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ADRENAL INSUFFICIENCY

Michail Savvas K. Magklis, MD, michael.magklis@icloud.com
Nicolas C. Nicolaides, MD, PhD, Medical School, University of Cyprus, nicolaides.nicolas@ucy.ac.cy
George P. Chrousos, MD, PhD, MACP, MACE, FRC. (UK), Professor of Pediatrics and Endocrinology, holder, UNESCO Chair on Adolescent Health Care, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, and Director, Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens and Distinguished Visiting Scientist, NICHD, NIH Bethesda, Maryland 20892. Chrousos@gmail.com

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ABSTRACT

Adrenal insufficiency (AI) is an uncommon clinical condition resulting from inadequate glucocorticoid secretion or action, either at the basal state or during stress. Hypothalamic-pituitary-adrenal (HPA) axis disturbance or primary adrenal failure itself are responsible for this condition. AI presentation can range from asymptomatic hormonal dysfunction to adrenal crisis. Prompt diagnosis and management are crucial since AI may be fatal if unrecognized or untreated. Among the various investigations, the appropriate tests should be performed in a timely manner to reverse hormonal and metabolic disturbances, treat associated conditions, and prevent acute crises. In this review, we provide background knowledge regarding pathophysiology, clinical manifestations, underlying etiologies, hormonal investigations, and related treatments in adrenal insufficiency.

EPIDEMIOLOGY

Adrenal insufficiency (AI) is a life-threatening condition characterized by the failure of adrenocortical function. This failure results in impaired secretion of glucocorticoids (GCs) only and/or of GCs and mineralocorticoids (MCs) and adrenal androgens, which are crucial for energy, salt and fluid homeostasis, and androgenic activity. The disorder may be caused by adrenocortical disease, primary adrenal insufficiency (PAI), known as Addison disease (AD), which is a rare condition with reported prevalence in Europe ranging from 39 cases/million in England in 1968 (1) to 221 cases/million in Iceland in 2016 (2), the highest prevalence reported. The current general prevalence of Addison disease is about 82-140 cases per million, depending on the study (3,4). This number illustrates a great increase from about 40-70 cases per million in the 1960s and data supports that this upwards trend continues, particularly in women (3). Some parts of the world appear to have a lower prevalence of Addison disease, for example in Japan the prevalence is 5 cases/million (5).Depending on the study, the annual incidence of AD in Europe is estimated to range between 4 and 6.2 new cases per million people (3, 5, 6, 7).

AI may be secondary in the setting of conditions affecting the pituitary gland and the secretion of adrenocorticotropic hormone (ACTH) (secondary AI) and/or the hypothalamus and the secretion of corticotropin-releasing hormone (CRH) and/or other ACTH secretagogues such as vasopressin (tertiary AI). Secondary and/or tertiary AI is estimated to have a prevalence between 150 and 280 per million, making

it more prevalent than primary adrenal insufficiency (4, 8-10). A prevalence of AI after pituitary surgery varies, with higher rates of up to 90% after craniopharyngioma surgery, while hypopituitarism has high prevalence after cranial radiation for non-pituitary tumors, but may take several years to develop. It should be noted that almost all patients that developed hypophysitis, a result of immune checkpoint inhibitor therapy (especially when treated with Anti-CTLA4 and Anti-PD-1/PDL-1), also developed persistent secondary adrenal insufficiency (11). An interesting finding in recent studies is that long Covid is often accompanied by pituitary dysfunction (12).

CLINICAL RECOGNITION

The clinical manifestations of AI depend upon the extent of loss of adrenal function, and whether mineralocorticoids and androgen production are preserved, as the renin-angiotensin-aldosterone system (RAAS) is intact in central AI. The presentation can be acute or insidious, depending on the underlying cause of the adrenal failure. The diagnosis may be delayed until an intercurrent illness, such as serious infection, acute stress, bilateral adrenal infarction, or hemorrhage, precipitates a life-threatening adrenal crisis. The symptoms of primary adrenal insufficiency are pleiotropic and non-specific, except for salt craving (Table 1).

Adrenal crisis is an acute deterioration in health which is associated with hypotension, acute abdominal symptoms, and marked laboratory abnormalities, which resolve after parenteral glucocorticoid administration. In primary adrenal insufficiency, the patients may have more severe symptoms which are due to concomitant mineral corticoid deficiency. This condition is commonly presented in primary adrenal insufficiency, but less common in central AI, in which a typical example would be pituitary apoplexy. Retrospective and prospective analysis revealed a prevalence of adrenal crises 6.6-8.3 cases/100 patient-years, with mortality 0.5/100 patient-years,mainly due to gastrointestinal and other infectious diseases (13). A recent retrospective case-control analysis of the European Adrenal Insufficiency Registry (EU-AIR) reported an incidence of adrenal crisis of 6.53 cases per 100 patient-years for primary adrenal insufficiency and 3.17 cases per 100 patient-years for central AI (14).

A significant feature to clinically differentiate primary adrenal insufficiency (PAI) from central AI is skin pigmentation, which is nearly always present in long-standing PAI. The most probable cause of the pigmentation seems to be the increased stimulation of the melanocortin-1 receptor (MC1R) by elevated levels of ACTH itself with its intrinsic α-melanocyte stimulating hormone activity. The rest of the clinical features of secondary and tertiary AI are like those of PAI type (Table 1). Rarely, the presentation may be more acute in patients with pituitary apoplexy. Hyponatremia and compensatory water retention may be the result of an “inappropriate” increase in vasopressin secretion. The clinical manifestations of a pituitary or hypothalamic tumor, such as symptoms and signs of deficiency of other anterior pituitary hormones, headache or visual field defects, may also be present.

Another condition with a dissociation in GCs and MCs secretion presenting as AI is congenital adrenal hyperplasia (CAH), with a frequency of adrenal crisis of 5.8 cases/100 patient-years (4.9 cases/100 patient-years after correction for a neonatal salt-wasting crisis), often occurring after respiratory infections, firstly in early childhood, followed by gastrointestinal infections at older ages (15).

Table 1. Symptoms, Physical Findings, and Laboratory Findings Associated with Adrenal Insufficiency	
SYMPTOMS AND PHYSICAL FINDINGS	
Adrenal crisis: hypotension (<110mmHg systolic) and syncope/ shock (>90%); volume depression **Non-specific symptoms:** Gastrointestinal symptoms: abdominal pain, flank pain, back pain, or lower chest pain: 86%- may mimic acute abdomen Fever (66%) Anorexia (early feature), nausea, vomiting (47%) Abdominal rigidity or rebound tenderness (22%) Diarrhea, which may alternate with constipation Neuropsychiatric symptoms: Confusion, lethargy, disorientation, coma (42%)	PAI>SAI/TAI
Psychiatric symptoms: memory impairment, depression, anxiety, psychosis, reduced consciousness, delirium	Chronic AI
General malaise, weakness, fatigue, lassitude, generalized weakness	PAI/SAI
Hypoglycemia; increased risk in children, thin women, alcohol abuse, GH deficiency	SAI>>PAI
Sudden severe headache, loss of vision or visual field defect	SAI (pituitary apoplexy)
Skin: Hyperpigmentation: sun-exposed or pressure areas, recent scars (after AI manifestation), axillae, nipples, palmar creases, mucous membranes as buccal mucosa Vitiligo (as marker of autoimmune disease)	Chronic PAI
Postural hypotension due to volume depletion, or improvement in blood pressure control in previously hypertensive patients, postural dizziness	PAI>>SAI
Salt craving (22%)	PAI
Autoimmune manifestations: vitiligo, autoimmune thyroid disease, type 1 diabetes, primary ovarian failure, autoimmune gastritis	PAI
Weight loss	Chronic PAI/SAI
Decreased axillary and pubic hair, loss of libido in females (DHEA deficiency), amenorrhea in women (in 25% due to chronic illness, weight loss or associated premature ovarian failure)	PAI/SAI
Auricular calcification	
Low grade fever	PAI
Associated endocrinopathies in the context of autoimmune polyglandular syndrome	PAI
LABORATORY FINDINGS	

Electrolyte abnormalities: Hyponatremia: 85-90% (PAI: MCs deficiency; CAI: dilutional effect) Hyperkalemia: 60-65% due to MCs deficiency Metabolic acidosis Mild hypercalcemia (uncommon)	 PAI/SAIPAI PAI PAI
Azotemia	PAI
Liver enzymes abnormalities: may be observed in autoimmune hepatitis	PAI
Changes in blood count: Mild anemia (normocytic normochromic) Eosinophilia Lymphocytosis	
↑TSH with normal or low normal T4 (transient with ↑ACTH; permanent with autoimmune thyroiditis)	PAI
↑Erythrocyte Sedimentation Rate	

ACTH: adrenocorticotropic hormone; AI: adrenal insufficiency; DHEA: dehydroepiandrosterone); GCs: glucocorticoids; GH: growth hormone; MCs: mineralocorticoids; PAI: primary AI, SAI: secondary AI, T4: thyroxine; TAI: tertiary AI; TSH: thyrotropin stimulating hormone.

