estimating the true incidence of adrenal crisis occurring in patients with known adrenal insufficiency, as well as the risk of death from adrenal crisis.

Initial studies in patients with both secondary[8,9] and primary adrenal insufficiency[10,11] used data registries and showed that they were at increased mortality risk, with some suggesting that endocrine and infectious causes contributed to this.[10,11] Subsequently, in a Swedish study[12] of patients with hypopituitarism, all 15 cases of death from infections occurred in patients with hypocortisolism. Eight of these patients had a documented adrenal crisis, and 7 of these 8 died at home or upon arrival to the hospital. Sudden death occurring in young patients with adrenal insufficiency was noted in 2 other studies,[13,14] with adrenal crisis a likely cause in >50%,[13] and in many cases associated with trivial infections.[14] This highlights the importance of prevention and early treatment.

CLINICAL SIGNIFICANCE

- Adrenal crisis remains an important cause of death in patients with adrenal insufficiency.
- Clinical deterioration may progress quickly, resulting in death at home or soon upon arrival in hospital.
- Early recognition and treatment of this endocrine emergency is crucial.
- Patient and family education about sick day rules and the availability of intramuscular hydrocortisone at home are crucial for prevention of an adrenal crisis.

The risk of adrenal crisis occurring in a patient with adrenal insufficiency has been estimated to be about 6-10 adrenal crises per 100 patient years (PYs).[15-17] These estimates were based on retrospective studies using questionnaires, and limited by reporting bias. A recent prospective study[18] found 64 episodes of adrenal crisis in 423 patients with primary and secondary adrenal insufficiency (8.3 adrenal crises/100 PYs), and, alarmingly, 4 adrenal crisis-related deaths were noted over a follow-up period of 2 years (0.5 adrenal crisis-related deaths per 100 PYs). Of concern, these cases occurred despite the fact that all the patients enrolled in this study had received, at baseline, patient education with written instructions on corticosteroid dose adjustments during stress, illness, and self-treatment with injectable hydrocortisone, which most physicians consider as adequate preventive measures.

Table 1 Common Causes of Adrenal Insufficiency

Primary adrenal insufficiency	Autoimmune adrenalitis
	Infections (tuberculosis, systemic fungal infections, AIDS)
	Metastasis (from lung, breast, kidney) (rare), lymphoma
	Congenital adrenal hyperplasia
	Adrenomyeloneuropathy/ adrenoleukodystrophy
	Bilateral adrenal hemorrhage
	Bilateral adrenalectomy
Secondary adrenal insufficiency	Pituitary or metastatic tumor
	Other tumors (craniopharyngioma, meningioma)
	Pituitary surgery or radiation
	Lymphocytic hypophysitis
	Head trauma
	Pituitary apoplexy/Sheehan's syndrome
	Pituitary infiltration (sarcoidosis, histiocytosis)
	Empty-sella syndrome
Glucocorticoid-induced adrenal insufficiency	Long-term exogenous glucocorticoid use

AIDS = acquired immunodeficiency syndrome.

CLINICAL PRESENTATION

There should be a high level of suspicion in all patients with known adrenal insufficiency or risk factors for any of the causes of adrenal insufficiency (Table 1). Adrenal crisis can be the first presentation of patients with adrenal insufficiency, occurring in up to 50% of patients with Addison's disease.[19] The diagnosis may be delayed, as most of the symptoms and signs of adrenal insufficiency occur insidiously and are nonspecific, such as anorexia, fatigue, nausea, fever, lethargy, and orthostatic hypotension (Table 2). Patients presenting with adrenal crisis are often in hypotensive shock, and may have altered sensorium. They frequently have gastrointestinal symptoms like abdominal pain, nausea, vomiting and diarrhea, leading to an erroneous diagnosis of an acute abdomen or gastroenteritis.

Hypotension occurs secondary to hypovolemia, but also due to hypocortisolism, as glucocorticoids exert a permissive effect on catecholamine action.[20] If not recognized, it may be refractory to fluids and inotropes. In secondary adrenal insufficiency, hyponatremia occurs due to failure to suppress vasopressin and impaired electrolyte-free water excretion in the kidneys.[21] In primary adrenal insufficiency, hyponatremia is due to concomitant aldosterone deficiency, which leads to natriuresis, volume depletion, and hyperkalemia. Other biochemical features include hypoglycemia and, rarely, hypercalcemia, which is due to decreased renal excretion of calcium and increased bone resorption[2,3] (Table 2).

