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SEEN guidelines for the management and prevention of acute adrenal insufficiency☆

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Abstract Acute adrenal insufficiency (AAI) is a potentially fatal medical emergency whose prevention and treatment should be known by all medical professionals.

AAI is an underdiagnosed condition because of its non-specific symptoms, but its diagnosis and early treatment with glucocorticoids is vital.

It may be triggered by a de novo deficiency in cortisol synthesis or occur secondarily to omission of hormone replacement therapy (corticosteroids) or inadequate adjustment of the dose required in stress situations in patients previously diagnosed with adrenal insufficiency.

AAI prevention significantly decreases death from cardiovascular diseases and infections in patients with adrenal insufficiency, and also improves their quality of life. Adequate education of patients, relatives, and all healthcare professionals is therefore essential.

Therefore, the Adrenal Disorders Group of the Neuroendocrinology Area of the Spanish Society of Endocrinology and Nutrition (SEEN) has prepared, at the proposal of the SEEN's board, a guideline for optimal management of acute adrenal insufficiency.

The guideline is intended to provide practical recommendations for all healthcare professionals who may be involved in the diagnosis, treatment, and prevention of AAI.

It is also intended to provide patients and their families with action guidelines for AAI management and prevention.

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Guía para el manejo y la prevención de la insuficiencia suprarrenal aguda

Resumen La insuficiencia suprarrenal aguda (ISA) es una urgencia médica potencialmente letal cuya prevención y tratamiento deberían ser conocidos por todos los profesionales médicos. La ISA es una condición infradiagnosticada debido a la inespecificidad de los síntomas de presentación, pero su diagnóstico y tratamiento con glucocorticoides es vital.

Puede ser desencadenada por una deficiencia *de novo* en la síntesis de cortisol o secundaria a la omisión del tratamiento hormonal sustitutivo con corticoides o al ajuste inadecuado de la dosis requerida en situaciones de estrés en el paciente ya diagnosticado.

La prevención de la ISA disminuye de forma significativa la mortalidad cardiovascular y por infecciones de los pacientes con insuficiencia renal y mejora su calidad de vida. Por ello, es fundamental la adecuada educación del paciente, sus familiares y del personal sanitario.

El Grupo de Trabajo de Patología Suprarrenal del Área de Conocimiento de Neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición (SEEN) ha elaborado, a partir de una propuesta de la Junta Directiva de la SEEN, esta guía para el óptimo manejo de la insuficiencia suprarrenal en fase aguda. Esta guía tiene el objetivo de ser eminentemente práctica y dar recomendaciones orientadas a todos los profesionales sanitarios que pueden estar involucrados en el diagnóstico, tratamiento y la prevención de la ISA. Así mismo, pretende facilitar pautas de actuación para el paciente y sus familiares en su manejo y prevención.

Introduction

Acute adrenal insufficiency (AAI), or adrenal crisis, is caused by corticosteroid deficiency due to ''de novo'' failure of the adrenal gland cortex or inadequate glucocorticoid (GC) replacement therapy dose adjustment in the face of an intercurrent stress event.

Acute adrenal insufficiency is a medical emergency, with a high mortality rate, and treatment should be started immediately at the slightest suspicion of AAI,[1–7] without waiting for prior laboratory confirmation.[1–8]

Patients with primary adrenal insufficiency (secondary to direct adrenal gland failure) and secondary adrenal insufficiency (secondary to hypothalamic-pituitary axis failure) require lifelong replacement therapy with GCs and, in the case of primary insufficiency, also mineralocorticoids (MCs).

The overall prevalence of adrenal gland insufficiency in the European Union is 2.1–4.2 cases per 10,000 individuals, with an incidence of AAI of 5–10 cases per 100 patients/year (higher in primary insufficiency) and a mortality rate of 0.5/100 patients.[1,2,8]

Acute adrenal insufficiency manifests in 50% of all cases at disease onset.

Table 1 describes the possible causes of adrenal insufficiency.[2]

The main cause of AAI being triggered in patients with chronic deficiency subjected to hormone replacement therapy is usually infection, particularly acute gastroenteritis.[1–7,9] Table 2 summarizes these circumstances.