PATHOPHYSIOLOGY

Adrenal Insufficiency is an umbrella term that includes several conditions. It is divided into:

1) Primary Adrenal Insufficiency (PAI), in which the adrenal cortex fails to produce enough glucocorticoids and/or mineralocorticoids.
2) Secondary Adrenal Insufficiency (SAI), which is due to a hypothalamic or pituitary dysfunction that leads to ACTH deficiency.
3) Tertiary Adrenal Insufficiency (TAI), which is caused by an HPA axis dysfunction, primarily due to the administration of large doses of exogenous steroids over a prolonged period.

Primary Adrenal Insufficiency

Most cases of PAI are the result of gradual destruction of all three layers of the adrenal cortex. In around 80% of cases of PAI, there is autoimmune adrenal gland destruction (16). Less commonly, the cause is a defective enzyme in the cortisol biosynthesis pathway (16). More precisely, Addison disease is the most common cause of PAI in adults in industrialized countries, while in children the number one cause of PAI is CAH, specifically caused by 21-alpha hydroxylase deficiency (17). Autoimmunity falls just behind CAH, being the second most common cause of PAI in children in industrialized countries (17).

The hypothalamic-pituitary-adrenal (HPA) axis's main end-product is cortisol, while it secondarily produces adrenal androgens as well (16). Cortisol is secreted both in a circadian fashion and has an ultradian rhythm (16). As part of its circadian rhythm, cortisol has an anticipatory awakening rise peaking 20 minutes after awakening, and a nadir at around 11pm, the former helping us face the day's challenges and the latter associated with rest (16). The ultradian rhythm of cortisol secretion is much more complex and associated with discreet ACTH and cortisol secretory pulses approximately every 90 min with peak amplitudes in the early morning hours (16). Practically, the circadian rhythm is made up of different, multiple ultradian rhythms that vary in magnitude (18). This is true for both the circadian and ultradian secretion of cortisol (18). Data supports the importance of the ultradian rhythm of ACTH and cortisol secretion, due to its observed effects on gene expression (18). This hormonal rhythmicity has a transcriptional effect, which allows tissue specific effects of the ultradian rhythm in the brain, the immune system, and the liver,

among other tissues (16). Abnormalities of this system have been associated with obesity, atopic/allergic diseases, autoimmunity, depression, atherosclerosis and cardiovascular diseases (16). All the above clearly demonstrate the need for a cortisol replacement therapy that mimics the anticipatory morning rise, as well as the natural ultradian rhythmicity (16).

The development of cortisol's circadian rhythm starts at 6-12 months of life and is stabilized at 3 years of age (19). This makes confirming the diagnosis of AI with laboratory evidence challenging before the age of 3, while the clinical presentation of adrenal insufficiency can range from insidious, non-specific symptoms to circulatory collapse (19). In addition to the above, neonates have low physiological levels of steroids, as well as endogenous compounds causing assay interference (19). We should always keep in mind whether the infant in question is preterm or not, as preterm infants have a functional deficiency of some adrenal steroidogenic enzymes (19).

Clinical manifestations of PAI appear when the loss of the adrenocortical tissue of the combined glands is greater than 90%. In the initial phase of chronic gradual destruction, adrenal reserve is decreased, and although the basal steroid secretion is normal, the secretion in response to stress is suboptimal, resulting in inadequate GCs, MCs and androgen production, leading to partial AI; this is manifested by an inadequate cortisol response during stress. Any major or even minor stressor can precipitate an acute adrenal crisis, followed by complete AI, since with further loss of adrenocortical tissue, even basal steroid secretion is decreased, leading to the clinical manifestations of the disease. Adrenal hemorrhage or infarction may lead to adrenal crisis, a medical emergency manifesting as hypotension and acute circulatory failure crisis due to MCs deficiency when the appropriate doses of GCs are not met to cover MCs requirements. On the other hand, GCs deficiency may also contribute to hypotension by decreasing vascular responsiveness to angiotensin II, norepinephrine/noradrenaline, and other vasoconstrictive hormones, reducing the synthesis of renin substrate, and increasing the production and effects of prostacyclin and other vasodilatory hormones. Combined GCs and MCs deficiency leads to increased urinary sodium loss and hypovolemia resulting in hypotension and electrolyte imbalance including hyponatremia and hyperkalemia. 'Inappropriate' anti-diuretic hormone (ADH) release and action on the renal tubule due to GCs deficiency contributes to the hyponatremia, although it could be argued that this attempt at volume maintenance is far from inappropriate. Low plasma cortisol concentrations reduce GCs negative feedback, which in turn increases the production and secretion of ACTH and other POMC-peptides. These mechanisms are responsible for the well-recognized hyperpigmentation by acting on the melanocortin-1 receptor (MC1R) in the skin.

Hyperpigmentation of pressure points (like axillae, palmar creases, nipples, etc.) and sun exposed areas has always been considered a basic feature of Addison's disease. This is primarily due to the stimulation of the MC1R in the skin by ACTH directly, as it has been established there is an overproduction of ACTH in PAI.

Central Adrenal Insufficiency

Conversely, ACTH deficiency in central AI leads to decreased secretion of cortisol and adrenal androgens, while MCs production remains normal, as MCs are principally regulated by the RAAS. In the early stages, basal ACTH secretion is normal, while its stress-induced release is impaired. With further loss, there is atrophy of zonae fasciculata and reticularis of the adrenal cortex. Therefore, basal cortisol secretion is decreased but aldosterone secretion by the zona glomerulosa is preserved. However, hypotension in central AI can still occur due to decreased vascular tone because of reduced vascular responsiveness to angiotensin II and noradrenaline.

Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

In critical illness, the body increases the activity of the HPA axis to ensure the cortisol it needs to adapt to stress, suppress inflammation, and maintain cardiovascular stability (19). During Critical Illness-related Corticosteroid Insufficiency (CIRCI) glucocorticoid secretion is inadequate for the level of stress present in the organism (19). Some explanations for this event are the decrease in number and affinity of glucocorticoid receptors, the decrease in tissue sensitivity to glucocorticoids due to inflammatory cytokine presence, and last but not least because of changes in the metabolic clearance of cortisol (19). This is probably equivalent to secondary adrenal insufficiency (19). In practice, blood work of patients with CIRCI may reveal levels of corticosteroids that are considered normal, but inadequate for the critical illness circumstances present. For example, organ hypoperfusion and subsequent failure, are feared outcomes in critically ill patients with sepsis or shock, which can be exacerbated by the inadequacy of cortisol which renders vessels less responsive to catecholamines and other vasoconstrictive hormones,

It is noteworthy that in the state of critical illness there is loss of the diurnal variation of cortisol, due to changes in HPA axis activation (19). Serum cortisol levels increase to 40-50mcg/dL (19). The HPA axis activation has been linked to decreased cortisol clearance by reducing the enzymes of cortisol metabolism, to increased affinity of glucocorticoid receptor to cortisol, and to increased conversion of cortisol precursors to cortisol in the periphery (19). Cortisol synthesis can be regulated by factors other than ACTH. In critical illness cortisol synthesis is boosted by inflammatory cytokines, such as IL-6 (19). Many factors can also disrupt the HPA axis, such as trauma, drugs, and central nervous system suppression. Peripheral tissues may exhibit cortisol resistance as well, which is at least partially due to the increased expression of the beta-isoform of the glucocorticoid receptor (hGR-β), which has been associated with glucocorticoid resistance (19).

