Approach to the patient with Addison's disease

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Summary

Addison's disease (AD) is the manifestation of adrenal glucocorticoid and mineralocorticoid deficiency from T-cell mediated destruction of the adrenal cortex, and the commonest cause of primary adrenal insufficiency in adults. Due to its vague presentation, diagnosis of AD is often delayed, and in some cases, people can present in adrenal crisis. Despite the use of corticosteroid replacement therapy, people with AD suffer from increased mortality and reduced quality of life. There are thought to be multiple contributory factors to this including inadequacy of adrenal crisis management as well as an inability of existing therapies to mimic circadian and ultradian rhythms of cortisol release. Current research strategies are focussed on understanding social and behavioural factors which contribute to adrenal crises, developing therapies that can better replicate rhythms of physiological cortisol secretion, and developing interventions to restore adrenal steroidogenesis. This review discusses the clinical features, investigation and management of AD.

Introduction

Addison's disease (AD) is the clinical manifestation of adrenal glucocorticoid and mineralocorticoid deficiency caused by autoimmune destruction of the adrenal cortex. Whilst the term AD is sometimes used interchangeably with primary adrenal insufficiency (PAI) (1), in accordance with its conventional definition, in this review AD is defined as autoimmune PAI (2, 3). AD is distinct from other causes of PAI including congenital adrenal hyperplasia (CAH) and PAI from tuberculosis or metastatic disease. AD is estimated to affect between 131 and 221 individuals per million within Europe (4-8), whereas outside Europe the estimated prevalence appears to be lower, with 5 individuals per million in Japan (9) and 3.1 individuals per million in South Africa (10). Since its first description by Thomas Addison in 1855, dramatic advancements have been made in the management of AD, transforming it from a predominantly lethal disease to a manageable condition with, in most cases, expected long-term survival. However, people with AD still experience delays in diagnosis and increased mortality. In this review, we discuss the presentation and aetiology of AD and propose an approach to its diagnosis and management. The potential benefits and limitations of newer and emerging therapies for people with AD are also discussed, including extended-release hydrocortisone and subcutaneous pump therapy. Finally, cutting-edge management strategies in development including cellular therapy and regenerative medicine will be discussed.

Symptoms, signs and presentation of Addison's disease

The symptoms of AD are predominantly non-specific, develop insidiously, and overlap with other conditions. Delayed diagnosis is common and in one study 40% of people were

diagnosed more than 6-months from the onset of symptoms (5). The clinical features of AD can be grouped into those resulting from deficiency of glucocorticoids, mineralocorticoids and adrenal androgens (Figure 1). In AD, impaired negative feedback to the hypothalamic-pituitary axis from cortisol results in increased release of adrenocorticotropic hormone (ACTH) and other pro-opiomelanocortin derived peptides from the anterior pituitary gland. Hyperpigmentation and features of mineralocorticoid deficiency (hyponatraemia, hyperkalaemia, salt craving) are distinguishing features of AD from secondary adrenal insufficiency (SAI). A multicentre retrospective study described the most common biochemical features of autoimmune AD as hyponatraemia < 137 mmol/L (84%), raised thyroid stimulating hormone (TSH) (52%), hyperkalaemia > 5mmol/L (34%) and hypoglycaemia (11% of those without T1DM) (11). Raised TSH levels in people with a new diagnosis of AD are likely to be due to either the lack of the inhibitory effect of cortisol on thyrotropin-releasing hormone (where TSH levels often normalise with glucocorticoid replacement alone) or co-existent autoimmune thyroid disease (2).

The first presentation of AD to healthcare services is often a life-threatening adrenal crisis, occurring in up to 50% of people with the condition (12). Whilst various definitions of adrenal crisis exist (12-16), there is a broad consensus that hypotension, driven by hypovolaemia and hypocortisolism, is a main feature, and that people experiencing adrenal crisis present systemically unwell and rapidly deteriorate. Many of the other features of adrenal crisis are vague and overlap with features of untreated glucocorticoid or mineralocorticoid deficiency . People in adrenal crisis can also present with nausea, vomiting, abdominal pain/tenderness, altered mental status, syncope and fever. As features of AD can be non-specific, delayed diagnosis is common leading to an increased risk of presentation with adrenal crisis. Adrenal crises can be triggered by a precipitating event,

most frequently gastrointestinal illness, but also infections/febrile illnesses, non-compliance with medication, physical trauma, strenuous exercise and medical procedures. In addition to physiological stress, psychological or emotional stress can also trigger adrenal crises, and was attributed to cause 16% of adrenal crisis cases in a study in people with PAI and SAI (17, 18). In individuals with co-existent hypothyroidism, introducing levothyroxine can increase metabolic demand and requirement for cortisol, whilst also accelerating cortisol clearance which may precipitate adrenal crisis (19, 20). However, the precipitant remains unknown in approximately 10% of cases (12, 17, 18). The incidence of adrenal crisis is higher in people with AD compared to those with SAI (21) and this may be due to concomitant deficiency in mineralocorticoids, which are key regulators of blood pressure (22).

Aetiology and Pathogenesis

AD is the commonest cause for PAI in adults in Europe and is underpinned by autoimmune destruction of adrenocortical cells (5, 23); 90% of adrenocortical cells need to be destroyed before AD clinically manifests (1, 24). Although autoimmune AD may present at any age, it most frequently presents between the 3rd and 5th decades of life and is more common in women than men (1).

