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Guidelines for diagnosis and treatment of adrenal insufficiency in adults

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Abstract Adrenal insufficiency (AI) is a disease characterized by a deficient production or action of glucocorticoids, with or without deficiency in mineralcorticoids and/or adrenal androgens. It can result from disease intrinsic to the adrenal cortex (primary AI), from pituitary diseases that hamper the release of corticotropin (secondary AI) or from hypothalamic disorders that impair the secretion of the corticotropin-releasing hormone (tertiary AI).

It is a disease with a low prevalence but its impact on the affected individual is very high as it can be life-threathening if not treated or lead to health problems if inadequately treated. However, currently there are no specific guidelines for the management of this disease. Therefore, at the proposal of the Spanish Society of Endocrinology and Nutrition (SEEN) board, a task-force under the Neuroendocrinology Knowledge Area of the SEEN was established, with the mandate of updating the diagnosis and treatment of AI. In fulfilment of this mandate the task-force has elaborated the present guide, that, based on a comprehensive review of literature, is intended to provide an answer to questions related to the management of this disease. It is, therefore, an essentially practical document, mainly aimed at guiding the health professionals involved in the care of IA patients.

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PALABRAS CLAVE
Insuficiencia adrenal;
Diagnóstico;
Tratamiento

Guía para el diagnóstico y tratamiento de la insuficiencia suprarrenal en el adulto

Resumen La insuficiencia suprarrenal (IA) es un trastorno que se caracteriza por un déficit de GC, al que se asocia en ocasiones un déficit de mineralocorticoides y/o andrógenos adrenales. Puede ser consecuencia de enfermedades intrínsecas del córtex adrenal (IA primaria), de procesos hipofisarios que afecten a la secreción de corticotropina (IA secundaria) o de trastornos hipotalámicos que afecten la secreción de la hormona liberadora de corticotropina (IA terciaria).

Se trata de una entidad de baja prevalencia pero con elevado impacto sobre la salud individual, dado que entraña riesgo vital en ausencia de tratamiento y efectos deletéreos para la salud en caso de tratamiento inadecuado. En la actualidad no hay ninguna guía de práctica clínica para el manejo de esta enfermedad, por este motivo, a partir de una propuesta de la junta directiva de la Sociedad Española de Endocrinología y Nutrición (SEEN), se constituyó un grupo de trabajo dependiente del Área de Conocimiento de Neuroendocrinología de la SEEN, al que se encomendó la tarea de actualizar el diagnóstico y tratamiento de la IA del adulto. En cumplimiento de esta labor, el grupo de trabajo ha elaborado la presente guía, que, basándose en una revisión exhaustiva de la bibliografía, pretende dar respuesta a los interrogantes que se platean en el manejo de esta enfermedad. Se trata, por tanto, de un documento de carácter eminentemente práctico, cuya intención principal es servir de guía a los profesionales que se dedican al cuidado de los pacientes con IA.

Introduction

AI was first described in 1885 by Thomas Addison, who defined the disease as a disorder characterized by impaired adrenocortical function with resultant glucocorticoid (GC), mineralocorticoid (MC) and/or adrenal androgen deficiencies[1]. AI may result form conditions affecting the adrenal cortex (primary AI). pituitary conditions affecting secretion of adrenocorticotropic hormone (ACTH) (secondary AI), or hypothalamic disorders affecting secretion of corticotropin releasing hormone (CRH) (tertiary AI).

Prevalence of primary AI (PAI) in the Western world has been estimated at 35-60 cases per million population, but according to some studies, it may be as high as 144 cases per million[2-4]. The overall estimated prevalence of secondary AI (SAI) ranges from 150-280 cases per million population[5].

PAI results from progressive destruction of adrenal cortex. At least 80% of adrenal parenchyma should be lost for clinical manifestations to occur. At the initial stage of this destructive process, there is only a decreased adrenal reserve, so that basal cortisol secretion is normal, but stress response is suboptimal. Therefore, any event that increases steroid demand in this early stage may trigger an acute adrenal crisis. Basal secretion decreases in parallel to progressive adrenal tissue, and clinical manifestations of the disease eventually occur. Decrease plasma cortisol levels lead to increased plasma ACTH levels due to loss of the negative feedback exerted by cortisol on ACTH secretion. Increased ACTH levels are responsible for the hyperpigmentation seen in patients with PAI. In addition, atrophy of the zona glomerulosa of adrenal cortex induces MC deficiency, which causes the water and electrolyte changes and hypotension seen in most these patients. Gland atrophy also causes a marked deficiency in adrenal sex steroids, mainly secreted in the zona reticularis and, to a lesser extent, in the zona fasciculata.

The relative frequency of the different causes of PAI has changed over time. Until the 1920s, the most common cause was tuberculosis infection. From the 1950s, most cases (approximately 80%) are due to autoimmune adrenalitis, either isolated or in the setting of an autoimmune polyglandular syndrome.

Secondary AI (SAI) may be due to any condition involving the anterior pituitary gland and interfering with ACTH secretion. Tertiary AI (TAI) results from conditions involving the hypothalamus and interfering with CRH secretion. Differentiation between SAI and TAI has no diagnostic or therapeutic implications in clinical practice. Thus, they will be henceforth jointly discussed under the name of SAI. In early disease stages, basal ACTH secretion is normal, but a decreased stress response already exists. As the disease progresses, basal ACTH secretion gradually decreases, leading to progressive atrophy of the zona fasciculata and zona reticularis of the adrenal cortex. The glomerular layer, however, remains unchanged because its dependence on the trophic effect of ACTH is minimal. Adrenal cortisol and androgen secretion therefore decreases, with no significant impairment in aldosterone secretion.

Clinical symptoms and signs associated to AI depend on the extent of adrenal involvement and on whether the mineralocorticoid axis is preserved or not. AI usually occurs slowly, and its manifestations usually become evident after physical stress conditions such as intercurrent diseases of some severity[1,5,6]. Patients with PAI usually show symptoms derived from GC and MC deficiency, while patients with SAI only have symptoms of GC deficiency. PAI is also associated to signs derived from excess ACTH such as skin and mucosal hyperpigmentation, which is especially apparent in palmoplantar furrows, scars (if formed after the start of the disease), and oral mucosa (Table 1).

Table 1 Symptoms and signs of adrenal insufficiency

Symptoms	Signs	Laboratory
Derived from GC deficiency • Gastrointestinal symptoms: — Nausea, vomiting — Constipation/diarrhea — Abdominal pain • Asthenia, anorexia, weakness, • Headache • Fasting hypoglycemia	• Weight loss • Hypotension • Hyperpigmentation (in PAI)	• Water and electrolyte disorders — Hyponatremia — Hyperkalemia (in PAI) • Hypercalcemia • Azotemia • Hypoglycemia • Anemia • Eosinophilia
Derived from MC deficiency (in PAI only) • Dizziness, hypotension • Weight loss • Dehydration		
Androgen deficiency • Decreased pubic and axillary hair in women • Decreased libido in women		
Derived from excess ACTH in PAI • Skin and mucosal hyperpigmentation		

ACTH: adrenocorticotropic hormone; GC: glucocorticoid; MC: mineralocorticoid; PAI: primary AI.

PART I. GUIDELINES FOR DIAGNOSIS OF AI

Diagnostic evaluation of a patient at risk of or with suspected AI includes three diagnostic processes: 1) confirmation of presence of AI (syndromic diagnosis); 2) identification of the level of the hypothalamic-pituitary-adrenal (HPA) axis where the responsible defect is located (diagnosis of location); and 3) identification of the cause (etiological diagnosis). For didactic purposes, the three conditions are sequentially discussed, although it is not rate for them to occur at the same time or in a different order.

1. Syndromic diagnosis

The gold standard test for diagnosis of AI is the insulin hypoglycemia test. This is however a relatively expensive test which is uncomfortable for patients and not devoid of risks. It is therefore reserved for patients in whom diagnosis cannot be made using simpler methods. Diagnostic workup usually starts with basal hormone measurements, followed by dynamics tests if needed.

1.1. Basal hormone measurements

1.1.1. What is the value of serum basal cortisol measurements?

Serum basal cortisol levels should initially be measured if AI is suspected, because they may confirm or rule out the condition without the need for additional studies in a significant proportion of patients.

1.1.2. What serum basal cortisol levels allow for confirming AI diagnosis?

Using response to the insulin hypoglycemia test as gold standard, it has been shown that plasma cortisol levels less than 3 μg/dL (100 nmol/L) according to some authors[7], or less than 5 μg/dL (138 nmol/L) according to other authors[8], have 100% specificity for AI diagnosis. Thus, plasma cortisol levels less than 3 μg/dL confirm diagnosis of AI, and no additional confirmation tests are required. Levels ranging from 3 and 5 μg/dL are highly suggestive of AI, although a small proportion of healthy subjects may have values in that range.

1.1.3. What serum basal cortisol levels allow for ruling out AI diagnosis?

Approximately 60% of patients with AI diagnosed based on an insulin hypoglycemia test have plasma cortisol levels higher than 5 μg/dL (138 nmol/L), and approximately 40% have levels higher than 10 μg/dL (275 nmol/L)[8]. However, cortisol levels above 15 μg/dL (414 nmol/L) predict for a normal response in the insulin hypoglycemia test in virtually all patients, and values higher than 18 (496 nmol/L) are even more reliable[8]. According to some experts, the cut-off point is 10 μg/dL[9,10]. Cortisol levels higher than 15 μg/dL would thus rule out AI with high certainty, and no further diagnostic tests would be required. Levels ranging from 10 and 15 μg/dL are highly suggestive of a normal adrenal axis, although a small proportion of patients with AI may have serum cortisol levels in this range.

1.1.4. What precautions are required when plasma cortisol results are interpreted?

It is well known that cortisol secretion follows a circadian rhythm characterized by a nadir occurring between 23:00 and 2:00 h and a gradual increase from 2:00-3:00 h until an early peak is reached at 6:00-8:00 h. The above reported normal values come from measurements made between 8:00 h and 9:00 h and cannot be extrapolated to other times of the day. Thus, adequate interpretation of cortisol levels requires knowing the time of the day at which the sample was taken.

Approximately 90% of serum cortisol is bound to plasma protein, and only 10% circulates as free cortisol; this is the biologically active fraction. Cortisol binding protein (CBG) is the main responsible for cortisol transport in plasma. Increased or decreased CBG levels are associated to increased or decreased protein-bound cortisol levels respectively. This leads to parallel changes in total cortisol levels with no change in free cortisol levels. However, procedures used in clinical practice to measure serum cortisol levels do not differentiate the protein-bound fraction from the free fraction. Plasma cortisol levels should therefore be interpreted with caution in patients with CBG increase or decrease (Table 2) because in these cases, abnormal cortisol levels (at the expense of the protein-bound fraction) do not necessarily mean that adrenal dysfunction exists.

Finally, since cortisol secretion is increased in physical stress situations, the finding of elevated plasma cortisol levels under these conditions is usually only the expression of an adequate response of the body to stress. By contrast, normal plasma cortisol levels in stress situations may be inappropriate and actually reflect low hormone secretion.

1.1.5. What is the diagnostic value of salivary cortisol levels?

Cortisol levels in saliva show a good correlation to serum cortisol levels[11,12], and various studies have shown a marked decrease in salivary cortisol in patients with hypoadrenalism[11,13,14]. Measurement of salivary cortisol has therefore been proposed as a potentially helpful procedure for AI diagnosis.

Measurement of salivary cortisol levels has two main advantages as compared to serum cortisol measurements: 1) sampling does not require an invasive procedure and may be done by patients themselves at home; 2 the test is not affected by changes in plasma proteins because it measures free cortisol, rather than total cortisol. This may therefore be a suitable test for cases where abnormal levels of transporter proteins make interpretation of serum cortisol levels difficult.

Various cut-off points have been proposed to rule out or confirm AI with 100% specificity[15]. It is usually accepted that morning (8:00 AM) salivary cortisol levels higher than 0.58 μg/dL (16 nmol/L) rule out AI, and values less than 0.18 μg/dL (5 nmol/L) strongly predict for AI. However, this test has not been duly standardized yet, and there is no universal agreement on its use for AI diagnosis.

1.1.6. What is the role of measurement of urinary free cortisol levels in AI diagnosis?

Measurement of urinary free cortisol (UFC) levels has a low diagnostic sensitivity because approximately 20% of subjects with AI have normal values[16]. Therefore, it is not a valid test for diagnosis, and should not be used for this purpose.

1.1.7. Is ACTH measurement helpful for AI diagnosis?

Measurement of plasma ACTH levels has no value for syndromic diagnosis of AI because low, normal, or high levels may be found depending on the level of the HPA axis where the defect responsible for AI is located. It may only be helpful in cases with suspected PAI and basal cortisol levels in the non-diagnostic range. Under these circumstances, clearly increased ACTH levels confirm at least subclinical AI (and suggest primary adrenal gland involvement as its cause).

1.1.8. What should be done in subjects with suspected AI and plasma cortisol levels in the indeterminate or non-diagnostic range?

As noted above, plasma cortisol levels ranging from 3 and 15 μg/dL (and especially from 5-10 μg/dL) in the absence of stress are indeterminate and may correspond to both normal and AI subjects. Subjects with indeterminate cortisol levels and clinical suspicion of AI therefore require additional dynamic tests to confirm or rule out diagnosis.

1.2. Dynamic tests

1.2.1. What dynamic tests are available for AI diagnosis?

Table 3 lists the dynamic tests helpful for diagnosis of AI.

Insulin hypoglycemia test. As stated above, the insulin hypoglycemia test is considered as the gold standard for AI diagnosis. The test measures serum cortisol response to

Table 2 Circumstances that may alter serum cortisol measurements by modifying transporter proteins.

Mechanism	Condition responsible	Effect
Decreased CBG synthesis	Liver disease Hypothyroidism Sepsis	Falsely decreased cortisol
Increased CBG losses	Nephrotic syndrome	Falsely decreased cortisol
Increasing CBG synthesis	Oral contraceptives Pregnancy Hyperthyroidism	Falsely increased cortisol

hypoglycemia induced by insulin administration. It is based on the strong stimulus exerted by hypoglycemia on CRH and ACTH secretion by hypothalamus and pituitary gland respectively, which finally results in increased serum cortisol levels. Thus, both defective ACTH secretion due to hypothalamic-pituitary-adrenal damage and defective cortisol secretion due to primary adrenal gland damage will cause a subnormal serum cortisol response. For the test to be valid, effective hypoglycemia, i.e. plasma glucose levels less than 40 mg/dL (2.2 nmol/L) associated to hypoglycemic signs and/or symptoms, should be achieved. Peak cortisol levels higher than 18 μg/dL according to some authors, or higher than 20 μg/dL according to others[17] guarantee the normality of the HPA axis.

Advantages of this test include: 1) high sensitivity and specificity; 2) its ability to assess, unlike other tests, the whole HPA axis, which makes it useful in newly starting SAI conditions where other test may give false negative results (see below); and 3) its ability to simultaneously assess GH secretion, which may be of interest in patients with hypothalamic-pituitary disease. Its disadvantages include the need for medical supervision during the test to avoid severe hypoglycemia with risk of severe complications and occurrence of contraindications. This limits its use under certain conditions, such as subjects older than 60 years, cardiovascular disease, stroke, severe high blood pressure, epilepsy, and pregnancy[18].