Precipitating Factors

In more than 90% of cases of adrenal crisis, there is a known precipitating event.[15-18] Gastrointestinal illness is consistently the largest precipitating factor for adrenal crisis

Table 2 Clinical Features of Chronic Adrenal Insufficiency (AI) and Adrenal Crisis (AC)

	Chronic Adrenal Insufficiency	Adrenal Crisis (Acute Adrenal Insufficiency)
Symptoms	Fatigue, anorexia, weight loss, myalgia, arthralgia	Severe weakness
	Dizziness	Acute abdominal pain, nausea, vomiting
	Nausea, vomiting, diarrhea	Altered sensorium
	Salt craving (in primary AI only)	
Signs	Orthostatic hypotension	Hypotension
	Fever	Fever
	Hyperpigmentation of the skin creases and buccal mucosa (in primary AI only)	Abdominal tenderness or guarding
		Reduced consciousness
Biochemical	Hyponatremia	Hyponatremia
	Hyperkalemia (primary AI)	Hyperkalemia (primary AI)
	Hypoglycemia	Hypoglycemia
	Hypercalcemia	Hypercalcemia
	Mild normocytic anemia, lymphocytosis, eosinophilia	

(Table 3),[15-18] greater than other infections or febrile illnesses. This is likely because it directly affects the intestinal absorption of glucocorticoids taken orally. Surgical stress is also a frequent cause. Hence, appropriate stress doses and close monitoring of all patients peri-procedure is important, along with timely intervention in the event of deterioration. In about 10% of cases, medications had been stopped, due to either noncompliance or cessation by the patient or doctor. It is pertinent to note that not only physical stress, but emotional stress can also precipitate an adrenal crisis.[18] Less common causes like accidents, flight delays, and wasp bites illustrate that patients always have to be prepared for the unexpected. As patients with adrenal insufficiency are unable to increase endogenous cortisol production, they have to be advised to increase exogenous intake during illness or severe stress.

Risk Factors

It is important to be aware of conditions that increase the risk of adrenal crisis in patients with adrenal insufficiency (Table 4). Patients with primary adrenal insufficiency may be at higher risk of adrenal crisis than patients with secondary adrenal insufficiency, due to the lack of mineralocorticoids and greater risk of dehydration and hypovolemia.[15,16,18] The true risk of adrenal crisis in patients with glucocorticoid-induced adrenal insufficiency is difficult to determine, as they form a heterogeneous group and only limited case reports are available.[22,23] It is important, nevertheless, to recognize that the most common cause of adrenal insufficiency is use of exogenous steroids,[3] and these patients are similarly at risk of adrenal crisis. Sudden, and often inadvertent, withdrawal of steroids can lead to adrenal crisis. Hence, a detailed drug history is

Table 3 Precipitating Factors for Adrenal Crisis

	White & Arlt, 2010[17]	Hahner et al, 2010[16]	Hahner et al, 2015*[18]
Gastrointestinal illness	56%	29%	23%
Other infections	17%	22%	25%
Peri-surgical	6%	10%	16%
Physical stress/pain	8%	7%	9%
Psychological stress	1%	3%	16%
Inadequate medication	2%	12%	14%
Accident	NA	3%	3%
Unknown	1%	9%	10%
Others	9%	5%	9%
	Blackout/unconscious	Severe migraine	Alcohol intoxication
			Dehydration/diuretics
			Chemotherapy
	Dehydration from hot weather	Long-distance flight	Wasp sting
		Incident atrial fibrillation	Medication-induced diarrhea
		Hot weather	Pregnancy
		Grand mal epilepsy	

*Multiple answers were allowed.

