Autoimmune Addison’s disease

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Summary

Addison’s disease is a rare autoimmune disorder. In the developed world, autoimmune adrenalitis is the commonest cause of primary adrenal insufficiency, where the majority of patients have circulating antibodies against the key steroidogenic enzyme 21-hydroxylase. A complex interplay of genetic, immunological and environmental factors culminates in symptomatic adrenocortical insufficiency, with symptoms typically developing over months to years. Biochemical evaluation and further targeted investigations must confirm primary adrenal failure and establish the underlying aetiology. The diagnosis of adrenocortical insufficiency will necessitate lifelong glucocorticoid and mineralocorticoid replacement therapy, aiming to emulate physiological patterns of hormone secretion to achieve well-being and good quality of life. Education of patients and healthcare professionals is essential to minimise the risk of a life-threatening adrenal crisis, which must be promptly recognised and aggressively managed when it occurs. This article provides an overview of our current understanding of the natural history and underlying genetic and immunological basis of this condition. Future research may reveal novel therapeutic strategies for patient management. Until then, optimisation of pharmacological intervention and continued emphasis on education and empowerment of patients should underpin the management of individuals with autoimmune Addison’s disease.

Addison’s disease is a rare autoimmune condition arising from a complex interplay of genetic, immunological and environmental factors, manifesting as symptomatic adrenocortical insufficiency and necessitating lifelong corticosteroid replacement therapy. In developed countries, the underlying aetiology of primary adrenal insufficiency is most commonly autoimmune adrenalitis (AA). This can present as isolated Addison’s disease (AD), or as AA within an autoimmune polyendocrine syndrome (APS) [1,2]. Less frequently
encountered causes include malignancy and haemorrhage; the possibility of adrenoleukodystrophy, a rare X-linked condition, should be considered in males. Last century, tuberculous infiltration of the adrenal glands was the major cause of primary adrenal insufficiency worldwide [3], and still represents a significant cause in the developing world today [4]. The first description of adrenocortical failure dates back to the mid-nineteenth century, when Dr. Thomas Addison, a physician at Guy’s Hospital, London, described symptoms of adrenocortical insufficiency and changes in the adrenal glands at the time of autopsy [5]. Although the majority of patients had tuberculosis or tumours of the adrenal glands at this time, at least one case was attributed to ‘idiopathic’ adrenal atrophy, which we now recognise as autoimmune Addison’s disease (AAD) [5]. Although this article will focus on AAD, secondary adrenal insufficiency is more commonly encountered, usually arising as a consequence of chronic administration of exogenous steroids [6], with an estimated prevalence of 150–280 per million [7–11]. Primary adrenal insufficiency is rare, with a prevalence of 93–140 per million and an annual incidence of 4.7–6.2 per million in white populations [7,12,13]. It occurs more frequently in women, and can occur at any age, though most often presents between the ages of 30 and 50 years [12]. This article will review the aetiology and pathogenesis of AAD, and our current understanding of the immunological basis and genetic implications of this condition. Clinical presentation, diagnostic considerations and management in the routine and acute setting are also addressed.

**Aetiology**

In developed countries, primary adrenal insufficiency is caused by autoimmune Addisonitis in 80–90% of cases, arising as an isolated disease, or within an APS [1,6]. APS type 1 accounts for only 5–10% of AAD cases in most populations, and is characterised by childhood onset of primary adrenal insufficiency, hypoparathyroidism and mucocutaneous candidiasis [1,14]. It is also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), and is inherited in an autosomal recessive pattern, arising as a result of mutations in the AIRE gene [1,14]. It is extremely rare in most countries, with a prevalence of three cases per million in the UK, and has an equal male and female preponderance [15]. However, APS1 is more frequent in certain populations such as in Finland or Sardinia, due to ancient founder genetic effects. APS type 2 is the most frequently encountered APS, and signifies the presence of adrenal insufficiency, with either autoimmune thyroid disease or type 1 diabetes. A spectrum of other autoimmune conditions are frequently found in APS2 including primary ovarian insufficiency, pernicious anaemia/atrophic gastritis or coeliac sprue. In contrast to type 1 APS, it is inherited as a complex multigenic trait [16]. The spectrum of APS is dealt with more comprehensively in another article in this issue. Other causes of primary adrenal failure are summarised in box 1 [17,18].

