



Clinical features, investigation, and management of Addison's disease

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Addison's disease is the manifestation of adrenal glucocorticoid and mineralocorticoid deficiency from T-cell mediated destruction of the adrenal cortex, and is the commonest cause of primary adrenal insufficiency in adults. Due to its vague presentation, diagnosis of Addison's disease is often delayed, and in some cases, individuals present in adrenal crisis. Despite the use of corticosteroid replacement therapy, people with Addison's disease have increased mortality and reduced quality of life. Multiple features are thought to contribute to these outcomes, including inadequacy of adrenal crisis management and the inability of existing therapies to mimic circadian and ultradian rhythms of cortisol release. Current research strategies focus on understanding social and behavioural factors that contribute to adrenal crises, developing therapies that more closely mimic rhythms of physiological cortisol secretion, and developing interventions to restore adrenal steroidogenesis. This Review discusses the clinical features, investigation, and management of Addison's disease.

Introduction

Addison's disease is the clinical manifestation of adrenal glucocorticoid and mineralocorticoid deficiency caused by autoimmune destruction of the adrenal cortex. Although the term Addison's disease is sometimes used interchangeably with primary adrenal insufficiency,¹ in accordance with its conventional definition, in this Review, Addison's disease is defined as autoimmune primary adrenal insufficiency.^{2,3} Addison's disease is distinct from other causes of primary adrenal insufficiency, including congenital adrenal hyperplasia and primary adrenal insufficiency from tuberculosis or metastatic disease. Addison's disease 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 Japan⁹ 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 Addison's disease, transforming it from a predominantly lethal disease to a manageable condition with, in most cases, expected long-term survival. However, people with Addison's disease still experience delays in diagnosis and increased mortality. In this Review, we discuss the presentation and aetiology of Addison's disease and propose an approach to its diagnosis and management. The potential benefits and limitations of newer and emerging therapies for people with Addison's disease 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 Addison's disease 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 after the onset of symptoms.⁵ The clinical

features of Addison's disease can be grouped into those resulting from deficiency of glucocorticoids, mineralocorticoids, and adrenal androgens (figure 1). In Addison's disease, 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, and salt craving) are distinguishing features of Addison's disease from secondary adrenal insufficiency. A multicentre retrospective study described the most common biochemical features of Addison's disease as hyponatraemia under 137 mmol/L (207 [84%] of 247), raised thyroid stimulating hormone (TSH; 79 [52%] of 153), hyperkalaemia over 5 mmol/L (82 [34%] of 242) and hypoglycaemia (15 [11%] of 135) of those without type 1 diabetes.¹¹ Raised TSH levels in people with a new diagnosis of Addison's disease are likely to be due to either the absence 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 Addison's disease to health-care services is often a life-threatening adrenal crisis, occurring in up to 50% of people with the condition.¹² Although 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 with 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 or tenderness, altered mental status, syncope, and fever. As features of Addison's disease 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 or febrile

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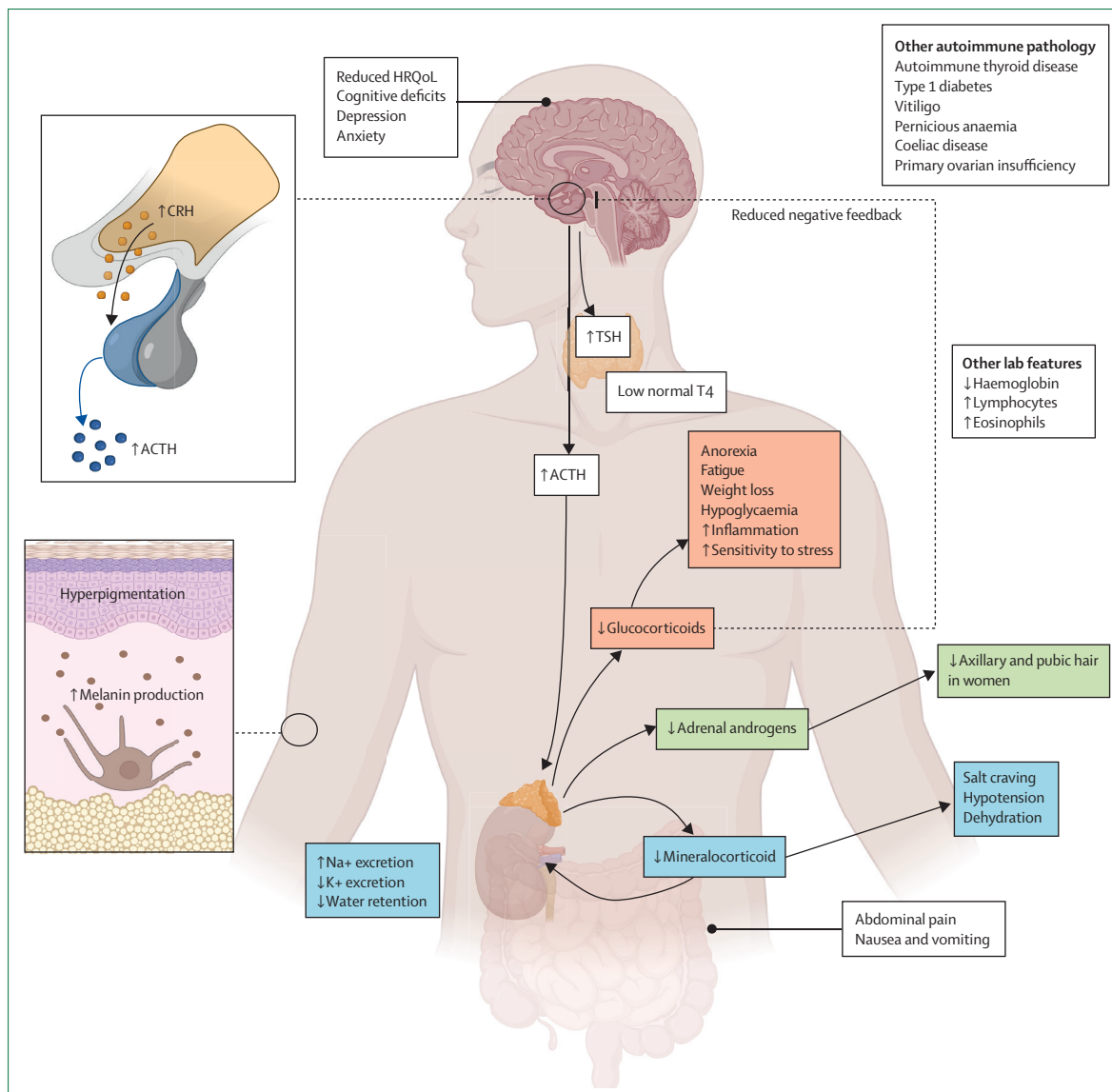


Figure 1: Features of Addison's disease

Addison's disease is characterised by reduced adrenal steroid production. Symptoms can be grouped based on steroid class (glucocorticoid: orange, mineralocorticoid: blue, and 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 CRH and secretion of 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 or biochemical abnormalities. ACTH=adrenocorticotropic hormone. CRH=corticotropin releasing hormone. HRQoL=health-related quality of life. K+=potassium. Na+=sodium. T4=thyroxine. TSH=thyroid-stimulating hormone.

illnesses, non-compliance with medication, physical trauma, strenuous exercise, and medical procedures. In addition to physiological stress, psychological stress can also trigger adrenal crises, and was a precipitating factor in 16% of adrenal crisis cases in a study in people with primary and secondary adrenal insufficiency.^{17,18} In individuals with co-existent hypothyroidism, introducing levothyroxine can increase metabolic demand and requirement for cortisol, while also accelerating cortisol clearance which might 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 Addison's disease compared with those with secondary adrenal insufficiency,²¹ which might be due to concomitant deficiency in mineralocorticoids, which are key regulators of blood pressure.²²

Aetiology and pathogenesis

Addison's disease is the most common cause of primary adrenal insufficiency in adults in Europe and is underpinned by autoimmune destruction of adrenocortical cells,^{5,23} 90% of adrenocortical cells need to be

destroyed before Addison's disease clinically manifests.^{1,24} Although autoimmune Addison's disease can present at any age, it most frequently presents between the third and fifth decades of life and is more common in women than men.¹

The presence of autoantibodies directed against 21-hydroxylase (21OH) in primary adrenal insufficiency 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 Addison's disease.^{1,5,27} However, although prevalent at disease onset, positivity of 21OH autoantibodies fades over time and might yield a negative result upon retesting.^{5,28} Adrenal cortex autoantibodies, which were used historically in the investigation of Addison's disease, 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 (8·4%), are far lower in people with Addison's disease.⁵

