Chapter 6

ADRENAL INSUFFICIENCY

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Data de aceite: 02/09/2024

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Adrenal insufficiency (AI) is a critical clinical condition characterized by the adrenal cortex›s inability to adequately synthesize or secrete cortisol. This disorder has a prevalence of 82 to 144 cases per million and can be classified as primary, affecting the adrenal glands directly, or secondary and tertiary, resulting from

deficiencies in the stimulation of the pituitary or hypothalamus. Primary adrenal insufficiency (PAI) results from direct adrenal gland failure due to the destruction or damage of the adrenal glands. Common causes include autoimmune adrenalitis, also known as Addison›s disease, and infections such as tuberculosis and HIV (Julie Martin Grace *et al.*, 2020). Secondary adrenal insufficiency (SAI) occurs due to diseases of the pituitary or hypothalamus, such as tumors and their therapies, hypophysitis, or granulomatous infiltration. Tertiary adrenal insufficiency (TAI) is often a consequence of prolonged administration of exogenous glucocorticoids, leading to suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Julie Martin Grace *et al.*, 2020).

Identifying the etiology of adrenal insufficiency is crucial for choosing the appropriate treatment and detecting underlying diseases such as tuberculosis, autoimmune syndromes, or pituitary tumors, which can have significant clinical implications (Lynnette K Nieman *et al.*, 2024). Despite diagnostic advances and the availability of replacement therapies, adrenal crisis (AC) remains a potentially lethal condition that contributes to increased mortality in patients with AI. Failure to administer adequate doses of glucocorticoids during periods of acute stress is one of the main causes of AC, highlighting the need for continuous education for patients and healthcare professionals (Lousada; Mendonça and Bachega, 2021).

AI is associated with increased morbidity and mortality, as well as reduced quality of life for patients, making early diagnosis and appropriate management essential to prevent acute adrenal crises, which can be fatal if not treated adequately (Lousada; Mendonça and Bachega, 2021). The prevalence and incidence of the different forms of AI vary, with Addison›s disease being the most common cause in adults and congenital adrenal hyperplasia (CAH) in children. Population studies indicate high mortality among patients with AI, especially due to adrenal crises (Stefanie *et al.*, 2021).

Adrenal events have an age-related pattern, with respiratory infections being the main trigger in childhood and gastrointestinal infections in older ages. AI has nonspecific symptoms, making early diagnosis and treatment challenging. The main clinical manifestations of an adrenal crisis include hypotension, dehydration, extreme fatigue, nausea, vomiting, abdominal pain, and hypoglycemia. Proper management of adrenal crises requires immediate therapeutic action with intravenous administration of hydrocortisone, fluid infusion, and monitored support (Stefanie *et al.*, 2021).

In recent years, there have been significant advances in understanding and managing AI. New diagnostic techniques, such as the measurement of plasma free cortisol using tandem mass spectrometry, have improved diagnostic accuracy. The introduction of innovative immunological therapies has brought additional challenges in managing adverse effects, such as adrenal insufficiency induced by immune checkpoint inhibitors. Treatment strategies continue to evolve, focusing on personalizing hormone replacement therapy and minimizing risks during intercurrent illnesses. Recent updates also highlight the importance of patient education programs, using questions to guide patients about the importance of

medication use and the use of emergency glucocorticoid injection kits, aiming to improve the early recognition of adrenal crisis symptoms and the appropriate administration of glucocorticoids in emergency situations (Lousada; Mendonça and Bachega, 2021). These trends reinforce the need for a comprehensive understanding of AI, from its physiological bases to the most advanced therapeutic approaches, with the aim of improving clinical outcomes and the quality of life of patients affected by this debilitating condition.

EPIDEMIOLOGY

Acute adrenal insufficiency is more common in patients with primary adrenal insufficiency due to the severity of hypocortisolism and lack of aldosterone. However, it can also occur in secondary adrenal insufficiency. The incidence of adrenal crisis is 5 to 10 per 100 patients per year and accounts for 15 to 40% of deaths related to adrenal insufficiency (Rushworth; Torpy, 2023).