The presence of autoantibodies directed against 21-hydroxylase (21OH) in PAI indicates that the underlying cause is autoimmunity, and 21OH antibodies are detected early on in the natural history of the disease before symptoms arise (25, 26). 21OH antibodies are present in approximately 90% of people with newly diagnosed AD (1, 5, 27). However, whilst prevalent at disease onset, positivity of 21OH autoantibodies fades over time and may yield a negative result upon retesting (5, 28). Adrenal cortex autoantibodies (ACA) which were

used historically in the investigation of AD have largely been replaced by 21OH autoantibodies due to their higher specificity (29). The prevalence of autoantibodies directed against other steroidogenic enzymes such as 17-hydroxylase (14%) and side-chain cleavage enzyme (SCC) (8.4%) are far lower in people with AD (5).

Whilst 21OH autoantibodies are sensitive and specific indicators of autoimmunity and a defining feature of autoimmune PAI, they are not mediators of disease. 21OH antibodies do not suppress the enzymatic activity of 21OH *in vivo* (30, 31). Furthermore, whilst 21OH autoantibodies are able to cross the placenta and become detectable in the neonate, they do not appear to impair adrenocortical function (32). Instead, tissue destruction in autoimmune AD is largely T-cell mediated and 21OH epitopes are believed to be T-cell autoantigens (31, 33). Post-mortem examinations of autoimmune AD reveal a histological picture of lymphocytic infiltration and atrophy of the adrenal cortex with fibrosis (34, 35). Findings from genetic studies have provided additional insight into the T-cell mediated nature of AD pathogenesis. A genome wide association study (GWAS) identified risk loci implicated in thymic T-cell selection and peripheral regulation of T-cell activity (PTPN22, CTLA4, IKZF4), many of which are also associated with other organ-specific autoimmune disease (36, 37).

Whilst little is known about the environmental factors that drive AD pathogenesis, a number of observations point to viral involvement. A Swedish nationwide cohort study reported a bimodal distribution of AD diagnoses among people with T1DM over the calendar year, peaking in February/March and September/October (38). A study in Polish and British cohorts suggests that being born in the winter months is associated with an excess risk of developing autoimmune AD, whereas being born in the summer months may be protective

(39). Viral infections are endemic during winter months and the T-cell lymphocytic immune response in AD is characteristic of viral infections. It is hypothesised that viral pathogens could promote the development of AD either by affecting regulation of the immune system or by directly infecting steroidogenic cells in the adrenal cortex, driving chronic inflammation and autoimmunity in individuals who are unable to eradicate the virus (40). Vitamin D deficiency could partly explain these associations with winter months and risk of AD. Vitamin D receptors are expressed on T-cells and modulate T cell proliferation and function (41), whilst variants in genes for the vitamin D receptor and 1-α-hydroxylase have been linked with AD (42-44).

The majority of people with AD develop another organ-specific autoimmune disease in their lifetime, of which autoimmune thyroid disease is the most common (5, 23). Other associated diseases include T1DM, vitiligo, pernicious anaemia, coeliac disease and primary ovarian insufficiency (Figure 1) (5). AD can occur in the context of autoimmune polyendocrine syndrome (APS). APS-II, the most common APS, is linked with class II HLA antigens (HLA-DQ2, HLA-DQ8, HLA-DR3, HLA-DR4). In APS-II, AD arises in association with T1DM and autoimmune thyroid disease. For individuals with APS-II, levothyroxine replacement should not be introduced before glucocorticoid replacement as this may precipitate adrenal crisis (19, 20). More rarely, AD can occur in the context APS-I, an autosomal recessive syndrome caused by a collection of variants in the autoimmune regulator (*AIRE*) gene. APS-I presents with at least 2 of the following 3 features: AD, hypoparathyroidism and chronic mucocutaneous candidiasis.

Diagnosis

Tests of adrenocortical function

Due to the non-specific presentation of AD, having a low threshold for testing is advised (45). Once clinically suspected, biochemical testing is readily available and generally uncomplicated, provided there is correct interpretation and appreciation of the limitations of the assays.

Initial assessment for AD should include measurement of an 8-9 am morning serum cortisol, which can be paired with a simultaneous measurement of an ACTH concentration. The combination of low morning serum cortisol paired with increased ACTH is sufficient for diagnosis of PAI, although the precise magnitude of ACTH elevation may be variable (15, 45, 46). Guidelines provide thresholds for morning serum cortisol of 100-150 nmol/L (3.6-5.4 µg/dL), below which adrenal insufficiency should be suspected (15, 45, 47). However, it is important to recognise that thresholds for morning cortisol concentrations vary based on the specific immunoassay used and therefore local reference ranges should be followed (48, 49). Furthermore, thresholds for assays are often set based on a sensitivity of less than 100% and therefore cases of AD could be missed if decisions are based on the results of the cortisol concentration alone (47-49). Importantly, exogenous glucocorticoids from any route (including inhaled and topical routes) may suppress cortisol concentrations and therefore a detailed drug history must be taken. In addition, there are situations where corticosteroid binding globulin (CBG) levels are altered and may affect the morning cortisol immunoassay concentration. Only 5-10% of circulating cortisol is free and therefore biologically active, whereas 80-90% of circulating total cortisol is bound to CBG and 5-10% is bound to albumin (50, 51). Widely-available immunoassays measure total cortisol including both protein-

bound and biologically active free cortisol, and as a consequence in situations where CBGs levels are increased (oral oestrogen) or decreased (cirrhosis, sepsis and SERPINA6 variants), interpretation of serum cortisol assays becomes more challenging (15, 52).