Although 21OH autoantibodies are sensitive and specific indicators of autoimmunity and a defining feature of autoimmune primary adrenal insufficiency, they are not mediators of disease. 21OH antibodies do not suppress the enzymatic activity of 21OH *in vivo*.^{30,31} Furthermore, although 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 Addison's disease is largely T-cell mediated and 21OH epitopes are believed to be T-cell autoantigens.^{31,33} Post-mortem examinations of autoimmune Addison's disease 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 Addison's disease pathogenesis. A genome-wide association study identified risk loci implicated in thymic T-cell selection and peripheral regulation of T-cell activity (*PTPN22*, *CTLA4*, and *IKZF4*), many of which are also associated with other organ-specific autoimmune diseases.^{36,37}

Although little is known about the environmental factors that drive Addison's disease pathogenesis, a number of observations point to viral involvement. A Swedish nationwide cohort study reported a bimodal distribution of Addison's disease diagnoses among people with type 1 diabetes 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 Addison's disease, whereas being born in the summer months could be protective.³⁹ Viral infections are endemic during winter months and the T-cell lymphocytic immune response in Addison's disease is characteristic of viral infections. It is

hypothesised that viral pathogens could promote the development of Addison's disease 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 Addison's disease. Vitamin D receptors are expressed on T cells and modulate T-cell proliferation and function,⁴¹ whereas variants in genes for the vitamin D receptor and 1- α -hydroxylase have been linked with Addison's disease.^{42–44}

The majority of people with Addison's disease develop another organ-specific autoimmune disease in their lifetime, of which autoimmune thyroid disease is the most common.^{5,23} Other associated diseases include type 1 diabetes, vitiligo, pernicious anaemia, coeliac disease, and primary ovarian insufficiency (figure 1).⁵ Addison's disease 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, and HLA-DR4). In APS-II, Addison's disease arises in association with type 1 diabetes and autoimmune thyroid disease. For individuals with APS-II, levothyroxine replacement should not be introduced before glucocorticoid replacement as this could precipitate adrenal crisis.^{19,20} More rarely, Addison's disease can occur in the context of APS-I, an autosomal recessive syndrome caused by a collection of variants in the autoimmune regulator (*AIRE*) gene. APS-I presents with at least two of the following three features: Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis.

Diagnosis

Tests of adrenocortical function

Due to the non-specific presentation of Addison's disease, 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 Addison's disease 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 primary adrenal insufficiency, although the precise magnitude of ACTH elevation might be variable.^{15,45,46} Authors recommend thresholds for morning serum cortisol of 100–150 nmol/L (3·6–5·4 μ g/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 Addison's disease 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) might suppress cortisol concentrations and therefore a detailed drug history should be taken. In addition, there are situations where corticosteroid binding globulin concentrations are altered and might 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 corticosteroid binding globulin 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 corticosteroid binding globulin concentrations 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 Although some centres choose to measure stimulated cortisol concentrations only at 30 min after ACTH administration, some individuals have a slower stimulated cortisol response, passing the test at 60 min but not 30 min, and measuring cortisol at both 30 and 60 min 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 min:^{54,55} 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). Although the ACTH stimulation test is considered the gold standard test for adrenal insufficiency and is 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 salivary cortisone concentrations had a positive and negative predictive value of 95% and 96%, respectively, for detecting adrenal insufficiency in one prospective study.⁵⁸ However, the specific performance of the test in Addison's disease is

unclear as these outcomes were measured in a cohort of individuals at risk of primary, secondary, or tertiary adrenal insufficiency. Although this emerging tool promises to be less invasive and more convenient when compared with ACTH stimulation testing, challenges with implementation exist, particularly with access to an LC–MS/MS laboratory capable of reporting salivary cortisol and cortisone.⁵⁸ Further confirmatory studies on the performance of salivary cortisone combined with LC–MS/MS will determine the performance of the test in Addison's disease and clarify its role in Addison's disease management.

Other adrenal steroid concentrations can be helpful in supporting a diagnosis of primary adrenal insufficiency but are not required as a confirmatory test. Mineralocorticoid deficiency is a feature of primary adrenal insufficiency since the entire adrenal cortex is affected, and a raised plasma renin concentration combined with an inappropriately normal or low serum aldosterone is also suggestive of primary adrenal insufficiency.⁵⁹ Concentrations of dehydroepiandrosterone sulphate (DHEA-S) that are below the expected age-adjusted and sex-adjusted range are also indicative of primary adrenal insufficiency, but not required for diagnosis, and are less reliable with recent glucocorticoid use in the past 2 months, in postmenopausal women, and in older ages.^{15,60}

Testing for aetiology

Once primary adrenal insufficiency is confirmed, further tests should always be performed to identify aetiology, which will determine further management and follow-up (figure 2). The presence of 21OH antibodies should be measured and if positive will confirm a diagnosis of Addison's disease. In autoantibody negative cases, it is important to consider other causes of primary adrenal insufficiency. Adrenal cross-sectional imaging might shed light on the cause, as many causative processes of primary adrenal insufficiency have characteristic appearances of infiltrative adrenal disease on imaging. In infants with primary adrenal insufficiency (and select older individuals), a morning 17-OHP level should be measured to determine the presence of congenital adrenal hyperplasia, 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 Addison's disease, whereas 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

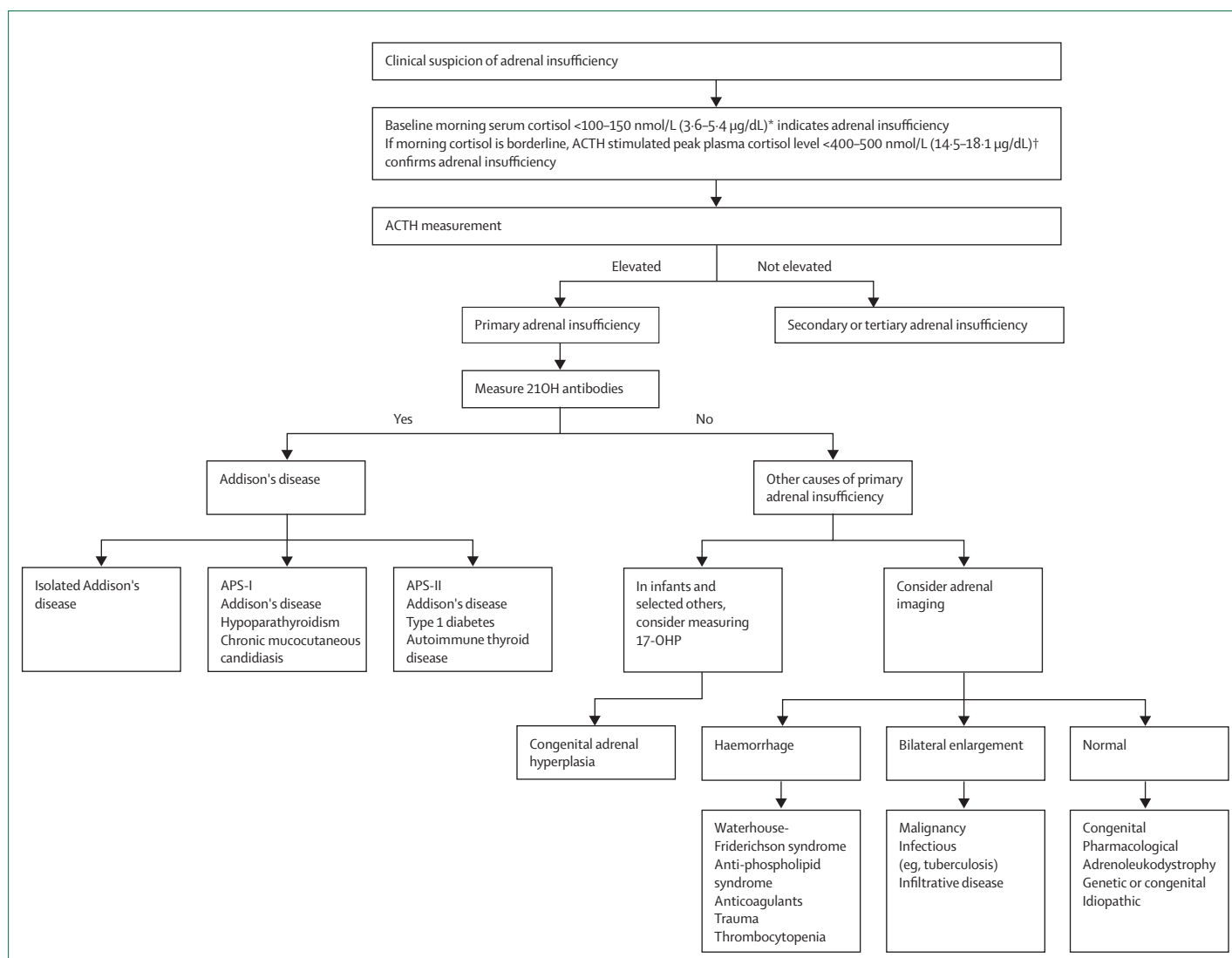


Figure 2: Approach to diagnosis of Addison's disease and other causes of primary adrenal insufficiency