Physiopathology

The physiopathology of AAI is only partially understood. The absence of the enhancing effect of GCs upon α1-adrenergic receptor expression induces hypotension, while MC deficiency conditions volume depletion due to the lack of sodium and water reabsorption. Hypovolemia may be aggravated by vomiting, diarrhea and hyperhidrosis, etc. Acute adrenal insufficiency under conditions of strenuous physical or psychological-emotional stress, trauma, or major surgery appears to be secondary to the absence of the suppressive effect of GCs upon the toxicity of the inflammatory and innate immune hyper-response.[1,2,9]

Clinical manifestations and diagnosis of acute adrenal insufficiency

The diagnosis of AAI is fundamentally clinical. If possible, blood sampling for cortisol and ACTH determination is advised before treatment is started, but it is not indispensable and should never be allowed to delay the start of patient management.[1–7,9]

The symptoms and signs of AAI depend on the degree and rate of onset of hormone deficiency, but are nonspecific, and patients characteristically suffer from severe and acute malaise.

Table 3 summarizes the main symptoms and signs of AAI.[7]

Physical examination and personal or family history

In cases of primary adrenal insufficiency, mucocutaneous hyperpigmentation (predominant in scars, the breast areolar region, photoexposed areas), as well as diminished pubic and axillary hair, is noted in women.

In both the personal and the family history, and in the physical examination, it is important to look for signs or symptoms of other autoimmune disorders (goiter, vitiligo, hypothyroidism, celiac disease, etc.).[1–5]

Table 1 Etiology of adrenal insufficiency.[2,4–7,9]

Primary
Autoimmune adrenalitis
Isolated (Addison)
Autoimmune polyglandular syndrome type 1 or 2
Immunotherapy (anti-CTLA4, anti-PD1, anti-PDL1)
Infections: tuberculosis, mycoses, parasitosis, syphilis, VIH, CMV
Bilateral adrenal metastases: lung, breast, melanoma, colon, lymphoma
Infiltrating diseases: hemochromatosis, amyloidosis, sarcoidosis
Vascular disorders: bilateral adrenal hemorrhage or thrombosis
Genetic causes
Congenital adrenal hyperplasia, salt-losing forms
Adrenoleukodystrophy, congenital (partial forms) or lipoid adrenal hypoplasia
Lack of response to ACTH due to receptor insensitivity
Surgical: bilateral adrenalectomy
Drugs
Bleeding: anticoagulants, sunitinib
Secondary to destruction: mitotane
Due to enzymatic inhibition: ketoconazole, metyrapone, etomidate, fluconazole, itraconazole
Due to increased metabolism: rifampicin, phenytoin, thyroxine, carbamazepine, phenobarbital, oxcarbazepine
Due to peripheral glucocorticoid resistance: mifepristone, chlorpromazine, imipramine
Miscellaneous: Mitochondrial disease, Wolman, etc.
Secondary
Due to suppression of the hypothalamic-pituitary axis:
Abrupt discontinuation of long-term treatment with glucocorticoids: systemic, topical, inhaled, intra-articular, and even eye drops. Chronic or repeated for over a total of 3 weeks or continuous nocturnal treatment for over 2 weeks; any dose that has induced a cushingoid phenotype
Other drugs: megestrol acetate, opioids, medroxyprogesterone, topiramate
After treatment for endogenous Cushing syndrome
Due to hypothalamic-pituitary involvement:
Primary (pituitary adenomas, craniopharyngiomas, gliomas, meningioma) or metastatic tumors (breast, lung, melanoma)
Infections: abscesses, tuberculosis, others
Infiltrating diseases: sarcoidosis, histiocytosis, hemochromatosis, Wegener
Hypophysitis: lymphocytic, granulomatous, others
Traumatic brain injuries
Postpartum hemorrhage (Sheehan)
Genetic diseases with isolated ACTH deficiency or panhypopituitarism, Prader-Willi syndrome
Iatrogenic: surgery, radiotherapy, immune therapy (anti-CTLA4, anti-PD1, anti-PDL1)

Some groups propose the use of a *diagnostic algorithm* for AAI (Table 4).[1]

Four severity degrees of AAI are defined according to the clinical scenario in which patient care is required, and to the final outcome[1]:

- Grade 1: outpatient care;
- Grade 2: in-hospital care;
- Grade 3: Intensive Care Unit (ICU);
- Grade 4: death due to adrenal crisis.