A low peak stimulated serum cortisol concentration (relative to local reference ranges) after a 250 µg corticotropin bolus injection confirms adrenal insufficiency (46). Whilst some centres choose to measure stimulated cortisol concentrations only at 30 minutes after ACTH administration, some individuals have a slower stimulated cortisol response, passing the test at 60 minutes but not 30 minutes, and measuring cortisol at both 30 and 60 minutes after ACTH administration is sometimes advised (15, 53). A threshold for stimulated serum cortisol of 500 nmol/L was based on older assays. Recent studies using newer assays suggest lower thresholds for stimulated cortisol at 30 and 60 minutes: 403-426 nmol/L (14.6-15.4 µg/dL) and 485 nmol/L (17.6 µg/dL) respectively for a second generation immunoassay (*ElecsysCort II*), 400-411 nmol/L (14.5-14.9 µg/dL) and 470 nmol/L (17.0 µg/dL) respectively for liquid chromatography-tandem mass spectrometry (LC-MS/MS) (54, 55). Whilst the ACTH stimulation test is considered the gold standard test for adrenal insufficiency and recommended by the Endocrine Society when the patient's condition and circumstances allow (15), the ACTH stimulation test is expensive, can delay diagnosis, and is arguably only needed when the morning serum cortisol concentration is equivocal (46).

Salivary cortisone concentrations are an emerging tool in the diagnosis of adrenal insufficiency. Salivary cortisol concentrations are frequently undetectable at low serum cortisol concentrations due to the activity of salivary gland 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which converts cortisol to cortisone. In contrast, salivary cortisone concentrations correlate well with circulating free cortisol (56, 57). Home waking

229 salivary cortisone concentrations have a positive and negative predictive value of 95% and
230 96% respectively for detecting adrenal insufficiency in one prospective study (58). However,
231 the specific performance of the test in AD is unclear as these outcomes were measured in a
232 cohort of individuals at risk of primary, secondary or tertiary adrenal insufficiency. Whilst
233 this emerging tool promises to be less-invasive and more convenient when compared with
234 ACTH stimulation testing, challenges with implementation exist, particularly with access to
235 an LC-MS/MS laboratory capable of reporting salivary cortisol and cortisone (58). Further
236 confirmatory studies on the performance of salivary cortisone combined with LC-MS/MS will
237 determine the performance of the test in AD and clarify its role in AD management.

238 Other adrenal corticosteroid concentrations can be helpful in supporting a diagnosis of PAI
239 but are not required as a confirmatory test. Mineralocorticoid deficiency is a feature of PAI
240 since the entire adrenal cortex is affected, and a raised plasma renin concentration
241 combined with an inappropriately normal or low serum aldosterone is also suggestive of PAI
242 (59). Levels of dehydroepiandrosterone sulphate (DHEAS) which are below the expected
243 age- and sex-adjusted range are also indicative of PAI, but not required for diagnosis and less
244 reliable with recent glucocorticoid use, in postmenopausal women and in older ages (15,
245 60).

246

247 <u>Testing for aetiology</u>

248 Once PAI is confirmed, further tests should always be performed to identify aetiology, which
249 will determine further management and follow-up (Figure 2). The presence of 21OH
250 antibodies should be measured and if positive will confirm a diagnosis of AD. In
251 autoantibody negative cases it is important to consider other causes of PAI. Adrenal cross-

sectional imaging may shed light on the aetiology as many causative processes of PAI have characteristic appearances of infiltrative adrenal disease on imaging. In infants with PAI (and select older individuals) a morning 17-OHP level should be measured to determine presence of congenital adrenal hyperplasia (CAH), which is screened for in most high-income countries excluding the UK (15, 61). Autoantibody-negative young males should be screened for very long chain fatty acids, the presence of which suggests a diagnosis of adrenoleukodystrophy (46).

Management

Glucocorticoid and mineralocorticoid replacement therapy are recommended in all patients with AD, while the role of dehydroepiandrosterone (DHEA) replacement in women is less clear.

Glucocorticoid replacement

Circulating cortisol concentrations rise in the late night and early morning before declining gradually over the course of the day, with pulses of cortisol secretion superimposed on this rhythm, highest in the morning (Figure 4A) (62, 63). Conventional glucocorticoid replacement therapy utilises immediate-release glucocorticoid preparations such as hydrocortisone acetate and cortisone acetate. Due to the short half-life of these drugs (~90 minutes), multiple daily administrations are required (15). In order to mimic the peak in cortisol after waking, the highest dose of glucocorticoid is administered upon awakening, whilst the last dose in the evening is the lowest to avoid undesirable effects on sleep and

insulin sensitivity (15, 64). The consensus statement of the Euradrenal European Consortium recommends either 15-25 mg/day hydrocortisone or 25-37.5 mg/day cortisone acetate (25-37.5 mg/day) in divided doses (46). The Endocrine Society recommends either 15-25 mg hydrocortisone or 20-35 mg/day cortisone acetate (15, 65). In the UK, the National Institute for Health and Care Excellence (NICE) recommend oral hydrocortisone replacement as first line treatment at 15-25 mg/day in 2 to 4 divided doses (47). Cortisone acetate is an inactive glucocorticoid precursor that requires activation via hepatic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), and therefore has a slightly delayed onset of action compared to hydrocortisone (46). Hydrocortisone is favoured in most industrialized countries and some believe that precursor glucocorticoids such as cortisone result in a greater degree of person-to-person variation, although evidence for this is lacking (15, 66).

Prednisolone or prednisone (3-5 mg/day) can be used as an alternative replacement glucocorticoid with a longer half-life (15). However, longer acting glucocorticoids are avoided in growing individuals due to their suppressive effects on bone growth (67, 68). Dexamethasone should be avoided due to its long half-life and potent glucocorticoid receptor activation, placing patients at a high risk of Cushingoid side effects (15, 69).