**Pathology, immunology and genetics**

Most autoimmune endocrine diseases, including AAD, are complex traits where interplay of genetic and environmental factors is thought to contribute to the underlying disease proclivity, and the subsequent development and symptomatic presentation, respectively. In AAD, this process is not yet fully understood, but pathogenesis is likely to reflect a long, multi-step process preceding the development of overt autoimmune failure and apparent clinical manifestation. On pathological examination, the adrenal glands are small and atrophic in cases of established AAD. Histological assessment shows that all three layers of the adrenal cortex are destroyed, correlating with the clinical picture of aldosterone, cortisol and adrenal androgen deficiency. It is often stated that more than 90% of the adrenal cortex is destroyed before symptoms develop, although the exact basis for this estimate is elusive. In earlier cases cortical cells are atrophic and surrounded by a dense mononuclear cell infiltrate, along with occasional islands of hyperplastic adrenocortical cells [19]. Most of the cellular infiltrate is T lymphocytes, with a small proportion of B cells. There is abundant MHC class II expression in AAD and in tuberculous adrenal infiltration, suggesting direct adrenocytomediated antigen presentation. This immunohistochemical evidence of antigen presentation is similar to that reported in the target organ in other autoimmune endocrine diseases, such as Hashimoto thyroiditis or type 1 diabetes. The adrenal medulla is preserved in AAD.

**Humoral immunity**

Twenty years ago, the key steroidogenic enzyme 21-hydroxylase (21-OH), was identified as being the target of the immune attack in AAD [20], and about 85% of patients with

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**Glossary**

- **AA**: autoimmune adrenalitis
- **AAD**: autoimmune Addison’s disease
- **ACTH**: adrenocorticotropic hormone
- **AD**: Addison’s disease
- **ALD**: adrenoleukodystrophy
- **APECED**: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
- **APS**: autoimmune polyendocrine syndrome
- **CAH**: congenital adrenal hyperplasia
- **CBG**: corticosteroid-binding globulin
- **DHEA**: dehydroepiandrosterone
- **21-OH**: 21-hydroxylase
- **21-OH Abs**: 21-hydroxylase autoantibodies
- **PRA**: plasma renin activity
Box 1

Aetiology of primary adrenal insufficiency

Inherited/Genetic causes:
- inherited defects in cholesterol biosynthesis;
- inherited defects in steroid biosynthesis:
  - steriodogenic acute regulatory protein mutations,
  - 21-hydroxylase enzyme defects,
  - other forms of congenital adrenal hyperplasia;
- others (including agenesis, hypoplasia):
  - adrenoleukodystrophy (X-linked),
  - scavenger receptor B1 mutations [17],
  - DAX1 mutations (X-linked),
  - SF1 mutations,
  - ACTHR mutations,
  - GPX1,
  - NNT;
- mitochondrial mutations;
- autoimmune adrenalitis:
  - APS1 (monogenic; AIRE gene mutations),
  - isolated Addison’s/APS2 (complex; HLA & others).

Acquired causes:
- haemorrhage;
- infection (including TB, HIV, fungi);
- metastatic malignancy;
- amyloidosis;
- sarcoidosis.

DAX1: dosage-sensitive sex reversal-adrenal hypoplasia gene; SF1: steroidogenic factor 1; ACTHR: adrenocorticotropic hormone receptor gene; GPX1: glutathione peroxidase 1; NNT: nicotinamide nucleotide transhydrogenase [18].