ACTH=adrenocorticotropic hormone. APS=autoimmune polyendocrine syndrome. 17-OHP=17-hydroxyprogesterone. 21OH=21-hydroxylase. *Thresholds for morning serum cortisol are laboratory and assay-dependent, and are often set based on a sensitivity of less than 100%. Therefore, cases of Addison's disease 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 min, and local guidelines should be followed.

course of the day, with pulses of cortisol secretion superimposed on this rhythm, highest in the morning (figure 3A).^{62,63} Conventional glucocorticoid replacement therapy uses immediate-release glucocorticoid preparations, such as hydrocortisone acetate and cortisone acetate. Due to the short half-life of these drugs (approximately 90 min), multiple daily administrations are required.¹⁵ To mimic the peak in cortisol after waking, the highest dose of glucocorticoid is administered upon awakening, whereas 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 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 recommend oral hydrocortisone replacement as first-line treatment at 15–25 mg/day in two to four divided doses.⁴⁷ Cortisone acetate is an inactive glucocorticoid precursor that requires activation via hepatic 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), and therefore has a slightly delayed onset of action compared with hydrocortisone.⁴⁶ Hydrocortisone is favoured in most industrialised countries and some believe that precursor glucocorticoids such as cortisone result in a greater degree of person-to-person variation, although there is little evidence for this.^{15,66} Prednisolone or prednisone (3–5 mg/day) can be used as an alternative replacement

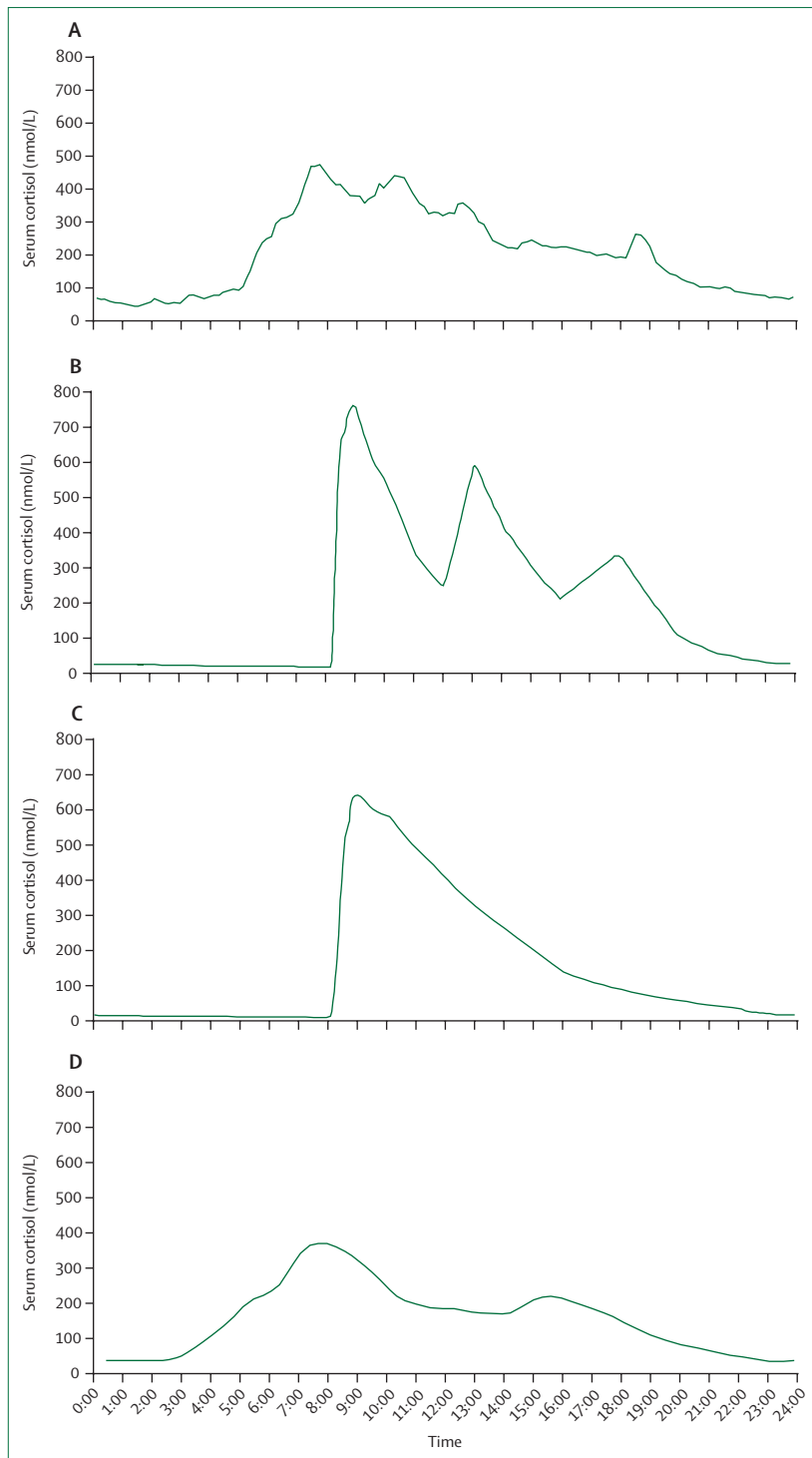


Figure 3: 24 h serum cortisol levels physiologically and during glucocorticoid replacement regimens.

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

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 doses and regimens. Dose adjustments following clinical assessment can be made,^{15,47} but there is currently no robust or reliable marker of glucocorticoid action. 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 were reviewed by Caetano and Malchoff in 2022.⁷⁰ Signs of glucocorticoid under-replacement include nausea, weight loss, early satiety or decreased appetite, muscle weakness, low energy levels affecting activities of daily living, and worsening hyperpigmentation. Signs of over-replacement include weight gain, increased appetite, increasing blood pressure, worsening glycaemic control, disturbed sleep, cushingoid appearance, acne, thrush, fragility fractures, and reduced height.⁷¹ There are currently no validated, objective biomarkers that guide decision making on glucocorticoid dose-titration in Addison's disease.

Modified-release hydrocortisone

Multiple daily doses of immediate-release hydrocortisone result in discrete peaks of serum cortisol with intervening periods of hypocortisolaemia and therefore fail to accurately mimic the circadian and pulsatile ultradian rhythm of physiological glucocorticoid secretion (figure 3B). Modified-release preparations of hydrocortisone have been developed to try to address some of the shortcomings of conventional immediate-release hydrocortisone. Plenadren is composed of a controlled-release core and an outer immediate-release coating, and upon ingestion in the morning leads to a rapid increase in cortisol concentrations, followed by a gradual decline over the course of the day (figure 3C).^{62,72}

Studies have shown beneficial effects of Plenadren on bodyweight and composition compared with conventional hydrocortisone in people with Addison's disease.^{73,74} Some studies report an improvement in HbA_{1c},^{73,75,76} insulin sensitivity,^{77,78} Homeostatic Model Assessment for Insulin Resistance,⁷⁷ and blood pressure⁷³ in people with Addison's disease using Plenadren. There are conflicting reports on the effect of Plenadren on cholesterol levels.⁶² Some studies have reported a progressive decrease in total and low-density lipoprotein cholesterol,⁷⁹ whereas others have reported unfavourable changes such as a reduction in high-density lipoprotein cholesterol.⁸⁰ Plenadren is also associated with more physiological immune cell profiles and reduced susceptibility to infections compared with 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 with baseline, whereas conventional regimens were associated with a decrease in bone mineral density.⁸² Quality of life was reported to decline with immediate-release hydrocortisone,⁶² whereas Plenadren use has been associated with improvements in health-related quality of life (HRQoL). Findings from some of the above studies should be interpreted with caution due to lack of blinding.^{75,80}

Plenadren is licensed by the European Medicines Agency for the treatment of Addison's disease, but despite promising findings from existing studies it is only used in a minority of people with Addison's disease in some countries, such as the UK. This decision not to use Plenadren might reflect the cost of modified-release hydrocortisone, and its unknown effects on important long-term cardiometabolic outcomes. The 24-h 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 might 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 a day 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 primary adrenal insufficiency is currently being investigated (NCT05222152), and it is currently only licensed for people with congenital adrenal hyperplasia.^{62,84}

Mineralocorticoid replacement

People with Addison's disease 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 might be influenced by treatment adherence, posture, timing of last dose, and concomitant medication.^{85,86} In individuals newly diagnosed with Addison's disease 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 blood pressure remains high.⁸⁷ A daily dose of 50–200 µg fludrocortisone is usually sufficient.^{15,46} In addition to pharmacological therapy, people with Addison's disease are advised to consume salt as desired without restriction (while avoiding salts with high concentrations of potassium).⁴⁶ Dose increments or increased salt intake can be recommended temporarily in hot conditions that stimulate excessive sweating.