Short stimulation test with synthetic ACTH at standard dose. This test assesses serum cortisol response to acute ACTH stimulation, for which 250 μg of tetracosactide (Synacthen, Novartis Pharma) or cosyntropin (Cortrosyn, Amphastar Pharmaceuticals), both synthetic ACTH analogues, are administered by the IV or IM route. Unlike the insulin hypoglycemia test, this is a test with no risks for the patient and no contraindications.

It may be used to identify patients with both PAI and SAI. In SAI, the value of the test lies in that long-term absence of stimulation with endogenous ACTH induces adrenal cortex atrophy, which results in loss of the capacity of the adrenal cortex to respond to an acute stimulus.

Peak serum cortisol levels less than 18 μg/dL are considered diagnostic of AI. This cut-off point has 97.5% sensitivity and 95% specificity for diagnosis of PAI[19]. A flat response is frequently seen in PAI because cortisol secretion is already maximally stimulated at baseline (pre-stimulus) due to elevated ACTH levels resulting from loss of the negative feedback exerted by cortisol.

Table 3 Dynamic tests to assess adrenal function

Test name	Compound to be administered	Sampling	Parameter tested	Remarks
Insulin hypoglycemia test	Regular insulin 0.1-1.15 U/kg i.v	0-30-45-60-90 min	Plasma cortisol	Gold standard Assesses integrity of the whole HPA axis Contraindicated at ages >60 years, cardiovascular or cerebrovascular disease, severe HBP, pregnancy Need for medical supervision
Standard dose ACTH stimulation	Tetracosactide (Synacthen®) 250 μg i.v	0-30-60 min	Plasma cortisol	Simple and safe Poor sensitivity in partial or recent onset SAI
Low dose ACTH stimulation	Tetracosactide (Synacthen®) 1 μg i.v	0-30-60 min	Plasma cortisol	Need for manual preparation of solution Its superiority over standard dose in SAI is questioned
Metyrapone stimulation	Metyrapone 30 mg/kg p.o. at 0:00 h	8 h post-metyrapone	11-deoxycortisol	Assesses integrity of the whole HPA axis Alternative to insulin hypoglycemia when contraindicated Contraindicated in pregnancy
Glucagon stimulation	Glucagon 1 mg i.m.	90-120-150-180-210-240 min	Plasma cortisol	Assesses integrity of the whole HPA axis Less diagnostic accuracy than the former

ACTH: adrenocorticotropic hormone; HBP: High blood pressure; HPA: hypothalamic-pituitary-adrenal; SAI: Secondary Adrenal insufficiency; i.m.: intramuscular; i.v.: intravenous; p.o.: orally.

In SAI, the cut-off point of 18 μg/dL appears to have a somewhat lower sensitivity than that reported for PAI because a small proportion of patients with SAI confirmed by insulin hypoglycemia have a cortisol peak higher than this threshold[20], In these cases, cortisol values less than 23 μg/dL have shown 100% sensitivity, and SAI cannot therefore be ruled out with certainty in subjects who exceed this threshold. Severe, long-standing SAI may be ruled out in subjects with cortisol levels ranging from 18 and 23 μg/dL, but mild or recently starting SAI cannot be excluded in these patients. This group of patients therefore represent a risk category, and an insulin hypoglycemia test or a repeat ACTH test after approximately 6 months are recommended in them.

Short stimulation test with synthetic ACTH at low dose. One of the main criticisms made to the standard ACTH stimulation test is use of a pharmacological dose of ACTH, which induces plasma ACTH levels at least one thousand times higher than those seen in stress situations in healthy subjects. This is therefore considered to be an unphysiological stimulus, able to induce adrenal response in cases of partial gland atrophy (resulting from partial ACTH deficiency), which may lead to false negative results in SAI diagnosis. To avoid this disadvantage, the low dose ACTH stimulation test was introduced in the early 90s. The ACTH dose administered in this test is 1 μg, which achieves plasma ACTH levels closer to physiological values and to those induced by the insulin hypoglycemia test in healthy subjects, which should theoretically contribute to a lower false negative rate. Using a cut-off point of 18 μg/dL, 100% sensitivity has been reported for AI diagnosis with this test, as compared to 97.7% sensitivity with the standard test[21]. However, the superiority (higher sensitivity) of the low dose test over the standard dose test for AI diagnosis[22-25] has not been supported by all studies[26,19].

A disadvantages of this test is that no commercial products containing 1 μg of ACTH are available, and the solution should therefore be prepared manually from the available commercial preparations, which provide 250 μg of ACTH per vial as solution or as freeze-dried powder.

Other tests.

- Metyrapone test. This test is based on the inhibitory effect exerted by metyrapone on the enzyme 11β-hydroxylase, responsible for conversion of 11-deoxycortisol into cortisol. In healthy subjects, reduction in cortisol synthesis induced by metyrapone results in increased ACTH secretion. This stimulates synthesis of adrenal steroids proximal to enzymatic blockade, which finally leads to increased plasma 11-deoxycortisol levels. The metyrapone test is a good alternative when the insulin hypoglycemia test is contraindicated[26].
  11-deoxycortisol levels higher than 7 μg/dL (190 nmol/L) eight hours after administration of metyrapone in the presence of cortisol levels less than 5 μg/dL (138 nmol/L) (indicating adequate enzyme inhibition) are considered normal. Potential interference by certain drugs in metyrapone metabolism, which may lead to false positive results, should be taken into account.
- Glucagon test. This test measures cortisol response to IM administration of 1 mg of glucagon. It is based on the capacity of glucagon to stimulate ACTH secretion. Serum cortisol levels higher than 21.5 μg/dL (599 nmol/L) after stimulation guarantee an adequate corticotroph reserve[27], but lower levels do not rule it out, because 10%-20% of healthy subjects do not exceed this threshold. The glucagon test has a low reliability in subjects with diabetes mellitus[28]. It may be of value in patients in whom the insulin hypoglycemia test is contraindicated and, as the latter, allows for simultaneous evaluation of GH secretion. However, it has a lower diagnostic yield as compared to the metyrapone test[29].
- Short ACTH stimulation test with cortisol measurement in saliva. Salivary cortisol response after stimulation with 1 μg of ACTH correlates to serum cortisol response[11]. Measurement of salivary cortisol levels after stimulation with low ACTH doses has therefore been proposed as a potential alternative to the conventional test, especially when abnormal CBG levels exist. Complete correspondence has also been shown between serum and salivary cortisol responses to stimulation with 25 μg of ACTH IM[13]. However, other studies show a low sensitivity and specificity of salivary as compared to serum cortisol levels[30], and use of this test for AI diagnosis currently appears premature.

1.2.2. What are the determinant factors for selecting one or the other test?

When the need arises to assess adrenal function using a dynamic test to confirm or rule out AI, the origin (primary or secondary) of AI is often already suspected. In these cases, suspicion may determine the choice of one of the other test.

1.2.3. What is the most adequate stimulation test when PAI is suspected?

When PAI is suspected, the short ACTH test is probably the most adequate diagnostic option, because it has a similar diagnostic accuracy to the insulin hypoglycemia test[19] without the disadvantages of the latter.

1.2.4. What is the most adequate stimulation test when SAI is suspected?

The ACTH stimulation test using standard doses is helpful for diagnosis of SAI only when the duration and degree of ACTH deficiency have been sufficient to cause significant adrenal cortex atrophy. Short-lasting (less than 4-6 weeks) or mild ACTH deficiency leads to subnormal steroid secretion, at baseline and/or in response to stress, but is not sufficient to cause significant adrenal cortex atrophy. The gland therefore retains its ability to respond to stimulation with exogenous ACTH, which causes false negative results (normal responses) in the ACTH test.

Use of the stimulation test with standard ACTH doses for SAI diagnosis must therefore be avoided in the 4-6 weeks following pituitary surgery and in the 9-12 months following radiotherapy on the hypothalamic-pituitary area. This test is not recommended either in patients with partial ACTH deficiency or when the time of start of the deficiency is unknown. Applicability of this test in a clinical scenario of suspected SAI is therefore very limited, because the test is unnecessary in the event of complete ACTH deficiency (where basal cortisol levels are often conclusive) and is unreliable in the event of partial deficiency. The low dose stimulation test may have greater sensitivity for detecting partial or short-lasting SAI, but there is no universal agreement on the subject.

Unlike previous tests, the insulin hypoglycemia test is able to demonstrate SAI regardless of its severity and duration because of its ability to assess the whole HPA axis. The insulin hypoglycemia test is therefore of choice when SAI is suspected (Fig. 1).

1.2.5. What precautions should be considered when performing a stimulation test?

Since response to stimulus is assessed in terms of plasma cortisol levels in most dynamic tests used for AI diagnosis, it should not be forgotten that conditions associated to increased or decreased CBG levels (Table 2) may lead to errors in interpretation of results and should therefore be corrected before the test is performed. In women on estrogen therapy, this should be discontinued for at least 6 weeks before any test is performed. Conditions such as hypothyroidism and hyperthyroidism should also be corrected sufficiently in advance.

In subjects with AI, stimulated cortisol secretion does not appear to be subject to circadian rhythm, because response to stimulation tests is independent from the time of day at which they are performed[31]. These procedures may therefore be done at any time during the day without this influencing interpretation of results.

1.2.6. What serum basal cortisol levels allow for confirming or ruling out AI after pituitary surgery?

After pituitary surgery, it is imperative to assess adrenal function because of potential corticotroph cell damage during the surgical procedure. When this evaluation is done in the early postoperative period, it should be reminded that physical stress inherent to this situation causes a physiological increase in cortisol secretion. Cut-off points for plasma cortisol levels established for AI diagnosis in the absence of stress may therefore not be valid under stress conditions.

Thus, a study on this subject established that levels less than 7 μg/dL on days 2 and 3 after surgery, less than 8 μg/dL on day 4, less than 6 μg/dL on day 5, and less than 3 μg/dL on day 6 have a 100% positive predictive value for AI (although their sensitivity is low, not exceeding 28%). It has similarly been established that basal cortisol levels higher than 15-16 μg/dL in the early postoperative period (from the first to the third day) after pituitary surgery predict for preserved adrenal function at the first and third months after surgery, as validated by stimulation tests[32,33]. Intermediate values between 7 and 15 μg/dL are indeterminate and do not allow for confirming or ruling out diagnosis.

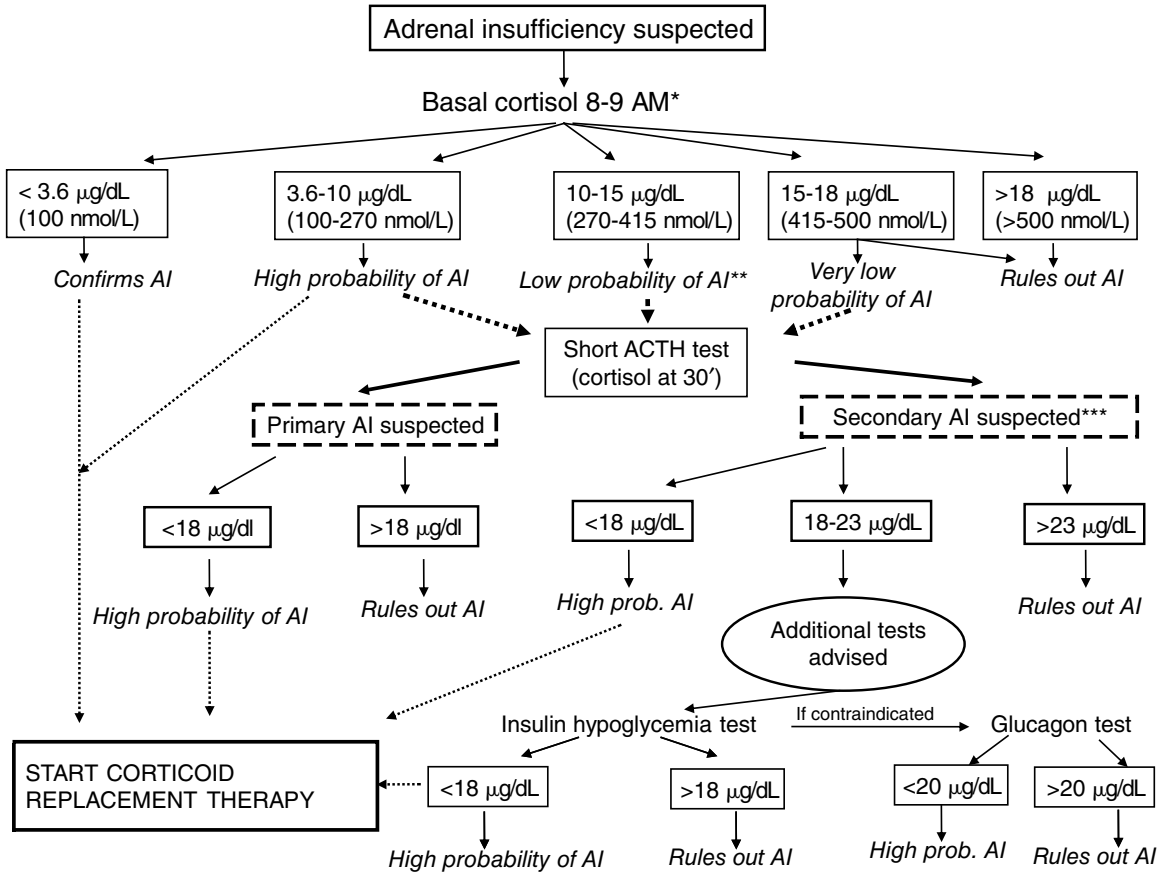

Figura 1 Diagnostic algorithm for adrenal insufficiency. ACTH: adrenocorticotropic hormone; AI: adrenal insufficiency.

1.2.7. Should dynamic tests be performed in the postoperative period of pituitary surgery?
Stimulation tests are not advised in the early postoperative period after pituitary surgery: the ACTH stimulation test may provide false negative results (normal responses) because no adrenal gland atrophy exists yet, and the insulin hypoglycemia test may be abnormal due to the presence of subtle HPA axis dysfunction that may spontaneously normalize after a few months[23]. Thus, if basal cortisol levels in the indeterminate range are found, repeat adrenal function testing is advised at least two months after surgery, maintaining physiological replacement doses of hydrocortisone until final axis assessment.

2. Diagnosis of location (differentiation between PAI and SAI)

AI is sometimes suspected when a compatible clinical picture suggesting its origin is seen in a subject with no history of adrenal or hypothalamic-pituitary disease. The clinical picture, however, often leads to suspect both AI and its primary or secondary origin (e.g. history of hypothalamic-pituitary surgery). In the first case, clinical and biochemical data will suggest the origin of AI, and in both cases this must be confirmed by ACTH measurement.

2.1. What clinical and biochemical parameters lead to suspect the primary or secondary origin of AI?
Skin and mucosal hyperpigmentation, resulting from elevated ACTH levels, is characteristic of PAI and is absent in SAI. In PAI, hyperpigmentation occurs even in the most mild or subclinical cases because ACTH increase is one of the earliest events during the course of disease.

Hyperkalemia is a prevalent biochemical finding in PAI. Hyperkalemia results from the mineralocorticoid deficiency inherent to PAI and is therefore absent in SAI. By contrast, hyponatremia may occur both in PAI and SAI because GC deficiency, common to both conditions, is associated to increased ADH secretion, which causes a condition clinically and biochemically identical to SIADH. In PAI, MC deficiency is added to GC deficiency, contributing to hyponatremia through its effect on urinary sodium excretion.