newly presenting idiopathic adrenal failure in Europe have circulating autoantibodies against this enzyme [21]. Autoantibodies against other steriodogenic enzymes are present in some patients [1], including steroid 17α-hydroxylase [22] and the cholesterol side-chain cleavage enzyme [23] but these are less sensitive markers of disease. Circulating 21-hydroxylase autoantibodies (21-OHAbs) are a reliable predictor of the development of AAD [16] indicating auto-immunological processes underway within the adrenal glands. These autoantibodies can be detected even before clinical features of adrenal insufficiency are present, when a gradual decline in adrenal function is already underway. At this stage, laboratory features of rising renin and/or ACTH levels may become apparent prior to any decline in circulating aldosterone or cortisol levels. Subsequently, overt symptoms will appear, heralding the clinical presentation of AAD, alongside a demonstrable suboptimal cortisol response [16]. About 50% of people with detectable 21-hydroxylase autoantibodies will go on to develop overt adrenal failure, over a time course ranging from 3 months to 11 years [24]. Overt clinical presentation is likely to be more rapid in patients with high autoantibody titres [16], however, as the 21-hydroxylase enzyme is an intracellular protein, it is not believed that 21-hydroxylase antibodies have a direct inhibitory effect on enzymatic function. Uncertainty remains over what proportion of patients with ‘idiopathic’ AAD, but without detectable circulating 21-OH-Abs, have a disease with an autoimmune basis [16], as the possibility of non-steriodogenic enzyme-positive AAD remains under-investigated.

Cellular immunity

Experimental findings support the hypothesis that a cell-mediated autoimmune response is the primary pathogenic mechanism in AAD [25–27]. Along with the histopathological finding that the major infiltrating immune cell type in AAD is the T lymphocyte, T lymphocytes from patients with AAD also exhibit abnormal proliferative responses to 21-hydroxylase protein antigen in vitro [28]. Furthermore, murine modelling suggests that one key region of 21-hydroxylase, the substrate binding domain, forms the major T cell epitope [29]. The circulating antibodies directed against 21-hydroxylase are predominantly of the IgG1 isotype, also suggesting a Th1 dominant immune response in AAD [30].

Genetics

In common with many other complex autoimmune conditions, alleles of the major histocompatibility complex were the first and remain the strongest genetic association of AAD [31]. In particular, HLA-DR3 is over-represented among Caucasian individuals with AAD [31,32]. Interestingly, a rare HLA allele, DRB1*0404 seems to be more highly over-represented in AAD patients than any other allele, with an odds ratio of more than 20 for compound heterozygote carriers of one DRB1*0404 and one DRB1*0301 allele compared to healthy subject [32]. Furthermore, weaker, but independent associations within the MHC region extend to the class I region, including HLA-B alleles [33]. Allelic variants at several other genetic loci have been associated with AAD, including PTPN22 and CTLA4, which are also independently associated with the other APS2 manifestations (i.e. autoimmune thyroid disease and type 1 diabetes). Additional loci that are implicated in AAD susceptibility include NALP1, CYP27B1, CIITA, CD226 and PD-L1, highlighting that variation in both the adaptive and innate immune systems contribute to disease pathogenesis. The reader is referred to a recent detailed review of this subject for more information [16].

Natural history and clinical presentation

The adrenal cortex is composed of three distinct zones which are responsible for secretion of the individual hormones under the direct control of well-recognised feedback mechanisms.
synthesis of aldosterone, the major mineralocorticoid, occurs in the outermost layer, the zona glomerulosa, and is predominantly regulated by the renin-angiotensin system and extracellular potassium concentrations, and therefore secretion is unaffected in secondary adrenal insufficiency. Glucocorticoids are secreted from the middle layer, the zona fasciculata, and regulated by pituitary adrenocorticotropin hormone (ACTH) via the cell-surface melanocortin-2 receptor. Glucocorticoids are secreted into the systemic circulation in a pulsatile manner, with a peak in the morning representing a well-recognised circadian rhythm [34]. Androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) are adrenal androgens synthesised in the innermost zona reticularis.