There are varying approaches to individualising glucocorticoid replacement does and regimens. Dose adjustments following clinical assessment can be made (15, 47), but currently a robust and reliable marker of glucocorticoid action to guide replacement is lacking. Starting doses of hydrocortisone 20-25 mg/day are most commonly used. The optimal method for individualising the dose regimen from then onwards is not clear, and the pros and cons of existing approaches are reviewed elsewhere (70). Signs of glucocorticoid under-replacement include nausea, weight loss, early satiety/decreased appetite, muscle

297 weakness, low energy levels affecting activities of daily living and worsening
298 hyperpigmentation. Signs of over-replacement include weight gain, increased appetite,
299 increasing blood pressure, worsening glycaemic control, disturbed sleep, cushingoid
300 appearance, acne, thrush, fragility fractures and reduced height (71). There are currently no
301 validated, objective biomarkers that guide decision-making on glucocorticoid dose-titration
302 in AD.

303

304 Modified-release hydrocortisone

305 Multiple daily doses of immediate-release hydrocortisone result in discrete peaks of serum
306 cortisol with intervening periods of hypocortisolaemia, and therefore fail to accurately mimic
307 the circadian and pulsatile ultradian rhythm of physiological glucocorticoid secretion (Figure
308 4B). Modified-release preparations of hydrocortisone have been developed to try to address
309 some of the shortcomings of conventional immediate-release hydrocortisone. Plenadren is
310 composed of a controlled-release core and an outer immediate-release coating, and upon
311 ingestion in the morning leads to a rapid increase in cortisol concentrations, followed by a
312 gradual decline over the course of the day (Figure 4C) (62, 72).

313 Studies have demonstrated beneficial effects of Plenadren on body weight and composition
314 compared to conventional hydrocortisone in people with AD (73, 74). Some studies report
315 an improvement in HbA1c (73, 75, 76), insulin sensitivity (77, 78), HOMA-IR (77) and blood
316 pressure (73) in people with AD using Plenadren. Reports on the impact of Plenadren on
317 cholesterol levels are conflicting (62). Some studies have reported a progressive decrease in
318 total and low-density lipoprotein (LDL)-cholesterol (79) while others have reported
319 unfavourable changes such as a reduction in high-density lipoprotein (HDL) cholesterol (80).

Plenadren is also associated with more physiological immune cell profiles and reduced susceptibility to infections compared to conventional hydrocortisone (80). Treatment with Plenadren for up to 6-years does not adversely affect markers of bone turnover or bone mineral density (81). In a head-to-head comparison with conventional replacement, Plenadren was associated with a significant increase in bone mineral density compared to baseline, whereas conventional regimens were associated with a decrease in bone mineral density (82). Quality of life has been reported to decline with immediate-release hydrocortisone (62), while Plenadren use has been associated with improvements in HRQoL (although findings should be interpreted with caution due to lack of blinding in some studies) (75, 80).

Plenadren is licensed by the European Medicines Agency (EMA) for the treatment of AD, but despite promising findings from existing studies it is used in a minority of people with AD in some countries . This may reflect the cost of modified-release hydrocortisone, and its unknown impacts on important long-term cardiometabolic outcomes. The 24-hour area under the curve for circulating cortisol is approximately 20% lower when an equivalent dose of conventional hydrocortisone is substituted for Plenadren, and it is speculated that some of the beneficial effects of Plenadren may be related to decreased cortisol exposure rather than improved pharmacokinetics (62, 72, 73).

Efmody is another extended-release hydrocortisone, composed of an inert core surrounded by a hydrocortisone layer with a delayed release outer coating (83). A twice daily regimen of Efmody with a higher evening dose leads to a late night/early morning serum cortisol peak, followed by a lower peak in the afternoon (Figure 3D). The role of Efmody in the

management of PAI is currently being investigated (NCT05222152), and it is currently only licensed for people with CAH (62, 84).

Mineralocorticoid replacement

People with AD who have confirmed mineralocorticoid deficiency should receive fludrocortisone replacement at a starting dose between 50-100 µg/day (15) which is then adjusted in steps of 25-50 µg/day according to clinical features. Features of mineralocorticoid under-replacement include salt craving and light-headedness whereas features of over-replacement include high blood pressure and ankle swelling. There is no clear consensus on the validity of using plasma renin concentrations to titrate fludrocortisone dose, and the relationship between renin concentration and mineralocorticoid replacement dose may be influenced by treatment adherence, posture, timing of last dose and concomitant medication (85, 86). In individuals newly diagnosed with AD who have pre-existing hypertension, starting doses towards the lower end of the recommended range could be used initially. When individuals develop hypertension on fludrocortisone, both the glucocorticoid and mineralocorticoid doses should be reviewed and optimised, and antihypertensive medications should be considered if the blood pressure remains high (87). A daily dose of 50-200 µg is usually sufficient (15, 46). In addition to pharmacological therapy, people with AD are advised to consume salt intake as desired without restriction (whilst avoiding salts with high levels of potassium) (46). Dose increments or increased salt intake can be recommended temporarily in hot conditions which stimulate excessive sweating.

Adrenal androgen replacement

DHEA and dehydroepiandrosterone sulphate (DHEAS) are the major corticosteroids produced by the zona reticularis of the human adrenal gland. Their concentrations peak around the third decade of life before declining again and they act indirectly, mainly through conversion to androgens and estrogens in target cells (15). They may also act as neurosteroids, modulating neurotransmitter receptors, displaying neuroprotective and anti-inflammatory effects (88).