2.2. What is the role of ACTH in elucidation of PAI origin?
In PAI, loss of feedback on corticotroph cells resulting from decreased cortisol levels causes increased ACTH secretion leading to elevated plasma levels, usually more than two times higher than normal. In SAI, ACTH levels are low or normal, so that no overlap exists between ACTH levels in both conditions. Plasma ACTH levels are therefore the key element in differentiation between PAI and SAI.

3. Etiological diagnosis

3.1. Etiological diagnosis of PAI

Once established that AI results from a primary failure in the adrenal gland, the cause of the failure should be identified. Table 4 lists the causes of PAI.

3.1.1. What is the role of demonstration of adrenal cortex autoimmunity?
Autoimmune adrenalitis accounts for 70%-90% of PAI cases, and demonstration of autoimmunity against the adrenal cortex usually represents the first step in etiological diagnosis of this condition.

Adrenal cortex antibodies (ACA) and antibodies to the enzyme 21-hydroxylase (anti-21OH Ab) are markers of autoimmune PAI. Presence of ACA is tested on human or animal adrenal tissue preparations using immunofluorescence. The main antigen recognized by ACA is the enzyme 21-hydroxylase, and presence and levels of antibodies against this enzyme

Table 4 Causes of primary adrenal insufficiency in adults

Global adrenal insufficiency
- Acquired disorders
  - Autoimmune adrenalitis
  - Infections: tuberculosis, fungal infections, parasitoses, HIV
  - Bilateral adrenal metastases (lung, breast, melanoma, lymphoma)
  - Bilateral adrena hemorrhage (sepsis, coagulopathies, anticoagulant therapy, phospholipid Ab, abdominal trauma, postoperative period after major surgery)
  - Granulomatous and deposition diseases (exceptional): sarcoidosis, amyloidosis, hemochromatosis
- Genetic diseases (with AI occurring at adult age)
  - Congenital adrenal hyperplasia (partial forms)
  - Adrenoleukodystrophy
- Iatrogenic
  - Drugs (see Table 5)
  - Surgery: bilateral adrenalectomy

Selective mineralocorticoid deficiency
  - Hypoaldosteronism: primary and secondary
  - Pseudohypoaldosteronism

AI: adrenal insufficiency; HIV: human immunodeficiency virus.

may currently be measured by radioimmunoassay. Anti-21OH antibodies have higher diagnostic sensitivity as compared to ACA: in subjects with disease starting less than 15 years before, anti-21OH antibodies are found in 100%, and ACA in approximately 70%. Prevalence of both types of antibodies is highest at the start of the disease and decreases over time. ACA antibodies show a more marked decrease, so that prevalence rates of anti-21OH and ACA antibodies in patients with disease duration longer than 15 years are 60% and 10% respectively[34].

3.1.2. What is the role played by imaging tests in etiological diagnosis of PAI?

Tuberculosis infection (TBC) is the second most common cause of PAI, and should therefore be investigated in the absence of autoimmunity against the adrenal cortex. The tuberculin test (Mantoux skin test) simply indicates contact with the tubercle bacillus, but provides no information on the presence of active or latent tuberculosis, and samples for microbiological testing cannot be taken if there is no extra-adrenal involvement. Diagnosis therefore often relies on findings made in imaging tests, either CT or MRI.

Enlargement of both adrenal glands is the most common finding in adrenalitis, made in approximately 90% of cases. Enlargement is unilateral in 10% of patients, and a normal size of both glands is seen in 2%. Enlarged glands have a preserved normal morphology in approximately half the cases, and a tumor appearance in the other half. Calcifications are a characteristic finding, but only occur in 50% of cases, and ring enhancement after contrast administration is common (50-80%). Presence of calcifications and preservation of gland morphology increase with disease duration, while ring enhancement and tumor appearance are seen less frequently[35].

3.1.3. What other diseases should be considered in the presence of adrenal gland enlargement?

Bilateral metastatic infiltration, bilateral adrenal hemorrhage, and various fungal infections are causes of PAI associated to bilateral adrenal gland enlargement.

In the absence of more characteristic signs, such as calcifications, TBC-induced adrenalitis may be radiographically indistinguishable from metastatic adrenal involvement. TBC also shows a high avidity for fluorodeoxyglucose (FDG), and positron emission tomography with FDG (FDG-PET) therefore appears to have no value for differentiating both conditions. However, absence of extra-adrenal uptake or a ring enhancement pattern in extra-adrenal lesions suggest TBC infection[36,37].

Bilateral adrenal hemorrhage should be considered an etiological possibility in the event of acute PAI and bilateral adrenal enlargement. The clinical picture supports etiological suspicion because it usually occurs as the result of disseminated infection (typically, but not only, by meningococci), coagulation disorders (anticoagulant treatment or coagulopathies), trauma, or after major surgery. MRI with specific sequences is helpful to differentiate between adrenal hematoma and other conditions, including bleeding from an underlying tumor[38]. Gradual normalization of radiographic image helps confirm diagnosis. Radiographic monitoring during the subsequent weeks or months is therefore helpful.

3.1.4. What causes of PAI should be considered in the absence of autoimmunity and radiographic abnormalities?

3.1.4.1. Adrenoleukodystrophy

PAI is present in more than 70% of patients with *adrenoleukodystrophy* (ADL), is the only manifestation of disease in 10% of patients, and is the initial presentation in a significant proportion of subjects. Although ADL is rare, accounting for only approximately 5% of all cases of PAI, its prevalence in PAI with no autoimmunity or radiographic abnormalities is very high, almost 60% in some series[3]. Frequency is even higher when PAI occurs in males, especially if these are younger than 15 years[39], although PAI has also been reported as the initial manifestation of ADL in adult males[3].

Ninety percent of patients with PAI secondary to ADL will experience neurological symptoms within a variable time period, which may range from years to decades. Adequate etiological diagnosis of PAI in these patients is very important because it allows for early therapeutic intervention to prevent or minimize development of neurological signs.

Measurement of very long chain free fatty acids in plasma is a highly sensitive diagnostic test[40]. Genetic testing is helpful to confirm diagnosis in patients with borderline levels[41].

3.1.4.2. Drugs

Rarely, PAI with no evidence of autoimmunity and no radiographic abnormalities may be the consequence of use of certain drugs (Table 5).

Imidazole derivatives, particularly ketoconazole, may cause AI due to inhibition of various enzymes involved in adrenal steroidogenesis. However, this is a very rare effect at doses usually given to treat fungal infections, and more commonly occurs with higher doses such as those used to treat hypercortisolism. Other imidazole preparations, such as fluconazole or itraconazole, have few adrenostatic effects, but some cases of adrenal insufficiency have also been reported when used at high doses[42,43].

Etomidate is a potent hypnotic drug used for inducing anesthesia which is able to inhibit various adrenal cortex enzymes. Occurrence of AI after a single dose of etomidate is very unlikely, because it has a transient effect on cortisol synthesis, but patients who receive etomidate as a continuous infusion for prolonged sedation may experience clinically evident AI.

Mitotane, an adrenolytic drug used for the treatment of adrenal carcinoma and refractory Cushing's syndrome, almost invariably causes adrenal insufficiency due to its cytotoxic effect on the adrenal cortex.

Drugs that accelerate cortisol metabolism do not usually cause AI in subjects with normal adrenal reserve because increased cortisol degradation is compensated by increased ACTH secretion and the resultant increase in cortisol synthesis. They may however cause AI in patients with decreased adrenal reserve, or trigger an adrenal crisis in patients with AI on treatment. These drugs include rifampin and the anticonvulsant agents phenytoin, carbamazepine, and phenobarbital[44,45].

In experimental animals, the tyrosine kinase inhibitor *sunitinib* is able to induce various histopathological changes in adrenal glands such as hemorrhage, inflammation, or necrosis[46]. In humans, approximately 2% of patients treated

Table 5 Drugs that may induce adrenal insufficiency

Mechism	Drug
Primary Adrenal Insufficiency	
Hemorrhage	Anticoagulants (heparin, warfarin)
	Tyrosine kinase inhibitors (sunitinib)
Adrenal cortex destruction	Mitotane
Inhibition of enzymes involved in cortisol synthesis	Ketoconazole, fluconazole
	Etomidate
	Aminoglutetimide
	Metyrapone
	Trilostane
	Suramin
Induction of enzymes involved in cortisol synthesis	Phenobarbital
	Phenytoin
	Carbamazepine
	Rifampin
Secondary Adrenal Insufficiency	
Inhibition of CRH and ACTH synthesis	Glucocorticoids (topical or systemic), megestrol acetate, medroxyprogesterone, opiates
Peripheral resistance to glucocorticoids	
Glucocorticoid receptor blockade	Mifepristone
Inhibition of gene transcription induced by glucocorticoids	Antipsychotics (chlorpromazine)
	Antidepressants (imipramine)

ACTH: adrenocorticotropic hormone; CRH: corticotropin releasing hormone.

with sunitinib show an inadequate cortisol response in the ACTH test. Although these abnormalities have no clinical consequences in patients with intact adrenal reserve[47], they may lead to frank PAI in those with a decreased adrenal reserve or under stress conditions.

3.1.5. Is genetic testing required for PAI of an unidentified cause?

In addition to ADL, various genetic abnormalities may cause PAI (Table 6). In most these cases, PAI is diagnosed in the neonatal period or in early infancy. Only PAI associated to partial forms of congenital adrenal hypoplasia may occur in adults[48]. Diagnosis should be suspected in young males with concomitant hypogonadotropic hypogonadism, and may be confirmed by genetic testing. In the absence of associated disorders, PAI with no identifiable cause starting in adulthood is usually an autoimmune adrenalitis in which antibodies cannot be detected in serum.

3.1.6. Is screening for other autoimmune conditions warranted in autoimmune adrenalitis?

Approximately 50%-80% of patients with autoimmune PAI have evidence of autoimmunity against other organs[49-51]. Thyroid autoimmunity, occurring in approximately 50% of cases, is most common, followed by chronic gastritis (30%). Other conditions such as pernicious anemia, type 1 diabetes, vitiligo, and early ovarian failure occur with frequencies ranging from 7%-10%[49,51]. Although no overall agreement exists, some authors recommended screening for these autoimmune disorders by measurement of organ-specific antibodies when tests are available[49,51].

3.2. Etiological diagnosis of SAI

In SAI, etiological diagnosis often precedes syndromic diagnosis because identification of a potential cause of AI (e.g. a pituitary lesion) leads to adrenal function evaluation and eventual confirmation of AI. By contrast, diagnosis of SAI in a patient with no prior evidence of hypothalamic-pituitary disease prompts a search for the underlying cause (Table 7). Evaluation of integrity of all other pituitary axes is the first step in etiological diagnosis in these cases. Deficiencies of other pituitary hormones associated to ACTH deficiency should prompt performance of imaging tests of the hypothalamic-pituitary area, while isolated ACTH deficiency requires that a pharmacological origin is ruled out before imaging tests are performed. MRI is the test of choice because of its greater anatomical definition, while CT of the head should be reserved for patients in whom MRI is not feasible.

3.2.1. Etiological diagnosis of SAI associated to other pituitary hormone deficiencies

3.2.1.1. What etiologies should be considered in the event of SAI associated to other hormone deficiencies and radiographic abnormalities?

When SAI coexists with other pituitary hormone deficiencies and pathological MRI, the first cause to be considered should be tumoral lesions in the hypothalamic-pituitary area, especially pituitary macroadenomas. Among hormone deficiencies caused by pituitary macroadenomas, ACTH deficiency is one of the least common. However, as these

represent the most prevalent pathology in the pituitary gland, they are the most common cause of SAI when this is associated to other hormone deficiencies.

Lymphocytic or autoimmune hypophysitis is another common cause of combined deficiency of ACTH and other pituitary hormones associated to a pituitary image suggestive of tumor. Unlike in adenomas, ACTH deficiency is the most common hormone disorder in these cases, and has been shown in a very high proportion of them.

Differentiation between pituitary adenoma and hypophysitis is important, because the therapeutic approach to both conditions is different (surgical vs non-surgical). Although a diagnosis of certainty may only be made based on histological study. The clinical context, hormone pattern, and radiographic findings often allow for presumptive diagnosis, so that biopsy is not usually needed for adequate patient management.

Other less common causes of SAI combined with other hormone deficiencies and MRI abnormalities include: tumors other than pituitary adenomas, either primary (craniopharyngioma, glioma) or metastatic, pituitary abscesses, granulomatous disease (sarcoidosis, Wegener granulomatosis), tuberculosis, fungal infections (histoplasmosis), and internal carotid aneurysms.

3.2.1.2. What are the clinical and hormonal differences between hypophysitis and adenomas?

Lymphocytic hypophysitis is more common in females as compared to males, often occurs during pregnancy or after delivery, and is commonly associated to other autoimmune endocrine diseases. Pituitary adenomas, by contrast, have a similar incidence in both sexes, are not related to pregnancy or delivery, and are not associated to other autoimmune disorders.

Table 6 Genetic defects associated to primary adrenal insufficiency

Congenital adrenal hyperplasia

Disease	Deficiency 21-Hydroxylase	β-Hydroxylase deficiency	17α-Hydroxylase deficiency	3β-hydroxysteroid dehydrogenase deficiency	Lipoid hyperplasia
Genetic defect	CYP212A (p450c21)	CYP18B1 (p450c11)	CYP17 (p450c17)	HSD3B2 (3-betaHSD)	StAR
Incidence	1/11,000-22,000	1/100,000	Rare	Rare	Rare
Hormones:					
Glucocorticoids	↓	↓	↓	↓	↓
Mineralocorticoids	↓	↑	↑	↓	↓
Androgens	↑	↑	↓	↓ male ↑ female	↓
Estrogens	↓	↓	↓	↓	↓
Metabolite	17-OH-P	DOC, 11-Desoxycortisol	DOC, corticosterone	DHEA, 17 5 pregnenolone	None

Other genetic changes

Disease	Genetic defect	Clinical characteristics
Congenital adrenal hypoplasia	Transcription factor (NR0B1)	Hypogonadotropic hypogonadism in males
Congenital adrenal hypoplasia	Transcription factor (NR5A1)	Gonadal dysgenesis (females 46XY)
Kearns Sayre syndrome	Mitochondrial abnormality (unknown gene)	Ophthtalmoplegia, retinal degeneration, cardiac conduction defects, endocrine changes
Wolman's d.	Deposition disease	Bilateral adrenal calcification, hepatosplenomegaly
Sitosterolemia	Sterol secretion: ATP-binding cassette, subfamily G (ABCG5, ABCG8)	Xanthomas, early coronary disease, arthritis, low height, adrenal and gonadal insufficiency
Adrenoleukodystrophy	Peroxysomal disorders: ATP-binding cassette, subfamily D (ABCD1, ABCD2)	Adrenal insufficiency, weakness, spasticity, dementia, blindness, tetraparesis,
Familial glucocorticoid deficiency type 1	ACTH receptor: melanocortin type 2 receptor (MC2R)	Hyperpigmentation, facial changes, tall height, muscle weakness, lethargy, normal BP
Familial glucocorticoid deficiency type 2	ACTH receptor: Melanocortin 2 receptor (accessory protein (MRAP)	Hyperpigmentation, normal height, hypoglycemia, muscle weakness, lethargy, normal BP
Triple A syndrome	Unknown	Achalasia, alacrima, adrenal insufficiency, mental retardation, hyperkeratosis, deafness

ACTH: adrenocorticotropic hormone; BP: blood pressure; GC: glucocorticoid; DHEA: dehydroepiandrosterone; MC: mineralocorticoid; StAR: steroid acute regulatory protein.