The vast majority of episodes of AAI in which medical care is sought correspond to grade 1, except in cases of trauma or accidents.[1]

Complementary tests

The *laboratory tests* in particular reveal electrolyte alterations in the form of hyponatremia, in primary adrenal insufficiency, and hyperpotassemia and azotemia (secondary to prerenal failure), normocytic anemia, lymphocytosis with neutropenia, eosinophilia, hypoglycemia (especially in children) and hypercalcemia.

From the *hormonal* perspective, decreased cortisol levels are observed, with ACTH levels that are elevated in primary adrenal insufficiency, and low or inappropriately normal in secondary adrenal insufficiency. Cortisol values should be interpreted in relation to situations of stress and, if malnutrition or sepsis is suspected, correction for total albumin/protein should be made. However, a level below

Table 2 Possible triggering causes of an adrenal crisis in patients with known adrenal insufficiency.

Medical-surgical conditions
Acute infections, especially gastroenteritis with vomiting and diarrhea
Myocardial infarction
Trauma, severe pain, wounds
Severe allergic reactions
Severe hypoglycemia in diabetic patients
Underlying psychiatric disorders
Invasive diagnostic tests
Major surgery
Drugs that increase cortisol metabolism or inhibit its synthesis (Table 1)
Patient suspension of therapy or abrupt termination of corticosteroid treatment
Drugs that increase the metabolism of mineralocorticoids or inhibit their action (lithium, progesterone, drospirenone, phenytoin)
Low salt intake and chronic mineralocorticoid under-replacement in primary adrenal insufficiency (recurrent AAI)
Non-disease conditions:
Pregnancy
Significant emotional stress
Strenuous exercise
Exposure to unusual heat and humidity
Change in circadian rhythm or eating rhythm (travel, Ramadan, work shifts, duty shifts)

Table 3 Major symptoms and signs of acute adrenal insufficiency.[7]

Severe hemodynamic instability with signs of hypovolemia, dehydration and hypotension
Asthenia with proximal muscle weakness, myalgia and cramps
Anorexia, nausea, vomiting, abdominal pain (sometimes with signs of peritoneal irritation) and altered bowel transit (diarrhea versus constipation)
Febricula/fever (idiopathic or associated with infection)
Weight loss
Cognitive impairment with headache or altered level of consciousness (from drowsiness to coma in cases of severe or prolonged alteration)
Cardiomyopathy with reversible acute myocardial failure
Previous psychiatric diagnosis of anorexia nervosa, depression

3.6 μg/dl (<100 nmol/l) is strongly suggestive of adrenal insufficiency, while concentrations above 15 μg/dl rule out the diagnosis, and levels between 5 and 15 g/dl require correlation with the clinical condition of the patient.

The *electrocardiogram* in turn can reveal bradycardia or signs of acute myocardial dysfunction.

Table 4 Diagnostic criteria of acute adrenal insufficiency.[a]

A. Markedly/severely impaired general condition + at least 2 of the following:
Systolic blood pressure < 100 mmHg (hypotension)
Nausea or vomiting
Drowsiness or disorientation and slowness
Febricula/fever
Ion disorders: hyponatremia (< 132 mEq/l) or hyperpotassemia
Hypoglycemia
B. Rapid improvement/remission of symptoms after parenteral administration of glucocorticoids (hydrocortisone). In cases of prolonged deficiency, recovery may take >24 h

[a] A type A or B criterion is required for the diagnosis of AAI.

Treatment of acute adrenal insufficiency

All healthcare professionals, and in particular emergency service professionals, should be aware of the management protocol applicable to AAI, since it is a potentially fatal condition if not identified and treated adequately and quickly.