Table 4 Risk Factors for Adrenal Crisis (AC)

	Detail	Mechanism
History	Known patient with adrenal insufficiency (AI) or risk factors for developing AI (Ref Table 1)	
	History of previous adrenal crisis	
Drugs	Exogenous steroids (glucocorticoid therapy, fluticasone, megestrol acetate, medroxyprogesterone)	Suppress hypothalamus-pituitary-adrenal axis (sudden withdrawal can lead to adrenal crisis)
	Levothyroxine	Increases cortisol metabolism
	P-450 cytochrome enzyme-inducers: phenytoin, rifampicin, phenobarbitone	Increases cortisol metabolism
	P-450 cytochrome enzyme-inhibitors: ketoconazole, fluconazole, etomidate	Reduces endogenous production of cortisol
	Anticoagulants	Increased risk of adrenal hemorrhage
Medical conditions	Thyrotoxicosis	Increases cortisol metabolism
	Pregnancy	Increased requirements in 3rd trimester of pregnancy
	Diabetes insipidus	May increase dehydration
	Type 1 and type 2 diabetes mellitus	Unknown
	Type 1 and type 2 diabetes mellitus	Unknown
	Premature ovarian failure	Unknown
	Hypogonadism	Unknown

important, particularly for surreptitious use of steroids. Use of glucocorticoids in the forms of topical, inhaled, nasal, injectable, intraarticular, intradermal (eg, keloid), paraspinal, or rectal preparations have all been described to cause suppression of the hypothalamus-pituitary-adrenal axis. Megestrol and medroxyprogesterone also have significant glucocorticoid action at pharmacological doses.[24] Concomitant use of steroids with itraconazole[25] or ritonavir[26] (which inhibit hepatic CYP3A metabolism of steroids) can increase this risk. Generally, longer duration, higher dosages, and oral and intraarticular preparations increase the risk of adrenal suppression. However, there is no dose, duration, or administration form that can predict adrenal insufficiency, and physicians should exercise a high level of suspicion.[27]

In undiagnosed patients with adrenal insufficiency, cytochrome P-450 enzyme inhibitors like ketoconazole or fluconazole can reduce endogenous adrenal production and precipitate adrenal crisis.[28] Levothyroxine can accelerate the peripheral metabolism of cortisol, and precipitate adrenal crisis in patients with undiagnosed adrenal insufficiency or those already on replacement,[2] which is relevant, as patients with type 2 autoimmune polyglandular syndrome may have concomitant thyroid and adrenal deficiency.[29] Cytochrome P-450 enzyme inducers (phenytoin, rifampicin, phenobarbitone) may similarly precipitate an adrenal crisis.[30] Hence, in patients with tuberculosis-associated adrenal failure being initiated on rifampicin, glucocorticoid doses should be appropriately increased.[31]

Diabetes insipidus was also associated with higher risk of adrenal crisis in patients with secondary adrenal insufficiency, which could be due to the higher risk of dehydration, or the lack of V1-receptor mediated vasoconstriction during severe stress.[16] Other medical conditions (eg, type 1 and type 2 diabetes mellitus, hypogonadism) were associated with higher risk of adrenal crisis in some studies, although the mechanism is not clear (Table 4).[15,17]

The life-time risk of adrenal crisis in a patient with adrenal insufficiency is about 50%,[17] and those with previous adrenal crisis appear to be at greater risk of subsequent episodes.[17,18] While some patients may go through life without an episode of adrenal crisis, the first may be fatal, as was the case in 3 of 4 patients in a recent prospective study, highlighting the need to be vigilant in managing all patients with adrenal insufficiency.[18]

INVESTIGATIONS

In patients with known adrenal insufficiency presenting with symptoms typical of adrenal crisis, treatment should be instituted immediately without delay. In patients where the diagnosis has not yet been made, treatment should also not be delayed for the purpose of diagnostic tests (eg, adrenocorticotropic hormone [ACTH]-stimulation test) in a patient who is medically unstable.[3] Serum cortisol, ACTH, aldosterone, dehydroepiandrosterone-sulfate, and renin can be taken just before hydrocortisone administration and may be useful in the diagnosis of adrenal insufficiency. A high cortisol level of >20 μg/dL (550 nmol/L) can exclude the diagnosis,[7] while a low cortisol level of <5 μg/dL (138 nmol/L) done in the early morning or in a state of stress, strongly supports the diagnosis of adrenal insufficiency.[32] A concomitant high ACTH level is present in cases of primary adrenal insufficiency,[2,3] while low or inappropriately normal

ACTH is consistent with secondary or tertiary adrenal insufficiency. In all cases of uncertainty, glucocorticoid therapy should be continued until the patient has recovered, after which a diagnostic test such as an ACTH-stimulation test can be conducted safely. This test should be performed as early as possible, because prolonged glucocorticoid treatment can influence the activity of the hypothalamic-pituitary-adrenal axis.