A study found that women are more likely to be hospitalized for adrenal crisis than men (Rushworth; Torpy, 2023). An increased risk of early death has also been observed in younger patients, those under 40 years of age (Stefanie *et al.*, 2021). Primary adrenal insufficiency (PAI) is more common in women, as is adrenal crisis, and is usually diagnosed between the third and fifth decades of life, although it can manifest at any age (Chabre *et al.*, 2017). Specifically, the prevalence of PAI varies geographically, ranging from 1.4 cases per 100,000 in South Africa to 9-22 cases per 100,000 in Europe (Stefanie *et al.*, 2021).

In the 20th century, the main cause of adrenal insufficiency was tuberculosis. However, recent studies have not documented cases of AI resulting from this cause. Conversely, infections remain a leading cause of primary adrenal insufficiency in areas with high rates of tuberculosis, HIV infection, and opportunistic infections such as cytomegalovirus (Stefanie *et al.*, 2021). The increasing prevalence of primary adrenal insufficiency is associated with a rise in cases of autoimmune origin (Chabre *et al.*, 2017).

Adrenal crisis can occur in patients with undiagnosed or inadequately treated chronic adrenal insufficiency, or when corticosteroid administration is abruptly stopped. The incidence of this pathology can increase with the use of low-dose, short-duration glucocorticoids. Additionally, initiating L-thyroxine therapy in patients with thyroid disease and the development of hyperthyroidism due to Graves› disease can trigger a crisis due to faster inactivation of cortisol than in individuals without thyroid disease (Stefanie *et al.*, 2021).

Primary adrenal insufficiency is mainly caused by autoimmunity, which is the most common cause in adults. It can also be associated with factors such as tuberculosis, HIV, or fungal infections that can damage the adrenal glands. In children, congenital adrenal hyperplasia prevails, while hereditary conditions such as adrenoleukodystrophy are also relevant. Secondary adrenal insufficiency is related to prolonged use of

exogenous corticosteroids in high doses and for long periods, which can suppress ACTH (adrenocorticotropic hormone) production by the pituitary gland, being twice as prevalent as primary insufficiency. The prevalence of primary adrenal insufficiency is rare, affecting 10-20 people per 100,000 population. In industrialized countries like Iceland, the prevalence of Addison›s disease has increased from 3.9 cases per 100,000 in 1968 to 22 cases per 100,000 in 2016 (Stefanie *et al.*, 2021).

There is a clear geographical difference in the prevalence of Addison›s disease. In underdeveloped countries such as South Africa, the prevalence is 1.4 cases per 100,000 population. In contrast, in developed countries like those in Europe, the prevalence increases to 9 to 22 cases per 100,000 population. The prevalence of congenital adrenal hyperplasia varies according to the population, being approximately 0.5 to 1 person per 10,000 inhabitants (Stefanie *et al.*, 2021). Secondary adrenal insufficiency is more prevalent than primary, with 42 cases per 100,000 European inhabitants.

Adrenal crisis accounts for 15 to 40% of reported deaths from adrenal insufficiency. Each year, 5 to 10 patients per 100 population suffer adrenal crises, being more prevalent in those previously diagnosed with PAI. The mortality from adrenal crises is low, at 0.5 patients per 100 population per year. The mortality from adrenal emergencies is lower, being below 1% of cases after hospital admission (Stefanie *et al.*, 2021).

DIAGNOSIS

The identification of adrenal insufficiency (AI) involves both clinical analysis and consideration of the patient›s social and financial circumstances. In addition to facing higher risks of morbidity and mortality due to adrenal crises, these patients are subject to other medical disorders such as autoimmune syndromes, infectious conditions, and congenital deficiencies responsible for the adrenal insufficiency itself. This concern justifies the importance of early and swift diagnostic investigation (He; Findling and Auchus, 2018).