In the emergency room, in the event of a strong clinical suspicion of adrenal insufficiency in a patient with no previous diagnosis of the disorder, or in situations of severe intercurrent episodes in a patient with confirmed adrenal insufficiency, urgent treatment is required and, if possible, peripheral blood sampling should be performed for hormone determination (cortisol and ACTH) before treatment is started.

Acute emergency treatment (24 h)

The basic key to management is immediate treatment with intravenous hydrocortisone at stress doses and the rapid correction of hypovolemia and water and electrolyte alterations (Table 5).

Mineralocorticoid replacement is not required on an acute basis, since high GC stress doses have an MC effect.

After starting GC treatment and hydration, an attempt should be made to identify and treat the triggering factor or disease.

With appropriate treatment, hemodynamic recovery occurs in the first 6–12 h, and clinical recovery in the first 24 h. Recovery may be slower in cases of prolonged corticosteroid deficiency with impaired consciousness.

Subacute treatment (24–48 h)

Once hemodynamic stabilization of the patient has been achieved, intravenous hydration should be continued for the next 24–48 h (total 72 h), with the administration rate being reduced and the dose of intravenous GC being gradually lowered. Finally, this should lead to a return to the usual dose via the oral route when so allowed by the underlying condition or factor causing AAI.

In the case of the onset of adrenal insufficiency, in addition to identifying and treating the triggering factor or

Table 5 Acute treatment of adrenal crisis.

General life support measures, peripheral line catheterization, cardiac monitoring and, if possible, CVP monitoring	
Intravenous corticosteroids	Hydrocortisone 100 mg as initial bolus followed by 200–300 mg/24 h as a continuous i.v. infusion in 5% glucose saline or bolus 50 mg i.v./6 h If hydrocortisone is not available, methylprednisolone (20 mg/12 h) or dexamethasone 4 mg/12 h i.v. may be used.[a] The i.m. route may be used in cases of vascular shock Children: hydrocortisone 50 mg/m^2 initial bolus followed by 50–100 mg/m^2 daily or every 6 h
Intravenous hydration	2–3 l of saline solution (0.9%) in the first 24 h: if the patient is in shock: 1000 ml in 1 st h, then 500 ml in 2nd and then adjust rate as needed Children: bolus of isotonic saline solution (0.9%) at 20 ml/kg. Up to 50 ml/kg in 1 h may be repeated in the case of shock Also administer glucose saline (10%) in the event of hypoglycemia Control of water balance, electrolytes (sodium, potassium, glomerular filtration) to avoid overload, rapid sodium correction[b] and subsequent hypopotassemia
Treatment of the underlying disease	Antibiotics, etc.
General support measures	Admission to intensive care Prophylactic dose heparin PPI (prevention of gastric stress ulcers)

HR: heart rate; PPI: proton pump inhibitor; i.m.: intramuscular; i.v.: intravenous; BP: blood pressure; CVP: central venous pressure.

[a] Avoid dexamethasone in cases of K > 6 mEq/l in primary adrenal insufficiency, due to the lack of a mineralocorticoid effect. Although an advantage of dexamethasone use is that it allows for the diagnosis of adrenal insufficiency even after administration, because it does not interfere with the method for measuring endogenous cortisol, its suppressive effect upon the hypothalamic-pituitary-adrenal axis may result in falsely low cortisol values.

[b] The correction of hyponatremia should be made with caution: a corrective rate of no more than 10 mmol/l is recommended in the first 24 h, and 18 in the first 48 h. In cases of an increased risk of brain edema (women, elderly subjects, children and malnourished patients), it is advisable not to exceed 6–8 mmol/l in the first 24 h and 15 mmol/l in the first 48 h. Close monitoring of electrolytes is recommended in the first 24–48 h and, if the correction rate exceeds that recommended, do not hesitate to increase the glucose saline perfusion rate and prescribe desmopressin intravenously or subcutaneously in a timely manner (1–2 mg).

disease, an etiological diagnosis should be established (see Table 1).