Symptoms of adrenal insufficiency include fatigue, nausea, anorexia, postural dizziness and muscle cramps. A history of weight loss, reduced strength and salt craving may also be found. The non-specific nature of many of these symptoms can hamper recognition of the underlying diagnosis, and prolongs the timescale between presentation and detection by healthcare professionals, thereby delaying instigation of essential treatment. Hyperpigmentation is a specific sign of primary adrenal insufficiency, predominantly affecting areas of skin subjected to increased friction, such as the elbows, knuckles, palmar creases, lips and buccal mucosa. Stimulation of the melanocortin-1 receptor in the skin by high circulating ACTH is responsible for this finding [6]. In addition, women may lose pubic and axillary hair, due to adrenal androgen deficiency. Laboratory findings of hyponatraemia and hyperkalaemia are manifestations of mineralocorticoid deficiency, which are often associated with postural hypotension, dehydration and polyuria. Hypoglycaemia, anaemia, lymphocytosis and eosinophilia are mediated by glucocorticoid deficiency. In addition, an elevated serum thyrotropin concentrations may be detected - adequate circulating cortisol levels physiologically suppress thyrotropin release, so levels should return to normal once adequate glucocorticoid treatment is instigated [35]. In a small proportion of patients, hypercalcaemia is also present, probably reflecting abnormal tubular cation handling [36].

A life-threatening adrenal crisis is often the first presentation of undiagnosed adrenal insufficiency. Clinical features include vomiting, abdominal pain, back or leg cramps and severe hypotension, which can culminate in hypovolaemic shock. The acute presentation may be precipitated by physiological stressors such as surgery, trauma or intercurrent infection. Management of adrenal crisis is dealt with in more detail below.

The pre-clinical time course of AAD can span many years after detection of early metabolic changes by screening [37], even in the presence of high specific autoantibody titres and significantly elevated ACTH [38]. The use of biochemical markers to predict progression in patients with positive 21-OH Abs is discussed further in the following section.

Diagnosis

If there is any concern that a patient’s clinical presentation represents acute adrenal insufficiency, the administration of steroids should never be delayed pending investigation and formal diagnosis. In the investigation of suspected adrenal failure, there are two essential questions that must be answered: firstly, is there adrenocortical failure? Secondly, if adrenal insufficiency is confirmed, what is its underlying aetiology? The answer to the latter question will impact on management and prognosis.

A suggested diagnostic pathway is summarised in the figure 1. If the patient is unwell, appropriate treatment must be instigated promptly, with parenteral hydrocortisone and rapid infusion of saline solution. If time allows, blood samples should be obtained to assay cortisol and ACTH; these results can be interpreted in the context of the clinical picture to confirm or refute the diagnosis in the fullness of time. In the presence of a suggestive clinical picture, biochemical testing may provide diagnostic clues in terms of hyponatraemia or hyperkalaemia. In advanced disease, cortisol levels will usually be low, or undetectable; though there is currently no clear consensus on what value constitutes a biochemical diagnosis of adrenocortical insufficiency. In the context of an acutely unwell patient a serum cortisol level below 250 nmol/L, together with an elevated plasma ACTH, is diagnostic of primary adrenal failure. In the same situation, a serum cortisol level below 400 nmol/L is also suspicious of adrenal insufficiency. In AAD, further investigations will reveal elevated plasma renin activity, whereas serum aldosterone and dehydroepiandrosterone sulphate (DHEA-S) levels will be low.

A more formal assessment is required where the clinical picture and corresponding laboratory results are not straightforward, or where the question of partial adrenocortical insufficiency is raised. A Synacthen (tetracosactide) test requires the administration of 250 micrograms of Synacthen intravenously or intramuscularly, with measurements of serum cortisol drawn at 30 minutes and at 60 minutes. For diagnostic purposes, one of these values should exceed 550 nmol/L to be deemed a satisfactory response. In the context of primary adrenal insufficiency, it is a highly sensitive diagnostic tool [39]. Results should be interpreted with caution when the test has been performed during pregnancy or in women taking the oral contraceptive pill, where increased oestrogen impacts on levels of corticosteroid-binding globulin (CBG), and resulting cortisol measurements [40].