Critically ill patients can either have absolute or partial adrenal insufficiency. Only up to 3% have absolute adrenal insufficiency (19).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Table 2. Etiology of Primary Adrenal Insufficiency (20-26)	
Autoimmune	Sporadic: not associated with other autoimmune disorders APS type 1or autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED): Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism, dental enamel hypoplasia, pernicious anemia, alopecia, primary gonadal failure APS type 2 or Schmidt's syndrome: Addison's disease, autoimmune thyroid disease, primary gonadal failure, type 1 diabetes, celiac disease, pernicious anemia, myasthenia gravis, vitiligo APS type 4: Addison's disease with other autoimmune diseases excluding autoimmune thyroid disease and type 1 diabetes
Infections	Tuberculosis Fungal infections: histoplasmosis, cryptococcosis, candidiasis, African trypanosomiasis, paracoccidioidomycosis (South America) Syphilis

	Cytomegalovirus, HIV (up to 5% of patients with AIDS)
Metastases	From lung, breast, kidney, colon cancers, melanoma, lymphoma
Infiltrations	Sarcoidosis Amyloidosis Hemochromatosis
Intra-adrenal hemorrhage	Drugs: anticoagulant, tyrosine kinase inhibitor Trauma Waterhouse-Friderichsen syndrome: mostly associated with meningococcal septicemia
Infarction	Anti-phospholipid syndrome
Hematological disorders	Lymphoma
Adrenoleukodystrophy (*ABCD1* and *ABCD2* gene mutations): X-linked disorder of very long chain fatty acid (VLCFA) metabolism, presents in childhood, may progress to severe spinal cord problems, adrenomyeloneuropathy (AMN), and cerebral demyelination causing dementia.	
Kearns-Sayre syndrome (mitochondrial DNA deletions): progressive external ophthalmoplegia, bilateral pigmentary retinopathy, cardiac conductions, CNS dysfunction, endocrine abnormalities (Addison's disease, hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus)	
Wolman's disease (LIPA gene mutations): inherited disorder of lysosomal enzyme, presented with abdominal distension from accumulation of foamy lipid droplet in various organs, along with adrenal calcification and malabsorption.	
Congenital adrenal hyperplasia (CAH)	Autosomal recessive disorders of enzyme deficiency in adrenal steroidogenesis pathway, which can have various manifestations depending on their subtype and severity. Hence, this disease may be diagnosed in older individuals. 21-Hydroxylase deficiency (*CYP21A2* gene mutation): the most common type, may be presented with salt wasting form in infancy, or simple virilizing form in later life if neonatal screening is not performed 11β-hydroxylase deficiency (*CYP11B1* gene mutation): hyperandrogenism with hypertension in older children and adults 3β-hydroxysteroid dehydrogenase 2 deficiency (*CYP3B2* gene mutation): neonatal wasting, ambiguous genitalia in boys, hyperandrogenism in girls P450 oxidoreductase deficiency (*POR* gene mutation): abnormal genitalia with or without skeletal malformations, and with or without maternal virilization P450 side-chain cleavage deficiency (*CYP11A1* mutations): may be presented with neonatal salt wasting with 46, XY under-androgenization, or later onset of PAI and ambiguous genitalia Congenital lipoid adrenal hyperplasia (*StAR* gene mutations): may be presented with varied severity of PAI and 46, XY DSD
Congenital adrenal hypoplasia	X-linked form (*NR0B1* mutations or deletion): variable manifestations, hypogonadotropic hypogonadism, impaired spermatogenesis, hypoaldosteronism, shock

	Xp21 contiguous gene syndrome (deletion of *NR0B1*, glycerol kinase and genes for Duchenne muscular deficiency): with psychomotor retardation, hepatic iron deposition SF-1 linked (*NR5A1* mutations or deletions): range from isolated adrenal failure to isolated gonadal failure, XY sex reversal, 46, XX DSD, gonadoblastoma, gonadal insufficiency IMAGe syndrome (*CDKN1C* pathogenic variant): Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital abnormalities in males MIRAGE syndrome (*SAMD9* pathogenic variant): Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy) Familial steroid-resistant nephrotic syndrome with AI (*SGPL1*mutations)
Inherited unresponsiveness to ACTH syndromes	Familial glucocorticoid deficiency (FGD): autosomal recessive cause of childhood onset AI, hyperpigmentation, hypoglycemia with normal MCs activity. Type 1 variant (*MC2R* gene mutations) Type 2 variant (*MRAP* gene mutations) Other variants (*MCM4, NNT, TXNRD2, GPX1, PRDX3*, partial mutation of *StAR* and *CYP11A1*) Triple A or Allgrove syndrome (*AAAS* gene mutations): Addison's disease, Achalasia, Alacrima, along with neurodegenerative change with or without mental retardation
Iatrogenic	Bilateral adrenalectomy
Drugs	Inhibition of steroidogenesis: ketoconazole, fluconazole, etomidate, aminoglutethimide, suramin Acceleration of cortisol metabolism: phenytoin, phenobarbital, thyroxine, rifampicin, St John's Wort (*Hypericum perforatum*) Promotion of adrenolytic activity: mitotane Enhancement of autoimmunity: CTLA-4 inhibitors

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; APS, autoimmune polyglandular syndrome; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DSD, disorders of sexual development; GCs, glucocorticoids; GH, growth hormone; HPA, hypothalamic-pituitary-adrenal; MCs, mineralocorticoids; PAI, primary AI; POMC, pro-opiomelanocortin; TSH, thyrotropin stimulating hormone.

Table 3. Etiology of Central Adrenal Insufficiency (27,28)	
Pituitary, parasellar and hypothalamic masses	Pituitary adenomas, rarely carcinomas Parasellar lesions: cysts, craniopharyngioma Non-adenomatous neoplasms: meningioma, chordoma, glioma, germinoma, pituicytoma Metastases: breast, lung, prostate, colon, lymphoma
Infections	Pituitary abscess: Gram-positive cocci Tuberculosis Syphilis, leptospirosis

	Fungal infections: candidiasis, aspergillosis Herpes/Varicella infection, SARS-CoV-2 virus
Infiltrations	Hypophysitis: lymphocytic, granulomatous, xanthomatous, necrotizing, IgG4-related, immunotherapy-induced, other autoimmune-associated Hemochromatosis Sarcoidosis Histiocytosis X Wegener's granulomatosis
Hemorrhage	Pituitary apoplexy
Infarction	Sheehan's syndrome
Iatrogenic	Pituitary surgery Pituitary irradiation
Drugs	Steroid Mifepristone: impaired GCs signal transduction Somatostatin analogues Opiates Antipsychotics and antidepressants
Trauma	Traumatic brain injury
Transcription factor mutations	Hereditary ACTH deficiency can manifest as an isolated pituitary defect or as a combination of pituitary hormone deficiencies. HESX1: panhypopituitarism, cognitive change, septo-optic dysplasia OTX2: panhypopituitarism, neonatal hypoglycemia, pituitary hypoplasia, ectopic posterior pituitary LHX4: panhypopituitarism PROP1: panhypopituitarism SOX3: panhypopituitarism, infundibular hypoplasia, mental retardation TBX19: isolated ACTH deficiency
POMC and related processing	POMC gene mutations: AI, severe early-onset obesity, hyperphagia, red hair, pale skin PC1 mutations: AI, abnormal glucose metabolism, early-onset obesity, hypogonadotropic hypogonadism, neonatal-onset persistent malabsorptive diarrhea
Prader-Willi syndrome: hypotonia, failure to thrive, obesity, multiple endocrine abnormalities (GH deficiency, central hypothyroidism, hypogonadotropic hypogonadism, central AI)	
Familial corticosteroid binding-globulin deficiency: unexplained fatigue, hypotension	
Idiopathic hypopituitarism	

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; APS, autoimmune polyglandular syndrome; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DSD, disorders of sexual development; GCs, glucocorticoids; GH, growth hormone; HPA, hypothalamic-pituitary-adrenal; MCs, mineralocorticoids; PAI, primary AI; POMC, pro-opiomelanocortin; TSH, thyrotropin stimulating hormone.

When an adrenal crisis is present, there is no need for immediate investigation to confirm AI, but treatment should be initiated without delay as soon as clinically suspected. A study revealed that among patients aged between 20 and 29 years, adrenal crises caused an admission rate of 8.3/million/year (29). Clinical suspicion could be the case of a cancer patient under treatment with immunotherapy, particularly with the anti-CTLA-4 agent ipilimumab and signs and/or symptoms suspicious for AI, where the differential diagnosis of the rare metastatic involvement of adrenal or pituitary gland has to be also considered (30,31). Moreover, several immune checkpoint inhibitors, such as ipilimumab, pembrolizumab, etc, lead to endocrine toxicities in 25%-50% of patients, ranging from mild asymptomatic thyroid dysfunction to a fatal adrenal crisis (32). Of course, clinical suspicion should be high in patients with known adrenal insufficiency, as adrenal crises are often a major cause of hospitalization in these patients. An Australian retrospective study showed that adrenal crises were responsible for up to 38.9% of acute medical admissions in adult patients with PAI aged between 20 and 29 years (33). In any case, confirmatory testing should be deferred until the patient has been stabilized; however, a blood sample taken at this time for cortisol and ACTH levels is extremely helpful for later assessment. In cases of insidious presentation, clinical suspicion of AI should be followed by diagnostic dynamic tests to confirm the inappropriately low cortisol secretion and whether cortisol deficiency is dependent or independent of ACTH deficiency by measuring ACTH levels (Table 4). In PAI, cortisol deficiency results in decreased feedback to the HPA axis, leading to increased secretion of ACTH to stimulate the adrenal cortex. Simultaneously, MCs deficiency causes increased release of renin by the juxtaglomerular apparatus of the kidneys.