It is advisable to consult the Endocrinology Department to ensure due assessment in the event of the onset of adrenal insufficiency, and to reinforce educational measures and adjust the basal regimen in special situations.

In cases of primary adrenal insufficiency, MC replacement should be restarted with fludrocortisone (0.1 mg daily via the oral route) when saline infusion is suspended and the hydrocortisone dose is less than 50 mg/day.

It should be noted that the diagnostic algorithm and the management of chronic replacement therapy in adrenal insufficiency are not the objective of this guide, but can be found in the documents cited in the references.

Prevention of acute adrenal insufficiency

In the management of patients with adrenal insufficiency, it is essential for both the patients and their relatives to have the basic tools to prevent, identify, and treat an adrenal crisis. This involves the following:

- An awareness of those situations that can trigger hormone deficiency and of the reasons why early treatment is so important. Likewise, the administration of high GC doses is not intended to mimic the mean values of normal subjects during stress, but to mimic the maximum cortisol increase that may be required in order to cover additional unexpected needs. The damage caused by these doses has not been demonstrated, and there are no direct studies indicating which lowest doses are safe.
- Education and regular follow-up (annually or more often in patients with a recent history of AAI), reviewing how to increase the GC dose according to the severity of intercurrent illness, and when and how to administer hydrocortisone via the intramuscular, subcutaneous or rectal route at home.
- Table 6 summarizes the main recommendations that healthcare professionals should be familiar with so that they can adjust the GC dose in relation to stress and medical or therapeutic procedures.
- If hydrocortisone is not available for intramuscular or intravenous administration, replacement with the equivalent dose of methylprednisolone or dexamethasone is advisable. Table 7 summarizes the characteristics of the GCs recommended for administration via these routes for the treatment and prevention of AAI.
- Education to recognize the warning signs and symptoms of a possible adrenal crisis, and to ensure awareness of the need to attend the nearest hospital and start treatment quickly.
- An awareness of how to use and ensure the availability of emergency material and treatment tools.

Table 6 Recommendations for corticosteroid dose adjustment in stress situations and medical/therapeutic procedures.

Condition	Treatment
Disease with fever, requiring home rest (e.g., respiratory tract infection) or antibiotics, after vaccination (influenza)	Hydrocortisone: double (>38 °C) or triple (>39 °C) the oral dose while fever persists, and then reduce it to the usual dose in 1–2 and 2 days, respectively. Increase the intake of fluids with electrolytes (isotonic drinks)[a]
Gastroenteritis with persistent vomiting or diarrhea, oral intolerance	Hydrocortisone 50 mg/12 h i.m. or i.v.[a] Hydration: saline solution 0.9% 1000 ml 1st hour; 500 ml 2nd hour, subsequent continuous infusion. Consider hospital admission Children: hydrocortisone 50 mg/m^2 i.m. (or 25 mg in preschool children, 50 mg in schoolchildren, 100 mg in adolescents)[a]
Wound with considerable bleeding, severe trauma, fracture, or severe disease (e.g., pneumonia, altered level of consciousness, severe sepsis, myocardial infarction, pancreatitis, etc.)	Hydrocortisone i.v. 50–100 mg/8 h or continuous i.v. perfusion of 150–300 mg/24 h, decreasing to half daily when improvement is seen[a] Children: hydrocortisone 50 mg/m^2 i.v., followed by hydrocortisone 50–100 mg/m^2 daily or divided and given every 6 h[a]
Pregnancy	Increase the dose by 20–50% of the initial dose (an increase in hydrocortisone of 2.5–10 mg/day) in the third trimester (from week 24)
Anticonvulsants and barbiturates, tuberculostatic agents, etomidate, topiramate, growth hormone, tamoxifen, estrogens, thyroxine	Assess the need for increased fludrocortisone after increased hydrocortisone Increase the dose (start with 10–20%)
Liquorice, grapefruit juice and colestipol	Reduce the dose (start by 10–20%)
Antifungal drugs	Dose adjustment may be required
Prolonged or severe emotional or mental stress (university or workplace exams, death of a family member, grief, acute depression) Exercise of unusual intensity or duration (marathon, match)	An additional hydrocortisone dose of 5–20 mg 30–60 min before. In the case of physical exercise: additional fluid and salt intake[b]
Working in shifts or travel with changes in time zone	Adapt the hydrocortisone dose to the sleep-wake cycle
Ramadan	Instead of hydrocortisone, longer-acting glucocorticoids, such as prednisolone or dexamethasone, should be considered for fasting compliance (approximately 15 h) A combination of prednisolone in the morning and hydrocortisone in the afternoon-evening may also be considered. If possible, it should be started a few weeks earlier for appropriate dose adjustment. During fasting hours, strenuous work and excessive heat should be avoided, and attempts should be made to rest during this period to avoid stress
Lithium, progesterone (synthetic non-progestins), drospirenone, phenytoin, beta-blockers	Increase the dose of fludrocortisone (start with 20%)
Exposure to excessive humidity and heat (tropical climate)	Increase the intake of fluids with electrolytes (isotonic drinks); free access to salt Increase the dose of fludrocortisone (start with 20–50%)