MANAGEMENT OF ADRENAL CRISIS

The principles of therapy are fluid resuscitation and steroid replacement. Intravenous fluid resuscitation with isotonic sodium chloride 0.9% will correct the hypovolemia and hyponatremia, while intravenous dextrose may also be required to correct hypoglycemia. One liter of saline 0.9% should be given over the first hour, and further replacement fluids should be guided by frequent hemodynamic monitoring and measurement of serum electrolytes.[7,33] Cortisol replacement can induce water diuresis and suppress antidiuretic hormone (in secondary adrenal insufficiency), which together with sodium replacement can lead to rapid correction of hyponatremia, and osmotic demyelination syndrome. Hence, caution has to be exercised to correct sodium by <10 mEq over the first 24 hours.[21]

Parenteral hydrocortisone, which can be administered at home intramuscularly, before arriving at a hospital, is fundamental to avert further clinical deterioration. In the hospital, hydrocortisone can be given intravenously or intramuscularly 100 mg as a bolus, followed by 100-300 mg per day for another 2 to 3 days, either as boluses every 6 hours or as continuous infusion until full recovery.[7] At hydrocortisone doses of >50 mg/day, there is sufficient action at the mineralocorticoid receptor, and it is generally accepted that additional mineralocorticoid therapy is not required.[7] With subsequent tapering of the doses, fludrocortisone should be started in patients with primary adrenal insufficiency, with a dose of 50-200 μg per day sufficient in most patients.[33]

PREVENTION OF ADRENAL CRISIS

Glucocorticoid Stress Doses and Peri-procedural Recommendations

It is widely accepted that all patients with established adrenal insufficiency should have adequate glucocorticoid replacement during periods of stress, although the required dose has been debated. Previously accepted stress doses of hydrocortisone (300 mg/day) have been challenged.[34] Cortisol requirements have been best studied in patients undergoing surgery. Mean cortisol production in a normal person increases from 10 mg/day to 50 mg/day with minor operations (<1 hour), and to 75-200 mg/day after major surgery,[35] and return to high normal values by about 48-72 hours after surgery.[36] Current guidelines (**Table 5**) are based on expert opinion, and dosages of glucocorticoid replacement depend on the expected stress. While the exact regimens may differ, most concur that in uncomplicated surgery, stress doses should be rapidly tapered and last no more than 3 days, because unnecessary steroid excess may predispose to hyperglycemia, infections, and impaired wound healing.

In medical stress, the recommendations are more variable, as the clinical course is more unpredictable and there is greater controversy on the normal physiological response.[37] Because gastroenteritis is a frequent precipitant (or presentation) of an adrenal crisis,[15-18] and an increase in oral glucocorticoids does not always avert an adrenal crisis,[18,38] there should be a low threshold for early parenteral hydrocortisone administration to ensure adequate systemic absorption in patients who cannot tolerate oral medications or fail to respond to stress doses. Physicians should also consider giving additional doses in severe emotional stress (eg, bereavement) if required.

It is worthwhile to note that some patients (eg, those with glucocorticoid-induced adrenal insufficiency) may be on low maintenance doses of hydrocortisone, and advice to double or triple their doses may be inadequate if they had a febrile illness.[39] A stress dose of at least 60 mg hydrocortisone daily in divided doses may be more prudent.