Adrenal androgen replacement

DHEA and DHEA-S are androgens 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 oestrogens in target cells.¹⁵ They can also act as neurosteroids, modulating neurotransmitter receptors, displaying neuroprotective and anti-inflammatory effects.⁸⁸

The exact role of DHEA replacement in women with Addison's disease is unclear. The adrenal glands are the primary source of DHEA and in women are a major contributor to circulating androgen concentrations. 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 Addison's disease are inconsistent.^{90–92} A systematic review which indicated that DHEA replacement might slightly improve HRQoL and depression in women with adrenal insufficiency (with no significant effect on anxiety or sexual well-being) concluded that there is insufficient evidence to support its routine use.⁹³

A pragmatic approach might be 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 Addison's disease are not known and should be discontinued after 6 months if there is no sustained, beneficial effect. Sexual dysfunction in Addison's disease correlates poorly with androgen concentrations and is frequently multifactorial in origin. It requires a holistic approach beyond replacement of sex steroids, but further research as to its coexistence in Addison's disease and optimal management are needed.⁹⁴

Testing for other autoimmune conditions

Periodic screening for other autoimmune conditions is recommended in people with Addison's disease and should be guided by clinical features. Routine surveillance for conditions that frequently co-occur, such as thyroid disease (thyroid function tests and thyroid peroxidase antibodies), type 2 diabetes (plasma glucose and HbA_{1c}), pernicious anaemia (full blood count and vitamin B12), and coeliac disease, is recommended

annually.⁴⁶ The presence of side-chain cleavage 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 Addison's disease have increased mortality in addition to reduced HRQoL and working ability.^{5,91,96–99} Although these outcomes might partly be 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 increases the risk of an adrenal crisis.¹⁷ Chronic over-replacement induces a Cushing's syndrome-like state with increased cardiovascular risk. It was suggested that the observed increase in mortality from infections and altered pattern of cancer incidence⁹⁶ might be related to the effect of chronic glucocorticoid therapy on immunity¹⁰¹ and, as such, vigilance for these complications should be encouraged. Cognitive deficits in Addison's disease, such as impaired memory and executive function, might 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,¹⁰⁴ and a failure to mimic pulsatile ultradian release of cortisol with existing replacement regimens might 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 1.^{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 (eg, 10 mg), 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

Panel 1: 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

Physiological stress

During febrile illness, oral hydrocortisone dose should be doubled (or tripled if fever >39°C) until recovery.¹⁵ While suffering from physical trauma requiring medical attention, use at least double dose of glucocorticoid until resolution.⁴⁷

Lack of effective oral route

Early administration of parenteral hydrocortisone is recommended (100 mg intramuscular or subcutaneous) and the patient should be advised to attend the emergency department.^{15,47}

Onset of vomiting

For vomiting under 30 minutes after taking an oral dose, take a further dose at twice the original dose once vomiting subsides. If vomiting recurs within 30 min, give intramuscular hydrocortisone, and advise the patient to attend the emergency department.⁴⁷

Psychological stress (eg, bereavement, major examination, marriage, or divorce)

Minor dose increases, eg, 10 mg hydrocortisone, as an additional dose.¹⁴ Sick day dosing for 1–2 days.⁴⁷

Severe mental health crisis (eg, a psychotic episode)

Consider sick day dosing and 100 mg intramuscular 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.¹⁰⁶

Labour

100 mg hydrocortisone intravenous or intramuscular at the onset of labour followed by 200 mg hydrocortisone every 24 h via continuous infusion or 50 mg boluses every 6 h.¹⁰⁶

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.¹⁰⁶

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 Addison's disease should be given a steroid emergency card (figure 4) and provided with and trained to use a glucocorticoid injection kit. Of concern, patients with chronic adrenal insufficiency who have received education still have 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 Addison's disease have parenteral glucocorticoid at home, and even when available it is underused for various reasons.^{17,107,108} The complex, multistep nature of preparing and administering a hydrocortisone injection is a challenge and over 50% of people with Addison's disease who responded to a survey in the USA reported that they never had the opportunity to practice preparation and administration.¹⁰⁸ Previous practice of parenteral hydrocortisone administration is likely to improve confidence and success, but repetition and adaptation of training to the individual is necessary.¹⁰⁹ The effects of the

intercurrent illness and confusion are additional barriers to administration and assistance might sometimes be required.

Education sessions could be improved by providing 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 premeasured injection of hydrocortisone, similar to autoinjectors used for anaphylaxis, could remove barriers to prehospital parenteral hydrocortisone delivery, and there is considerable demand from people with Addison's disease for such a device.¹¹⁰ There are early suggestions that self-injection could positively influence the course and outcome of adrenal crises.¹¹¹

Comorbidities, such as type 1 diabetes, diabetes insipidus, asthma, and primary ovarian insufficiency, increase the risk of adrenal crisis in people with Addison's disease.^{112,113} 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 Addison's disease and type 1 diabetes,¹¹⁴ and therefore patient education should take comorbidities into consideration and cover dose adaptation of concomitant medications where appropriate.

Studies published since 2020 have provided evidence that psychosocial factors play an important role in the onset of adrenal crises in people with adrenal insufficiency. Financial pressures, psychiatric comorbidities, and drug or alcohol misuse, as well as the disruption of social

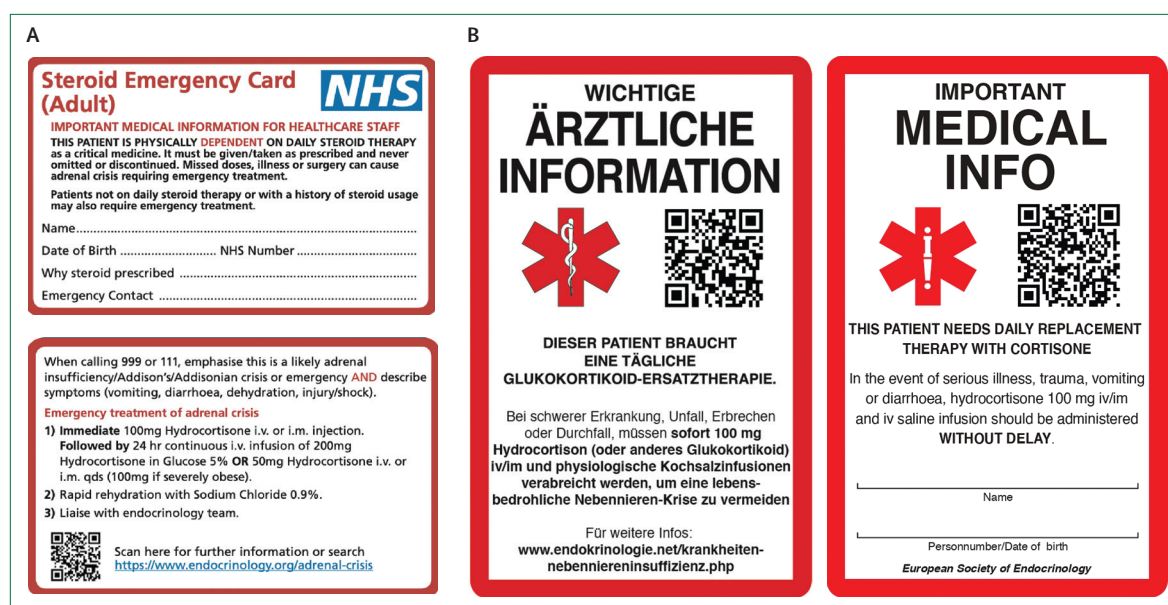


Figure 4: Steroid emergency cards from different world regions.

(A) National Health Service 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 or necklace is used.

structures around the individual, are pressures for adrenal crisis in younger or middle-aged individuals.^{115,116} 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.¹¹⁷ Such evidence suggests that educational measures alone might not be sufficient in preventing adrenal crisis, and that there is a need to address the wider psychological and social barriers to prevent adrenal crisis with targeted interventions.