Table 7 Causes of secondary adrenal insufficiency in adults

ACTH deficiency associated to other pituitary hormone deficiencies
- Tumors
  - Primary (pituitary adenoma, craniopharyngioma, glioma, other)
  - Metastatic (breast, lung, melanoma)
- Hyphopysitis (lymphocytic, other)
- Iatrogenic: pituitary surgery, radiotherapy
- Infections (abscesses, tuberculosis, syphilis, fungal)
- Infiltrative lesions (sarcoidosis, Wegener, histiocytoma)
- Hemochromatosis
- Pituitary infarct (Sheehan syndrome, pituitary apoplexy)
- Internal carotid aneurysm
- Head trauma
- Genetic diseases: PROP1 mutations

Isolated ACTH deficiency
- Sudden discontinuation of chronic exposure to supraphysiological glucocorticoid doses
  - Sudden discontinuation of long-term steroid treatment
  - Successful surgery for Cushing s.
- Autoimmune
- Head trauma
- Partial pituitary infarct
- Drugs (see Table 5)

ACTH: adrenocorticotropic hormone.

ACTH and TSH deficiencies are the most common and earliest occurring hormone changes, while GH and gonadotropin deficiencies are more rare and occur later. Macroadenomas have a reverse pattern: secretion of GH and gonadotropins is affected first, while secretion of TSH and ACTH is affected late. Hence, ACTH deficiency with preservation of the gonadotropic and somatrotropic axes is common in hypophysitis and exceptional in adenomas. Diabetes insipidus is also relatively common in hypophysitis and absolutely exceptional in pituitary adenoma. Marked hypopituitarism with a pituitary gland with a relatively preserved radiographic appearance is another finding suggesting hypophysitis.

3.2.1.3. What are the radiographic differences between pituitary macroadenoma and lymphocytic hypophysitis?
Diffuse, symmetrical pituitary gland enlargement with no pituitary stalk deviation or sellar floor erosion is highly suggestive of hypophysitis. By contrast, pituitary adenomas cause asymmetrical pituitary gland enlargement, pituitary stalk deviation, and sellar floor erosion. The enhancement pattern after contrast also helps differentiate both conditions, because it is diffuse and homogeneous in hypophysitis and more heterogeneous in adenomas. Extension of the inflammatory process to the infundibulum and/or neurohypophysis (infundibulo-neurohypophysitis) is associated to pituitary stalk thickening and disappearance of the bright signal of neurohypophysis, abnormalities which are not seen in adenomas.

3.2.1.4. Is measurement of pituitary gland antibodies helpful to differentiate autoimmune hypophysitis from pituitary adenoma?
Antibodies against adenohypophysis are detected in 30%-70% of patients with lymphocytic hypophysitis[52], but their diagnostic value is currently not clear because conflicting results have been found with the different methods used to test these antibodies. Moreover, sensitivity and specificity of pituitary antibodies when measured by immunofluorescence (the standard method used) are limited. Thus, these antibodies have been reported to be absent in patients with histologically documented hypophysitis, while they have been detected in up to 20% of patients with pituitary macroadenomas. Some authors suggest that high titers of pituitary antibodies suggest hypophysitis, while low titers suggest macroadenoma[52]. Antibody titers usually decrease gradually over time, and antibodies may eventually disappear[53].

3.2.1.5. What condition should be suspected in an adult with SAI associated to other pituitary hormone deficiencies in the absence of radiographic abnormalities?
Hypopituitarism with normal pituitary MRI ("idiopathic" hypopituitarism) accounts for approximately 10% of all cases of hypopituitarism[54]. When hormonal involvement includes ACTH deficiency, a significant proportion of cases are probably due to lymphocytic hypophysitis. Other conditions that may be responsible for this presentation include hemochromatosis, sarcoidosis, and head trauma[54,55].

Mutations in the PROP1 (Prophet of Pit-1) gene are another cause of SAI starting in adulthood associated to other hormone deficiencies and to normal pituitary MRI. The PROP1 gene encodes for a transcription factor implicated in pituitary gland development, and its mutation is the most common genetic cause of multiple hormone deficiency. ACTH secretion is the last to be affected (at a mean age of 18 years), so that SAI often occurs at an adult age[56]. Low height or history of GH deficiency in childhood and absence of spontaneous pubertal development should alert to the possibility of this condition in an adult with SAI and normal pituitary MRI. Other genetic causes of combined deficiency of ACTH and other pituitary hormones only occur in childhood (Table 8).

3.2.2. Etiological diagnosis of isolated ACTH deficiency

3.2.2.1. What is the first step in etiological diagnosis of isolated ACTH deficiency?
The most common cause of isolated ACTH deficiency (and SAI in general) is undoubtedly sudden discontinuation of long-term treatment with exogenous GCs at supraphysiological doses. By virtue of the negative feedback exerted by steroids on corticotroph cells, long-term treatment at supraphysiological doses with these drugs induces inhibition of CRH and ACTH secretion which takes days or weeks to subside after treatment discontinuation, causing during this time a subnormal production of endogenous steroids. Comprehensive questioning to show prior GC exposure should therefore be the first step for etiological identification in patients with isolated ACTH deficiency.

Table 8 Genetic causes of SAI

Disease	Gene involved	Clinical characteristics
Panhypopituitarism	HESX1	Low height, cognitive impairment, septo-optic dysplasia, delayed puberty
	OTX2	Neonatal hypoglycemia, pituitary hypoplasia, ectopic neurohypophysis
	LHX4	GH, TSH, and ACTH deficiency
	SOX3	Infundibular hypoplasia, hypopituitarism, mental retardation
	PROP1	Enlarged sella turcica, late onset ACTH deficiency
Isolated ACTH deficiency	TPIT (TBX19)	None specific
	POMC	Obesity, red hair
Prader-Willi syndrome	IPW	Mental retardation, hypotonia, obesity, hypogonadism

ACTH: adrenocorticotropic hormone; GH: Growth hormone; IPW: imprinted in Prader Willi; TSH: thyroid-stimulating hormone.

3.2.2.2. What are the factors determining the risk of HPA axis suppression in patients treated with GCs?

Dose received, dosing time (morning vs evening), and treatment duration are the factors that determine the probability of HPA axis suppression in patients treated with GCs. Risk of suppression of the hypothalamic-pituitary-adrenal axis is rated as probable, intermediate/uncertain and improbable based on these three parameters (Table 9), and this rating determines in turn adequate management to prevent SAI[57,58].

3.2.2.3. Can corticoids administered by non-oral routes suppress the HPA axis?

Like oral corticoids, those administered by oral inhalation and very potent topical corticoids may suppress the HPA axis when administered long-term.

Although individual susceptibility to the effect of inhaled GCs is variable, the possibility of axis suppression with beclomethasone, triamcinolone, or budesonide increases from 800 μg/day (mean doses in clinical practice) and is

Table 9 Risk of suppression with chronic treatment with glucocorticoids, recommendations

Suppression probable.	Intermediate/uncertain risk of suppression.	Suppression improbable.
• Prednisone dose ≥20 mg/day, or equivalent treatment for more than 3 weeks. • Dose ≥5 mg of prednisone administered during the evening/night for more than two weeks. • Clinical signs of Cushing Sydrome.	• Dose ≤20 mg of prednisone/day or equivalent for more than 3 weeks, (provided that it is not taken in the evening for more than two weeks).	• Treatment with any dose of glucocorticoid, not parenteral, less than 3 weeks. • Dose <10 mg of prednisone or equivalent, administered on alternate days.
Recommended attitude.		
• No evaluation of axis required. • They should be treated as patients with secondary adrenal insufficiency. • Treatment with glucocorticoids should gradually decrease to enable axis recovery.	• Decrease treatment gradually. • Routine evaluation of the HPA axis is unnecessary. • If treatment is going to be abruptly discontinued, perform ACTH test to evaluate adrenal function. • If the patient is going to be exposed to acute stress, such as surgical intervention, perform ACTH test, if possible, or treat with glucocorticoid dose for stress.	• Treatment can be discontinued without any special measures. For frail or seriously ill patients, proceed with more caution.

ACTH: adrenocorticotropic hormone; HPA: hypothalamic-pituitary-adrenal.
The suppression of the HPA axis with a prednisone dose <5 mg/day is uncommon.

very common (greater than 30%) from 1500 μg/day (high doses in clinical practice). Equivalent fluticasone doses are 400 and 750 μg/day respectively[59]. While the fluticasone dose required for axis suppression is lower than those of beclomethasone, triamcinolone, or budesonide, the risk in practice is likely to be similar or only slightly greater, because fluticasone is used at lower doses as compared to other compounds due to its greater anti-inflammatory potency. Prednisone and fluticasone are equivalent in their axis suppression capacity in a 10:1 mg ratio.

More potent topical corticoids (class I) such as clobetasol or betamethasone may suppress the axis even at low doses[60]. Young people are more susceptible to this effect. Other predisposing factors besides potency of the compound used and treatment duration include application to scalp and folds, treatment of extensive surfaces, and occlusive bandages.

3.2.2.4. What should be done when faced with an isolated ACTH deficiency in the absence of GC exposure?

Once prior GC exposure has been ruled out, identification of an isolated ACTH deficiency should be followed by radiographic examination of the hypothalamic-pituitary area. As noted above, pituitary adenoma with associated ACTH deficiency and no involvement of other pituitary axes is exceptional. By contrast, isolated ACTH deficiency is common in lymphocytic hypophysitis and is the most common form of pituitary deficiency in these cases[61]. Therefore, the finding of a pituitary mass in a patient with isolated ACTH deficiency should suggest hypophysitis, rather than pituitary adenoma.

3.2.2.5. What causes should be considered in the event of an isolated ACTH deficiency (not due to GC therapy) in the absence of radiographic pituitary abnormalities?

Isolated ACTH deficiency in the absence of radiographic pituitary changes, also called idiopathic isolated ACTH deficiency, is a rare condition of which few cases have been reported in the literature. Its frequent association to autoimmune disorders[62] and detection of antibodies to pituitary antigens[63] suggest that a high proportion of cases are due to autoimmune hypophysitis.

Head trauma may cause adenohypophysial hypofunction, and isolated ACTH deficiency has been reported in 1% of cases[64]. Finally, some progestogens, such as megestrol or medroxyprogesterone[65], may cause prolonged suppression of the HPA axis when administered long-term, because they have a significant glucocorticoid activity derived from its binding capacity to the glucocorticoid receptor. Sudden discontinuation of these treatments is an often unrecognized cause of isolated ACTH deficiency (Table 5).

3.2.2.6. Is genetic testing required in cases of isolated ACTH deficiency with no apparent cause?

Mutations in the TPIT gene, which encodes for a gene selectively expressed in corticotroph cells during embryonic development, and in the POMC gene are associated to isolated ACTH deficiency[66,67]. In these cases, SAI occurs in the neonatal period or in early childhood, and is associated to characteristic phenotypic traits (obesity and red hair) when POMC mutation exists. This condition has not been reported in adults, and genetic testing is therefore not currently recommended in adults with SAI with no evidence of an apparent cause. Many such cases possibly correspond to autoimmune hypophysitis (Table 8).

PART II. GUIDELINES FOR TREATMENT OF AI

1. Replacement treatment with glucocorticoids

1.1. Long-term treatment

1.1.1. Treatment rationale

Regardless of AI etiology, the aim of glucocorticoid replacement therapy is to mimic as much as possible endogenous cortisol secretion in healthy subjects.

In healthy subjects, this daily endogenous cortisol secretion has been estimated at 5-7,4 mg/m^2, and although it varies depending on sources consulted, is lower than initially estimated. This amount would be equivalent to an oral replacement dose of 15-20 mg/day of hydrocortisone. Doses of 30 mg or greater used in the past should be considered supraphysiological and may cause undesirable side effects[68].

In the past seven years, various studies have demonstrated that patients with AI of any etiology have a high standardized mortality ratio, essentially due to increased cardiovascular disease, especially if diagnosis is made before 40 years of age[69]. Increased cardiovascular risk is related to total daily dose of hydrocortisone[70] and absence of physiological cortisol rhythm. It is essentially due to increased insulin resistance and lipid profile changes[71,72].

In PAI, other diseases such as cancer or infectious diseases have a greater incidence than in the general population[73,74].

The harmful effect of glucocorticoid therapy on bone metabolism is well known[75,76]. A recent study by Lovas[77] showed reduction in bone mineral density in the femoral neck and lumbar spine of patients with PAI; this reduction does not appear to be influenced by treatment duration or type of glucocorticoid used, but by total daily glucocorticoid dose[78]. Patients receiving doses higher than 20 mg of hydrocortisone who have additional risk factors for osteoporosis or with very long disease duration (leading to suspect administration of higher glucocorticoid replacement doses in the past) should be evaluated in this regard. Low scores in quality of life questionnaires in these patients also confirm that current replacement therapy is far from optimal[79-81]. This decreased quality of life persists in many patients even when dehydroepiandrosterone (DHEA) is added to treatment. Failure to achieve circadian physiological rhythm may partly be responsible for the poor results achieved with standard treatment, but level of evidence is poor because of the lack of randomized, placebo-controlled studies. These scores especially refer to areas such as vitality and perception of general well-being. Chronic fatigue is an often reported symptom whose causes may include, in addition to absence of the cortisol peak before waking up, poor quality of fragmented sleep, with decreased REM phase, in undertreated patients, or difficulty sleeping in overtreated patients[82]. In addition to this, low

epinephrine levels in PAI contribute to fatigue due to a limited glucose response during exercise and neuroglycopenic symptoms. These changes may apparently improve with administration of small carbohydrate doses before exercise[83]. In SAI, additional etiological factors include association of other hormone deficiencies.

AddiQoL, a specific questionnaire for patients with primary adrenal insufficiency that may contribute to easier monitoring and treatment optimization in these areas, has recently been published[84,85].

Unfortunately, it should also be noted that individual dose optimization during follow-up is difficult because, in the absence of adequate objective analytical parameters, clinicians should rely on observations of symptoms and signs to assess potential overdosing (weight gain and skin changes) or underdosing (fatigue, myalgia, and nausea) not specific of adrenal insufficiency.

1.1.2. What is the glucocorticoid of choice?

The ideal glucocorticoid would be one that mimicked endogenous rhythm, had little variability in its metabolism, and was easy to titrate and monitor.

Various glucocorticoid schemes and types have been used, including hydrocortisone, cortisone acetate, prednisone, and dexamethasone[86] (Table 10). The latter were used in the past with the argument of preventing marked fluctuations in serum glucocorticoid levels; however, their disadvantages, such as great between- and within-subject variability in metabolism, risk of overdose, and null simulation of circadian rhythm, have limited their use, and they have been relegated to patients with very poor compliance of multiple dose therapeutic regimens.

Tabla 10 Table 10 Equivalences between corticoids

Glucocorticoid	Equivalent dose (mg)	Duration of action (h)
Hydrocortisone	20	8-12
Cortisone acetate	25	8-12
Prednisone	5	12-36
Methylprednisolone	4	12-36
Triamcinolone	4	12-36
Deflazacort	7.5	18-36
Betamethasone	0.6	36-72
Dexamethasone	0.75	36-72

1.1.3. What is the most widely recommended replacement scheme with hydrocortisone?

Hydrocortisone is currently recommended as the glucocorticoid of choice[87]. In Spain, only the 20 mg dose is marketed, which makes individual dose adjustment and divided dosing difficult.