Self-administration of Intramuscular Hydrocortisone

Intramuscular hydrocortisone should be administered to a patient with vomiting, persistent diarrhea, or an impending adrenal crisis. As patients can deteriorate quickly, it is crucial that patients are equipped to administer it at home. However, while many patients may have a hydrocortisone ampoule at home, not all will have practiced the injection before,[40] and a majority of patients rely on emergency medical personnel to administer it during an episode of adrenal crisis.[17] Significant physical or cognitive impairment of patients can occur during illness, which can affect their ability to make the correct decisions or administer medications.[41] Hence, patients, along with a close family member or friend, should be educated to recognize an adrenal crisis and trained on intramuscular hydrocortisone administration. In the future, a user-friendly subcutaneous hydrocortisone pen may help to improve proficiency of patients. Subcutaneous hydrocortisone administration has been recently shown to achieve adequately high serum cortisol levels in only 11 minutes longer than intramuscular administration.[42] While absorption may be reduced in a patient with shock, if more patients are able to administer hydrocortisone at an earlier time, then this may prove to be beneficial.[43]

Emergency Help

If a patient with adrenal insufficiency becomes unconscious, it is crucial that appropriate medical help is administered. Patients should be reminded to wear or carry a MedicAlert bracelet or emergency card at all times.[44] A huge concern is the reluctance of some health care professionals to treat the

Table 5 Recommendations for Glucocorticoid Doses during Illness or Peri-procedural

During medical illness*

Expected Stress	Recommended Doses
Illness with fever of >37.5°C (>99.5°F), or infection/ sepsis requiring antibiotics	Double the normal HC replacement doses until recovery
Severe nausea, severe stress (physical injury)	Take HC 20 mg orally immediately
In event of vomiting	Intramuscular HC 100 mg immediately and to contact doctor saying "Addison's emergency"

During surgery and medical procedures†,‡,§,‖,¶,**

Procedure	Preprocedure Requirements	Postprocedure requirements††
Major surgery with long recovery time (eg, open heart surgery, procedures requiring stay in intensive care)	100 mg IM or 50-100 mg IV HC just before anesthesia	Continuous IV infusion 200 mg/24 h, or 100 mg IM or IV every 6 h until able to eat and drink Then double oral dose for 48+ h, then taper to normal dose
Major surgery with rapid recovery (eg, joint replacement)	100 mg IM or 50-100 mg IV HC just before anesthesia	Continuous IV infusion 200 mg/24 h, or 100 mg IM or IV every 6 h for 24-48 h Then double oral dose for 24-48 h, then taper to normal dose
Labor and vaginal birth	100mg IM HC at onset of active labor	Double oral dose for 24-48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery (eg, hernia repairs, dental extraction under general anesthesia)	100 mg IM HC just before anesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives (eg, colonoscopy)	Admission overnight with 100 mg IM HC and IV fluids during purgative preparation 100 mg IM HC at commencement	Double oral dose for 24 h, then return to normal dose
Other invasive procedures (eg, gastroscopy)	100 mg IM HC just before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental surgery (eg, root canal work under local anesthesia)	Double dose (up to 20 mg HC) 1 h before surgery, or 50-100 mg IM HC just before anesthesia	Double oral dose for 24 h, then return to normal dose.
Minor procedure (eg, dental filling replacement, skin biopsy)	Usually not required	Extra dose if hypoadrenal symptoms occur afterwards

HC = hydrocortisone; IM = intramuscular; IV = intravenous.

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†Material reproduced and developed by UK Addison's disease self-help group and physicians of the Addison's disease clinical advisory panel; www.addisons.org.uk. Endorsed by a European expert consensus statement.[33]

‡Ensure patients are given the same "first on the list" priority for scheduled surgery as patients with insulin-dependent diabetes.

§Ensure the proposed steroid-cover regime has been agreed by the patient's endocrinologist, with specific assessment of the potential for interactions from any drugs for comorbidities.

‖Patients taking CYP-3A4 accelerants, eg, phenytoin, should always be placed on infusion cover to avoid rapid decompensation.

¶For any nil-by-mouth regime, arrange IV saline infusion to maintain mineralocorticoid stability and prevent dehydration.