Once the diagnosis of adrenal insufficiency has been made, attention must be given to the underlying aetiology (figure 1). Where primary adrenal insufficiency is confirmed, the next step should be measurement of 21-OH Abs. If this assay yields positive results, further diagnostic evaluation is rarely necessary. Further evaluation is indicated if 21-OH Abs are not
detected, and cross-sectional imaging such as an upper abdominal CT scan is the next step in order to disclose less frequent diagnoses such as haemorrhage, infiltrative disease or infection. Specific conditions, such as tuberculosis, will have typical imaging appearances–bilateral adrenal enlargement is demonstrated initially, with calcification apparent later [41]. In younger males, screening for adrenoleukodystrophy (ALD) should be performed by assay of serum very long chain fatty acids [42]. This is particularly important in the presence of neurological dysfunction, which may be as mild as a subtle ataxia that may be passed off as clumsiness. However, the clinical presentation can be highly variable; adrenal insufficiency can precede the onset of neurological symptoms of ALD, and may be the sole clinical manifestation in 15% of cases [43]. In childhood (<10 years of age), the probability of a non-autoimmune cause is much higher and a variety of inherited conditions may be responsible (box 1). Consideration of an underlying diagnosis of congenital adrenal hyperplasia (CAH) should also be considered in the presence of suggestive clinical features.

It is well-recognised that the emergence of AD can follow a protracted sub-clinical course. Early detection of metabolic abnormalities is possible months to years prior to overt clinical manifestation [37]. The biochemical marker thought to best represent this initial functional impairment in adrenocortical function is rising plasma renin activity (PRA), with a normal or low aldosterone [24,44]. In patients with positive 21-OH Abs, biochemical monitoring can be a helpful adjunct in predicting progression to clinical disease. However, it has recently been proposed that ACTH may me a more useful indicator of impending AD: individuals with positive 21-OH Abs who progressed to AD were significantly more likely to have an elevated ACTH, without significant difference in mean plasma renin activity, in the 24 to 30 months prior to clinical manifestation [37]. Making the diagnosis of adrenal insufficiency in acutely unwell patients is an imperative but challenging problem. The steroid axis is significantly up-regulated in the presence of critical illness [45,46]. This, in conjunction with the interplay of multiple other compounding factors, makes diagnosis of adrenal insufficiency in this setting highly complex. It remains axiomatic that where clinical concern exists, a blood sample for serum cortisol and plasma ACTH should be obtained, and immediately followed with hydrocortisone administration [6].

**Treatment**

A diagnosis of AAD necessitates lifelong glucocorticoid and mineralocorticoid therapy. Maintenance treatment should be
tailored to the individual on the basis of thorough clinical assessment, accompanied by continuing patient education and clear guidance on how to manage a potential crisis.

**Maintenance**

Glucocorticoid replacement regimens are constructed to attempt to reflect physiological patterns of secretion. Individuals with intact adrenal function produce 5–10 mg/m² of body surface area of cortisol in a day [47–50], equating to a total daily dose of 15–25 mg hydrocortisone, the preferred choice of glucocorticoid treatment. Other steroids (prednisolone, dexamethasone) have longer half-lives, and are usually avoided to minimise unphysiological exposure to glucocorticoid in the afternoon and evening.

Hydrocortisone is administered in two or three divided doses each day, with the larger proportion of the total daily dose taken immediately on waking. Subsequent doses should be 4–6 hours after the initial dose, with the last dose of the day ideally being 4–6 hours before bedtime. Thorough clinical assessment is central to optimising treatment regimens. Patients may describe symptoms of adrenal insufficiency, such as weight loss, lack of appetite, nausea and fatigue, in the instance of under-replacement. Conversely, clinical features of steroid excess including weight gain, hypertension, oedema, striae and insomnia, indicate over-replacement. Normal skin colour should be apparent in most patients on adequate glucocorticoid replacement. To date, there is no validated method for exact assessment of glucocorticoid dose, although a clinical scoring system has been proposed [51]. Important questions about the timing of hydrocortisone doses, whether doses are taken strictly by the clock, and whether symptoms occur if a dose is missed or late, allow an optimal daytime dosing regimen to be devised. If patients report not taking their last glucocorticoid dose of the day intermittently, it should be considered whether this dose is indeed required. There should be no harm in reducing patients to a lower total daily dose of glucocorticoids after adequate clinical assessment, as long as they are prescribed sufficient mineralocorticoid replacement. Patients should be managed on the lowest total daily dose of glucocorticoid that is compatible with their well-being.