Moreover, the management of the disease depends on diagnostic clarification since adrenal insufficiency has various etiologies that differ in clinical and therapeutic approaches. Currently, the prevalence of secondary and tertiary adrenal insufficiencies is significantly higher compared to primary adrenal insufficiency (PAI), whose investigation relies on specific and dynamic methods such as clinical manipulation of the patient. This underscores the essential role of clinical and complementary analysis in managing this disease (He; Findling and Auchus, 2018).

The symptomatology of AI is quite diverse, presenting with nonspecific symptoms such as nausea, vomiting, and fatigue, mimicking other diseases, or manifesting as a catastrophic adrenal crisis, evolving with circulatory shock and coma. Therefore, a detailed medical history, medication history, high suspicion, and appropriate laboratory evaluation are of utmost importance (Shaikh *et al.*, 2023).

Furthermore, the clinical presentation helps differentiate the multiple etiologies responsible for acute adrenal insufficiency. PAI is accompanied by typical symptomatic characteristics resulting from glucocorticoid and mineralocorticoid deficiency, such as fatigue, salt craving, nausea, loss of appetite, weight loss, myalgia, and abdominal pain. In contrast, secondary (SAI) and tertiary (TAI) dysfunctions exhibit symptoms restricted to the mass effect of a hypothalamic-pituitary lesion, such as headache, visual field defects, galactorrhea, and even amenorrhea (Martin-Grace *et al*., 2020).

In AI induced by glucocorticoids, patients may present with skin pallor due to alterations in the melanocortin 1 receptor located in the skin by ACTH, leading to decreased activation (Pelewicz; Miskiewicz, 2021). Hyperpigmentation observed during physical examination is prominent in regions such as skin folds, areolas, and palmar creases, and may also involve the oral mucosa and gums (Charoensri; Auchus, 2024). In PAI, androgen deficiency in women can result in decreased body hair and reduced libido, as androgens produced by the adrenals constitute a significant portion of the total body amount in women. In contrast, in men, the primary source of androgens responsible for body hair is the testes, not the adrenals (Charoensri; Auchus, 2024).

However, the nonspecific nature of adrenal insufficiency symptoms contributes to delayed diagnostic elucidation and increases medical diagnostic errors, with about 68% of patients leaving consultations with gastrointestinal or psychiatric suppositions. For these reasons, it is determined that investigation should never delay the immediate treatment of an acute condition, which is done with the use of parenteral hydrocortisone (Martin-Grace *et al*., 2020).

Laboratory methods can be used to differentiate AI and its various etiologies. The main alterations are found through routine tests such as a complete blood count and electrolytes. In primary AI, a specific hydroelectrolytic alteration is hyperkalemia. A biochemical alteration frequently found in all types of AI is hyponatremia. This results from a physiological phenomenon due to cortisol deficiency, resulting in the inability to suppress arginine vasopressin in the hypothalamus. Thus, the kidneys› ability to excrete free water is compromised, leading to greater water retention despite decreased plasma osmolality. The lack of aldosterone also contributes to hypovolemic hyponatremia in primary adrenal insufficiency, resulting from renal loss of water and sodium, along with prerenal azotemia. Additionally, in primary and central AI, occasional laboratory analyses may show normocytic anemia, eosinophilia, lymphopenia, and hypercalcemia (Charoensri; Auchus, 2024).

If there is clinical suspicion of AI, it is extremely important to conduct diagnostic investigation. However, this should never delay the initiation of glucocorticoid treatment. Knowledge of physiology is essential for early diagnosis and understanding of screening tests. A commonly used screening method in clinical practice is the measurement of basal serum cortisol. Its secretion follows the circadian cycle, peaking between 6 am and 9 am. Therefore, a reference time interval for collection has been established, specifically between

8-9 am. External factors such as pregnancy, inflammation, and critical illnesses should be considered as they can alter the results, as 90% of cortisol is bound to CBG (Pelewicz; Miskiewicz, 2021).