Use of hydrocortisone allows for reaching optimum cortisol levels 30 minutes after oral intake. Hydrocortisone has a mean plasma half-life of 95 minutes. Its high oral bioavailability and short half-life result in a profile with high peaks 1-2 hours after administration, followed by a rapid decline after 5-7 hours, very different from the physiological profile[88].

Although the current rapid release presentations of hydrocortisone are not able to mimic circadian rhythm, an attempt is made to approximate this by giving divided doses. In order to avoid glucocorticoid overexposure, especially from mid afternoon (because of its relationship to insulin resistance and the untoward metabolic consequences), various schemes have been proposed. Options include dividing the: dose into two fractions (2/3 of the total dose in the morning upon awakening and 1/3 in mid afternoon) or three fractions (10 mg at 7 AM, 5 mg at 12 AM, and 2.5-5 mg at 4:30 PM), avoiding administration later than 6 PM[86]. Although there is no convincing evidence to support three instead of two divided doses, three divided doses may partly correct the afternoon nadir in cortisol levels which occurs if two doses are administered[88-90] (Table 11).

Dose adjustment based on body weight has been routinely used in children. Debono proposed weight-adjusted dosing in adults also, preparing a nomogram for subsequent modifications; using this approach, the author found reductions in total dose in 77.5% of patients[91] (Table 12).

These fractionated are however far from being optimal. In addition to the risk of evening overdose and the frequent sensation of fatigue before the first dose, treatment compliance. Missing any dose represents a problem for 38% of patients, with the resultant negative impact on quality of life, and is associated to an increased risk of acute crisis, as shown by a recent study on 1245 patients with adrenal insufficiency[82].

Table 11 Recommendations for GC dosage and distribution

Glucocorticoid	Characteristics	Half-life (h)	Recommended dose	Recommended frequency
Hydrocortisone	Physiological glucocorticoid. Modified release: Plenadren	1-2	20-25 mg in PAI 15-20 mg en SAI	2 or 3 doses/day
Cortisone acetate	Prohormone (conversion to cortisol after passage through liver)		25-37.5 mg	Once, in the morning
Prednisolone	Greater anti-inflammatory potency than mineralocorticoids	12-36	3-5 mg	Once, in the morning
Dexamethasone	No mineralocorticoid effect	36-72	Not recommended	Not recommended

PAI: primary adrenal insufficiency; SAI: secondary adrenal insufficiency.
Modified table red. 67.

Table 12 Suggested daily hydrocortisone dose in a weight-adjusted regimen

Weight of patient (kg)	Total daily dose (mg)	1st dose (morning)	2nd dose (midday)	3rd dose (evening)
50-54	10.0	5.0	2.5	2.5
55-74	15.0	7.5	5.0	2.5
75-84	17.5	10.0	5.0	2.5
85-94	20.0	10.0	7.5	2.5
95-114	22.5	12.5	7.5	2.5
115-120	25.0	15.0	7.5	2.5

*Modified from ref. 67.

1.1.4. What should be taken into account when planning treatment?

When planning treatment, it should be reminded that various drugs may interfere with and require adjustment of hydrocortisone therapy, mainly by interfering with its transport or increasing its inactivation by induction of the CYP3A4 enzyme[92] (Table 13).

Dose modifications in other circumstances are specified in the section devoted to special circumstances.

1.1.5. New modified-release hydrocortisone preparations. What are the advantages of new modified release formulas?

Despite fractionation of hydrocortisone dose, simulation of circadian rhythm has not been achieved. New presentations of modified-release hydrocortisone have been designed to address this problem. Plenadren®, already marketed in Europe, is a new dual-release formula of hydrocortisone approved by the EMA on November 2011 as an orphan drug for use in patients with AI over 18 years of age[93].

It novel formulation consists of an outer layer that releases the drug immediately, providing optimum cortisol levels 45 minutes after intake, and an extended, gradual release core that maintains gradually decreasing levels for the rest of the day, thus allowing for single daily administration in most cases. This new formulation meets the two major requirements: rapid increase in cortisol levels in the morning and slow decrease over the day. Its bioavailability is 20% lower as compared to rapid-release hydrocortisone[94].

Dual-release hydroaltesone is supplied as 20 and 5 mg tablets. A single daily 20 mg dose, taken between 6 and 8 AM without chewing at least 30 minutes before breakfast, preferably in a straight position, will usually be required.

The reported studies with dual -release hydrocortisone showed improvement in some areas in quality of life questionnaires, and in small group with AI and type 1 diabetes mellitus, a significant reduction was noted in HbA1c levels (-0.6%)[95].

A new delayed-release, presentation of hydrocortisone with microparticle technology, Chronocort®, which may address the absence of the early cortisol peak before waking up and be the basis of treatment for congenital adrenal hyperplasia is on the premarketing testing phase. Its formula allows for the start of cortisol increase 4 hours after oral administration. Peak cortisol levels are reached after 8 hours. In the different trials reported, 20 mg of this drug, administered between 10 PM and 11 PM, induced progressive increases in cortisol levels until a peak was reached at 6-7 AM. This is very similar to the normal cortisol rhythm[96,97].

Table 13 Drugs interfering with GC treatment

Drugs affecting hydrocortisone metabolism	Changes in hydrocortisone dose
Anticonvulsants and barbiturates	Increase dose
Antifungal drugs	Adjustment may be required
Tuberculostatics	Increase dose
Etomidate	Increase dose
Topiramate	Increase dose
Growth hormone	Increase dose
Licorice and grapefruit juice	Reduce dose
Colestipol	Reduce dose
Estrogens	Increase dose
Tamoxifen	Increase dose

1.1.6. Are there other options available for optimization of GC treatment?

Continuous subcutaneous hydrocortisone infusion. Finally, the possibility of administering hydrocortisone as a subcutaneous (SC) infusion should be mentioned. This is currently reserved to clinical trials on small patient samples because of its complexity. In these trials, a total dose of 10 mg/m^2 restores normal circadian rhythm in most patients.

After publication of a small study on seven patients with AI treated with SC pump[98], Lovas recently completed a new open label, randomized, crossover 8-month study of hydrocortisone SC compared to oral standard therapy. Results of this study have not been reported yet[99].

1.1.7- What formulation of hydrocortisone should be used to start GC treatment?

Because of the current lack of evidence, it appears reasonable to start glucocorticoid treatment with immediate release hydroaltesone, because of experience with its use, price, and availability, until the new modified-release formulations become available and new studies supporting the potential benefits of their use are reported. However, treatment should be individualized, and each clinician will consider the need to

modify it in each patient. In cases where treatment compliance or dose adjustment are difficult, and in patients with frequent decompensations or other associated conditions that make dosing with the immediate release molecule difficult, such as diabetic patients, the benefit provided by the dual-release molecule may be considered.

1.2. Monitoring of long-term GC treatment

1.2.1. What clinical data are used to assess GC dose?
Monitoring of GC treatment and, thus, decision to modify GC dose is mainly based on clinical symptoms and signs, although clinical data that may reflect excess or inadequate dosage are not specific[88]. There are no objective parameters to assess the quality of replacement therapy.

The lowest dose that relieves symptoms of glucocorticoid deficiency should be used, avoiding symptom and signs of overdose[100]. Dose calculation based on weight may help prevent overdosing[101]. It is important to estimate daily dose and its distribution, and to adjust treatment to stress and intercurrent diseases[88].

If patients have symptoms of glucocorticoid deficiency (fatigue, lack of energy, nausea, myalgia, weight loss, hyperpigmentation in PAI), dose should be increased, but if symptoms do not improve, treatment should be resumed at the previous dose and other potentially responsible causes should be assessed[100].

Dose will be excessive if symptoms or signs of Cushing syndrome occur (weight increase, central obesity, striae, osteoporosis, insomnia, edema, HBP, impaired glucose metabolism)[90].

Arlt et al. proposed a structured clinical assessment using a clinical score system (Table 14)[102].

1.2.2. Is there any role for ACTH measurement?
In patients with SAI, ACTH is decreased, and its measurement during follow-up therefore provides no information.

In patients with PAI on standard treatment, ACTH is elevated before the morning dose is taken, and decreases after dose administration. An attempt to normalize ACTH level may lead to treatment overdose[92]. ACTH measurements are not required in routine monitoring of patients with primary adrenal insufficiency, but may detect treatment with excess GC doses. Low or suppressed ACTH levels in the morning suggest an excess GC dose[100,103].

1.2.3. What is the value of cortisol measurement?
Cortisol measurements have no value if the time of treatment administration is not known. Salivary cortisol levels are no helpful either because they are highly variable, which limits their use to adjust treatment dose[103].

Some authors recommend serial serum cortisol measurements over several hours to assess treatment dose (patients take hydroaltesone upon waking up and cortisol is tested a 9 AM, 12:30 PM, before lunch, and 5:30 PM, before the evening dose), combined with measurement of UFC levels in sample taken the day before[104]. This is expensive and time-consuming, and only helps identify markedly excessive or deficient doses. This approach is therefore of limited value in routine treatment monitoring[92]. The value of UFC levels in monitoring will be discussed later. Other authors recommend that cortisol is measured 4 hours after taking a weight-based hydrocortisone dose administered upon awakening under fasting conditions, and that treatment is adjusted based on a nomogram[91,101]. Other authors think that cortisol curves have a limited value, and recommend monitoring of treatment with a scoring system for structured clinical assessment (Table 14). Cortisol curves may have some value in selected patients, e.g. if treatment noncompliance or malabsorption is suspected[102].

1.2.4. What is the value of urinary free cortisol measurement?
Although its value for treatment monitoring has been reported[103], after GC administration, CBG saturates rapidly, causing a transient, but marked, elevation of urinary cortisol excretion. Results may therefore suggest, for example, adequate levels despite the presence of low cortisol levels for long time periods[91]. Urinary cortisol excretion shows a great interindividual variability[92].

Measurement of UFC levels is not helpful for monitoring these patients.

2. Mineralocorticoid replacement therapy

2.1. In what cases is treatment with mineralocorticoids required?

Mineralocorticoid (MC) deficiency only occurs in PAI. In SAI, by contrast, MC production is preserved because aldosterone secretion is mainly regulated by the renin-angiotensin system, with minimal dependence on ACTH. Patients with SAI do not therefore require MC replacement.

2.2. What preparations are used to replace MC deficiency?

Natural MCs, aldosterone and DOCA, are difficult to synthesize and have a short half-life. They are therefore not adequate for clinical use. Although cortisol has the same affinity as aldosterone for the MC receptor in the kidney, cortisol access to this receptor is limited by action of the enzyme 11 beta-hydroxysteroid dehydrogenase (11bHSD, type 2 isoform), because this enzyme, located in renal tubule together with the MC receptor, converts cortisol into cortisone, which has minimal affinity for the MC receptor. The only preparation available for aldosterone replacement is the synthetic MC 9 alpha-fluorhydrocortisone or fludrocortisone (FC), resulting from addition of a fluorine atom at the alpha position to carbon 9 of the cortisol molecule. Fluorination at the 9-alpha position protects cortisol from degradation by 11bHSD[105] and confers it a MC activity similar to that of aldosterone. Although FC also has GC activity, this is negligible at the doses routinely used.

2.3. What dose of fludrocortisone is required to replace the mineralocorticoid deficiency?

The standard FC dose ranges from 0.05 and 0.2 mg/day given as a single daily dose early in the morning[6,7,106-109]. Treatment usually starts with a dose of 0.1 mg/day[92,110,111], which may be subsequently adapted to the individual needs of each patient.

Table 14 Recommendations for long-term monitoring in patients with AI

Treatment.	Monitoring.	Recommendation.
Glucocorticoids.	• Clinical assessment: – Weight control. – Clinical signs of adrenal insufficiency (weight loss, fatigue, lack of energy, myalgia, nausea, hypotension, hypoglycemia, hyperpigmentation (in primary AI). – Clinical signs of hypercortisolism (weight increase, trunk obesity, HBP, striae, osteoporosis, insomnia, edema, hyperglycemia). • Routine measurement of ACTH or cortisol curves is not required; assess under certain circumstances.	• Increase if underdosing is suspected, ruling out other causes of clinical signs. • Decrease dose if excess dose is suspected.
Mineralocorticoids (only in patients with primary adrenal insufficiency).	• Assess clinical signs of orthostatic hypotension. • Resting and standing BP. • Explore edema. • Sodium and potassium measurements. • Measurement of PRA. • Consider ANP measurement if overdosing is suspected.	• Increase dose if underdosing is suspected: orthostatic hypotension (≥20 mmHg decrease in standing BP), hyperkalemia, elevated PRA (if normal kalemia and patient is asymptomatic. slightly elevated levels need not be corrected). • Decrease dose if excess dose is suspected: HBP, edema, hypokalemia, PRA suppression. • Recommend dose increase with hot weather. • Free salt consumption, especially with exercise. Restrict if HBP.
DHEA-S (not recommended for routine treatment, consider in patients with significant impairment in quality of life, mood and, in women, sexuality).	• Clinical assessment: monitoring for benefits and side effects (clinical signs of hyperandrogenism). • Measurement of DHEA-S and, in women, androstenedione, testosterone and SHBG also.	• Maintain treatment for at least 4-6 months to assess potential benefits. • Decrease dose if side effects or elevated levels occur.
Other	• Assess quality of life. • Check that patient wears plate/bracelet with diagnosis and emergency card. • Check that patient knows and applies adjustments in special situations. • Bone densitometry: in patients treated with high-dose glucocorticoids or at risk of osteoporosis. • Cardiovascular risk factor monitoring. • In patients with autoimmune Addison disease: regular TSH measurement, assess data suggesting other autoimmune diseases, measurement of antibodies. • Check potential drug interactions.	• Use specific questionnaires. • Consider flu, pneumococcal, and travel-specific vaccines.

ACTH: adrenocorticotropic hormone; ANP: atrial natriuretic peptide; DHEA: dehydroepiandrosterone; HBP: high blood pressure; HPA: hypothalamic-pituitary-adrenal; PRA: plasma renin activity.

2.4. What are the consequences of MC underdosing or overdosing?

Administration of MC doses adequate to the needs of each patient is of paramount importance. Underdosing of MCs results in a persistent state of hypovolemia which, if severe enough, causes postural dizziness due to orthostatic hypotension and tachycardia, together with elevation of plasma urea and potassium levels. Lesser degrees of hypovolemia may be asymptomatic, but place patients at risk of circulatory insufficiency when exposed to conditions involving sodium and water losses, such as diarrhea and vomiting.

By contrast, MC overdosing results in hypertension and potassium depletion. Lesser degrees of overdosing may cause no symptoms, but involve a risk for patients if they suffer diarrhea or other disorders associated to potassium loss.

2.5. Are clinical symptoms and signs helpful to guide MC replacement therapy?

The value of clinical symptoms and signs as predictors of FC underdosing or overdosing has been assessed by giving increasing FC doses to subjects with PAI. Using this approach, no consistent relationship was found between symptom occurrence or severity and the different FC doses, except for an increase in weakness (but not in postural dizziness, thirst, or craving for salt) in the absence of treatment[112, 113]. Similarly, changes in blood pressure, heart rate, and body weight also showed no consistent relationship with FC dose[112, 113]. It was only found that BP was lower in untreated as compared to treated patients, but no significant differences in BP levels were seen between the different FC doses[113].

Clinical symptoms and signs therefore appear to have a limited value for monitoring MC treatment, and are in any case more sensitive for detecting underdosing than overdosing.