**Give bolus HC over 10 minutes to avoid vascular damage.

††Monitor electrolytes and blood pressure postoperatively. If patient becomes hypotensive, drowsy, or peripherally shut down, administer 100 mg HC IV or IM immediately. If any postoperative complications arise (eg, fever), delay the return to normal dose.

condition even after it is presented to them, as illustrated in a recent survey of 46 patients. While 86% of patients were quickly attended to by a health care professional within 45 minutes of a distress call, only 54% received glucocorticoid administration within 30 minutes of arrival.[45] This may be because it is an uncommon condition with which health care professionals are often unfamiliar. The introduction of a pan-European Emergency card with clear instructions on the necessity of early treatment will hopefully empower allied health care providers and physicians to institute treatment.[46] For physicians who are less familiar with this uncommon condition, it is prudent to listen to patients and their families who often do know best, and in times of uncertainty, heed patients' requests for more hydrocortisone.[47] Increased

Table 6 Practical Checklist for Managing a Patient with Adrenal Insufficiency to Prevent Adrenal Crisis

Education (to re-evaluate at each visit)
Sick day rules (see **Table 5**)
Education of self-injection to patient and partner/family member/close friend
Symptoms and signs to watch out for, and need to seek emergency attention after hydrocortisone injection
Emergency phone number to contact (must be contactable at all times)
Leaflets and Web sites for further information
http://www.nadf.us/
https://www.youtube.com/user/adrenalchannel
Items to carry along at all times
Medic alert bracelet/card/necklace
Extra doses of hydrocortisone (adequate to last 48 h)
Items that should be easily accessible
Emergency hydrocortisone injection set
Hydrocortisone 100-mg ampoules (ensure not expired). To keep 0-25°C
Syringes and needles
Surgery
Patient should be provided letter of condition to any new attending surgeon or physician
Adjusting glucocorticoid dose is indicated for almost all surgeries (the extent depends on grade of surgery)
If admitted, endocrinologist/internist should be consulted
Before travel
Need to bring oral medication (on board plane)
Injection set
Letter from doctor (including translation in English/local language if necessary)
Prescription in case of lack of medications
Identify hospital or emergency facilities/helpline
Vaccinations and to avoid areas with higher risk of gastroenteritis

glucocorticoid doses in the short term are generally safe, while the consequences of inadequate doses can be disastrous. However, in the long-term management of a patient with adrenal insufficiency, it is also important to evaluate the frequency of stress doses used by the patient. Frequent use may indicate overzealous response to minor illness (which requires additional counseling about sick day rules), or a requirement for adjustments in basal regimens.

Education

Apart from patients, others, including the endocrinologist, primary physician, nurse, and family members, all play an important role. Nurse educators or patient group education meetings about sick day rules can improve patients' knowledge of their condition, and improve their response to illness.[40] However, in a recent prospective study, 18% of patients still failed to adjust their doses despite having received prior education.[18] Hence, it is important to constantly re-evaluate patients' understanding and to assess their reaction to illness.

Many patients with adrenal insufficiency suffer from impaired quality of life.[48] The National Adrenal Diseases Foundation has multiple local patient support groups, and their Web site[49] also provides a good deal of useful information for general practitioners and patients. The Dutch patient support group has also aided the provision of short and simple instructive online videos,[50] which are suitable for all ages above 4 years.

Travel advice should also be dispensed to all patients. For instance, adequate medication should always be carried with the patient, including on board the airplane in case of baggage delays. Hydrocortisone injections should be kept at 0-25°C (on board a plane without ice). Memos (in English, and possibly local language) about a patient's condition should be provided for the airline or any attending physicians. The new European Emergency Card provides information in both English and 8 different local languages.[46] Emergency numbers and directions to hospitals should be identified before travel, and they should be discouraged from traveling to places where medical care is limited. Appropriate vaccinations should be administered, and caution should be exercised in prevention of gastrointestinal infections. A useful checklist for managing patients with adrenal insufficiency is provided in **Table 6**.

CONCLUSION

Although adrenal insufficiency is a treatable disease in the 21st century, failure to recognize an adrenal crisis and institute appropriate and timely intervention has led to preventable deaths. Current glucocorticoid therapy fails to replicate the physiological requirements during times of stress. Hence, all physicians should be familiar with increased doses required in illness or stress. It is important to recognize that patients may not respond to oral therapy, and in those instances, early parenteral hydrocortisone administration and referral to an emergency department is

warranted. Adrenal crisis remains a real and constant danger to all patients with adrenal insufficiency throughout their lifetime. Because there is more than adequate availability of necessary health care in most countries, we should aim to eliminate mortality from adrenal crisis.

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