If basal serum cortisol levels are below 4 μg/dL (110 nmol/L) along with plasma ACTH above the normal reference (>100 pg/mL), the diagnosis of primary adrenal insufficiency can be confirmed without dynamic tests. Conversely, diagnosing central adrenal insufficiency is more complex than primary due to the lack of dynamic tests in most published diagnostic criteria studies. Generally, when morning serum cortisol is below 4 μg/dL and plasma ACTH is below or near the lower limit of the normal range (typically <10 pg/mL), it may suggest some degree of central adrenal insufficiency (Charoensri; Auchus, 2024). However, it is important to remember that cortisol-binding globulin deficiency, glucocorticoid resistance, and hypersensitivity can affect adrenocortical function tests (Bornstein *et al.*, 2016).

Certain conditions can predispose patients to primary adrenal insufficiency, including autoimmune diseases such as type 1 diabetes, autoimmune gastritis, pernicious anemia, and vitiligo, as well as infectious diseases like tuberculosis, HIV, cytomegalovirus, candidiasis, and histoplasmosis. Additionally, inhibitors of adrenal enzymes and medications that act on the central nervous system, such as phenytoin and carbamazepine, can induce PAI by increasing cortisol metabolism. Therefore, if the patient is taking these medications, the diagnostic threshold should be kept low (Bornstein *et al.*, 2016).

Diagnostic tests for AI include the synthetic ACTH stimulation test (SST), insulin tolerance test (ITT), metyrapone stimulation test, glucagon stimulation test, and also CRH stimulation (Pelewicz; Miskiewicz, 2021). The insulin tolerance test has been considered the reference method for diagnosing forms of adrenal insufficiency, particularly when central causes are suspected, whether they stem from hypothalamic or pituitary dysfunctions, as the corticotropin stimulation test can produce falsely negative results. In this test, an intravenous bolus of insulin (0.1 IU/kg) is administered to induce severe hypoglycemia, activating a counter-regulatory response and evaluating the entire HPA axis. The lowest blood glucose level occurs between 30 to 45 minutes after insulin administration, with the criterion for central adrenal insufficiency being a peak serum cortisol level below 18 μg/dL (500 nmol/L) at 60 to 90 minutes (Charoensri; Auchus, 2024).

Despite ITT being the gold standard for secondary adrenal insufficiency, it is possible to observe risks for patients, requiring a high level of supervision and being contraindicated for those with a history of cardiovascular disease or seizures. Additionally, reference values have not been established for modern cortisol assays. Consequently, it has been less used in clinical practice (Charoensri; Auchus, 2024). Metyrapone stimulation tests, glucagon stimulation tests, and CRH stimulation are used less frequently and lack sufficient investigation, although they are useful in evaluating ACTH axis function and are highly valuable for diagnosing glucocorticoid-induced AI (Pelewicz; Miskiewicz, 2021).

The corticotropin stimulation method is used for confirming the diagnosis of PAI. Two synthetic corticotropin analogs can be used: cosyntropin (Cortrosyn, Amphastar, etc.) and tetracosactrin (Synacthen, Novartis Pharma, etc.). Both have the same dose of 250 μg administered parenterally (IV or IM). This dose is considered standard for practicality and is recommended by the Endocrine Society›s clinical practice guideline. Serum cortisol levels are measured 30-60 minutes after administration to assess the peak cortisol level. In primary AI, 30-minute dosing diagnosed 95% of cases with high accuracy. In central AI, 60-minute post-injection dosing showed better diagnostic accuracy. This method can be used in patients suspected of adrenal crisis, with morning serum cortisol <140 nmol/L and plasma ACTH >2 times the normal value or >66 pmol/L. This finding is highly predictive of PAI. In healthy individuals, a peak cortisol concentration >500 nmol/L is expected, suggesting AI in those where the peak cortisol remains <500 nmol/L (the cutoff value may vary depending on the assay used), as the zona fasciculata is already being excessively stimulated by the elevated level of endogenous ACTH. Additionally, the adrenal cortex is replaced by fibrous tissue (Younes; Bourdeau and Lacroix, 2021).