The effect of glucocorticoid therapy on bone mineral density is an important consideration. Studies have demonstrated reduced bone density at the femoral neck and lumbar spine in patients with AD in a hydrocortisone dose-dependent manner [52]. Furthermore, bone mineral density has been shown to not be significantly reduced in those maintained on lower doses of glucocorticoids [53]. Nevertheless, AAD patients treated over the last 20 to 30 years using what have historically been higher doses of hydrocortisone do show an excess of hip fractures [54]. Timed measurement of serum cortisol is worthwhile only if intestinal malabsorption is a significant possibility. Regular monitoring of serum cortisol levels, or a serum cortisol ‘day curve’, are not reliable methods to guide dose adjustment. Peak serum cortisol conditions will vary greatly between individuals and are dependent upon several factors including whether tablets are taken with food and circulating cortisol-binding globulin concentration (which is oestrogen dependent). Physicians need to understand that tissue glucocorticoid receptor occupancy, which presumably most closely correlates to symptoms of hypoadrenalism, has significantly different kinetics to the blood cortisol concentration.

In some instances, an alternative glucocorticoid replacement will need to be considered. Prednisolone can be tried as a single daily dose on waking (e.g. 3–5 mg), or as a split dose between morning and lunchtime (e.g. 3 mg on waking, 1 mg at midday); with cortisone acetate as a further alternative. A combination tablet containing both immediate and slow release hydrocortisone is about to become available in Europe. It’s place in management remains to be established, although the potential for once daily dosing may be a key advantage [55].

Appropriate mineralocorticoid therapy in individuals with primary adrenal insufficiency is paramount and inadequate replacement is a clear risk-factor for adrenal crisis. In the majority of adults, a daily fludrocortisone dose between 50–300 micrograms will be appropriate. In certain circumstances, including in younger people, in the latter stages of pregnancy, or in the setting of substantial fluid or salt loss, higher doses may be indicated. It is also important to tell patients to ignore ‘healthy eating’ advice about a low-salt diet, and to eat salt and salty foods as they feel the urge.

Monitoring mineralocorticoid replacement also relies on thorough clinical assessment. Reports of salt craving (e.g. salted potato crisps, olives, soy sauce), as well as of postural dizziness, signify a higher dose requirement. Examination should incorporate measurement of postural change in blood pressure, and assessment of peripheral oedema, in addition to laboratory assessment of sodium, potassium and PRA. Postural hypotension represents inadequate mineralocorticoid replacement. Concentrations of PRA taken while recumbent in the lower normal range support optimal dosing [56]. Insufficient mineralocorticoid dosing is commonly encountered, and may be inappropriately compensated for by higher than necessary doses of glucocorticoids. If patients are hypertensive, the fludrocortisone dose should not be automatically lowered or stopped. Following thorough clinical assessment, a dose reduction may be appropriate as long as the continued regimen represents adequate mineralocorticoid replacement. Essential hypertension can be managed by addition of a vasodilating anti-hypertensive agent, such as an ACE-inhibitor or calcium channel blocker. Diuretics should be avoided.

Androgen replacement is a further consideration, particularly in women, where the adrenal glands are the major sources of androgens. Replacement with oral DHEA may boost general
well-being or sex drive in some women, although the evidence of significant clinical benefit is weak [57]. Furthermore, there is a theoretical risk of breast cancer through oestrogenic effects. Where optimal glucocorticoid and mineralocorticoid treatment is achieved, but well-being is still impaired, a three month therapeutic trial of DHEA replacement can be considered [6,58]. A starting dose of 25 mg daily is suggested, and women should be advised to report any androgenic side-effects, such as greasy skin or acne [59].