The exact role of DHEA replacement in women with AD is unclear. The adrenal glands are the primary source of DHEA and in women are a major contributor to circulating androgen levels. DHEA secretion has been associated with mood and DHEA supplementation has been shown to improve mood in cohorts without adrenal disease (89). Findings from studies on the effect of DHEA replacement on sexual function, depression and HRQoL in AD are inconsistent (90-92). A systematic review which indicated that DHEA replacement may slightly improve HRQoL and depression in women with adrenal insufficiency (with no significant effect on anxiety or sexual well-being) concluded that here is a lack of evidence to support its routine use (93).

A pragmatic approach maybe to consider a trial of DHEA replacement (10-50 mg/day) in women with low libido, depression, and low energy levels despite optimal glucocorticoid and mineralocorticoid replacement (15). However, DHEA replacement should be used with caution as the long-term effects in people with AD are not known and should be discontinued after 6 months if there is no sustained, beneficial effect. Sexual dysfunction in AD correlates poorly with androgen levels and is frequently multifactorial in origin. It

requires a holistic approach beyond replacement of sex steroids, but further research as to its coexistence in AD and optimal management are needed (94).

Testing for other autoimmune conditions

Periodic screening for other autoimmune conditions is recommended in people with AD and should of course be guided by clinical features. Routine surveillance for conditions that frequently co-occur such as thyroid disease (TFTs, thyroid peroxidase antibodies), diabetes mellitus (plasma glucose, HbA1c), pernicious anaemia (FBC, B12) and coeliac disease is recommended annually (46). The presence of SCC autoantibodies is associated with increased risk of developing primary ovarian insufficiency in women and should be used to guide counselling (5, 46, 95).

Long term consequences and challenges

Despite oral corticosteroid replacement therapy, people with AD suffer from increased mortality in addition to reduced health-related quality of life (HRQoL) and working ability (5, 91, 96-99). Although this may be partly a result of increased burden of comorbidities, the inability of currently available corticosteroid replacement therapies to mimic physiological circadian and ultradian cortisol rhythmicity is also likely to be responsible (97, 100). Corticosteroid under-replacement during times of stress will increase the risk of an adrenal crisis (17). Chronic over-replacement induces a Cushing syndrome-like state with increased cardiovascular risk. It has been suggested that the observed increase in mortality from infections and altered pattern of cancer incidence (96) may be related to the effect of

chronic glucocorticoid therapy on immunity (101) and as such, vigilance for these complications should be encouraged. Cognitive deficits in AD such as impaired memory and executive function may be related to the role of glucocorticoid and mineralocorticoid signalling in the hippocampus and prefrontal cortex (102, 103). In addition, studies implicate cortisol pulsatility in the regulation of neural processing underlying behaviour and cognition, and a failure to mimic pulsatile ultradian release of cortisol with existing replacement regimens may contribute to suboptimal health outcomes related to emotional and cognitive ability (104).

Stress dosing

Increased physiological stress from acute gastrointestinal illness, infections, invasive procedures and trauma in addition to inadequate delivery of corticosteroid therapy are major precipitants of adrenal crisis (12, 13). Increased glucocorticoid replacement dosing recommended to prevent adrenal crisis at times of increased physiological stress is detailed in Panel 1A. (12, 13). The approach to psychological stress is challenging as these situations are harder to define and the experience between different individuals varies greatly. However, recent guidelines recommend that for emotional stress such as a bereavement or major examination, either a single additional dose (e.g. 10mg), or sick-day dosing for 1-2 days is recommended (14, 47). There are inconsistencies in the exact dose adjustments recommended under certain circumstances and these guidelines are largely influenced by expert opinion rather than evidence from well-designed clinical studies (12). Separate guidelines are available to guide the perioperative administration of glucocorticoid (105). Further research to inform evidence-based guidelines on the optimal approaches to

adjusting glucocorticoid dosing during times of stress and to standardise recommended doses for strenuous physical exercise would be welcomed.

Adrenal crisis prevention

Patient education on glucocorticoid stress dosing is key to the effective prevention of adrenal crises and their associated morbidity and mortality. All patients with AD should be given a steroid emergency card (Figure 3) and provided with and trained to use a glucocorticoid injection kit. Of concern, patients with chronic adrenal insufficiency who have received education still experience significant rates of adrenal crisis and adrenal crisis-related mortality (17). One possible explanation is that there are shortcomings in education on adrenal crisis prevention strategies. Studies have consistently reported that not all people with AD have parenteral glucocorticoid at home, and even when available it is underutilised for various reasons (17, 106, 107). The complex, multi-step nature of preparing and administering a hydrocortisone injection is a challenge and over 50% of people with AI who responded to a survey in the USA reported that they never had the opportunity to practice preparation and administration (107). Prior practice of parenteral hydrocortisone administration is likely to improve confidence and success, but repetition and adaptation of training to the individual is necessary (108). The effects of the intercurrent illness and confusion are additional barriers to administration and assistance may sometimes be required.

Education sessions could be improved by allowing more opportunities to provide patients with the opportunity for hands-on practice of injection preparation and administration, and also to train carers and family members. Approval and development of a device which can

deliver a pre-measured injection of hydrocortisone, similar to autoinjectors used for anaphylaxis, could remove barriers to pre-hospital parenteral hydrocortisone delivery, and there is considerable demand from people with AD for such a device (109). There are early suggestions that self-injection could positively influence the course and outcome of adrenal crises (110).

Comorbidities such as T1DM, diabetes insipidus, asthma and premature ovarian insufficiency increase the risk of adrenal crisis in people with AD (111, 112). The interplay between comorbidities and adrenal crises is complex and one important challenge is the complexity of adapting multiple drug regimens during an intercurrent illness. For instance, titrating insulin and glucocorticoids simultaneously when unwell is a careful balance in people with AD and T1DM (113), and therefore patient education should take comorbidities into consideration and cover dose adaptation of concomitant medications where appropriate.