Finally, basal morning cortisol is used as a first-line investigation for SAI/TAI. Levels <3 μg/dL (83 nmol/L) indicate AI, and levels >15 μg/dL (413 nmol/L) exclude the diagnosis. Given this etiological origin, the pituitary profile type is identified by requesting laboratory tests for prolactin, LH, FSH, TSH, Free T4, estradiol, testosterone, and insulin-like growth factor (IGF-1). Simultaneous measurement of renin and aldosterone is also requested to confirm mineralocorticoid deficiency (Younes; Bourdeau and Lacroix, 2021).

After confirming primary adrenal insufficiency, anti-adrenal antibodies, including 21-hydroxylase antibodies (routinely assessed to rule out autoimmunity), screening for tuberculosis exposure in endemic areas, and cross-sectional imaging, such as MRI of the adrenal glands, are proposed to exclude infectious, hemorrhagic, and neoplastic etiologies (Shaikh et al., 2023). In some situations, standard tests may not be reliable. Patients with abnormalities in cortisol-binding globulin (CBG) or albumin, women using oral contraceptives (high CBG), or those with cirrhosis or nephrotic syndrome (low CBG) may have cortisol thresholds leading to misdiagnosis (De Miguel Novoa *et al.*, 2014).

If CBG is high, as in scenarios of oral contraceptive use or pregnancy, CBG measurement should be performed. If levels are normal, usual tests can be conducted. If CBG is elevated, morning serum cortisol should be measured (De Miguel Novoa *et al.*, 2014).

The metyrapone test is one possible alternative to ITT for evaluating HPA axis function. Metyrapone can inhibit the enzyme 11β-hydroxylase and, when administered at night, prevents the normal morning cortisol rise, increasing ACTH and steroid precursor secretion. For adequate inhibition of 11β-hydroxylase, a serum cortisol level below 5 μg/dL is required. If there is an increase in plasma 11-deoxycortisol, it may indicate an intact HPA axis. However, metyrapone has limited availability due to high cost and heterogeneity

of 11-deoxycortisol assays, restricting its widespread use. Additionally, it may precipitate an adrenal crisis in symptomatic patients (Charoensri; Auchus, 2024).

Non-invasive tests are also available, such as basal and stimulated salivary cortisol testing, which is currently being explored as an approach for diagnosing AI. Studies have shown that salivary cortisol values after cosyntropin stimulation are comparable to serum cortisol. Salivary cortisol is a highly promising test, especially in pediatrics, as it is simple, non-invasive, and easy to administer (Charoensri; Auchus, 2024).

A recent retrospective study with 370 patients in Spain highlighted the importance of considering sex-specific and test-type-specific cutoff values when interpreting the corticotropin test. This is necessary to minimize false-positive results and improve specificity. Both the corticotropin stimulation test and the metyrapone test, commonly used to diagnose central adrenal insufficiency, cannot replace the insulin tolerance test (gold standard for evaluating the HPA axis) (Younes; Bourdeau and Lacroix, 2021).

TREATMENT

The treatment of adrenal insufficiency initially involves intervention aimed at stabilizing the patient, achieving optimal management to replace adrenal hormones to mimic physiological secretion, thereby maintaining the patient›s quality of life without the adverse effects of excessive medication. Therefore, the goal in treating AI is hormone replacement, such as glucocorticoids and mineralocorticoids, correcting electrolytes, providing hemodynamic support, and managing any adverse effects (Charoensri; Auchus, 2024; De Miguel Novoa *et al.*, 2014; Nieman; Lacroix and Martin, 2012). The treatment regimen varies according to the etiology of AI; in cases of primary AI, full doses of glucocorticoids and mineralocorticoids should be replaced, whereas in central AI (secondary or tertiary), the glucocorticoid dose can be lower, without mineralocorticoids, as the patient still preserves part of the hormone secretion (Charoensri; Auchus, 2024; Bornstein *et al.*, 2016; De Miguel Novoa *et al.*, 2014; Nieman; Lacroix and Martin, 2012). Moreover, the etiology also determines the duration of treatment; primary AI requires lifelong replacement, while secondary or tertiary AI may also require lifelong treatment but is expected to be more prolonged (Kumar; Wassif, 2022).