Adrenal crisis management

In acutely unwell patients where Addison's disease is suspected, treatment should not be delayed pending test results.¹³ The two principles of management of adrenal crisis are prompt administration of intravenous fluid and of hydrocortisone (panel 2). 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 Addison's disease in pregnancy

Pregnancy is a challenging period for the management of Addison's disease, as many symptoms of Addison's disease and the corresponding signs of corticosteroid overtitration or undertitration overlap with normal features of pregnancy. Incident Addison's disease during pregnancy is rare, and interpretation of tests of adrenocortical function requires consideration of the normal physiological changes of pregnancy.^{15,106} There is a lack of studies on the optimal glucocorticoid dose and regimen in pregnancy and variability in clinical practice.¹⁰⁶

Panel 2: Management of adrenal crisis.

Modified from Bornstein and colleagues,¹⁵ with additional recommendations incorporated from other sources.^{14,46,47,106}

Immediate administration of intravenous or intramuscular 100 mg hydrocortisone for adults. An intramuscular 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 h or divided into boluses every 6 h. After the first 24 h, daily hydrocortisone dose is reduced to 100 mg per day.

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

Appropriate treatment of intercurrent illness.

Hydrocortisone is preferred to other glucocorticoids for Addison's disease in pregnancy and dexamethasone should be avoided. Neither hydrocortisone nor prednisone or prednisolone cross the placenta due to the activity of placental 11 β -HSD2, whereas dexamethasone is not susceptible to placental deactivation and can therefore affect the developing foetus.^{15,106} Daily glucocorticoid dosing is often increased by 20–40% after gestational week 24 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} Although some advocate for an increase of mineralocorticoid dosing during pregnancy in response to blood pressure and potassium concentrations,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 1).¹⁰⁶ Despite the availability of pregnancy-specific guidelines for management of Addison's disease, 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 primary adrenal insufficiency, and only 41% of women received an increase in hydrocortisone dose.¹²⁰ Although 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 with oral hydrocortisone, continuous subcutaneous hydrocortisone infusion (CSHI) can better mimic both physiological circadian and pulsatile ultradian rhythms.^{122,123} However, it is infrequently used in clinical practice.

Studies comparing the effect of CSHI on oral replacement in 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 with placebo.^{124,125} However, in PULSES, a double-blinded placebo-controlled crossover trial in people with Addison's disease, 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 effect of cortisol pulsatility on neural processing and mood seen in the

PULSES trial is consistent with previous studies showing 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 with oral hydrocortisone, and participants sometimes report pain from the catheter site.¹²⁴ In a study in patients with congenital adrenal hyperplasia, two of six people chose to switch back from CSHI to oral hydrocortisone.¹²⁶ CSHI might be suitable for a very small subset of people with Addison's disease 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

Personalisation and titration of corticosteroid therapy

Identifying biomarkers for dose titration and individualisation of corticosteroid dosing is challenging, at least in part due to the high degree of interindividual variability in cortisol physiology. Circulating whole blood gene expression (*DSIPI*, *MMP9*, and *FKBP5*),¹²⁷ osteocalcin, immunological markers,¹²⁸ and 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 that enable 24-h 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 concentrations, 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 with 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 expression 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 have 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 Addison's disease by restoring endogenous adrenal steroid production, removing the

need for corticosteroid replacement. Although still in preclinical phases of development, technologies associated with adrenocortical cell transplantation are developing swiftly.^{132,133} Graft tissue might be derived from primary cell isolates, animal-derived xenografts, induced pluripotent stem cells, or from cellular reprogramming of differentiated cells. Importantly, the high turnover rate of adrenocortical cells¹³⁴ necessitates the incorporation of adrenocortical progenitor cells to prevent graft exhaustion.¹³² The precise 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 and maintenance has improved in recent decades, including the role of the 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 the capability of differentiating into glucocorticoid-producing and mineralocorticoid-producing 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 responsiveness¹⁴⁶ 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 Addison's disease with anti-CD20 therapy, one of six 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), two of 13 people with Addison's disease 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 Addison's disease.

Although a study assessing combination therapy with anti-CD20 and tetracosactide did not restore normal adrenal steroidogenesis in any of the 13 participants with Addison's disease, it highlighted the potential for adrenal plasticity as four of 13 had residual adrenal function at 72 weeks.¹⁵¹ Elucidating why some individuals respond to regenerative therapy and identifying biomarkers of residual adrenal function should be a

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, covering the period from from Jan 1, 1974, to Sept 30, 2025. Reference lists of articles identified from this search were reviewed for other relevant articles. Only articles published in English were included. In addition, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform registry were also searched for clinical trials on Addison's disease therapies from database inception to Sept 30, 2025.

priority and studies are being conducted to further characterise residual adrenal function in Addison's disease (NCT06309498 and NCT03793114).

Conclusion 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 Addison's disease, and both treatments have their respective merits. Although there is optimism surrounding 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 Addison's disease are delayed diagnoses and the occurrence of adrenal crises, which in many cases are entirely preventable. Health-care providers should consider Addison's disease 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 on the use and administration of parenteral hydrocortisone and the importance of implementing established principles of Addison's disease 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 timely diagnosis, reduce the incidence of adrenal crises, and improve the morbidity and mortality of people with Addison's disease.

Contributors

All authors contributed to developing the structure of the review, literature search and drafting of the manuscript.

Declaration of interests

JD has no declarations of interest. JWT has been an advisory board member for Diurnal. IB reports consulting, advisory board or data safety and monitoring board participation (fees to institution) for Adrenas, Spruce, Neurocrine, Corcept, Camurus, Crinetics, AstraZeneca, NovoNordisk, Xeris, Recordati, HRA Pharma, Adaptyx, and Liford.

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References

- Betterle C, Presotto F, Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. *J Endocrinol Invest* 2019; **42**: 1407–33.
- Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol* 2015; **3**: 216–26.
- Hahner S, Ross RJ, Arlt W, et al. Adrenal insufficiency. *Nat Rev Dis Primers* 2021; **7**: 19.
- Lovås K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. *Clin Endocrinol* 2002; **56**: 787–91.
- Erichsen MM, Lovås K, Skiningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. *J Clin Endocrinol Metab* 2009; **94**: 4882–90.
- Björnsdóttir S, Sundström A, Ludvigsson JF, Blomqvist P, Kämpe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. *J Clin Endocrinol Metab* 2013; **98**: 2009–18.
- Komninos J, Kohler S, Karavitaki N, Wass J. Epidemiology of Addison's disease in the area of Banbury, Oxfordshire. *Endocr Abstr* 2011; **25**: P307 (abstr).
- Olafsson AS, Sigurjonsdóttir HA. Increasing prevalence of Addison disease: results from a nationwide study. *Endocr Pract* 2016; **22**: 30–35.
- Takayanagi R, Miura K, Nakagawa H, Nawata H. Epidemiologic study of adrenal gland disorders in Japan. *Biomed Pharmacother* 2000; **54** (suppl 1): 164s–68s.
- Ross IL, Levitt NS. Addison's disease symptoms—a cross sectional study in urban South Africa. *PLoS One* 2013; **8**: e53526.
- Saevik AB, Åkerman AK, Grønning K, et al. Clues for early detection of autoimmune Addison's disease - myths and realities. *J Intern Med* 2018; **283**: 190–99.
- Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal crisis: still a deadly event in the 21st century. *Am J Med* 2016; **129**: 339. e1–9.
- Rushworth RL, Torpy DJ, Falhammar H. Adrenal crisis. *N Engl J Med* 2019; **381**: 852–61.
- Allolio B. Extensive expertise in endocrinology. Adrenal crisis. *Eur J Endocrinol* 2015; **172**: R115–24.
- Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2016; **101**: 364–89.
- Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. *Endocrine* 2017; **55**: 336–45.
- Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab* 2015; **100**: 407–16.
- Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol* 2010; **162**: 597–602.
- Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. *Br Med J* 1986; **292**: 1185–86.
- Kang MS, Sandhu CS, Singh N, Evans T. Initiation of levothyroxine in a patient with hypothyroidism inducing adrenal crisis requiring VA ECMO: a tale of preventable disaster. *BMJ Case Rep* 2019; **12**: e230601.