Recent research has provided evidence that psychosocial factors play an important role in the onset of adrenal crises in people with adrenal insufficiency. Financial pressures, psychiatric comorbidities, drug or alcohol misuse, as well as the disruption of social structures around the individual are pressures for adrenal crisis in younger or middle-aged individuals (114, 115). Furthermore, the high incidence of adrenal crisis in older individuals is not just a result of increased burden of comorbidities, but also of age-related cognitive impairments and social isolation (116). Such evidence suggests that educational measures alone may not be sufficient in preventing adrenal crisis, and that there is a need to address the wider psychological and social barriers to preventing adrenal crisis with targeted interventions.

Adrenal crisis management

In acutely unwell patients where AD is suspected, treatment should not be delayed pending test results (13). The 2 principles of management of adrenal crisis are prompt administration of intravenous fluid and of hydrocortisone (Panel 1B). Parenteral hydrocortisone can be administered upon arrival to hospital, and administration of intramuscular hydrocortisone 100 mg can be delivered by non-medical individuals and by the patient themselves when necessary (15, 47). Additional mineralocorticoid dosing is not recommended for adrenal crisis as the high doses of hydrocortisone being administered will exert sufficient action at the mineralocorticoid receptor (12). The underlying trigger of adrenal crisis should be considered and prompt treatment of this cause should be provided.

Considerations for management of AD in pregnancy

Pregnancy is a challenging period for the management of AD as many symptoms of AD and the corresponding signs of corticosteroid over-/under-titration overlap with normal features of pregnancy. Incident AD during pregnancy is rare and interpretation of tests of adrenocortical function requires consideration of the normal physiological changes of pregnancy (15, 117). There is a lack of studies on the optimal glucocorticoid dose and regimen in pregnancy and variability in clinical practice (117). Hydrocortisone is preferred to other glucocorticoids for AD in pregnancy and dexamethasone should be avoided. Neither hydrocortisone nor prednisone/prednisolone cross the placental due to the activity of placental 11β-HSD2 whereas dexamethasone is not susceptible to placental deactivation and can therefore impact the developing foetus (15, 117). Daily glucocorticoid dosing is often increased by 20-40% after the 24th week to match the physiological increase in cortisol

observed in pregnancy (15). Mineralocorticoid requirement is likely to increase during pregnancy, partly due to the anti-mineralocorticoid effects of progesterone (15, 118). Whilst some advocate for an increase of mineralocorticoid dosing during pregnancy in response to blood pressure and potassium levels (119), others suggest that the increase in glucocorticoid replacement will frequently cover the mineralocorticoid requirements (15). Guidance is available on glucocorticoid stress dosing during delivery and the immediate post-partum period (Panel 1A) (117). Despite the availability of pregnancy-specific guidelines for management of AD, a recent multicentre study in the UK and Ireland reported that complications (including adrenal crisis, caesarean section and prematurity) are prevalent in pregnant women with PAI, whilst only 41% of women received an increase in hydrocortisone dose (120). Whilst evidence-based recommendations are challenging to establish due to the rarity of the disease, common-sense strategies such as specialist follow-up to tailor corticosteroid doses, closer liaison with the obstetric team to optimise intrapartum/peripartum dose adaptation and reinforcing patient education are likely to improve outcomes (121).

Continuous subcutaneous hydrocortisone infusion device

Compared to oral hydrocortisone, continuous subcutaneous hydrocortisone infusion (CSHI) can better mimic both physiological circadian and pulsatile ultradian rhythms (122, 123). It is however, infrequently used in clinical practice.

Studies comparing the impact of CSHI to oral replacement on patient-reported outcomes have yielded conflicting findings. In one unblinded study, improvements in the vitality domain of HRQoL were seen after using CSHI (124), but in a separate double-blinded study,

there was no difference in subjective health status after CSHI compared to placebo (124, 125). However, in PULSES, a double-blinded placebo-controlled crossover trial in people with AD, participants consistently reported subjective improvements in fatigue and mood. Differences were detected in functional MRI-measured neural processing of emotional cues and visual stimulation, and these changes were localised to glucocorticoid-sensitive brain areas including the amygdala (123). The impact of cortisol pulsatility on neural processing and mood seen in the PULSES trial is consistent with previous studies demonstrating the importance of ultradian rhythmicity on cognitive processing (104).

Although the use of CSHI is generally safe and well tolerated, it is more costly, time-consuming and requires greater user-commitment compared to oral hydrocortisone, and participants sometimes report pain from the catheter site (124). In a study in patients with CAH, two out of 6 people chose to switch back from CSHI to oral hydrocortisone (126). CSHI may be suitable for a very small subset of people with AD who are committed to device management, and CSHI is so far the only replacement strategy that has the potential to mimic pulsatile ultradian release of cortisol.

Management strategies in development

<u>Personalisation and titration of corticosteroid therapy</u>

Identifying biomarkers for dose titration and individualisation of corticosteroid dosing is challenging, at least partly due to the high degree of inter-individual variability in cortisol physiology. Circulating whole blood gene expression (DSIPI, MMP9, and FKBP5) (127), osteocalcin, immunological markers (128) and a microRNA (miR-122-5p) (129) vary in

response to glucocorticoid administration and have been proposed as potential biomarkers, but require validation in prospective studies.

Portable devices which enable 24-hour measurement of steroid profile that could facilitate accurate assessment of available corticosteroid regimes and personalisation of therapy are now in development (130). These devices enable ambulatory assessment of existing corticosteroid replacement therapies in people undergoing their normal activities, and by sampling adipose interstitial steroid levels, can provide an accurate measurement of the biologically active fraction of hormone (51). Dynamic measurement of steroid physiology might prove to be a more effective method of measuring glucocorticoid action compared to one-off serum markers, though far less convenient.