The management of the disease also includes continuous monitoring and patient education regarding «sick day rules,» to teach them to understand the signs of AI and that glucocorticoid replacement must always be adjusted to daily needs and stressful situations, such as surgical or invasive procedures (Simpson et al., 2020). Patients should also understand that excess medication can cause signs and symptoms characteristic of Cushing›s syndrome, while a lack of hormones can be fatal (Nieman; Lacroix and Martin, 2012).

The value of random cortisol measurement is considered a good marker of hypothalamic-pituitary-adrenal (HPA) axis activity and is directly proportional to the degree

of stress. However, randomized studies have not shown a minimum plasma cortisol level below which mortality increases in critical illnesses (Hamrahian & Fleseriu, 2017). Factors affecting plasma cortisol levels in sick patients include gender, type and duration of illness, patient volume status, differences in cortisol assays, levels of corticosteroid-binding globulins (CBG), glucocorticoid (GC) polymorphisms, different activities of ACTH, CRH, and 11-hydroxysteroid dehydrogenase enzyme subtypes (Hamrahian; Fleseriu, 2017).

Additionally, in patients with vasopressor- and fluid-refractory septic shock, glucocorticoids (GCs) may be used as standard treatment regardless of serum cortisol levels, as the benefit of GC therapy for patients may not be associated with AI. The most recent consensus on severe sepsis and septic shock recommends hydrocortisone therapy regardless of serum cortisol concentrations if hemodynamic instability is refractory to adequate volume resuscitation and vasopressor therapy (Hamrahian; Fleseriu, 2017).

Moreover, a brief trial of hydrocortisone treatment in critically ill patients with hemodynamic instability without septic shock but with borderline serum cortisol levels (10-15 μg/dL) may be reasonable as long as treatment is discontinued in the absence of any significant response to avoid harm (Hamrahian; Fleseriu, 2017).

After various studies, random cortisol and free cortisol measurements were recommended as the primary methods for evaluating adrenal function in critically ill patients. The cosyntropin stimulation test (CST) should not be used to define relative adrenal insufficiency (RAI) in critically ill patients. However, in patients without septic shock and with borderline random cortisol levels, performing the CST may be reasonable (Hamrahian; Fleseriu, 2017). A free cortisol level ≥ 1.8 mcg/dL was proposed as a criterion for normal adrenal function in critically ill patients without septic shock. However, more outcome-based studies are needed to validate free cortisol cutoff points in critically ill patients (Hamrahian; Fleseriu, 2017).

The ideal glucocorticoid replacement should mimic physiological secretion, be easy to administer and control, and have low metabolic variability. However, this is not always possible (De Miguel Novoa *et al*., 2014). Hydrocortisone is the drug of choice as it has both glucocorticoid and mineralocorticoid effects. Its administration is recommended in doses of 15-25 mg/day, divided into two or three times a day to simulate the circadian rhythm of cortisol (Charoensri; Auchus, 2024; Kumar; Wassif, 2022; Nieman; Lacroix and Martin, 2012; Nowotny *et al*., 2021). For emergency situations, the recommended dose is 100 mg intramuscularly (Charoensri; Auchus, 2024; Kumar; Wassif, 2022; Simpson *et al*., 2020; Bornstein *et al*., 2016; Nowotny *et al*., 2021).