- 21 Quinkler M, Murray RD, Zhang P, et al. Characterization of patients with adrenal insufficiency and frequent adrenal crises. *Eur J Endocrinol* 2021; **184**: 761–71.
- 22 Dineen R, Thompson CJ, Sherlock M. Adrenal crisis: prevention and management in adult patients. *Ther Adv Endocrinol Metab* 2019; **10**: 2042018819848218.
- 23 Dalin F, Nordling Eriksson G, Dahlqvist P, et al. Clinical and immunological characteristics of autoimmune Addison disease: a nationwide Swedish multicenter study. *J Clin Endocrinol Metab* 2017; **102**: 379–89.
- 24 Rosenthal FD, Davies MK, Burden AC. Malignant disease presenting as Addison's disease. *BMJ* 1978; **1**: 1591–92.
- 25 Winqvist O, Karlsson FA, Kämpe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet* 1992; **339**: 1559–62.
- 26 Laureti S, De Bellis A, Muccitelli VI, et al. Levels of adrenocortical autoantibodies correlate with the degree of adrenal dysfunction in subjects with preclinical Addison's disease. *J Clin Endocrinol Metab* 1998; **83**: 3507–11.
- 27 Betterle C, Coco G, Zanchetta R. Adrenal cortex autoantibodies in subjects with normal adrenal function. *Baillieres Best Pract Res Clin Endocrinol Metab* 2005; **19**: 85–99.
- 28 Betterle C, Volpato M, Rees Smith B, et al. I. Adrenal cortex and steroid 21-hydroxylase autoantibodies in adult patients with organ-specific autoimmune diseases: markers of low progression to clinical Addison's disease. *J Clin Endocrinol Metab* 1997; **82**: 932–38.
- 29 Betterle C, Scarpa R, Garelli S, et al. Addison's disease: a survey on 633 patients in Padova. *Eur J Endocrinol* 2013; **169**: 773–84.
- 30 Boscaro M, Betterle C, Volpato M, et al. Hormonal responses during various phases of autoimmune adrenal failure: no evidence for 21-hydroxylase enzyme activity inhibition in vivo. *J Clin Endocrinol Metab* 1996; **81**: 2801–04.
- 31 Hellesen A, Bratland E, Husebye ES. Autoimmune Addison's disease - an update on pathogenesis. *Ann Endocrinol* 2018; **79**: 157–63.
- 32 Betterle C, Pra CD, Pedini B, et al. Assessment of adrenocortical function and autoantibodies in a baby born to a mother with autoimmune polyglandular syndrome Type 2. *J Endocrinol Invest* 2004; **27**: 618–21.
- 33 Rottembourg D, Deal C, Lambert M, et al. 21-Hydroxylase epitopes are targeted by CD8 T cells in autoimmune Addison's disease. *J Autoimmun* 2010; **35**: 309–15.
- 34 Irvine WJ, Stewart AG, Scarth L. A clinical and immunological study of adrenocortical insufficiency (Addison's disease). *Clin Exp Immunol* 1967; **2**: 31–70.
- 35 al Sabri AM, Smith N, Busuttill A. Sudden death due to autoimmune Addison's disease in a 12-year-old girl. *Int J Legal Med* 1997; **110**: 278–80.
- 36 Eriksson D, Røyrvik EC, Aranda-Guillén M, et al, and the Norwegian Addison Registry Study Group, and the Swedish Addison Registry Study Group. GWAS for autoimmune Addison's disease identifies multiple risk loci and highlights AIRE in disease susceptibility. *Nat Commun* 2021; **12**: 959.
- 37 Røyrvik EC, Husebye ES. The genetics of autoimmune Addison disease: past, present and future. *Nat Rev Endocrinol* 2022; **18**: 399–412.
- 38 Chantzichristos D, Persson A, Eliasson B, et al. Incidence, prevalence and seasonal onset variation of Addison's disease among persons with type 1 diabetes mellitus: nationwide, matched cohort studies. *Eur J Endocrinol* 2018; **178**: 113–20.
- 39 Pazderska A, Fichna M, Mitchell AL, et al. Impact of month of birth on the risk of development of autoimmune Addison's disease. *J Clin Endocrinol Metab* 2016; **101**: 4214–18.
- 40 Hellesen A, Bratland E. The potential role for infections in the pathogenesis of autoimmune Addison's disease. *Clin Exp Immunol* 2019; **195**: 52–63.
- 41 Sirbe C, Rednic S, Grama A, Pop TL. An update on the effects of vitamin D on the immune system and autoimmune diseases. *Int J Mol Sci* 2022; **23**: 9784.
- 42 Pani MA, Seissler J, Usadel KH, Badenhoop K. Vitamin D receptor genotype is associated with Addison's disease. *Eur J Endocrinol* 2002; **147**: 635–40.
- 43 Jennings CE, Owen CJ, Wilson V, Pearce SH. A haplotype of the CYP27B1 promoter is associated with autoimmune Addison's disease but not with Graves' disease in a UK population. *J Mol Endocrinol* 2005; **34**: 859–63.
- 44 Lopez ER, Zwermann O, Segni M, et al. A promoter polymorphism of the CYP27B1 gene is associated with Addison's disease, Hashimoto's thyroiditis, Graves' disease and type 1 diabetes mellitus in Germans. *Eur J Endocrinol* 2004; **151**: 193–97.
- 45 Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. *Lancet* 2021; **397**: 613–29.
- 46 Husebye ES, Alolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. *J Intern Med* 2014; **275**: 104–15.
- 47 NICE. Adrenal insufficiency: identification and management. 2024. <https://www.nice.org.uk/guidance/ng243> (accessed Nov 16, 2025).
- 48 Sbardella E, Isidori AM, Woods CP, et al. Baseline morning cortisol level as a predictor of pituitary-adrenal reserve: a comparison across three assays. *Clin Endocrinol* 2017; **86**: 177–84.
- 49 Dong J, Tomlinson JW. Lessons to learn from the 2024 NICE guideline on adrenal insufficiency. *Lancet Diabetes Endocrinol* 2024; **12**: 872–73.
- 50 le Roux CW, Chapman GA, Kong WM, Dhillon WS, Jones J, Alaghband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 2003; **88**: 2045–48.
- 51 Bikle DD. The free hormone hypothesis: when, why, and how to measure the free hormone levels to assess vitamin D, thyroid, sex hormone, and cortisol status. *JBM Plus* 2020; **5**: e10418.
- 52 Verbeeten KC, Ahmet AH. The role of corticosteroid-binding globulin in the evaluation of adrenal insufficiency. *J Pediatr Endocrinol Metab* 2018; **31**: 107–15.
- 53 Cartaya J, Misra M. The low-dose ACTH stimulation test: is 30 minutes long enough? *Endocr Pract* 2015; **21**: 508–13.
- 54 Javorsky BR, Raff H, Carroll TB, et al. New cutoffs for the biochemical diagnosis of adrenal insufficiency after ACTH stimulation using specific cortisol assays. *J Endocr Soc* 2021; **5**: bvab022.
- 55 Okutan S, Jørgensen NT, Pedersen LE, et al. Determination of cortisol cut-off limits and steroid dynamics in the ACTH stimulation test: a comparative analysis using Roche Elecsys Cortisol II immunoassay and LC-MS/MS. *Endocrine* 2024; **85**: 321–30.
- 56 Debono M, Harrison RF, Whitaker MJ, et al. Salivary cortisone reflects cortisol exposure under physiological conditions and after hydrocortisone. *J Clin Endocrinol Metab* 2016; **101**: 1469–77.
- 57 Perogamvros I, Aarons L, Miller AG, Trainer PJ, Ray DW. Corticosteroid-binding globulin regulates cortisol pharmacokinetics. *Clin Endocrinol* 2011; **74**: 30–36.
- 58 Debono M, Elder CJ, Lewis J, et al. Home waking salivary cortisone to screen for adrenal insufficiency. *NEJM Evid* 2023; **2**: EVIDoa2200182.
- 59 Oelkers W, Diederich S, Bähr V. Diagnosis and therapy surveillance in Addison's disease: rapid adrenocorticotropin (ACTH) test and measurement of plasma ACTH, renin activity, and aldosterone. *J Clin Endocrinol Metab* 1992; **75**: 259–64.
- 60 Han AJ, Suresh M, Gruber LM, et al. Performance of dehydroepiandrosterone sulfate and baseline cortisol in assessing adrenal insufficiency. *J Clin Endocrinol Metab* 2025; **110**: e3117–24.
- 61 Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev* 2022; **43**: 91–159.
- 62 Steintorsdottir SD, Øksnes M, Jørgensen AP, Husebye ES. Extended-release hydrocortisone formulations-is there a clinically meaningful benefit? *J Clin Endocrinol Metab* 2025; **110**: e566–73.
- 63 Knutsson U, Dahlgren J, Marcus C, et al. Circadian cortisol rhythms in healthy boys and girls: relationship with age, growth, body composition, and pubertal development. *J Clin Endocrinol Metab* 1997; **82**: 536–40.
- 64 Plat L, Leproult R, L'Hermite-Baleriaux M, et al. Metabolic effects of short-term elevations of plasma cortisol are more pronounced in the evening than in the morning. *J Clin Endocrinol Metab* 1999; **84**: 3082–92.
- 65 Beuschlein F, Else T, Bancos I, et al. European Society of Endocrinology and Endocrine Society joint clinical guideline: diagnosis and therapy of glucocorticoid-induced adrenal insufficiency. *J Clin Endocrinol Metab* 2024; **109**: 1657–83.