There is the potential to have a more precise approach to the timing of replacement strategies, reflective of physiology and chronotype. Conventional immediate-release glucocorticoid therapy leads to dysregulated expression of circadian genes in peripheral blood mononuclear cells whereas Plenadren appears to largely revert these changes to levels seen in healthy people (131). Glucocorticoid replacement regimens should be personalised to each individual's sleep wake cycle rather than time of day, and this has particular relevance in shift workers as highlighted in recent clinical guidance (47).

Cell replacement therapy

Adrenocortical cell transplantation has the potential to transform the treatment of AD by restoring endogenous adrenal steroid production, removing the need for corticosteroid replacement. Whilst still in preclinical phases of development, technologies associated with

adrenocortical cell transplantation are developing swiftly (132, 133). Graft tissue may be derived from primary cell isolates, animal-derived xenografts, adult/embryonic stem cells or from cellular reprogramming of differentiated cells. Importantly, the high turnover rate of adrenocortical cells (134) necessitates the incorporation of adrenocortical progenitor cells to prevent graft exhaustion (132). The precise genetic/molecular signature of these progenitor cells is yet to be established, and neither is the optimal protocol for isolation and graft incorporation (132, 135). Progenitor cells are believed to reside in the capsular and subcapsular regions of the adrenal gland and migrate inwardly undergoing zone-specific differentiation, before undergoing apoptosis at the corticomedullary junction (136-138). Our understanding of molecular pathways involved in adrenocortical development/maintenance has improved in recent decades, including the role of sonic hedgehog (SHH) signalling pathway (139, 140) and SF1 activation (141, 142). Subpopulations of cells expressing combinations of Nestin, SHH and GLI1, appear to possess capability of differentiating into glucocorticoid and mineralocorticoid cells (143, 144). Application of adrenal cell transplantation has so far been limited to rodents, where biochemical evidence of graft glucocorticoid function has been reported (145, 146), although a lack of ACTH responsiveness (146) and mineralocorticoid secretion has been noted in some models (147, 148).

Regenerative therapy

In early-phase experimental studies, treatments aimed at enhancing or preserving residual adrenal function have achieved success in isolated cases.

In a study aimed at preserving adrenal function in people with recently diagnosed AD with anti-CD20 therapy, 1 out of 6 participants who received treatment displayed a gradual increase in adrenal steroidogenesis (149). Steroid replacement therapy was discontinued 15-months after treatment for this participant, and improvements in serum cortisol were observed 27-months after treatment (149). Following 20 weeks of tetracosactide (synthetic ACTH), 2 out of 13 people with autoimmune AD showed gradual improvement in adrenal steroidogenic function and were able to, at least temporarily, withdraw steroid replacement (150). The findings of these studies suggest that steroidogenic function is salvageable in a proportion of people with AD.

Although a study assessing combination therapy with anti-CD20 and tetracosactide did not restore normal adrenal steroidogenesis in any of the 13 participants with autoimmune AD, it highlighted the potential for adrenal plasticity as 4 out of 13 had residual adrenal function at 72-weeks (151). Elucidating why certain individuals respond to regenerative therapy and identifying biomarkers of residual adrenal function should be a priority and studies are being conducted to further characterise residual adrenal function in AD (NCT06309498, NCT03793114).

Conclusions and priorities for future research

It is challenging to envisage how developing novel oral glucocorticoid replacement drug therapy could accurately replicate the circadian and pulsatile ultradian rhythms of physiological cortisol secretion. Current evidence does not clearly favour Plenadren or conventional immediate-release hydrocortisone for the treatment of AD, and both treatments have their respective merits. Whilst there is optimism behind potential future

strategies to restore endogenous cortisol secretion, these treatments are in a very early stage of development.

The most immediate issues to address for the management of AD are delayed diagnoses and the occurrence of adrenal crises, which in many cases are entirely preventable. Healthcare providers should consider AD as a differential in a wide variety of presentations, and understand the correct interpretation and limitations of widely available cortisol assays. Education on corticosteroid stress dosing, particularly the use and administration of parenteral hydrocortisone, and the importance of implementing established principles of AD management in pregnancy, should be emphasised routinely. Social and behavioural factors contributing to adrenal crisis should also be addressed to tackle wider-ranging determinants of adrenal crises at an individual and population level. Focussing attention to these areas should facilitate a timely diagnosis, reduce the incidence of adrenal crises and improve the morbidity and mortality of people with AD.

Search strategy and selection criteria:

References were identified by searches using a combination of the terms including 'Addison', 'adrenal insufficiency' and 'adrenal crisis' on Medline and Embase from 1st January 1974 to 30th September 2025. Reference lists of articles identified from this search were reviewed for other relevant articles. Articles published in English were included. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) registry were also searched for clinical trials on AD therapies from conception to 30th September 2025.

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Figure 1. Features of Addison's disease

Addison's disease is characterised by reduced adrenal corticosteroid production. Symptoms can be grouped based on corticosteroid class (glucocorticoid: orange, mineralocorticoid: blue, adrenal androgen: green). Cortisol deficiency results in loss of negative feedback to the hypothalamic-pituitary-adrenal axis, and a consequent rise in hypothalamic secretion of corticotropic releasing hormone (CRH) and secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. Increased melanin production leads to hyperpigmentation. Other features of Addison's disease include reduced quality of life, cognitive deficits, depression, anxiety and laboratory/biochemical abnormalities.