Hydrocortisone has good bioavailability and a short half-life, but dose division and adjustment can be difficult (De Miguel Novoa et al., 2014). Long-acting glucocorticoids, such as prednisolone and dexamethasone, are not as recommended due to their long half-life and unfavorable nocturnal glucocorticoid activity. Prednisolone can be used in doses of 3-5 mg/day for better adherence and control (Nieman; Lacroix and Martin, 2012; Bornstein

et al., 2016; Charoensri; Auchus, 2024), but it can cause dyslipidemias, osteopenia, and osteoporosis (Charoensri; Auchus, 2024). Dexamethasone, although long-lasting, is not recommended due to the risk of Cushing›s syndrome and difficulty in titration (Nieman; Lacroix and Martin, 2012).

Patients with gastrointestinal disease or after major surgeries should receive parenteral glucocorticoids (Charoensri; Auchus, 2024; Bornstein *et al.*, 2016). Prednisone and dexamethasone should be used in patients with poor adherence to multiple doses due to metabolic variability and risk of intoxication (De Miguel Novoa *et al.*, 2014). Patients under treatment should be evaluated quarterly during dose titration and annually thereafter, including blood pressure measurement, heart rate, weight gain or loss, signs of lethargy or impaired sleep, and Cushingoid signs (Nieman, Lacroix; Martin, 2012; De Miguel Novoa *et al.*, 2014). Adequate glucocorticoid replacement control is achieved through clinical evaluation or cortisol curve (Kumar; Wassif, 2022). Patient education on «sick day rules» is essential to adjust the dose, such as doubling the dose when necessary or associating a fast-acting glucocorticoid during stress (Simpson *et al.*, 2020).

Patients on long-term supraphysiological glucocorticoid replacement are at higher risk of infections, increased hospitalization rates, and antimicrobial use due to the immunosuppressive activity of glucocorticoids. In women with primary adrenal insufficiency (PAI), high doses of glucocorticoids increase the risk of ischemic and cardiovascular heart disease, as well as compromise sleep quality (Nowotny *et al.*, 2021).

For primary adrenal insufficiency, it is necessary to associate mineralocorticoids from diagnosis to maintain volume levels, normal blood pressure, electrolyte balance, and reduce salt cravings. The drug of choice is fludrocortisone (FC), which mimics natural aldosterone secretion and should be administered in morning doses of 0.05 to 0.20 mg/day (Bornstein *et al.*, 2016; Kumar; Wassif, 2022; Charoensri; Auchus, 2024). The initial dose can be 0.05 to 0.1 mg/day, especially for patients on hydrocortisone or cortisone acetate (Nieman; Lacroix and Martin, 2012). The dose should be temporarily adjusted in hot climates and excessive sweating or stressful situations (Nieman; Lacroix and Martin, 2012; Bornstein *et al.*, 2016; Kumar; Wassif, 2022; Charoensri; Auchus, 2024; De Miguel Novoa *et al.*, 2014).

Treatment options also include gene therapy and the potential to restore the defect in certain forms of monogenic primary adrenal insufficiency (PAI); adrenal cortical transplantation, a promising area already with successful reports in the literature; and new cell replacement and encapsulation technologies, which may even achieve the cure of primary adrenal insufficiency with the restoration of hypothalamic-pituitary-adrenal (HPA) axis function. Stem cells offer the potential to regenerate adrenal cortical tissue in patients with AI, and this is currently an area of intense research (Kumar; Wassif, 2022; Bornstein *et al.*, 2016).

Finally, treatment options to reverse autoimmune adrenal insufficiency have been developed, which include B-lymphocyte-depleting immunotherapy with rituximab, regular

therapy with subcutaneous tetracosactide (ACTH1-24), and dual therapy with rituximab and repeated depot tetracosactide (Kumar; Wassif, 2022). More recent studies have reported a successful mother-to-daughter allograft in a pediatric patient who developed adrenal insufficiency after acquiring fulminant meningococcemia. However, these multi-organ transplants are only viable and/or indicated when recipients have severe comorbidities (Babot *et al*., 2015). A study conducted by Hornsby et al. demonstrated that the transplantation of human adrenal cortical cells into mice with severe combined immunodeficiency and adrenalectomy could be an effective technique for treating adrenal insufficiency (Babot *et al*., 2015).

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