- 66 Allolio B, Winkelmann W, Fricke U, Heesen D, Kaulen D. [Cortisol plasma concentration in patients with primary adrenal cortex insufficiency during substitution therapy with cortisone acetate]. *Verh Dtsch Ges Inn Med* 1978; **84**: 1456–58.
- 67 Whittle E, Falhammar H. Glucocorticoid regimens in the treatment of congenital adrenal hyperplasia: a systematic review and meta-analysis. *J Endocr Soc* 2019; **3**: 1227–45.
- 68 Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018; **103**: 4043–88.
- 69 Fadeev VV, Gitel EP, Mel'nichenko GA. The diurnal rhythm of adrenocorticotropic hormone secretion in the assessment of the adequacy of replacement therapy in primary chronic adrenal failure. *Neurosci Behav Physiol* 2001; **31**: 237–42.
- 70 Caetano CM, Malchoff CD. Daily glucocorticoid replacement dose in adrenal insufficiency, a mini review. *Front Endocrinol* 2022; **13**: 897211.
- 71 Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the side effects of exogenous glucocorticoids; can we separate the good from the bad? *Endocr Rev* 2023; **44**: 975–1011.
- 72 Johannsson G, Bergthorsdottir R, Nilsson AG, Lennernas H, Hedner T, Skrtic S. Improving glucocorticoid replacement therapy using a novel modified-release hydrocortisone tablet: a pharmacokinetic study. *Eur J Endocrinol* 2009; **161**: 119–30.
- 73 Johannsson G, Nilsson AG, Bergthorsdottir R, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *J Clin Endocrinol Metab* 2012; **97**: 473–81.
- 74 Dineen R, Martin-Grace J, Ahmed KMS, et al. Cardiometabolic and psychological effects of dual-release hydrocortisone: a cross-over study. *Eur J Endocrinol* 2021; **184**: 253–65.
- 75 Mongioli LM, Condorelli RA, La Vignera S, Calogero AE. Dual-release hydrocortisone treatment: glycometabolic profile and health-related quality of life. *Endocr Connect* 2018; **7**: 211–19.
- 76 Guarnotta V, Di Stefano C, Santoro A, Ciresi A, Coppola A, Giordano C. Dual-release hydrocortisone vs conventional glucocorticoids in adrenal insufficiency. *Endocr Connect* 2019; **8**: 853–62.
- 77 Guarnotta V, Mineo MI, Radellini S, Pizzolanti G, Giordano C. Dual-release hydrocortisone improves hepatic steatosis in patients with secondary adrenal insufficiency: a real-life study. *Ther Adv Endocrinol Metab* 2019; **10**: 2042018819871169.
- 78 Guarnotta V, Ciresi A, Pillitteri G, Giordano C. Improved insulin sensitivity and secretion in prediabetic patients with adrenal insufficiency on dual-release hydrocortisone treatment: a 36-month retrospective analysis. *Clin Endocrinol* 2018; **88**: 665–72.
- 79 Giordano R, Guaraldi F, Marinazzo E, et al. Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. *Endocrine* 2016; **51**: 360–68.
- 80 Isidori AM, Venneri MA, Graziadio C, et al. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* 2018; **6**: 173–85.
- 81 Hasenmajer V, Ferrari D, De Alcubierre D, et al. Effects of dual-release hydrocortisone on bone metabolism in primary and secondary adrenal insufficiency: a 6-year study. *J Endocr Soc* 2023; **8**: bvad151.
- 82 Guarnotta V, Di Stefano C, Giordano C. Long-term outcomes of conventional and novel steroid replacement therapy on bone health in primary adrenal insufficiency. *Sci Rep* 2022; **12**: 13280.
- 83 Whitaker M, Debono M, Huatan H, Merke D, Arlt W, Ross RJ. An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure. *Clin Endocrinol* 2014; **80**: 554–61.
- 84 Merke DP, Mallappa A, Arlt W, et al. Modified-release hydrocortisone in congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2021; **106**: e2063–77.
- 85 Pofi R, Bonaventura I, Duffy J, et al. Assessing treatment adherence is crucial to determine adequacy of mineralocorticoid therapy. *Endocr Connect* 2023; **12**: e230059.
- 86 Pofi R, Prete A, Thornton-Jones V, et al. Plasma renin measurements are unrelated to mineralocorticoid replacement dose in patients with primary adrenal insufficiency. *J Clin Endocrinol Metab* 2020; **105**: dgz055.
- 87 Esposito D, Pasquali D, Johannsson G. Primary adrenal insufficiency: managing mineralocorticoid replacement therapy. *J Clin Endocrinol Metab* 2018; **103**: 376–87.
- 88 Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Front Neuroendocrinol* 2009; **30**: 65–91.
- 89 Schmidt PJ, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry* 2005; **62**: 154–62.
- 90 Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341**: 1013–20.
- 91 Gurnell EM, Hunt PJ, Curran SE, et al. Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 2008; **93**: 400–09.
- 92 Lovås K, Gebre-Medhin G, Trovik TS, et al. Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. *J Clin Endocrinol Metab* 2003; **88**: 1112–18.
- 93 Alkatib AA, Cosma M, Elamin MB, et al. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94**: 3676–81.
- 94 Hasenmajer V, De Alcubierre D, Ferrari D, et al. Exploring sexual function in adrenal insufficiency: findings from the Dual Release hydrocortisone versus conventional glucocorticoid replacement therapy in hypocortisolism (DREAM) trial. *Andrology* 2025; **13**: 302–13.
- 95 Dal Pra C, Chen S, Furmaniak J, et al. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. *Eur J Endocrinol* 2003; **148**: 565–70.
- 96 Bensing S, Brandt L, Tabaroj F, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. *Clin Endocrinol* 2008; **69**: 697–704.
- 97 Johannsson G, Falorni A, Skrtic S, et al. Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy. *Clin Endocrinol* 2015; **82**: 2–11.
- 98 Hahner S, Loeffler M, Fassnacht M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. *J Clin Endocrinol Metab* 2007; **92**: 3912–22.
- 99 Lovås K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. *Clin Endocrinol* 2002; **56**: 581–88.
- 100 Stewart PM, Biller BM, Marelli C, Gunnarsson C, Ryan MP, Johannsson G. Exploring inpatient hospitalizations and morbidity in patients with adrenal insufficiency. *J Clin Endocrinol Metab* 2016; **101**: 4843–50.
- 101 Bancos I, Hazeldine J, Chortis V, et al. Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality. *Eur J Endocrinol* 2017; **176**: 471–80.
- 102 Tytherleigh MY, Vedhara K, Lightman SL. Mineralocorticoid and glucocorticoid receptors and their differential effects on memory performance in people with Addison's disease. *Psychoneuroendocrinology* 2004; **29**: 712–23.
- 103 De Alcubierre D, Ferrari D, Mauro G, Isidori AM, Tomlinson JW, Pofi R. Glucocorticoids and cognitive function: a walkthrough in endogenous and exogenous alterations. *J Endocrinol Invest* 2023; **46**: 1961–82.
- 104 Kalafatakis K, Russell GM, Harmer CJ, et al. Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. *Proc Natl Acad Sci USA* 2018; **115**: e4091–100.
- 105 Woodcock T, Barker P, Daniel S, et al. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. *Anaesthesia* 2020; **75**: 654–63.