In a non-acute setting, the diagnosis should be suspected based on the patient's history and physical examination along with low morning cortisol levels and confirmed by an ACTH stimulation test. The index of clinical suspicion should be high for PAI in patients with one or more of the following signs and symptoms: volume depletion, hyponatremia, hypotension, hyperkalemia, fever, abdominal discomfort, hyperpigmentation, or hypoglycemia (especially in children), that have no other clinical explanation (32,34). The same goes for patients who present with unexplained hyperpigmentation (34). This can be challenging to see in patients with naturally dark skin; thus physicians should ask the patients if they have observed changes in their skin color and assess the mucosa and possibly surgical scars (34). Basal morning cortisol levels lower than 3μg/dL suggest ACTH deficiency (34). Conversely, morning cortisol higher than 15μg/dL indicates sufficient ACTH reserve. However, random cortisol levels are not advised for the diagnosis of AI. Additional tests are required to establish the diagnosis of AI if the cortisol levels are in the range of these cut-offs. Based on the pathophysiology, different dynamic tests have been proposed to diagnose this condition. Typically, low basal morning cortisol levels confirmed with low stimulated cortisol levels are all that is necessary to make the diagnosis (17, 32).

The classic short *Synacthen* test (SST; 250μg of ACTH [1-24], i.m. or i.v.) is considered the standard diagnostic method to detect AI, with a sensitivity of 92% (95% confidence interval, 81–97%) for the diagnosis of AI (35). On the other hand, no statistically significant difference was found between low-dose and high-dose ACTH stimulation tests (36,37). Low levels for age and sex of dehydroepiandrosterone sulphate (DHEAS) concentration (or less frequently, dehydroepiandrosterone, DHEA) represents an additional marker to increase the level of suspicion of PAI, but it is not *per se* diagnostic (32). A CRH test may also be used, but is less common and has limited availability, while a prolonged ACTH stimulation test is rarely required other than to distinguish secondary or tertiary deficiency (Table 4).

The insulin-induced hypoglycemia or insulin tolerance test (ITT), also previously known as the gold standard test, is performed by injecting 0.1 or 0.15u/kg of short-acting insulin intravenously after overnight fast, followed by serial measurements of venous glucose and cortisol over 2 hours (38). Importantly, this procedure must only be used if there is adequate supervision and experience. However, the ITT is beneficial in assessing growth hormone (GH) response simultaneously in patients with suspected co-existing deficiency in secondary AI, in which GH may not exceed 3-5μg/dL. It must be emphasized that all normative values quoted are assay-dependent, and using immunoassays or liquid chromatography with tandem mass spectrometry (LC-MS/MS) may result in a lower cut-off than the historic value of 18μg/dL derived from polyclonal antibody assay (39). Further investigations such as imaging studies, auto-antibodies, or microbiological screening should be arranged accordingly to identify the underlying cause of AI.

The glucagon stimulation test is a safe alternative to ITT (38). Glucagon is subcutaneously administered at 0.03mg/kg (maximum 1mg) and, subsequently, serum cortisol and glucose levels are measured at 60, 90, 120, 150 and 180 minutes (38). It is believed that glucagon induced cortisol secretion stems from the initial blood glucose rise that leads to endogenous insulin secretion that is followed by a counter response made up by growth hormone and cortisol secretion (38). The peak cortisol levels are similar to those generated in ITT, but glucagon stimulation test is characterized by a higher percentage of false positives (23.7%) in children (38). It should be noted that a lower peak cortisol cutoff has been suggested in adults (38).

Table 4. Diagnostic Tests Used to Diagnose and Differentiate AI (17, 38, 40-54)

Test/ procedure	Interpretation of the result/ comments	Cortisol physiologic response
Adrenal testing		
Morning serum cortisol levels at 8-9am in combination with plasma ACTH	8-9am cortisol levels<3μg/dL (80nmol/L) suggest AI (40). In recent onset central AI within 4-6 weeks or severe stress such as sepsis, a 'normal' level may still indicate AI. ACTH levels >300ng/L (66pmol/L) or > 2-fold the ULN confirms PAI.	Cortisol levels>14.5μg/dL (400nmol/L) indicates normal HPA axis(27). Serum cortisol concetration≥18ug/dL virtually rules out AI (38). Morning cortisol levels in early postoperative pituitary surgery higher than 10μg/dL (275nmol/L) are a predictor of corticotroph reserve(42, 43).
SST or cosyntropin test or ACTH test; sampling at 8-9am for cortisol and ACTH level following by 250μg Synacthen for adults, children ≥ 2y of age (15μg/ kg for infants, 125μg for children <2y of age) ACTH i.v. or i.m.;	Peak cortisol levels < 18μg/dL indicate AI (depending on assay) (40). Indicated when morning cortisol levels 3-15μg/dL. Recent-onset central AI may produce a normal response. SST can be performed at any time of the day but testing for cortisol levels	Peak cortisol levels> 18μg/dL (430-500nmol/L)at 30 or 60 minutes (depending on assay). Pregnancy: higher diagnostic cortisol cut-offs of 25μg/dL (700 nmol/L), 29μg/dL (800 nmol/L), and 32μg/dL (900nmol/L) for the first, second, and third trimesters, respectively (44).

collect samples at 0, 30 and 60 min for cortisol levels.	should be collected at least 18–24 h after the last HC dose or longer for GCs.	
Low-dose SST; 1μg ACTH i.v.; collect samples at 0, 30min for cortisol levels (45).	Peak cortisol levels < 18μg/dL indicate AI (depending on assay). Indicated when suspected recent-onset central AI or a shortage of Synacthen itself. Insufficient response to low-dose SST should be considered for other dynamic tests.	Peak cortisol level >18μg/dL (500nmol/L)
Pituitary testing		
CRH stimulation test;1μg/kg or 100μg ovine or human CRHi.v.; collect samples at -5, -1, 0, 15, 30, 60, 90, and 120minfor cortisol and ACTH levels (46).	Central AI demonstrates low ACTH levels that do not respond to CRH. PAI shows high ACTH levels that rise after administration of CRH. Limited use due to wide variation of responses.	Peak ACTH response should be 2-4 folds above baseline at 15 or 30 min. Peak cortisol level > 20μg/dL between 30 and 60 min or incremental cortisol > 10μg/dL above baseline(47).
Prolonged ACTH stimulation test; (A) 8-h protocol - 1mg depot Synacthen i.m. or 250μg cosyntropin i.v. infusion over 8h; collect serum samples hourly for cortisol and additional samples at 0, 1, 7, 8h for plasma ACTH levels. (B)24-h protocol - cosyntropin 250μg i.v. infusion over 24h on 2 or 3 consecutive days; take blood sample for 9am cortisol and ACTH level; then blood sample for serum cortisol levels at 30min, 60min, 120min, 4h, 8h, 12h and 24h.	Central AI illustrates a delayed response and typically has a much greater value at 24 and 48 hours than at 4 hours. PAI shows no response at either time. Useful in differentiating primary from central AI when ACTH level is equivocal Helpful in detecting more subtle degrees of AI than standard SST.	A: serum cortisol levels > 20μg/dL (550nmol/L) at 30min, 60min; 25μg/dL (695nmol/L) at 6-8h after initiation of infusion(34,35). B:serum cortisol levels at 4h >36μg/dL (1000nmol/L) with no further increase beyond this time (50).
Hypothalamic testing		
ITT; insulin 0.1-0.15 U/kg i.v. is administrated after overnight to achieve symptomatic	AI is confirmed when a fall of glucose to less than 40mg/dL with a corresponding inability to demonstrate a cortisol response	Peak cortisol levels >18μg/dL (500nmol/L).

hypoglycemia and blood glucose level lower than 40mg/dL (<2.2mmol/L); collect blood samples at -15, 0, 15, 30, 45, 60, 90 and 120min for glucose, cortisol, ACTH. Repeat insulin dose if blood glucose does not fall to level of less than 40mg/dL at 45 min	higher than 18μg/dL (37). *Contraindications* in patients with basal cortisol < 3μg/dL, untreated hypothyroidism, electrocardiographic evidence or history of ischemic heart disease, or seizure. Useful in diagnosis of coexisting GH deficiency.	
Overnight metyrapone test; 30mg/kg (max 3g) metyrapone is given at midnight; serum cortisol, 11-deoxycortisol, and ACTH levels are measured at 8am the following day.	Alternative test when ITT is contraindicated. Test is valid only when cortisol levels fall to lower than 10μg/dL.	Peak ACTH response >200ng/L 11-deoxycortisol level >7mg/dL Sum of cortisol and 11-deoxycortisol should exceed 16.5μg/dL(52).