2.6. What is the role of serum electrolyte monitoring in adjustment of MC replacement therapy?

Serum sodium and potassium levels show a good correlation (positive and negative respectively) with FC dose in patients with PAI treated with increasing drug doses[114,115]. However, although electrolyte levels already normalize with low FC doses, higher doses are associated to minor additional changes. Electrolyte levels therefore appear to be poorly sensitive to MC overdosing and to have a limited value in fine adjustment of FC dose.

2.7. Is measurement of plasma renin helpful to guide MC replacement therapy?

In healthy subjects, activity of the renin-angiotensin system reflects sodium balance status. Thus, sodium retention or overload states are associated to inhibition of activity of this system, while sodium depletion stimulates the system. The possibility of using measurement of plasma renin activity (PRA) as a marker of MC status in PAI was examined by administering increasing FC doses (ranging from 0 and 200 μg/day) to patients with PAI[112-115]. Using this approach, an inverse, highly significant correlation was consistently shown between FC and PRA, which was greater than that seen between FC dose and sodium and potassium levels. In addition, both PRA and FC dose have been shown to be inversely related to plasma volume in patients with PAI[116,117]. PRA are therefore a parameter more sensitive to changes in FC dose than clinical parameters or potassium levels, and their measurement is helpful to guide MC replacement therapy.

2.8. What is the minimum time required for changes in FC dose to be reflected in changes in PRA?

When FC dose is modified, PRA takes several days to reach a new steady state[118] because the negative feedback exerted by MCs on PRA is not direct, but is mediated by changes in vascular volume and blood pressure. It is therefore recommended to wait at least two weeks after a change in FC before PRA is monitored[106].

2.9. What are the limitations of PRA measurement as a marker of MC status in PAI?

PRA level are highly dependent on sodium intake, and may therefore be undetectable in subjects with high sodium intake[112]. The relationship between sodium intake and PRA is preserved in the absence of aldosterone[119], so that in patients with PAI and high salt intake (and thus with suppressed renin), PRA levels are not able to discriminate between adequate and excess MC replacement[112].

On the other hand, although good correlation exists between PRA levels and FC dose, studies conducted on patients with PAI given increasing FC doses showed that in the higher dose range, PRA level was not significantly different between the different doses[113,115]. Finally, as stated below, clear signs of MC overdosing have been identified in patients with normal renin.

These data suggest that although PRA is a more helpful parameter to detect MC underdosing, it has little value to differentiate between adequate and excess dosing.

2.10. Is there any parameter useful to detect FC underdosing?

Atrial natriuretic peptide (ANP) is a hormone secreted in response to intravascular volume changes with a regulation opposite to that of renin, so that ANP levels increase when intravascular volume is expanded and decrease with hypovolemia. An analysis of the relationship between ANP levels and MC dose found a direct correlation between both[113]. However, although ANP levels were found to be significantly more elevated when patients received the highest FC doses than when they received the lowest doses, no differences were seen between the latter, which suggests that ANP, unlike renin, is more sensitive to MC overdosing than to MC underdosing. ANP may therefore be complementary to PRA in adjustment of MC dose, especially in the high dose range, where other parameters are of little value.

The reason why PRA is more sensitive to MC underdosing and ANP is more sensitive to MC overdosing is not clear, but may be related to nonlinear response of both hormones to intravascular volume changes and to a reduced discriminant power of test used to measure both hormones when their values are in the lower limit of normal[113].

2.11. Has measurement of plasma renin concentration any advantage over PRA measurement?

Similarly to what occurs with PRA, plasma renin concentration (RC) is inversely correlated to FC dose[113]. Thus, both PRA and RC have a similar value for monitoring FC dose. However, glucocorticoids (GCs) are known to modify plasma angiotensinogen levels[120], and these levels have been shown to influence PRA levels, but not plasma renin concentration, in adrenalectomized animals[121]. PRA may therefore appear falsely elevated in the event of GC overdosing. By the same reason, changes in PRA levels should be interpreted with caution if they are preceded by or associated with a change in GC dose. Under these circumstances, RC may reflect better than PRA the true MC status and suitability of FC dose.

2.12. What PRA target should be achieved with treatment?

Although some authors advocate the convenience of achieving normal renin values in subjects with PAI[116], it has been shown that, in patients on an apparently adequate FC dose (based on clinical and electrolyte signs) but with elevated PRA, an increase in FC dose to normalize PRA may lead to development of hypokalemia and edema[116,122]. Similarly, in patients with hypokalemia and low PRA, FC dose reduction intended to normalize potassium levels has been shown to lead to supranormal PRA levels[122]. These data suggest that overtreatment may exist in the presence of normal PRA levels. Normal PRA may therefore be inadequate in some patients with PAI on MC replacements therapy. It is thus recommended to titrate FC in order to achieve PRA at or slightly above the upper limit of normal[6,108,115,121,123].

In contrast to the general recommendation to maintain PRA levels in the upper limit of normal, in the particular case of AI associated to classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults, some authors recommend as the goal of MC treatment the lowest possible PRA levels that can be achieved without causing hypertension or hypokalemia[124]. This recommendation, for which no supportive scientific evidence is provided by the authors, appears surprising considering that adult patients with classical 21-hydroxylase deficiency are predisposed to develop high blood pressure[125].

2.13. Is treatment with FC required in any patient with PAI?

Hydrocortisone, the standard preparation used for GC replacement, has a MC activity 125-400 times lower than FC[112,115]. Thus, all subjects with PAI potentially require treatment with FC. However, some patients maintain normal PRA in the absence of MC treatment, which suggests that they do not need additional treatment with FC. This may be due to the fact that although the MC potency of GCs is low, their contribution to total MC activity is significant at the usual replacement doses. Thus, for example, a 20 mg dose of hydrocortisone has a MC activity equivalent to 0.05-0.16 mg of fludrocortisone, which may suffice to cover the needs of MC in some patients.

An additional factor that may contribute to the different MC requirements in patients with PAI is individual variation in residual aldosterone secretion by the adrenal cortex. This may in turn depend on PAI etiology, because not all causes are associated to the same risk of hypoaldosteronism. Thus, MC deficiency is virtually constant in PAI of an autoimmune origin, but is less common in post-TBC PAI or ADL[103].

2.14. What is the role of FC in the treatment of acute adrenal insufficiency?

From the pathogenetic viewpoint, MC deficiency plays a more significant role than GC deficiency in precipitation of an adrenal crisis. In fact, patients receiving adequate GC doses may develop acute adrenal insufficiency if their MC requirements are not adequately met[126]. However, treatment with FC during an adrenal crisis has little value because its sodium retention effect takes several days to become apparent. MC deficiency should instead be fought by administration of great volumes of saline. On the other hand, the high HC doses used provide adequate MC action.

2.15. Is modification of FC doses required in stress situations?

In contrast to cortisol, for which response to stress is widely documented, changes in aldosterone secretion in stress situations are not well known, and highly variable responses have been reported depending on the nature of the stressor, among other factors. In patients with PAI, however, increase in FC doses is not recommended in acute stress situations[127] because high hydrocortisone doses used in these situations have adequate MC activity to cover a potential increase in MC requirements[115]. Moreover, with hydrocortisone doses higher than 40 mg, MC treatment may be discontinued because this dose is equivalent to at least 0.1 mg of FC. In the uncommon event that steroid coverage in stress situations is performed with synthetic glucocorticoids, which have very low or no MC activity, an increased FC dose may possibly be required.

2.16. Should FC dose be increased in the summer months?

Environmental humidity and temperature, through their effects on perspiration, are determinant factors in salt loss. Therefore, under elevated temperature and humidity conditions, aldosterone levels increase to compensate salt loss. It is therefore recommended to increase FC doses by 50% during the hottest months of the year[91] in subjects living in countries with Mediterranean or tropical climates, although the evidence supporting this recommendation is scarce.

2.17. How should patients with PAI and high blood pressure be managed?

Subjects on MC replacement therapy who develop HBP represent a special challenge, and no evidence-based recommendations are available on the most adequate management in these cases. As an initial measure, it appears reasonable to verify that doses, both of FC and GC, are adequate. Even in the absence of overdosing, FC dose may be tapered while carefully monitoring sodium and potassium levels[5,91,87], but total drug discontinuation is not recommended[91]. If HBP persists, patients should be given standard antihypertensive treatment[128], avoiding, of course, MC receptor antagonists (spironolactone and eplerenone). PRA levels should be interpreted with caution in patients receiving antihypertensive treatment with drugs affecting the renin-angiotensin system.

2.18. What drugs may modify FC requirements?

As compared to cortisol, synthetic steroids have a reduce affinity for the MC receptor, and have therefore little (prednisone and prednisolone) or no (dexamethasone) mineralocorticoid activity. Hence, patients treated with synthetic GCs usually required higher FC doses than those treated with hydrocortisone.

Progesterone may increase FC requirements because of its antagonist effect on the MC receptor. By contrast, synthetic progestogens have no antagonist effect on the MC receptor[129] and do not therefore modify FC requirements. One exception, however, is a new progestogen, drospirenone, which has antimineralocorticoid activity similar to progesterone[103].

In subjects with normal adrenocortical function, lithium treatment induces an increase in PRA and aldosterone levels[130,131] which has been postulated to be due to inhibition of aldosterone action in the renal tubule[131]. In agreement with this hypothesis, several cases have been reported of patients with bipolar disorder and Addison disease treated with GCs and MCs who experienced signs and symptoms of MC deficiency concurrent with lithium treatment[132-134], which resolved after a marked increase in FC dose (up to 5 times the standard dose)[132,133] or lithium discontinuation[134].

Drugs that decrease renin levels may reduce endogenous aldosterone secretion and increase FC requirements in patients with partial destruction of the glomerular layer, who retain some grade of aldosterone secretion thanks to elevated renin levels. This effect has been reported for beta-blockers and NSAIDs[135].

Finally, phenytoin has been shown to increase FC requirements, probably due to increased drug metabolism[44].

3. Replacement therapy with dehydropiandrosterone

3.1. What is DHEA? Short reminder of physiology

Sex hormones come from three sources: gonads, adrenal glands, and peripheral conversion. Adrenal glands secrete approximately 90% of dehydropiandosterone (DHEA). DHEA is converted into dehydroepiandrosterone-sulfate (DHEA-S) in the adrenal glands and liver mainly. DHEA and DHEA-S secretion depends on age. DHEA is the most abundant steroid at birth, when their levels decrease. Levels subsequently increase between 6 and 10 years of age (adrenarche), and peak DHEA secretion is reached in young adults. Secretion subsequently decreases gradually and variably depending on individuals. DHEA secretion is stimulated by ACTH and follows a circadian rhythm. However, DHEA-S, which has a longer half-life, shows no diurnal variations. These are the most abundant steroids in adults, but are not vital[136]. The factors that modify their secretion during life and during intercurrent diseases are not known[128].

DHEA has multiple roles which are not fully known, some of them studied in vitro or in animals: it is a precursor of sex and intermediate steroids; at neurological level, it acts as a neurosteroid, a precursor of steroids that modulate neuron activity and interacts with different neurotransmitter receptors; in experimental studies, a protective effect on neuron survival has been seen; it has direct effects mediated by membrane receptor binding, stimulates nitric oxide synthase, and has effects on smooth muscle cells[136] and immune system[111]; it also acts as an antiglucocorticoid[137,138], antagonizing neurotoxicity induced by glucocorticoids in hippocampus. Its peripheral conversion to other steroids depends on presence in the tissue of the required enzymatic activity[139].

3.2. How are DHEA levels in patients with adrenal insufficiency?

Patients with PAI and SAI have marked DHEA and DHEA-S deficiency. Adrenal contribution to androgen production is very important in women, but not in men, who usually have preserved testicular function or receive replacement therapy for hypogonadism if required. For this reason, symptoms of adrenal androgen deficiency are usually more evident in women.

3.3. Why is treatment with DHEA considered?

Many patients with AI experience an impaired quality of life despite standard replacement therapy with glucocorticoids and mineralocorticoids. To avoid this, the need for more physiological glucocorticoid replacement therapy has been considered, and there has been speculation about the need for treatment with DHEA.

Conflicting results have been reported for DHEA treatment. Treatment normalizes DHEA, DHEA-S (within the normal range for young adults), and androstenedione levels. In women, treatment elevates testosterone and dihydrotestosterone levels to low normal limits, increases androstanediol glucuronide to high normal limits, and decreases SHBG levels[137,140,141]. The effect on testosterone and SHBG does not occur in males[137,138], and has not been reported in women in other studies[142,143].

Effects of treatment may result from direct DHEA action on central nervous system and/or increased peripheral androgen synthesis[137,140]. Most studies have been conducted in women. In studies where the effect of treatment has been assessed in men and has been positive, a non-androgenic effect is postulated. In patients in whom treatment improves depression of anxiety, this could be related to the effect of DHEA as a neurosteroid[137,140].

Although multiple studies suggest benefits on health-related quality of life and sexuality, DHEA is not part of routine replacement therapy, and large scale phase III trials are needed to establish its role.

Available results are often not fully consistent, which may be related to the following factors: both sexes should be analyzed separately because of the different impact of AI in terms of androgen deficiency depending on sex; long duration studies (benefits occurred in the long term in some studies) with adequate power to assess the actual role of DHEA in the treatment of these patients are required; and studies focused on health-related quality of life must recruit patients with impaired quality of life. Studies using specific tools validated for AI and assessing the optimal treatment dose, age of patients at which treatment would be indicated, and dose depending on age are also required[136,139,140,144,145].

3.4. What are the effects of DHEA on quality of life and sexuality?

The reported data are conflicting. Several clinical trials suggest that, in women with PAI and SAI, treatment with DHEA-S may improve mood, psychological well-being, fatigue, depression, anxiety, or sexuality to a greater or lesser extent[137-140,142,146-148], although some of them found no positive results in some of the above symptoms (e.g. no improvement was seen in sexuality in the Hunt, Gurnell, and van Thiel trial, but there were other more or less marked benefits). Some authors also reported in men psychological benefits[137,138,146,147] which were not seen by others[156]. Other studies showed no benefits[145,149,150].

A meta-analysis by Alkatib et al., assessing the effect of treatment with DHEA on quality of life, depression, anxiety, and sexuality, included 10 randomized studies conducted on patients, mostly women, with PAI or SAI from 1999 to 2008[138-142,145-148]. Treatment with DHEA (50 mg/day for 3-12 months in most studies; 20-30 mg/day in the Johansson study; and 25 mg in the Lovas study) slightly improved health-related quality of life and depression. Among trials assessing the effect of treatment on depression, the study using less than 50 mg found a significantly lower effect as compared to those using 50 mg. The benefits seen in anxiety and sexuality were not statistically significant[144].

No data are available on the effect of this treatment in women with isolated ACTH deficiency[100].

3.5. What are the effects of treatment with DHEA on IGF-I levels?

Studies conducted have reported conflicting results as regards effects of DHEA on IGF-I levels[136,147]. Increased levels have been reported in women with PAI[141] and in women with SAI treated with GH, an effect not seen in men and which has therefore been related to an androgenic effect of DHEA treatment[136,147]. A decrease in the GH dose required was also seen in women with hypopituitarism treated with DHEA, in whom maintenance of stable IGF-I levels during the study was intended[135]. Other studies found no effects on IGF-I levels in Addison disease/PAI[138,139,146], or in SAI[139,140,142,145].

3.6. What are the effects of treatment with DHEA on body hair?

Increased body hair is one of the potential side effects of treatment[137-140]. The androgenic effects reported are usually mild[140].

In some studies, DHEA treatment induced reappearance of pubic and axillary hair, an effect which is usually considered beneficial[92]. Increased pubic hair has been found in both girls and young women[148] and adult women[139] with hypopituitarism. Increased axillary hair has been reported in women with Addison disease treated with DHEA[138].