Procedure	Pre-procedure	Post-procedure
Major surgery with a long recovery time (e.g., intraabdominal surgery, cardiac surgery), general anesthesia, intensive care	100 mg of hydrocortisone i.v. or i.m. just before anesthesia and continue with 200 mg/day as a continuous infusion or bolus of 100 mg every 12 h or 50 mg every 6 h[a] Children: hydrocortisone 50 mg/m^2 i.v. followed by hydrocortisone 50–100 mg/m^2 daily or divided into every 6 h[a]	On the first day, 100 mg of hydrocortisone every 8–12 h or continuous i.v. infusion of 200–300 mg/24 h. After the uncomplicated procedure, gradually reduce the dose (30%) every day until the patient is able to drink and eat[a] Double the oral dose for 48 h, then reduce to the normal dose Children: hydrocortisone 50 mg/m^2 i.v. followed by hydrocortisone 50–100 mg/m^2 daily or divided into every 6 h[a]

Table 6 (*Continued*)

Procedure	Pre-procedure	Post-procedure
Major surgery with rapid recovery (joint replacement surgery, cesarean section)	100 mg of hydrocortisone i.v. or i.m. just before anesthesia[a] Children: hydrocortisone 50 mg/m^2 i.v.[a]	Hydrocortisone 50 mg/8 h i.v. on the day of surgery, halve in the next 24 h and return to the usual replacement doses in the following days[a] Children: hydrocortisone 50 mg/m^2 followed by hydrocortisone 25–50 mg/m^2 daily or divided and given every 6 h[a]
Prepartum and delivery maneuvering	Start of hydrocortisone with labor maneuvers: infusion of 100 mg in 12 h until delivery During labor: hydrocortisone i.v.[a] 25 mg every 6 h If labor is prolonged, 100 mg/8 h or continuous infusion (200–300 mg/24 h) until delivery	Double the oral dose for 24–48 h after delivery, then reduce to the normal dose
Minor surgery (cataracts, hernia) and major dental surgery (tooth extraction under general anesthesia, molars)	100 mg of hydrocortisone i.m. (or s.c.) just before anesthesia or i.v. infusion during surgery[a] Children: hydrocortisone 50 mg/m^2 i.m.[a]	Double the oral dose for 24 h, then return to the normal dose[b]
Invasive procedures requiring laxatives: colonoscopy, barium enema, etc.	Consider hospital admission the night before to administer 100 mg of hydrocortisone i.v. or i.m. (or s.c.) and fluids (isotonic saline solution), repeat the dose just before the procedure[a] Children: hydrocortisone 50 mg/m^2 i.m. before the procedure[a]	Double the oral dose for 24 h, then return to the normal dose[b]
Other invasive procedures: arteriography, endoscopy, etc.	100 mg hydrocortisone i.v. or i.m. just before the procedure	Double the oral dose for 24 h, then return to the normal dose[b]
Minor dental procedure (filling, skin lesion)	Not normally required. An extra dose can be administered 1 h before the procedure (10–20 mg of hydrocortisone in adults)	Extra dose in the event of symptoms of hypocortisolism[b]
Minor dental procedure (endodontic treatment)	An extra dose can be administered 1 h before the procedure (10–20 mg of hydrocortisone in adults)	Double the oral dose for 24 h, then return to the normal dose[b]