17-OHCS, 17-hydroxycorticosteroids; ACTH, adrenocorticophic hormone; AI, adrenal insufficiency; CBG, cortisol-binding globulin; CRH, corticotrophin releasing hormone; HC, hydrocortisone; h-CRH, human CRH; GCs, glucocorticoids; GH, growth hormone; i.m., intramuscular; ITT, insulin tolerance test; i.v., intravenous; MCs, mineralocorticoids; PAI, primary AI; SST, short Synacthen test; ULN, upper limit of normal.

The notion of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) emerged to describe impairment of the HPA axis during critical illness that is characterized by the dysregulated systemic inflammation caused by the inadequate intracellular GC-mediated anti-inflammatory activity. The Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) have updated the guideline for the diagnosis and management of CIRCI, which was originally proposed in 2008 (55). The task force makes no recommendation on whether to use delta cortisol after SST or random plasma cortisol levels of less than 10μg/dL to diagnose CIRCI. However, some cohort studies found that patients with CIRCI had poorer outcomes than patients without CIRCI when total cortisol levels are less than 10μg/dL or delta cortisol after SST < 9μg/dL. This evidence may be helpful in deciding upon replacement treatment when CIRCI is suspected(Table 5) (56, 57).Other diagnostic tests, such as salivary cortisol or serum ACTH, are not recommended to diagnose this condition. Additionally, markers of inflammation and coagulation, morbidity, length of intensive care unit (ICU) stay, and mortality should be taken into consideration. Nevertheless, this whole concept has been questioned, especially since cortisol-binding globulin and albumin are invariably decreased in severe critical illness, implying that simple measurement of total cortisol is likely to be an inaccurate reflection of the true state of the HPA axis. However, the guideline cautions against using plasma free cortisol levels rather than plasma total cortisol levels to diagnose CIRCI. Most recent evidence suggests that CIRCI is not a useful diagnostic or therapeutic description, and that during the acute phase of the response to severe sepsis there is no failure of the HPA axis and no need for corticosteroid therapy, although in the recovery phase this may become important. In 2024, SCCM alone provided a revision of the guidelines concerning CIRCI, which

was focused on the management of septic shock and community acquired bacterial pneumonia that required hospitalization and Acute Respiratory Distress Syndrome.

Table 5. Tests Used in Adrenal Insufficiency in Critical Illness (but see text above)	
Test	**Indicators for poorer outcome**
Cortisol	Random levels < 10μg/dL (275nmol/L)
SST	Delta peak/basal levels< 9μg/dL (250nmol/L)

SST: short Synacthen test

In the context of the different diseases associated with AI, additional investigations may be necessary (Table 6). CT scanning of adrenals should be performed to identify infectious diseases such as tuberculosis, tumors, or adrenal hemorrhage.

Table 6. Additional Studies Used in Patients with AI	
Primary AI	
Specific tests for autoimmune antibodies	Autoantibodies against CYP21A2 for the vast majority of autoimmune PAI cases. Other antibodies against 17-hydroxylase and side-chain-cleavage enzyme are also identified. It should be note that tests for autoantibodies are not standardized.
Other autoimmune markers and hormonal assays for evidence of APS	Autoantibodies against IFNα and IFNω for APS-1. Serum calcium and PTH for hypoparathyroidism. Autoantibodies for autoimmune thyroid disease and thyroid function test. Autoimmune for insulin, GAD65, ICA, and ZnT8 along with blood glucose for autoimmune diabetes. Antibody against parietal cells with or without intrinsic factor antibody for pernicious anemia. Antibodies to tissue transglutaminase and anti-endomysial IgA antibody for celiac disease. Liver function along with ANA, SMA, and anti-LKM1 antibodies for autoimmune hepatitis in those with abnormal liver biochemical tests.
Microbial and serological tests	Tuberculosis (tuberculin testing, early morning urine samples cultured for *Mycobacterium tuberculosis*). Other infective cause.
CT / MRI scan	Calcified adrenals can be found in infection, hemorrhage, and malignancy. Large adrenals with or without calcification can be seen in metastatic deposits and early phase of infection. Small atrophic glands with calcified foci are commonly illustrated in the chronic stage of infection.

	Adrenal hemorrhage shrinks and attenuates gradually on CT and has a variable appearance on MRI depending on the stage of blood products. Adrenal venous thrombosis, in turn raises internal pressure, resulting in the same hemorrhagic finding.
Chest radiograph	Clue for pulmonary manifestation of tuberculosis or fungal infection.
CT guided adrenal biopsy	Useful in confirming the diagnosis of adrenal metastasis from extra-adrenal malignancy or certain infiltrations such as histoplasmosis.
Adrenoleukodystrophy	Circulating levels of VLCFA.
17-OH progesterone and 24-hour urine steroid profile	Classic CAH.
Secondary AI	
Pituitary hormonal assessment	Pituitary hormone producing tumor or co-existing pituitary hormone deficiency.
Pituitary MRI scans	Pituitary or parasellarlesion.
Biopsy of pituitary	Occasionally necessary such as hypophysitis.
Other Investigations	
Measurement of plasma renin and aldosterone in PAI to determine MCs reserve	High renin levels in combination with an inappropriately normal or low aldosterone concentration suggests PAI. In early phase of evolving PAI, MCs deficiency may predominate and may be the only sign.
Measurement of serum DHEAS	Decreased DHEAS levels in women in both PAI (direct effect on adrenal cortex) and central AI (decrease in ACTH stimulus).

AI, adrenal insufficiency;ANA, antinuclear antibodies; anti-LKM, anti-liver microsomal; APS, autoimmune polyglandular syndrome; CAH, congenital adrenal hyperplasia; CT, computerized tomography; DHEAS, dehydroepiandrosterone sulphate; MRI, magnetic resonance imaging; SMA, anti-smooth muscle antibodies; VLCFA, very long-chain fatty acids.

As previously stated, laboratory tests should be interpreted with caution in specific situations, such as those affecting CBG (Corticosteroid-Binding Globulin) concentration. Low CBG levels are commonly found in conditions characterized by inflammation, nephrotic syndrome, liver disease, the immediate postoperative period or requiring intensive care, or rare genetic disorders, whereas estrogen, pregnancy and mitotane can raise CBG levels. Systemic estrogen-containing drug prescriptions should be discontinued at least four weeks prior to testing. However, using an estrogen patch has no effect on CBG levels. Different diagnostic criteria should be considered according to the cortisol assay. If patients are currently on GCs replacement, omitting the steroid dose before testing is advised. The evening and morning dose of HC or prednisolone should be omitted, whereas the duration of drug withdrawal in patients taking other synthetic GCs may be longer. In pregnancy, higher diagnostic cortisol cut-offs of 25µg/dL (700nmol/L), 29µg/dL (800nmol/L), and 32µg/dL (900nmol/L) should be considered for the first, second, and third trimesters, respectively (44). In pituitary diseases, testing of GCs reserve is suggested before and after initiation of GH replacement or upon

documentation of an unexplained improvement in co-existing diabetes insipidus (DI).

THERAPY

Acute Adrenal Insufficiency (Adrenal Crisis)

Adrenal insufficiency is a potentially life-threatening medical emergency when presented as an adrenal crisis, which requires prompt treatment with HC and fluid replacement. When clinical suspicion exists, treatment should be initiated without any delay while awaiting definitive proof of diagnosis. Blood samples should be obtained for later cortisol concentration measurements, and the management approach should be like that of any critically ill patient (Table 7, 8).

Table 7. Treatment of Acute Adrenal Insufficiency (Adrenal Crisis) - Management during Resuscitation of Critically Ill Patients.