3.7. What are the effects of treatment with DHEA on vascular markers and lipid and glucose metabolism?

Studies conducted have shown no cardiovascular or endothelial function changes[151,152].

As regards the effect on lipid profile, some studies found decreased HDL-C levels in patients with PAI[139] and SAI[153,154] and apolipoprotein A-1 reduction in SAI[154], while other studies reported decreased levels of total cholesterol, LDL-C, HDL-C, and triglycerides in AI of different causes[153], and similar findings in PAI, with an unfavorable lipoprotein profile[153]. Other authors found no lipid profile changes in PAI[137].

Data on the effect of DHEA treatment on carbohydrate metabolism are also conflicting. Some studies reported no changes in insulin sensitivity in PAI[154] and SAI[150,154]. However, other authors reported increased insulin sensitivity with DHEA treatment in patients with AI of different causes[154].

3.8. What are the effects of treatment with DHEA on body composition and bone?

Overall, DHEA treatment has shown no benefits on bone in patients with PAI[137,143] or SAI[139], but this could be due to short treatment duration (3-6 months). A single study showed reversion of continuous bone mass loss in femoral neck after treatment for 12 months, an effect not seen at other locations[138]. The effects of treatment with DHEA on body composition are not consistent: while some studies showed fat mass increase[138,143], this effect was not seen in other studies[137,141].

3.9. What are the effects of treatment with DHEA on the immune system?

Although additional long-term studies are required, treatment with DHEA appears to have immunomodulatory benefits[155].

3.10. What are the side effects of treatment with DHEA?

Some studies reported side effects common after androgen treatment, usually mild and transient: oily skin, hirsutism. acne, hair loss, itchy scalp, and increased sweating and body odor[137,139,140,150,144,146]. In some patients, side effects led to treatment dose reduction (to 25-30 mg)[140,140]. Other authors reported no side effects[142,140]. Other effects of treatment, including decreased HDL-C levels[139,140] reported as transient by

Johannsson[139], and mild, transient transaminase elevation[140], not seen in other studies[137,138,139,145] have been reported. Although no severe adverse effects have been reported, the long-term safety of DHEA treatment has not been established[144].

3.11. Are there contraindications for treatment with DHEA?

Since DHEA is a precursor of sex hormones (androgens and estrogens), treatment may be contraindicated in patients with hormone-dependent diseases such as breast[140] and prostate cancer.

3.12. What is the current recommendation for treatment with DHEA: to whom and in what dose?

There is therefore no adequate evidence to recommend treatment with DHEA in all patients with AI, especially men. Treatment with DHEA may be considered in patients with PAI or SAI with a significant impairment in mood, well-being, or sexuality (quantified using validated questionnaires) despite adequate glucocorticoid and mineralocorticoid replacement therapy, especially in women[144].

The starting dose is 25-50 mg as a single dose in the morning, and should be adjusted based on clinical response (improved libido, well-being, and side effects of treatment) and laboratory tests (see the monitoring section, 3.13). Arlt et al. recommend that treatment is started with 25 mg and dose is increased to 50 mg in 2-4 weeks. Patients should be instructed to decrease the dose to a half if they experience androgenic side effects in the skin persisting for more than one week[91]. Women may benefit from lower doses after menopause[145,146].

Minimal treatment duration should be 4-6 months. If no evident clinical benefit is seen at 6 months or adverse effects occur, treatment should be discontinued[100].

Treatment is experimental, and its potential risks should therefore be explained in detail.

DHEA is not marketed as an adequately controlled drug, which makes treatment difficult.

3.13. How is DHEA treatment monitored?

Monitoring is based on clinical signs and symptoms, side effects, and DHEA-S measurement. The target DHEA-S level is, for some authors, a mean normal value in young adults[91,143], and for other authors, normal values for age[111, 128]. Some authors recommend measurement of androstenedione, testosterone, and SHBG levels in women, in addition to DHEA-S[92,111].

A significant part of DHEA-S is generated in the liver by the action of sulfotransferase. If sulfotransferase is inhibited, e.g. by cytokines, DHEA-S level may be decreased, with normal or elevated DHEA levels. This may occur in sepsis[136].

3.14. Can testosterone be used in women as treatment for hypoandrogenism in adrena l insufficiency?

Miller et al. reported beneficial effects on bone density, body composition, and neurobehavioral function in women with hypopituitarism treated with testosterone (patches releasing 300 μg/day)[156]. Transdermal testosterone may be a treatment option[92]. Treatment with testosterone and DHEA has not been compared. DHEA, in addition to being an androgen precursor, has effects as a neurosteroid and immunomodulator[92]. Treatment with testosterone should be carefully assessed in Addison disease before it is recommended[128]. The long-term safety of testosterone therapy has not been established[128].

4. Long-term monitoring of patients with PAI and SAI

In addition to monitoring of drugs used, already discussed in the relevant sections, monitoring of patients with PAI and SAI requires some considerations, as explained below.

4.1. How is quality of life assessed?

In patients with adrenal insufficiency, decreased vitality and perception of well-being and increased concern about state of health have been reported, but results are based on questionnaires not specific for AI[103]. A specific questionnaire (AddiQoL) has been developed for patients with primary adrenal insufficiency. It may be helpful to assess quality of life in clinical trials and for patient monitoring. AddiQoL is a 30-item questionnaire and has a short 8-item version[84,85].

4.2. Should bone density be assessed?

Bone mineral density results reported in these patients are conflicting[103].

Osteoporosis is more common in patients treated with hydrocortisone doses of 30 mg/day or higher. Lower doses do not affect bone mineral density. Thus, routine controls of bone mineral density are not required in patients given adequate doses[92,102].

It is important to avoid excess doses. Today, it is generally recommended not to exceed the dose of 20-25 mg of hydrocortisone (recommended dose: 15-20 mg/day in secondary adrenal insufficiency, 20-25 mg/day in primary adrenal insufficiency). In patients treated with higher doses, with additional risk of osteoporosis (family history, history of fractures, hypogonadism, post-menopausal women) or with long-standing disease, and thus greater probability of having received high-dose treatment, bone mineral density should be assessed[89]. In any case, the recently published European consensus on management of Addison disease recommends that bone mineral density is tested every 3-5 years[157].

4.3. Should cardiovascular risk factors be controlled?

Increased mortality is seen in patients with PAI mainly as the result of infectious and cardiovascular diseases, and in patients with SAI as the result of cardiovascular disease[88]. Cardiovascular disease is the most common cause of increased mortality in both conditions[68]. According to the Filipsson et al study, conducted on patients with hypopituitarism, the cardiovascular risk profile is related to daily

hydrocortisone dose. Patients on replacement therapy for AI had greater waist circumference and higher total cholesterol, triglyceride, and HbA1c levels than patients not requiring such treatment. In addition, new cases of stroke, myocardial infarction, and diabetes occurred in patients treated with glucocorticoids. However, if the hydrocortisone dose used was 20 mg or less, metabolic changes were not different from those found in patients not requiring glucocorticoids[71].

Circadian rhythm of cortisol secretion may be partly responsible for physiological diurnal changes in glucose tolerance. Mimicking this rhythm with hydroaltesone treatment may be essential to maintain glucose homeostasis[68].

As noted above, the first step in patients with PAI who experience HBP is to consider the possibility of mineralocorticoid and glucocorticoid overdosing, and decrease fludrocortisone dose. If no evidence exists of treatment overdosing, patients should receive standard treatment for HBP, avoiding drugs such as spironolactone and eplerenone, which are aldosterone antagonists.

Although it is important to avoid overdosing in glucocorticoid therapy, underdosing should also be avoided because of the risk of adrenal insufficiency itself and the increased mortality associated to it[68].

While no specific goals are recommended in control of cardiovascular risk factors in these patients, and there is no evidence that control improves cardiovascular prognosis, it appears sensible to recommend, in addition to optimization of replacement therapy, emphasis on cardiovascular risk factor monitoring.

4.4. What are the effects of glucocorticoid treatment on the eyes?

Patients treated with glucocorticoids have an increased, dose-dependent risk of cataract and glaucoma[158].

The Li Voon Chong study, conducted on 17 patients with PAI or SAI with no history of intraocular hypertension or glaucoma, compared the effect of hydrocortisone doses of 20 and 10 mg on intraocular pressure. The 10 mg dose was associated to a more physiological intraocular pressure profile during the day. A marked increase in circulating cortisol levels may cause an increase in intraocular pressure approximately 4 hours later[159].

4.5. Are there recommendations about vaccination in patients with adrenal insufficiency?

There is no specific recommendation about vaccination in patients with AI. Because of the risk associated with infections in these patients, it is advisable to offer vaccination against flu and pneumococci, as well as specific vaccines for traveling, but this recommendation is not based on strict evidence[128]. What is established is the need for early and aggressive treatment of infections, in addition to increasing glucocorticoid dose[87].

In patients treated with high glucocorticoid doses for other diseases, vaccines recommended for immunosuppressed patients will be administered.

4.6. Should screening for other autoimmune diseases in patients with autoimmune Addison disease?

As discussed in previous sections, other autoimmune diseases are detected in two thirds of patients diagnosed with AI due to autoimmune Addison disease. There is no agreement on screening to be performed. Antibody tests may hep predict such diseases. Thyroid function, intestinal malabsorption data (possibly including vitamin B12 levels and celiac disease antibodies), menstrual cycle in women, and glucose/HbA1c should be monitored annually[89,92].

Relatives of these patients have an increased risk of autoimmune AI, and should therefore be assessed for symptoms of hypocortisolism[89].

4.7. What should education of patients and their families involve?

This is one of the main factors in long-term management of AI, because adequate patient behavior in special situations may prevent an adrenal crisis.

Patients should know:

1. The nature of hormone deficiency and the reason why treatment is required.
2. Maintenance treatment and treatment adjustments with intercurrent diseases.
3. When they should seek medical help.
4. When and how glucocorticoids should be injected.
5. Emergency precautions:

a) All patients should be recommended to wear a bracelet or a plate in the neck with disease diagnosis, and should be advised to take with them an emergency card with information about the cause of disease, usual treatment, and treatment to be administered in an emergency[87-89].

b) Each patient should have an emergency kit including: an injectable glucocorticoid (100 mg vials of hydrocortisone or 4 mg vials of dexamethasone), 0.9% vials of saline (if possible), and syringes. Patients and one or more of their relatives should be instructed on drug preparation and injection, either intramuscular or subcutaneous, if the patient experiences any of the following:

- A wound with substantial blood loss or a fracture.
- Nausea or vomiting, or inability to tolerate oral medication.
- Symptoms of acute adrenal insufficiency.
- Unconsciousness.

Patients should be advised to have a low threshold for glucocorticoid injection. This is indispensable in patients who travel or who live in areas with limited access to medical care.

At control visits, patient understanding of and compliance with recommended rules must be verified.

As drugs that accelerate cortisol clearance exist and their use requires modification of glucocorticoid dose[89], physicians in charge of these patients should know their potential interactions with treatment, and it would be advisable that patients informed about their disease before starting new treatments.

4.8. May steroid requirements in stress situations be predicted?

Because of the great variation in cortisol secretion in healthy subjects under stress, accurate prediction of steroid requirements under these conditions is difficult. Table 14 summarizes recommendations for glucocorticoid dose adjustment related to stress (Table 15)[103, 127].

4.9. What changes are recommended in treatment when exercise is performed?

Patients with AI who perform regular, routine, and time-limited physical activity do not usually need dose adjustment of glucocorticoid and mineralocorticoid. If unusual, strenuous, or prolonged exercise is performed, hydrocortisone dose and salt intake may have to be increased. To run a race, such as a marathon, an extra dose of 5 mg may be given before the race. Under very hot conditions or during strenuous physical activity, additional fluid and salt intake is required to replace losses through sweat. Patients who plan to perform strenuous or prolonged exercise are advised to try the proposed replacement regimen before the event. There are however no systematic studies of treatment replacement during strenuous physical activity[158].

4.10. What should be the frequency of control visits?

Patients diagnosed with AI must attend a specialized center for regular monitoring every 6-12 months[92]. This time interval must be adapted to the characteristics and different circumstances of each patient. Table 14 summarizes the recommendation for treatment monitoring and long-term follow-up.

5. Management of patients on long-term glucocorticoid therapy (TAI)

5.1. How should patients on long-term glucocorticoid therapy in whom treatment discontinuation is planned be managed?

Long-term glucocorticoid treatment is used because of its anti-inflammatory effect or immunosuppressant activity. Treatment discontinuation should be careful to prevent recurrence of the underlying disease and glucocorticoid deficiency derived from suppression of the hypothalamic-pituitary-adrenal axis caused by treatment[57].

Discontinuation of long-term glucocorticoid treatment is considered when the desired therapeutic benefit has been achieved, the expected benefit does not occur, or side effects which are severe or not controlled with treatment, such as osteoporosis or HBP, occur. There are two complications requiring immediate treatment discontinuation or reduction to physiological doses: acute steroid-induced psychosis not responding to antipsychotic treatment, and corneal ulcer induced by herpesviruses, because of the risk of corneal perforation and blindness[57].

5.2. What patients are at risk of suppression of the hypothalamic-pituitary-adrenal axis?

Risk of suppression of the HPA axis is classified as probable, intermediate/uncertain, and improbable depending on the characteristics of treatment received. Management will be decided based on risk (Table 9)[57,58].

Interindividual variability exists in GC kinetics, so that some patients may have more symptoms than others upon treatment discontinuation. Although potency, dose, and duration of GC treatment are important, they are not perfect predictors to establish the risk of suppression of the HPA axis[57]. HPA axis suppression is uncommon with prednisone doses less than 5 mg/day[57] (Table 10).

5.3. How is suppression of hypothalamic-pituitary-adrenal axis estimated?

HPA axis should be assessed when patients are being treated with daily doses of 5 mg of prednisone or less and further dose reduction is difficult because of symptoms unrelated to the underlying disease. The ACTH test is the method most commonly used. Furst et al. recommended use of low ACTH doses for the test[57].

5.4. What schemes may be followed to discontinue long-term glucocorticoid treatment?

There is little evidence to recommend a specific scheme.

In patients treated with glucocorticoids for at least 3 weeks, even at high doses, Furst et al. recommended treatment discontinuation with no need for a tapering scheme. In fragile or severely ill patients, however, a more cautious approach may be taken[57].

In patients treated with glucocorticoids for a longer time, who have cushingoid appearance or receive glucocorticoid treatment in the evening, Furst et al. propose a prednisone tapering scheme based on experience which considers patient state of health, age, stability of underlying disease, and therapeutic regimen used. Dose is reduced by 10%-20% every 1 to 4 weeks depending on clinical signs. The proposed scheme is as follows:

- 5 to 10 mg/day every 1-2 weeks if the initial dose of prednisone (or other GC at an equivalent dose) was >40 mg/day.
- 5 mg/day every 1-2 weeks with prednisone doses ranging from 40 and 20 mg/day.
- 2.5 mg/day every 2-3 weeks with prednisone doses ranging from 20 and 10 mg/day.
- 1 mg/day every 2-4 weeks with prednisone doses ranging from 10 and 5 mg/day.
- 0.5 mg/day every 2-4 weeks with prednisone doses ≤ 5 mg/day. This may be done by alternating daily doses (e.g. 5 mg on day 1, 4 mg on day 2).