i.m.: intramuscular; i.v.: intravenous; s.c.: subcutaneous: p.o.: oral.
Recommendations for glucocorticoid dose adjustment in medical and therapeutic procedures.
[a] If hydrocortisone administered via the intramuscular or intravenous route is not available, it is advisable to replace it with the equivalent dose of methylprednisolone or dexamethasone (100 mg hydrocortisone is equivalent to 20 mg of methylprednisolone or 4 mg of dexamethasone), adjusting the hourly regimen according to the specific pharmacokinetics of each GC. It is important to take into account that MC replacement is not required if the hydrocortisone dose exceeds 50 mg every 24 h.
[b] In the case of treatment with sustained-release and dual-release GC preparations (such as Plenadren®), in order to double or triple the total daily dose, the maintenance dose should be administered every 12 or 8 h, respectively (e.g., if the dose is 20 mg at breakfast and we want to triple it, raise it to 20 mg at breakfast, 20 mg at lunch and 20 mg at dinner time). In the case of treatment with Plenadren®, and if an extra dose is to be administered, an extra immediate-release dose of hydrocortisone is required (5–10 mg), particularly in the afternoon or evening (e.g.: Plenadren® 20 mg at breakfast and hydrocortisone 10 mg at the time of the afternoon snack).

Emergency materials and precautions

These are as follows:

1) An emergency card or identification (necklace or bracelet) which the patient should carry or wear at all times, so that it can be located by the healthcare personnel in the event of an adrenal crisis in order to know the cause of the disease, regular treatment, and the treatment to be administered in the event of an emergency: ''Adrenal insufficiency: I need glucocorticoids!''.

Both national and international (EU) emergency cards are available for printing in the adrenal disease section for patients of the SEEN (www.seen.es).

2) The patient should report his/her disease before starting new treatments, in case dose adjustment is required.
3) An emergency kit should be available for use by the patient or relatives, and should include the following: GC for injection (at least 2 vials of 100 mg hydrocortisone or 20 mg methylprednisolone or 4 mg of dexamethasone), vials of saline solution (0.9%), and syringes. An

Table 7 Glucocorticoids used in the prevention and treatment of acute adrenal insufficiency.

GC	Equivalent doses (mg)	Potency GC/MC	GC hourly regimen in the treatment of AAI	Hourly regimen in the prevention of AAI	Duration of GC action
Hydrocortisone	100	1/1	Every 6 h	Single – every 8–12 h	8–12 h
Methylprednisolone	20	5/0.3	Every 12 h	Single – every 12–24 h	12–36 h
Dexamethasone	4	25–50/0	Every 12 h	Single – every 12–24 h	36–72 h

GC: glucocorticoid; h: hour; AAI: acute adrenal insufficiency; MC: mineralocorticoid.

alternative is the use of suppositories of 100 mg prednisolone, or prednisolone enemas of 20 mg/100 ml or 10% hydrocortisone acetate (in the absence of diarrhea). Explain how the medication should be prepared and injected (intramuscular, subcutaneous or rectal). The subcutaneous and intramuscular injection of hydrocortisone presents similar pharmacokinetics, but the ease of subcutaneous administration makes this route the option of choice. It should be borne in mind that in the case of subcutaneous administration, two injections are needed (versus a single intramuscular injection), and more time is required to reach therapeutic levels (22 versus 11 min).

4) The availability of an *information leaflet with indications* for medical or therapeutic situations/events/procedures requiring dose adjustments or the intramuscular, subcutaneous or rectal administration of replacement therapy.

Supplementary informative material on AAI for patients and relatives is available in the adrenal disease section for patients of the SEEN (www.seen.es) and in the European support network (www.adrenal.eu).

5) The provision of a *phone number of the healthcare team* familiar with the management of this disorder.

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