Maintain airway and breathing.	Correct hypovolemia and reverse electrolyte abnormalities; caution should be taken in correcting chronic hyponatremia (not more than 12mmol in 24h, preferably < 8mmol) to prevent central pontine myelinolysis. Replace glucocorticoid; clinical improvement especially blood pressure should be seen within 4-6h. The half-life of HC is 90min after i.v. injection, and more prolonged after i.m. administration; switch to oral HC 40mg in the morning and 20mg in the afternoon if oral intake is resumed (offer at least 40mg daily divided into 2-4 doses); taper to a standard dose of 10-20mg on awakening and 5-10mg in the early afternoon if there is no other major illness. Some experts recommend dexamethasone while dynamic tests are awaited, as dexamethasone does not interfere with the assay, but HC is preferred for its MCs activity. Regarding the electrolyte imbalances, no need for fludrocortisone replacement in an acute crisis since the MCs activity of HC and 0.9% NaCl infusion is sufficient.
Establish i.v. access with two large bore cannulas.	
Collect venous blood samples for urea and electrolytes, glucose, full blood count, bicarbonate, infection screen, and store samples (plasma cortisol and ACTH measurement). Do not wait for blood results.	
Rapid infusion of 1L isotonic saline solution (0.9% NaCl) within the 1st hour, followed by continuous i.v. isotonic saline solution guided by individual patient needs; usually infuse 2-3L of normal saline solution within 12 hours; after this, fluid management should be guided by volume status, urine output and biochemical results; 50g/L (5%) dextrose in saline solution if there is evidence of hypoglycemia.	
Inject i.v.100mg of HC immediately (50-100mg/m^2 for children) and then followed by 200mg/day (50–100mg/m^2/d for children divided q 6h) of HC (via continuous i.v. therapy or 6-8 hourly i.v. injection) for 24h, reduce to HC 100mg/day on the following day; i.m. administration should be used if venous access is not possible; prednisolone may be used as an alternative drug if HC unavailable; dexamethasone is the least preferred and should be given only if no other glucocorticoid is available.There is no risk of overdose from hydrocortisone in an emergency situation.	
Use additional supportive measures as needed	

For hypoglycemia	Dextrose 0.5-1g/kg of dextrose or 2-4mL/kg of D25W should be infused slowly at rate of 2-3mL/min; standard initial glucose dose is 25g.
Cardiac monitoring.	
MCs replacement is not required if the HC dose exceeds 50mg/day.	

ACTH, adrenocorticotropic hormone; HC, hydrocortisone; i.m., intramuscular; i.v., intravenous; MCs, mineralocorticoid.

Table 8. Treatment of Acute Adrenal Insufficiency (Adrenal Crisis) - After Patient Stabilization
Continue i.v. 0.9% NaCl; rate may be slower and maintained for 24-48h.
Search for and treat possible infectious precipitating causes of adrenal crisis; treat any associated condition(s).
Perform SST to confirm the diagnosis.
Differential diagnosis if needed.
Taper parenteral glucocorticoids over 1-3 days, depending on precipitating illness. After the first 24 hours, HC dose can be reduced to 50mg q 6h and switched to oral HC 40mg in the morning and 20mg in the afternoon, then tapered to a standard dose of 10mg on awakening, 5mg at lunchtime and 5-10mg in the early afternoon.
In aldosterone deficiency, begin MCs replacement with fludrocortisone (100µg by mouth daily) when saline infusion ceased to prevent sodium loss, intravascular volume depletion, and hyperkaliemia. However, MCs replacement is not required if the HC dose exceeds 50mg/day.

ACTH, adrenocorticopic hormone; HC, hydrocortisone; i.m., intramuscular; i.v., intravenous; MCs, mineralocorticoids; SST, short Synacthen test.

Management of Chronic or Insidious Onset of Adrenal Insufficiency

The aim of replacement treatment in AI is to mimic the normal cortisol secretion rate, which is around 5-8mg/m^2/day (58, 59).Previously this rate was thought to be approximately 25-30mg/day of HC, but normal cortisol production rates seem to be about 8-15mg/day. Most patients can cope with less than 30mg/day (usually 15-25mg/day in divided doses) (34). Doses are usually given upon waking with a smaller dose at lunchtime and then one in late afternoon. Weight-adjusted dosing may be associated with a better safety profile. Despite the various types of cortisol replacement regimens, no head–to-head comparison data is available to advocate one over the other. Decisions regarding the form and dose of GCs replacement therapy are based on crude endpoints such as weight, well-being, and blood pressure, as well as on local availability, cost and clinical need (Table 9). Bone mineral density may be reduced on conventional doses of 30mg/day HC, highlighting the importance of aiming for effective but safe doses. Long-duration GCs can be administered once daily but may be associated with higher risk of side effects. Patients should be monitored for clinical symptoms.

Table 9. Glucocorticoid Replacement Schemes		
Drug profile		**Commonly used doses**
Immediate-release HC (Hydrocortisone)	Short acting, given in 2-3 divided doses; this biologically active GCs approximately mimics the endogenous diurnal rhythm; obese individuals may	15-25 mg or 5-8 mg/m^2/day; the highest dose in the morning on

	require more GCs replacement than lean individuals; higher frequency regimes and size-based dosing may be beneficial in individual cases; high doses in the evening may disturb sleep and alter metabolism.	awakening, the next in the early afternoon (2h after lunch) (2-dose regime) or at lunch and afternoon but not later than 4-6h before bedtime) (3-dose regime); usually 10mg upon awakening, 5mg at lunchtime and 5mg in the late afternoon.
Dual-release HC (combination of immediate-release HC in the outer-layer coat and extended-release core, Plenadren®)(60,61).	Given once daily in the morning; resulting in higher morning and lower evening cortisol levels with no overnight cortisol rise. This may be advantageous in patients with high risk of metabolic comorbidities and in patients with poor administrative compliance.	20-30mg; lower dose may be sufficient in patients with some remaining endogenous cortisol production; identical total daily dose may be given when switching and clinical response needs to be monitored due to lower bioavailability than HC.
Modified-release HC (Delayed and sustained release in multiple microcrystals with polymer sheathing, Chronocort®)(62,63, 64).	Given twice daily as a “toothbrush regime”, with 2/3 of the total daily dose before bedtime (11p.m.) and 1/3 administered in the morning (7a.m.), resulting in overnight rise with morning peak of cortisol and near physiological cortisol levels throughout the day. This is beneficial for CAH patients since it prevents the ACTH-driven excess production of adrenal androgens.	Usual dose of HC; then titrated based on symptoms and 17OHP along with androstenedione measurement. (Phase 3 study)
Cortisone acetate(65).	Short acting but longer than HC; the peak of serum cortisol level is delayed compared to HC since the oral form requires a conversion to cortisol in the liver to become active; available in oral preparation only.	20-35mg in 2-3 divided doses.
Prednisolone/prednisone	Long-acting, once-daily dose is sufficient; some may need additional 2.5mg in the evening; does not mimic diurnal rhythm of endogenous cortisol; better choice in patients with poor administrative compliance or in	3-5mg once daily on waking.

	patients with poor quality of life on HC replacement; prednisone must be processed in liver to become prednisolone which is then able to cross the cellular membrane; cross-reaction occurs in most cortisol assays.	
Dexamethasone	Inter-individual variable metabolism makes it difficult to predict the adequate dose; dose needs to be titrated if patient is on hepatic enzyme inducing medications; it is not recommended in PAI because of risk of Cushingoid side effects; concurrent fludrocortisone replacement is necessary in PAI patients.	0.25-0.75mg once daily.
Crinecerfont (66) (Corticotropin-releasing factor type 1 receptor antagonist)	It is an orally administered corticotropin-releasing factor type-1 receptor (CRF1) antagonist, that can be used in adolescents and adults with congenital adrenal hyperplasia as glucocorticoid replacement therapy.It allows glucocorticoid dose reduction to a target physiological range(≤11 mg/m2/day HCe), without increasing the rate of adrenal crises, while providing significant sustained reductions in androstenedione and 17OHP. This data for crinecerfont were provided from the phase 3 trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia (66).	8-10mg/m2/day HCe (66)
MCs replacement (Fludrocortisone)(67).	Required only in PAI; doses may need to be temporarily increased by 50-100% in hot weather or conditions that promote excessive sweating; available in oral preparation only; if parenteral action required, use DOCA if available.	50-200μg (median 100μg) once daily in the morning with starting dose at 50-100μg.
Androgen replacement (DHEA) (68, 69).	A trial of replacement can be offered to PAI women with low energy, low mood, and low libido, despite otherwise optimized GCs and MCs replacement; some evidence of	25–50mg as a single oral dose in the morning; replacement should be discontinued if no clinical

	benefit; not generally available as a prescription but obtained as a 'health food' supplement.	benefit after initial 6-month trial.

AI, adrenal insufficiency; DHEA, dehydroepiandrosterone; DOCA, deoxycorticosterone acetate; GCs, glucocorticoids; i.m., intramuscular; i.v., intravenous; HC, hydrocortisone; MCs, mineralocorticoids; PAI, primary adrenal insufficiency.

It should be noted that while HC and prednisolone are active GCs, cortisone acetate and prednisone require activation via hepatic 11β-hydroxysteroid dehydrogenase type 1 to become biologically active.