Other possibilities include: use schemes with dose reduction every other day, or gradual tapering of hydrocortisone, which could be discontinued when basal cortisol is >10 μg/dL; glucocorticoids may be required in stress situations, such as infections[57].

Alves et al. published clinical practice recommendations for discontinuation of glucocorticoid treatment in children[160].

Table 15 Recommendations for increasing hydrocortisone doses in patients with AI in different conditions:

Surgery, invasive or dental procedures and labor		
Procedure	Preoperative requirements	Postoperative requirements
Major surgery with long recovery time (e.g. abdominal surgery, cardiac surgery)	100 mg of hydrocortisone i.v. just before anesthesia	On the first day, 100 mg of hydrocortisone every 8 hours or a continuous intravenous infusion of 200-300 mg/24 h. After an uncomplicated procedure, decrease dose gradually (30%) every day to maintenance dose.
Major surgery with rapid recovery (joint replacement, cesarean section)	100 mg of hydrocortisone i.v. or i.m. just before anesthesia	Hydrocortisone 50 mg IV every 8 hours on the day of surgery, decrease to a half in the next 24 hours, and return to the usual replacement dose in the following days
Labor	During labor: hydrocortisone 25 mg i.v. every 6 hours. Si labor is prolonged, 100 mg/8 h or continuous infusion (200-300 mg/24 h) until delivery.	Double oral dose for 24-48 h after delivery, then reduce to the normal dose
Minor surgery (e.g. cataract, hernia) Major dental surgery: tooth extraction under general anesthesia	100 mg of hydrocortisone i.v. or i.m. just before anesthesia	Double oral dose for 24 hours*, then return to normal dose.
Minor dental surgery: endodontic surgery	Extra dose in the morning, 1 hour before surgery	Double oral dose for 24 hours*, then return to normal dose.
Minor dental procedure: tooth filling	Not normally required	Extra dose (e.g. 20 mg hydrocortisone) if symptoms of hypocortisolism†.
Invasive intestinal procedures requiring laxatives; e.g. colonoscopy, barium enema)	Consider hospital admission the night before administering 100 mg of hydrocortisone i.v. or i.m. and fluids, repeat the dose before the procedure	Double oral dose for 24 hours*, then return to normal dose
Other invasive procedures (e.g. endoscopy, arteriography)	100 mg of hydrocortisone i.v. or i.m. just before the procedure	Double oral dose for 24 hours*, then return to normal dose.
Intercurrent disease, psychological stress, and physical exercise		
Minor febrile disease (e.g. common cold, viral respiratory infection)		Double oral dose*. Decrease maintenance dose within 2-3 days of disease resolution. Do not change mineralocorticoid dose
Persistent vomiting and/or diarrhea (e.g. gastroenteritis)		Hydrocortisone 50 mg/12 h i.v. or i.m.. Consider hospital admission.
Severe medical disease (such as severe sepsis, myocardial infarction, pancreatitis) or severe trauma		Intravenous injection of 50-100 mg every 8 hours or continuous intravenous infusion of 150-300 mg/24 h, decreased to a half when improvement occurs.
Short-lasting stress: examination, interview		No dose increase required
If stress is prolonged and severe (grief for a relative, acute depression)		Consider an additional hydroaltesone dose
Shift work		Adapt hydrocortisone doses to sleep-wake cycle
Physical exercise		No dose increase is required for short-duration exercise. Increase dose 5-10 mg before sustained, strenuous exercise (marathon, football match) †

*If treatment with Plenadren® is used, increase in total daily dose should be made by giving the maintenance dose two or three times daily at 8-hour intervals.
†If treatment with Plenadren® is used, additional immediate-release hydrocortisone may be required, especially in the evening/night.
i.m.: intramuscular; i.v.: intravenous.
Adapted ref.102, 126, 156.

6. Adrenal crisis

Acute adrenal insufficiency (AAI) or adrenal crisis (AC) is a life-threatening medical emergency that requires urgent hospital admission for parenteral administration of glucocorticoids and crystalloids[161]. AC is the initial manifestation of Addison disease in almost half the patients[5]. AC rate is 6.3 crises per 100 patient-years, and crises are more common in PAI (6.6 in PAI and 5.8 in SAI)[161].

6.1. What conditions may trigger an adrenal crisis?

The most common precipitating factors include infection, particularly gastrointestinal (which cause vomiting and/or diarrhea), and fever (45%), as well as surgery, severe pain, wounds, myocardial infarction. severe allergic reactions, severe hypoglycemia in diabetic patients, significant emotional stress, and pregnancy. Other potential causes include strenuous physical activity, climate changes with exposure to unusual heat, and discontinuation of glucocorticoid replacement therapy in poorly educated or poorly compliant patients. Sometimes, a clear cause is not found (6.6% in PAI and 12.7% in SAI[161,162]).

6.2. What are the signs of an AC?

AC usually occurs suddenly. Symptoms may include nausea, vomiting, abdominal pain (sometimes with peritoneal irritation), muscle pain or cramps, fever with no other signs of infection, and dehydration leading to hypotension or shock that responds poorly to fluids and inotropic medications. Cognitive impairment is not uncommon (confusion, loss of consciousness, or coma). Biochemical findings include hyponatremia, in PAI hyperkalemia and azotemia caused by prerenal failure, and unexplained hypoglycemia mainly in children. Plasma count often reveals, lymphocytosis, and eosinophilia.

6.3. How should AC be treated?

6.3.1. Emergency measures in the first 24 hours[103, 107, 163]

6.3.1.1- What emergency measures should be taken in the first 24 hours?

1. Establish a large bore intravenous line.
2. Draw blood for plasma electrolyte, creatinine, and glucose tests and routine measurement of cortisol and ACTH in plasma before corticosteroid administration. Do not wait for laboratory results.
3. Infuse 2 to 3 liters of physiological saline (0.9% NaCl); if patient is in shock: 1000 mL over the first hour, 500 mL over the second hour, and subsequent infusion guided by frequent hemodynamic monitoring (CVP) and plasma electrolyte levels to avoid iatrogenic fluid overload. Administer also glucose solution to prevent potential hypoglycemia.
4. Intravenous glucocorticoid:

— In patients with no prior diagnosis of AI, dexamethasone is preferred: an intravenous 4 mg bolus over 1 to 5 min and every 12 hours thereafter, instead of hydrocortisone, because it is not measured by plasma cortisol tests.

— For patients with known diagnosis of AI, use dexamethasone (4 mg IV bolus), or preferably hydrocortisone, 100 mg IV immediately and then as a continuous infusion (200-300 mg of hydrocortisone for 24 hours in 5% glucose solution). If the intravenous route is not possible, an intramuscular 100 mg bolus should be given every 6-8 hours[92].

— Acute mineralocorticoid replacement is not required, because the sodium retention effects take several days to occur, and sodium may be adequately replaced with intravenous saline only. However, in patients with known primary adrenal insufficiency with potassium levels >6.0 mEq/L, hydrocortisone is preferred because of its mineralocorticoid activity by saturating type 2 11bHSD. Forty milligrams of hydrocortisone are equivalent to 0.1 mg of fludrocortisone.

5. Use other support measures depending on severity of the intercurrent disease, admission to an intensive care unit; prophylaxis of gastric stress ulcer, low dose heparin, and antibiotic treatment as needed.

If the reason for the clinical situation of the patient is adrenal insufficiency, clinical improvement should be seen within 4-6 hours, especially in blood pressure[111].

6.3.1.2- When hyponatremia occurs, at what rate should be corrected?

As in other conditions where hyponatremia occurs, we should be cautious with correction. Although recommendation may vary depending on patient circumstances, rapidity of onset of hyponatremia, age, and nutritional status of patient, a correction not greater than 10 mmol/L in the first 24 hours and 18 mmol/L in the first 48 hours is recommended (even no greater than 6-8 mmol/L and 14-16 mmol/L in the first 24 ahd 40 hours respectively in cases with greater risk such as women, the elderly, children, and malnourished patients). It is therefore recommended to closely monitor electrolytes for the first 24-48 hours and, if the correction rate is higher than recommended, do not hesitate in increasing the infusion rate of glucose solutions and eventually prescribing 1-2 μg of desmopressin IV or SC.

6.3.2. Subacute measures after patient stabilization

6.3.2.1. What measures should be taken after patient stabilization?

1. Continue physiological saline (0.9%) at a lower rate in the following 24 to 48 hours.
2. Investigate and treat potential precipitating causes of AC.
3. Perform a short stimulation test with ACTH to confirm diagnosis of AI, if patient has not been diagnosed.
4. Determine the type and cause of AI, if not known yet.
5. Gradually decrease glucocorticoid dose to the oral maintenance dose over 3 to 4 days if allowed by the precipitating disease or complication.
6. Start mineralocorticoid replacement with oral fludrocortisone, 0.1 mg daily, when saline infusion is stopped and hydrocortisone dose is <50 mg/day.

6.3.2.2. How can adrenal crisis be prevented?
Follow the recommendations given in the long-term monitoring section, patient education. Patient education should be reinforced to teach them to increase steroid dose when intercurrent diseases, vomiting, wounds, or other stressors occur, and the need to search for medical help before they reach a state in which they will not be able to care for themselves. Low salt consumption and chronic mineralocorticoid underreplacement could be the cause of recurrent adrenal crises. It should be investigated whether inadequate treatment compliance or underlying psychiatric changes are implicated[157].

7. Special circumstances

7.1. Pregnancy

7.1.1. When should AI be suspected in pregnancy?
The rarity of AI during pregnancy lies in the fact that PAI of an autoimmune origin is associated to chronic anovulation, leading to impaired fertility, while in SAI, due to hypopituitarism if this exists, growth hormone deficiency plays a role in decreasing pregnancy rates.

Diagnosis of PAI should be considered in a pregnant woman with persistent nausea, hypotension, and marked fatigue, particularly if there is a personal or family history of autoimmune endocrine disease. At the start of pregnancy. symptoms and signs of an adrenal crisis may be confused with hyperemesis gravidarum[164,165].

7.1.2. How is diagnosis made?
If PAI is suspected, paired blood samples should be taken for testing cortisol and ACTH and, if possible, an ACTH stimulation test should be performed before starting replacement treatment with hydroaltesone. Normal cortisol levels or response to stimulation tests of the HPA axis during pregnancy are not well established. Due to estrogen-induced CBG production in the liver, pregnancy is physiologically associated to a gradual, marked increase in CBG and, thus, in total plasma cortisol. Free cortisol also increases during the last trimester of pregnancy. Increased levels of bioavailable free cortisol may be due to: placental synthesis and release of biologically active CRH and ACTH, pituitary desensitization to cortisol feedback, and increased pituitary response to corticotropin releasing factors. Based on this increase in cortisol and UFC[166,167], it has been suggested that basal cortisol levels less than 11, 16.3, and 22 μg/dL during the first, second, and third trimesters respectively should lead to suspect AI. Cut-off points in the ACTH test proposed for the first, second, and third trimesters of pregnancy are 25, 29, and 32 μg/dL respectively[167,168]. The insulin hypoglycemia test, the metyrapone test and the CRH stimulation test and not recommended during pregnancy due to potential risk of AC and absence of validation. The insulin hypoglycemia test may be performed after delivery.

7.1.3. How should GC treatment be given and monitored?
Before glucocorticoid replacement therapy was available, pregnancy in women with PAI was associated to a maternal mortality rate of 35%-45%, and delayed growth was common. Today, most women with AI adequately treated complete pregnancy and delivery with no complications, and babies achieve a normal birth weight. Problems occur is AI is not recognized, because this often leads to greater maternal and fetal mortality rates during pregnancy and postpartum.

Treatment adherence is the cornerstone for a successful pregnancy. It is important to advise patients to continue with glucocorticoid replacement therapy despite nausea. Intramuscular dexamethasone may be needed at a slightly higher dose (1 mg daily) if nausea and vomiting are severe.

If AI is not diagnosed, risk of adrenal crisis is higher during the first trimester and labor, and until two weeks after delivery.

While some authors recommend close monitoring and dose adjustment based on clinical judgment[103,127], most authors advise a systematic increase in hydrocortisone dose by approximately 20%-50% as compared to the initial dose, i.e. a 2.5-10 mg/day increase during the third trimester, due to the abovementioned increase in free cortisol[107,166,168,169].

7.1.4. Is modification of FC dose required in pregnancy?
During pregnancy, progesterone secreted by the placenta competes with aldosterone for the MC receptor in the kidney[129] and, as the result, the sodium retention effect of aldosterone decreases. In healthy women, this progesterone action is compensated by increased activity of the renin-aldosterone axis, which results in increase PRA, angiotensinogen, angiotensin II, and aldosterone levels. This effect is already evident from the first trimester and becomes more marked over the course of pregnancy, so that aldosterone levels increase approximately five times in the second trimester and up to 10 times at the end of pregnancy. Women with Addison disease, in whom aldosterone levels cannot increase, may therefore need higher MC replacement doses during pregnancy, and requirements up to 0.6 mg/day have been reported in the third trimester[168]. Adjustment required in FC dose should mainly be based on BP levels, serum electrolyte levels, and clinical signs of volume depletion or expansion. PRA levels during pregnancy may be difficult to interpret because of their physiological increase. Most authors[92,111,127,128,168], but not all[170], therefore advise against their use for dose adjustment. If PRA levels are monitored, it is recommended that they do not decrease below 20-25 ng/mL/h, which are the levels usually found in healthy pregnant women. Immediately after delivery, the dose prior to pregnancy should be given again. If pregnancy is complicated by preeclampsia, treatment must be discontinued[170].

7.1.5. What is advised during labor?
During labor, adequate saline hydration and 25 mg of intravenous hydrocortisone every 6 hours should be administered. If labor is prolonged or cesarean section is performed, intravenous hydrocortisone should be administered at a dose of 100 mg every 6-8 hours or as a continuous infusion (200-300 mg/24 hours), which is more advisable to avoid peak-through. After delivery, dose may be reduced within three days to the maintenance dose prior to pregnancy.

7.1.6. Is newborn monitoring required?
Assessment of adrenal function in newborns to mothers with AI who received adequate physiological replacement is not required. However, formal assessment of the HPA is advised in

children born to mothers who have received high glucocorticoid doses during pregnancy, because glucocorticoids may cross the placenta and inhibit fetal glucocorticoid production, causing adrenal atrophy[168]. Breast-feeding is not contraindicated[166].

7.2. Management of adrenal insufficiency during Ramadan

Instead of hydroaltesone, longer acting glucocorticoids such as prednisolone or dexamethasone should be considered for compliance with fasting (for approximately 15 hours daily) during the month of Ramadan. A combination of prednisolone in the morning and hydrocortisone in the evening-night may also be considered to try and mimic the daily cortisol curve. If possible, corticoid replacement should start a few weeks before Ramadan, and patients should be clinically monitored for adequate dose adjustment[171]. During the fasting hours, strenuous work and excess heat should be avoided, and patients should try and rest during this time to avoid stress.

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Conflicts of interest

The authors state that they have no conflict of interest.

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Annex 1 Methodology to prepare these clinical guidelines

These guidelines were prepared at the proposal of the SEEN Board of Directors. A study group was formed to update diagnosis and treatment of primary and secondary adrenal insufficiency (AI).

As no prior guidelines were available, a comprehensive literature search was made on the subject using the PubMed and Embase databases, and original articles, meta analyses, and clinical recommendations prepared by expert groups of known repute were collected from them. These guidelines are therefore not based on levels of evidence. Our aim was to carry out a practical and updated review that is helpful in clinical practice for professionals who care for patients with adrenal insufficiency.