Special situations
In certain situations, usual replacement therapy will require adjustment. Concurrent type 1 diabetes may necessitate an amended hydrocortisone regimen to minimise risks of hypoglycaemia (for example, overnight hypoglycaemia, with an additional dose in the evening). The impact of lifestyle factors on the choice of regimen should be considered; individuals with varying work-shift patterns will need to tailor their dosing schedule accordingly. Physical activity demonstrates a variable effect on steroid demands, although patients who regularly undertake exercise will physiologically adapt, and often dose adjustment will not be required. Recognition of additional salt requirements to replace sweat losses in a hot environment, or during strenuous exercise, is important. Longer periods of strenuous exertion can be managed by administration of additional small doses of glucocorticoid, after each set time period (e.g. 2.5 or 5 mg every 3–4 hours).

In pregnancy, physiological changes in total serum cortisol and CBG may necessitate minor dose adjustments. CBG is increased, as is free cortisol, during the last trimester [6]; and a small daily dose increase, perhaps 2.5–5 mg of hydrocortisone, may be appropriate at this stage. Fludrocortisone replacement may also require titration in the latter stages of pregnancy, when increased serum progesterone concentrations exert anti-mineralocorticoid effects [6]. In this setting, monitoring replacement is more challenging - PRA cannot be relied upon as an indicator for adjustment of fludrocortisone dose [60]. Recognised symptoms of mineralocorticoid deficiency, such as salt craving, alongside clinical assessment of blood pressure and electrolytes, should be utilised in this scenario.

In the context of thyroid dysfunction, there are some imperative considerations. Hyperthyroidism increases cortisol clearance [59], and glucocorticoid replacement will need to be significantly increased in thyrotoxic patients. Crucially, in the setting of hypothyroidism, thyroxine must only be initiated once adequate glucocorticoid treatment has been instigated. Conversely, in the presence of untreated adrenal insufficiency, serum TSH is commonly elevated: this generally returns to the reference range following glucocorticoid treatment and does not indicate hypothyroidism.

Cytochrome P450 3A4 (CYP3A4) is a major enzyme involved in the metabolism and clearance of hydrocortisone, and consequently, concomitant administration of certain drugs will impact on pharmacokinetics. For example, glucocorticoid requirements will be increased in the presence of anti-epileptic drugs and anti-tuberculose drugs. Ingestion of selected food products may also affect bioavailability, with lower dose requirements commonly seen in the context of consumed liquorice or grapefruit juice. Glycyrrhetinic acid within natural liquorice also inhibits 11-beta-hydroxysteroid dehydrogenase [61], leading to unopposed agonism of the mineralocorticoid receptor by hydrocortisone; thus, liquorice should be avoided in AAD patients.

Managing crises
Patients, their families, and healthcare providers must be educated regarding the prompt recognition and immediate treatment of an adrenal crisis. An acute crisis represents a lifethreatening event and must be dealt with as an emergency. The frequency of this event varies depending on sex, age and the aetiology of the underlying adrenal insufficiency. In patients with AD, the frequency is around 6–8 per 100 patient years [62]. Women and individuals with primary adrenal insufficiency have a higher risk of crisis, most significant in females with autoimmune adrenalitis (6.5 per 100 years [6]). Precipitants of an adrenal crisis include intercurrent illness most commonly vomiting or diarrhoea, trauma or surgery (including dental procedures). Many result from insufficient dose adjustment in the context of increased steroid requirements by patients or general practitioners [6].

Presenting symptoms include fatigue, nausea, vomiting, abdominal pain and muscle cramps. Clinical assessment will reveal hypotension and ultimately, hypovolaemic shock, a consequence of significant dehydration. Acutely unwell patients may also present with a reduced consciousness level. Initial biochemical assessment will reveal recognised features of adrenal insufficiency - hyponatraemia, hyperkalaemia and potentially renal impairment and hypoglycaemia. Other laboratory features including elevated TSH, mild anaemia, lymphocytosis, eosinophilia and elevated transaminases may also be apparent [59].