Another novel aspect in the management of chronic AI is the development of glucocorticoid formulations. A dual-release HC preparation that can be administered once daily upon awakening, Plenadren® (developed by Duocort, Viropharma, Shire Pharmaceuticals), was approved for treatment of AI in adults since 2011. Moreover, another delayed- and sustained-release preparation of HC, Chronocort®, given twice daily before bedtime and in the morning, is currently undergoing the approval process for treatment of CAH patients (Table 9). Advances in understanding of the normal cortisol circadian rhythm in the setting of endogenous clock genes, as well as its importance in controlling innate immunity, metabolism, and stress may imply that some of these GCs replacement formulas will be superior over the traditional ones in the future.The superiority of hormone therapies that mimic physiology is also supported by evidence form the PULSES trial (16).

One important aspect of the management of chronic PAI is patient and family education. Careful instructions should be given to up-titrate the daily dose in the event of intercurrent febrile illness, accident, or severe mental stress, such as an important examination (Table 10). If the patient is vomiting and cannot take medication by mouth, parenteral HC must be given urgently. Ideally, patients should wear a 'medical alert' bracelet or necklace and carry the Emergency Medical Information Card, which should provide information on the patient's diagnosis, prescribed medications and daily doses, and the physicians involved in the patient's care. Patients should also have supplies of HC for emergencies and should be educated about how and when to administer them by the subcutaneous route. Rectal suppositories of prednisolone 100 mg, enemas of prednisolone 20mg/100mL, or HC acetate enema10% have also been used, but they are clearly ineffective when diarrhea is present.

Table 10. Glucocorticoid Replacement Schemes during Illness

		Examples of commonly used schemes
During minor illness	Increase dose by 2-3 times the usual dosage for 3 days; do not change MC dose.	HC 25-75mg/twice daily per oral, then taper rapidly to maintenance dose as patient recovers (usually 1-2 days); HC 50mg/m^2/day i.m. or double/triple HC replacement doses in children.
During minor-to-moderate surgery		HC 50-100mg/day twice daily per oral or i.v., then taper rapidly to maintenance dose as patient recovers.

During major illness	Increase dose up to 10 times usual dosage with continuous infusion of HC, or equivalent dexamethasone dosage, then decrease dose by half per day, to usual maintenance dose. Half dose 2nd postoperative day, maintenance dose 3rd postoperative day.	HC 100mg i.v., followed by continuous i.v. infusion of 200mg HC in 24h, then taper rapidly by half per day regarding course of illness; alternative administration of HC 50mg iv. or i.m. q 6h may be considered.
Major surgery with general anesthesia		HC 100mg i.v. just before induction of anesthesia,followed by continuous i.v. infusion of 200mg HC in 24h (alternatively 50mg every 6h i.v. or i.m.); then taper rapidly by half each day and switch to oral regime depending on clinical state; children: HC 50mg/m^2 i.v. followed by HC 50–100mg/m^2/d divided q 6h.Weight-appropriate continuous i.v. fluids with 5% dextrose and 0.2 or 0.45% NaCl.
Uncomplicated, outpatient dental procedures under local anesthesia and most radiologic studies	No extra supplementation is required.	
Severe stress or trauma	Inject prefilled dexamethasone (4-mg) syringe.	
Moderately stressful procedures (barium enema, endoscopy, or arteriography)	Extra supplementation is required only before the procedure.	100mg i.v. dose of HC just before the procedure
Pregnancy	HC should be increased 5-10mg/day in the last trimester (20–40% from the 24th week onward) to mimic physiologic increase in free cortisol; fludrocortisone dose adjustment in response to serum sodium and potassium levels; HC is preferred over the other GCs, whereas dexamethasone is contraindicated since it is not inactivated in the placenta and can transfer to the fetus.	Last trimester: 5-10mg/day of HC usually (20–40% from the 24th week onward) Labor: HC stress dosing with HC 100mg i.v. bolus, followed by continuous i.v. infusion of 200mg HC in 24h, and rapidly taper to pre-pregnancy doses after delivery.

HC, hydrocortisone; i.m., intramuscularly; i.v., intravenously; GCs, glucocorticoids

Regarding MC replacement therapy, the dose of fludrocortisone is titrated individually based on clinical examination, mainly body weight and blood pressure, and the levels of plasma renin activity (PRA).

Hydrocortisone is generally preferred for use in patients with AI because it has both GCs and MCs activity. Patients receiving prednisone or prednisolone, on the other hand, may require additional fludrocortisone due to their relatively low MCs activity. Notably, dexamethasone should not be used to treat PAI patients because its lack of MCs activity (70).After resolution of an adrenal crisis, the adequacy of MC replacement should be assessed by measuring supine and erect blood pressure, electrolytes, and PRA. Inadequate fludrocortisone dose may cause postural hypotension with elevated PRA, whereas excessive administration results in the opposite. Mineralocorticoid replacement therapy is frequently neglected in patients with adrenal failure. The dose may be temporarily increased in the summer along with an increase in salt intake, particularly if patients are exposed to temperatures above 30ºC (85ºF) or other conditions causing increased sweating. Newborns and children may also require higher fludrocortisone because MCs sensitivity is lower.

In chronic central AI, GCs replacement is like that in PAI; however, measurement of plasma ACTH concentrations cannot be used to titrate the optimal GCs dose. Replacement of other anterior pituitary deficits may be also necessary, while changing doses of growth hormone and thyroxine may affect GCs requirement. More specifically, the HPA axis should be evaluated prior to and following the initiation of GH replacement therapy since GH inhibits the conversion of cortisone to cortisol. Consequently, patients receiving GCs replacement may require higher doses once GH treatment is introduced (27,71). Thyroid hormone accelerates the metabolism of GCs.

For patients with either primary or central AI, the beneficial effects of adrenal androgen replacement therapy with 25 to 50mg/day of DHEA have been reported. To date, the reported benefit is principally confined to female patients and includes improvement in sexual function and well-being, but the effects are variable.

In children with PAI, HC in three or four divided doses with total starting daily dose of 8-10mg/m^2 body surface area are preferred over synthetic long-acting GCs, such as prednisolone or dexamethasone. In the case of documented aldosterone deficiency, fludrocortisone treatment with a typical dosage of 100µg/day (can range from 50µg to 300µg per day) without body surface area adjustment is suggested, while sodium chloride supplements are needed in the newborn period until the age of 12 months. Most experience has been gained from the treatment of children with CAH; however, since in this case under treatment is confirmed by hyperandrogenism higher GCs therapy is usually given (34, 35).

Other therapies have been studied such as rituximab with or without depot tetracosactide in newly diagnosed autoimmune PAI patients (72). The regenerative potential of adrenocortical stem cells combined with immunomodulatory treatment to stop the autoimmune destruction, adrenal transplantation, or gene therapy in forms of monogenic PAI may be a useful option in the future.

For CIRCI with septic shock in adults, it has been “suggested” to use i.v. HC < 400mg/day for at least 3 days at full dose (rather than high-dose and short-course regimes, which are “recommended against”) when they are not responsive to fluid and moderate-to high-dose vasopressor therapy (> 0.1µg/kg/min of norepinephrine or equivalent) (73). In hospitalized adults with “severe” community-acquired bacterial pneumonia a daily dose of < 400mg i.v. HC or equivalent has been “suggested” for 5-7 days. GCs are also suggested in patients suffering from meningitis, cardiac arrest (methylprednisolone given during resuscitation or HC given for post-resuscitation shock), and cardiopulmonary bypass surgery (CPB) (250mg i.v. of methylprednisolone at anesthesia induction and at onset of CPB) or dexamethasone (1mg/kg perioperatively). Corticosteroids are not suggested for patients after major trauma or suffering from influenza. Nevertheless, it should be emphasized

that this is a rapidly changing situation, and the use of corticosteroids in the ICU with severely ill patients remains controversial. Finally, for patients with early moderate to severe Acute Respiratory Distress Syndrome (ARDS), meaning onset <14 days and Pao2/Fio2 of < 200, the use of corticosteroids has been suggested (73).

Despite concerns that patients with AI were more vulnerable to infection during the recent COVID-19 pandemic, adequately treated and well-trained AI patients demonstrated the same incidence of COVID-19-suggestive symptoms and disease severity as the people without AI.