Other Abbreviations:

HRQoL: health-related quality of life, Na+: sodium, K+: potassium, Hb: haemoglobin, T1DM: type 1 diabetes mellitus, TSH: thyroid stimulating hormone, T4: thyroxine

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Panel 1.

A. Stress dosing. Guidelines for the administration of immediate-release hydrocortisone. Separate guidelines have been published for management of glucocorticoids during the perioperative period for patients with adrenal insufficiency by the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK (105).

B. Management of adrenal crisis. Modified from Bornstein et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(2):364-89 (15) with additional recommendations incorporated from other sources (14, 46, 47, 117).

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A. Stress dosing

Physiological stress:
During febrile illness, oral hydrocortisone dose should be doubled (or tripled if fever > 39°C) until recovery (15). Increased dosing should be administered during physical trauma requiring medical attention, using at least double dose of glucocorticoid until resolution (47)

Lack of effective oral route:
Early administration of parenteral hydrocortisone is recommended (100 mg IM or SC) and the patient should be advised to attend the emergency department (15, 47)

Onset of vomiting:
For vomiting < 30 minutes from taking an oral dose, take a further dose at twice the original dose once vomiting subsides. If vomiting recurs within 30 minutes, give IM hydrocortisone, and advise the person to attend the emergency department (47)

Psychological stress (e.g. bereavement, major examination, marriage, divorce):

- Minor dose increases e.g. 10mg hydrocortisone as an additional dose (14)
- Sick day dosing for 1-2 days (47)

Severe mental health crisis (e.g. a psychotic episode):
Consider sick day dosing and 100 mg IM hydrocortisone for someone in severe mental health crisis who is unable to take oral glucocorticoids (47)

Appropriate adjustment of hydrocortisone dose if concomitant drugs are prescribed that inhibit or stimulate CYP3A4 metabolism of cortisol

Exhaustive strenuous exercise
Add 5-10 mg hydrocortisone 30–60 min before starting exercise (14, 46)

Pregnancy
Based on the individual clinical course, during the second and third trimesters a 20-40% increase in dose of glucocorticoid is recommended (117)

Labour
100 mg hydrocortisone IV/IM at the onset of labour followed by 200 mg hydrocortisone every 24 hours via continuous infusion or 6-hourly 50 mg boluses (117)

Postpartum
If delivery and the immediate postpartum period is uncomplicated the oral dose should be doubled for the first 2-4 days before returning to pre-pregnancy doses (117)

B. Management of adrenal crisis

Immediate administration of IV or IM 100 mg hydrocortisone for adults. An IM dose can be administered by non-medical individuals if needed.

Following the 100 mg injection, 200 mg of hydrocortisone should be administered either as a continuous infusion over 24 hours or divided into boluses every 6 hours. After the first 24 hours, daily hydrocortisone dose is reduced to 100 mg per day.

Rapid infusion of intravenous fluids within the first hour (e.g. 1L 0.9% saline), followed by continuous maintenance therapy based on need, electrolyte levels and body weight

Appropriate treatment of intercurrent illness.

Figure 2. Approach to diagnosis of Addison's disease and other causes of primary adrenal insufficiency

*Thresholds for morning serum cortisol are lab and assay-dependent, and are often set based on a sensitivity of less than 100%. Therefore, cases of AD could be missed if decisions are based on the results of the cortisol level concentration alone.

**Thresholds for stimulated cortisol vary at 30 and 60 minutes, and local guidelines should be followed.

Abbreviations: ACTH = adrenocorticotropic hormone, APS = autoimmune polyendocrine syndrome, 17-OHP = 17-hydroxyprogesterone, 21OH = 21-hydroxylase, AD = Addison's disease, T1DM = type 1 diabetes mellitus, TB = tuberculosis, PAI = primary adrenal insufficiency

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Figure 3. Steroid emergency cards from different world regions.

(A) National Health Service (NHS) Steroid emergency card (UK). (B) European Society of Endocrinology bilingual steroid emergency card with German translation and QR code. In North America a medical alert bracelet/necklace is used.

Figure 4. 24 hourly serum cortisol levels physiologically and during glucocorticoid replacement regimens.

(A) Log-transformed serum total cortisol levels (geometric mean, 8 healthy males) modified from (152). (B) Thrice-daily immediate-release hydrocortisone (mean values from 64 patients with adrenal insufficiency using a total daily dose 20-40 mg) (62, 73). (C) Once-daily Plenadren mean values from 64 patients with adrenal insufficiency using a total daily dose 20-40 mg) (62, 73). (D) Twice-daily Efmody, 10 mg at 7am and 20 mg at 11 pm (62, 153). Efmody is not licensed for use in Addison's disease at the time of writing.

Panel A modified from Bhake et al. Continuous Free Cortisol Profiles-Circadian Rhythms in Healthy Men. J Clin Endocrinol Metab. 2019 Dec 1;104(12):5935-5947

Panel B reused from Steintorsdottir et al. Hydrocortisone Formulations-Is There a Clinically Meaningful Benefit? J Clin Endocrinol Metab. 2025 Feb 18;110(3):e566-e573. Original source: Johannsson et al, J Clin Endocrinol Metabol, 97(2):473-81.

Panel C reused from Steintorsdottir et al. Hydrocortisone Formulations-Is There a Clinically Meaningful Benefit? J Clin Endocrinol Metab. 2025 Feb 18;110(3):e566-e573. Original source: Johannsson et al, J Clin Endocrinol Metabol, 97(2):473-81.

Panel D reused from Steintorsdottir et al. Hydrocortisone Formulations-Is There a Clinically Meaningful Benefit? J Clin Endocrinol Metab. 2025 Feb 18;110(3):e566-e573. Original source: DeBono et al J Clin Endocrinol Metabol, 94(5):1548-54.