Treatment of a crisis requires prompt administration of intravenous or intramuscular steroids, and robust fluid resuscitation. A bolus of hydrocortisone 100 mg must be given as soon as a crisis is suspected, accompanied by large volumes of sodium chloride, initially at 1 L/h. This must not be delayed by formal diagnostic procedures. Subsequently, hydrocortisone should be continued at a total daily dose of 100–300 mg per day, either as a continuous infusion, or in divided doses 6-hourly. These boluses can be administered intravenously or intramuscularly, but must not be omitted. Mineralocorticoid replacement is not required at this stage, as a daily dose of more than 50 mg of hydrocortisone will provide adequate mineralocorticoid activity [56]. Close
patient monitoring is essential, and where indicated, admission to a critical care setting must be considered. Once the patient is clinically stable and tolerating oral intake, parenteral glucocorticoids can be converted to an oral regimen and tapered to a maintenance dose over the next 24–72 hours, depending on the severity of the intercurrent illness. Mineralocorticoid replacement should be reinstated when the total daily dose of hydrocortisone falls below 50 mg, or equivalent. After an adrenal crisis, it is essential that measures are introduced to minimise the risk of a further event. The precipitating cause should be identified and addressed appropriately. Education of patients and healthcare providers is the cornerstone of minimising this life-threatening complication, and is discussed in more detail in the following section.

**Education and follow-up**

**Education**

It is of paramount importance that patients and their relatives receive regular, clear instructions on what to do if they are vomiting, unable to take their oral steroids, or otherwise unwell.

Patients should be empowered to autonomously increase their own steroids during spells of intercurrent illness, and strongly advised to seek medical help early when required. Patients should carry a steroid alert card at all times, and be equipped with an emergency kit containing vials of hydrocortisone which they are taught to administer intramuscularly themselves, or by their relative, prior to seeking urgent medical attention [62]. A ‘medic alert’ form of identification (i.e. bracelet or necklace) should also be advised, enabling healthcare professionals to quickly recognise the underlying condition in the event of an emergency.

The need for greater education of healthcare providers should not be underestimated. Delays in recognising and treating acute adrenal insufficiency pose a significant risk to patients. Despite this, individuals may encounter resistance to prompt treatment in healthcare settings, even when they are empowered to advise on correct management of their condition.

**Follow-up**

A 6- or 12-monthly review by an endocrinologist provides an opportune setting for treatment optimisation, assessment of any complications and patient education. Subjective evaluation should be sought, and supported by thorough clinical assessment and directed laboratory investigations. Pharmacological treatment should be tailored to the individual, and patients should be empowered to self-manage their condition during intercurrent illness or adverse events. In particular, developments such as hypertension, impaired glycaemia and osteoporosis should be screened for. Although the evidence linking physiological replacement therapy to osteoporosis in AAD patients is not overwhelming, long-term epidemiological assessment does show an excess of hip fractures amongst AAD patients. It is reasonable, therefore, to assess bone mineral density at diagnosis, and then 5-yearly if the initial results are normal. In addition, the review represents a valuable opportunity for ongoing education of patients and their relatives, and direction towards additional resources from several recognised patient support organisations that are now established in many countries.

Further considerations should include screening for other autoimmune disorders; type 1 diabetes and autoimmune thyroid disease commonly co-exist. Surveillance can be undertaken within an ongoing outpatient care by assay of serum autoantibodies, where the possibility of premature ovarian failure in women of childbearing age, or potential clinical features of APS, should be addressed as indicated (see article on APS2 [63]).

**Conclusion**

Clinicians need to be constantly vigilant for adrenal insufficiency in acutely unwell patients as early detection of AAD remains key to improving the outcome of this life-threatening condition. Regular adrenal replacement therapy with hydrocortisone and fludrocortisone are likely to remain the mainstay of treatment in the foreseeable future. Our understanding of the natural history and underlying genetic and immunological basis of AAD continues to improve and may lead to future novel therapies. In the meantime, optimising therapeutic intervention and a strong emphasis on crisis prevention and continued patient empowerment and education are of paramount importance in the management of those with AAD.

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