FOLLOW-UP

Patients with chronic AI should be closely followed-up by an endocrinologist or a healthcare provider with endocrine expertise at least annually (for infants every 3 to 4 months) to ensure the adequacy of their GCs and/or MCs replacement dose (Table 11, 12), to reduce the risk of adrenal crisis, to provide necessary education to patients, and to confirm that they have a prompt updated emergency pack with HC to treat an emergency. Specifically, children and young people under 16 years should be offered an appointment every 6 months and an annual -in person- review to measure their height and weight (34). Clinical symptoms including body weight, postural blood pressure, and energy levels should be monitored in order to avoid signs of frank GCs excess and adjust accordingly the dose of steroids. The ‘mapping’ of the dose has been suggested to assess the compliance and also help decide when tablets should be taken in problematic cases of reduced quality of life where the detailed questioning for daily habits, working patterns, general feelings of energy, mental concentration, daytime somnolence, and energy dips. Hormonal monitoring of GCs replacement, such as serum or salivary cortisol ‘day-curves’is not routinelyrecommended, but can be useful in specific situations where the clinical response cannot be reliably used to adjust treatment or when malabsorption is suspected (74, 75).In addition, the use of ACTH levels to assess GCs replacement is not suggested since it leads to over-replacement.

Similarly, MCs replacement should be monitored based on clinical assessment, which includes postural hypotension as measured by lying and standing blood pressure and pulse, symptoms of salt craving, edema, and blood electrolyte measurements. Reported well-being, normal blood pressure without orthostatic hypotension, and electrolytes within the normal range indicate adequate replacement. PRA in the upper reference range has been found to be a useful predictor for a correct MCs dose (76, 77). Liquorice and grapefruit juice enhance the MC effect of HC and should be avoided. Phenytoin potentiates hepatic clearance of GCs and increases fludrocortisone metabolism; therefore, higher doses are needed when it is co-administered.

It is of note that in patients who develop hypertension while receiving fludrocortisone, the dose of fludrocortisone should be reduced, and HC replacement should be adjusted. If blood pressure remains uncontrolled, anti-hypertensive treatment should be initiated without fludrocortisone discontinuation. First-line anti-hypertensive drugs to be selected are the angiotensin II receptor blockers or angiotensin-converting enzyme blockers to counterbalance the vasoconstrictive effects of elevated angiotensin II; second-line a dihydropyridine calcium blocker, while diuretics should be avoided and aldosterone receptor blockers are contraindicated.

Since AI might mask the presence of partial DI, urine output should be monitored after starting GCs replacement, or conversely, when DI has unreasonably improved, patients have to be tested for HPA reserve. With DHEA replacement, morning serum DHEAS levels should be measured before the intake of the daily dose aiming at the mid-normal range. An annual screening for autoimmune diseases, which includes autoimmune thyroid disease, type 1 diabetes, premature ovarian failure, coeliac disease,

and autoimmune gastritis should be performed in PAI patients without other obvious cause of adrenal failure.

Special populations, like pregnant females, should be surveyed for clinical symptoms and signs of GCs over- and under-replacement including weight gain, fatigue, postural hypotension or hypertension, hyperglycemia, at least once per trimester. Only sodium and potassium can be reliably monitored in blood and urine for the adequacy of replacement. In contrast, PRA monitoring is not advised since plasma renin physiologically increases during this time.

In children, monitoring of GCs replacement includes clinical assessment such as growth velocity, body weight, blood pressure, and energy levels (78).

Although familial autoimmune PAI is less frequent, genetic counselling is suggested in particular situations due to monogenic disorders.

Table 11. Assessment of Glucocorticoid Replacement	
Under replacement	Lethargy, tiredness, nausea, poor appetite, weight loss, hyperpigmentation. Low serum cortisol level on cortisol day curve (useful in specific cases for HC or cortisone replacement only)
Over replacement	Cushingoid appearance, weight gain, insomnia, peripheral edema, low bone mineral density. High 24-h UFC, high serum cortisol on hydrocortisone day curve (useful in specific cases for HC or cortisone replacement only)

Table 12. Assessment of Mineralocorticoid Replacement	
Inadequate replacement	Postural hypotension, light-headedness High PRA (plasma renin activity, should be at the upper limit of normal)
Over replacement	Hypertension, peripheral edema, hypernatremia, hypokalemia

Patient Education

This is very crucial in the management of AI and for the prevention of adrenal crisis. All patients and their relatives should be educated about their condition and the emergency measures they should take at home to avoid crises, particularly concerning GCs adjustments in stressful events and preventive strategies including parenteral self- or lay-administration of emergency GCs particularly in situations of intercurrent illness, fever, or any type of stress. This information should be reinforced during annual follow-up visits by clinicians and if possible, through a structured patient education program. All patients should be given a steroid emergency card and medical-alert identification to inform health personnel of the need for increased GCs doses to avert or immediately treat adrenal crisis. Every patient should be equipped with a GCs injection kit for emergency use and be educated on how to use it (Table 13).

Table 13. Information and Equipment for Patients with AI
Steroid Sick Day Rules
Sick day rule 1: Patients should be advised to increase the oral GCs when the patient experiences fever or illness requiring bed rest, or when requiring antibiotics for an infection. For instance, the total oral GCs dose should be doubled (>38°C) or tripled (>39°C) for at least 72 hours; if the patient remains unwell after 72 hours, they should contact their physician. People aged 16 and older should

receive at least 40mg of hydrocortisone or at least 10mg of dexamethasone during significant physiological stress (34). There is no need to increase the MCs dose. **Sick day rule 2:** There should always be a supply of additional oral GCs for sick days and an HC emergency injection kit. **Sick day rule 3:** Every patient should carry a medical alert bracelet or leaflet with information stating their conditions, treatment, physician, emergency phone number of endocrine specialist team, and proposed GCs regimen during adrenal crisis. **Sick day rule 4:** Parenteral injection of GCs preparation, either i.m. or i.v.should be provided in case of severe illness, trauma, persistent vomiting, before moderately stressful procedure (i.e., barium enema endoscopy, arteriography), or before surgical intervention.
Steroid Emergency Pack
• Every patient should be provided with this pack to keep at home. • The pack contains a vial of 100mg HC or 4mg dexamethasone, syringes, needles, also oral HC or prednisolone suppositories. • The patient and/ or any responsible family member should be educated to administer this medication i.m. or s.c. during an emergency situation including severe accident, significant hemorrhage, fracture, unconsciousness, diarrhea and vomiting, and they should call the emergency medical personal immediately (adults, i.m. or s.c. HC 100mg; children, i.m. HC 50mg/m^2; infants, 25mg; school-age children, 50mg; adolescents, 100mg). • The expiry date on the pack should be checked regularly and replaced with a new pack if expired. • The patient should be advised to take the pack when travelling.
Medical-Alert bracelet or pendant and emergency steroid card
• Every patient should wear or carry these in which the diagnosis and daily medication should be clearly documented.
Follow up
• A regular visit in order to reinforce education and confirm understanding should be scheduled at least annually in a patient without specific problems or recent crises. Other circumstances, such as monitoring during infancy, may necessitate more frequent visits.

GCs, glucocorticoids; HC, hydrocortisone; i.m., intramuscularly; i.v., intravenously; HC, hydrocortisone; MCs, mineralocorticoids; s.c., subcutaneously

PROGNOSIS

The mortality of patients with PAI was increased in some studies and adrenal crisis was a significant cause of death, emphasizing the importance of educating patients with AI to prevent crises. Recent large cohorts confirmed the increased mortality of patients with AI, especially PAI. Although cardiovascular disease (CVD) was the leading cause of death, infectious diseases were found to pose the greatest risk in comparison to controls. Adrenal crisis was also found to be a common contributor, particularly in those with co-existing CVD. In addition, despite an adequate replacement dose, the quality of life of PAI patients remains impaired. This appears to be related to the delay in diagnosis.

ADRENAL FATIGUE: DOES IT EXIST?

Adrenal fatigue has become a popular term used to describe a group of non-specific symptoms, including tiredness, late falling asleep and/or early waking-up in the morning, generally in people who cope with chronic physical, emotional, or mental stressors (79). According to supporters of this theory, chronic stress leads to failure of the adrenal glands to respond properly to stressors through increased biosynthesis and release of cortisol. It is worth mentioning that a number of medical societies have recognized adrenal fatigue as a real disease (80) and have suggested screening people with the above-mentioned symptoms for adrenal fatigue using a questionnaire prepared by Dr. Wilson (81). However, adrenal fatigue has not been recognized by any endocrinology societies. Moreover, people with this condition are advised to measure serum basal cortisol concentrations and salivary cortisol circadian rhythm and are often treated with synthetic corticosteroids (80). It is clearly stated that scientific evidence does not exist to support adrenal fatigue as a real medical condition but rather a state that could be categorized under the Chronic Fatigue/Fibromyalgia Syndrome umbrella. A systematic review published in 2016 by Cadegiani and Kater included many studies related to adrenal fatigue. The authors found conflicting results in most of the studies and concluded that “adrenal fatigue is still a myth” (80).

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