- 106 Pofi R, Tomlinson JW. Glucocorticoids in pregnancy. *Obstet Med* 2020; **13**: 62–69.
- 107 Li D, Brand S, Hamidi O, et al. Quality of life and its determinants in patients with adrenal insufficiency: a survey study at 3 centers in the United States. *J Clin Endocrinol Metab* 2022; **107**: e2851–61.
- 108 Hover WJ, Krein AD, Kallet J, et al. People with adrenal insufficiency who are in adrenal crisis are frequently unable to self-administer rescue injections. *Endocr Pract* 2025; **31**: 625–30.
- 109 Burger-Stritt S, Eff A, Quinkler M, et al. Standardised patient education in adrenal insufficiency: a prospective multi-centre evaluation. *Eur J Endocrinol* 2020; **183**: 119–27.
- 110 Llahana S, Anthony J, Sarafoglou K, Geffner ME, Ross R. Patient and caregiver experiences with hydrocortisone injections in adrenal crisis: a mixed-methods cross-sectional study. *Front Endocrinol* 2025; **16**: 1544502.
- 111 Burger-Stritt S, Kardonski P, Pulzer A, Meyer G, Quinkler M, Hahner S. Management of adrenal emergencies in educated patients with adrenal insufficiency—a prospective study. *Clin Endocrinol* 2018; **89**: 22–29.
- 112 White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *Eur J Endocrinol* 2010; **162**: 115–20.
- 113 Claessen KMJA, Andela CD, Biermasz NR, Pereira AM. Clinical unmet needs in the treatment of adrenal crisis: importance of the patient's perspective. *Front Endocrinol* 2021; **12**: 701365.
- 114 Chantzichristos D, Eliasson B, Johannsson G. Management of endocrine disease: disease burden and treatment challenges in patients with both Addison's disease and type 1 diabetes mellitus. *Eur J Endocrinol* 2020; **183**: R1–11.
- 115 Rushworth RL, Falhammar H, Torpy DJ. Adrenal crisis and adrenal insufficiency admissions in patients 30–59 years: contribution of psychosocial factors. *Clin Endocrinol* 2025; **102**: 245–54.
- 116 Rushworth RL, Falhammar H, Torpy DJ. Factors underlying a disproportionate increase in hospital admissions for adrenal insufficiency in women aged 20–29 years. *Front Endocrinol* 2023; **14**: 1252577.
- 117 Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises in older patients. *Lancet Diabetes Endocrinol* 2020; **8**: 628–39.
- 118 Suri D, Moran J, Hibbard JU, Kasza K, Weiss RE. Assessment of adrenal reserve in pregnancy: defining the normal response to the adrenocorticotropic stimulation test. *J Clin Endocrinol Metab* 2006; **91**: 3866–72.
- 119 Quinkler M, Oelkers W, Remde H, Alolio B. Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. *Best Pract Res Clin Endocrinol Metab* 2015; **29**: 17–24.
- 120 Cauldwell M, Steer PJ, Ahsan M, et al. Pregnancy outcomes in women with primary adrenal insufficiency: data from a multicenter cohort study. *BJOG* 2025; **132**: 1122–29.
- 121 Bothou C, Anand G, Li D, et al. Current management and outcome of pregnancies in women with adrenal insufficiency: experience from a multicenter survey. *J Clin Endocrinol Metab* 2020; **105**: e2853–63.
- 122 Russell GM, Durant C, Ataya A, et al. Subcutaneous pulsatile glucocorticoid replacement therapy. *Clin Endocrinol* 2014; **81**: 289–93.
- 123 Russell G, Kalafatakis K, Durant C, et al. Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect and fatigue in adrenal insufficiency: The PULSES trial. *J Intern Med* 2024; **295**: 51–67.
- 124 Oksnes M, Björnsdóttir S, Isaksson M, et al. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of Addison's disease: a randomized clinical trial. *J Clin Endocrinol Metab* 2014; **99**: 1665–74.
- 125 Gagliardi L, Nenke MA, Thynne TR, et al. Continuous subcutaneous hydrocortisone infusion therapy in Addison's disease: a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2014; **99**: 4149–57.
- 126 Mallappa A, Nella AA, Sinaii N, et al. Long-term use of continuous subcutaneous hydrocortisone infusion therapy in patients with congenital adrenal hyperplasia. *Clin Endocrinol* 2018; **89**: 399–407.
- 127 Sævik AB, Wolff AB, Björnsdóttir S, et al. Potential transcriptional biomarkers to guide glucocorticoid replacement in autoimmune Addison's disease. *J Endocr Soc* 2021; **5**: bvaa202.
- 128 Ramadoss V, Choudhury SM, Meeran K. Feasibility of immunological markers and osteocalcin as a barometer of glucocorticoid replacement. *Endocr Abstr* 2018; **59**: P004 (abstr).
- 129 Chantzichristos D, Svensson PA, Garner T, et al. Identification of human glucocorticoid response markers using integrated multi-omic analysis from a randomized crossover trial. *eLife* 2021; **10**: 10.
- 130 Upton TJ, Zavala E, Methlie P, et al. High-resolution daily profiles of tissue adrenal steroids by portable automated collection. *Sci Transl Med* 2023; **15**: eadg8464.
- 131 Venneri MA, Hasenmajer V, Fiore D, et al. Circadian rhythm of glucocorticoid administration entrains clock genes in immune cells: a DREAM trial ancillary study. *J Clin Endocrinol Metab* 2018; **103**: 2998–3009.
- 132 Graves LE, Torpy DJ, Coates PT, Alexander IE, Bornstein SR, Clarke B. Future directions for adrenal insufficiency: cellular transplantation and genetic therapies. *J Clin Endocrinol Metab* 2023; **108**: 1273–89.
- 133 Balyura M, Gelfgat E, Ehrhart-Bornstein M, et al. Transplantation of bovine adrenocortical cells encapsulated in alginate. *Proc Natl Acad Sci USA* 2015; **112**: 2527–32.
- 134 Grabek A, Dolfi B, Klein B, Jian-Motamedi F, Chaboissier MC, Schedl A. The adult adrenal cortex undergoes rapid tissue renewal in a sex-specific manner. *Cell Stem Cell* 2019; **25**: 290–96.e2.
- 135 Gan EH, Pearce SH. Management of endocrine disease: regenerative therapies in autoimmune Addison's disease. *Eur J Endocrinol* 2017; **176**: R123–35.
- 136 Carsia RV, Macdonald GJ, Gibney JA, Tilly KI, Tilly JL. Apoptotic cell death in the rat adrenal gland: an in vivo and in vitro investigation. *Cell Tissue Res* 1996; **283**: 247–54.
- 137 Chang SP, Morrison HD, Nilsson F, Kenyon CJ, West JD, Morley SD. Cell proliferation, movement and differentiation during maintenance of the adult mouse adrenal cortex. *PLoS One* 2013; **8**: e81865.
- 138 Freedman BD, Kempna PB, Carlone DL, et al. Adrenocortical zonation results from lineage conversion of differentiated zona glomerulosa cells. *Dev Cell* 2013; **26**: 666–73.
- 139 Ching S, Vilain E. Targeted disruption of Sonic Hedgehog in the mouse adrenal leads to adrenocortical hypoplasia. *Genesis* 2009; **47**: 628–37.
- 140 King P, Paul A, Laufer E. Shh signaling regulates adrenocortical development and identifies progenitors of steroidogenic lineages. *Proc Natl Acad Sci USA* 2009; **106**: 21185–90.
- 141 Parker KL, Schimmer BP. Steroidogenic factor 1: a key determinant of endocrine development and function. *Endocr Rev* 1997; **18**: 361–77.
- 142 Buaas FW, Gardiner JR, Clayton S, Val P, Swain A. In vivo evidence for the crucial role of SF1 in steroid-producing cells of the testis, ovary and adrenal gland. *Development* 2012; **139**: 4561–70.
- 143 Steenblock C, Rubin de Celis MF, Delgadillo Silva LF, et al. Isolation and characterization of adrenocortical progenitors involved in the adaptation to stress. *Proc Natl Acad Sci USA* 2018; **115**: 12997–3002.
- 144 Finco I, Lerario AM, Hammer GD. Sonic Hedgehog and WNT signaling promote adrenal gland regeneration in male mice. *Endocrinology* 2018; **159**: 579–96.
- 145 Teebken OE, Scheumann GF. Differentiated corticosteroid production and regeneration after selective transplantation of cultured and noncultured adrenocortical cells in the adrenalectomized rat. *Transplantation* 2000; **70**: 836–43.
- 146 Tanaka T, Aoyagi C, Mukai K, Nishimoto K, Kodama S, Yanase T. Extension of survival in bilaterally adrenalectomized mice by implantation of SF-1/Ad4BP-induced steroidogenic cells. *Endocrinology* 2020; **161**: bqaa007.
- 147 Popnikolov NK, Hornsby PJ. Subcutaneous transplantation of bovine and human adrenocortical cells in collagen gel in scid mice. *Cell Transplant* 1999; **8**: 617–25.
- 148 Ciancio SJ, King SR, Suwa T, et al. Transplantation of normal and genetically modified adrenocortical cells. *Endocr Res* 2000; **26**: 931–39.
- 149 Pearce SH, Mitchell AL, Bennett S, et al. Adrenal steroidogenesis after B lymphocyte depletion therapy in new-onset Addison's disease. *J Clin Endocrinol Metab* 2012; **97**: E1927–32.
- 150 Gan EH, MacArthur K, Mitchell AL, et al. Residual adrenal function in autoimmune Addison's disease: improvement after tetracosactide (ACTH1-24) treatment. *J Clin Endocrinol Metab* 2014; **99**: 111–18.

- 151 Napier C, Gan EH, Mitchell AL, et al. Residual adrenal function in autoimmune Addison's disease-effect of dual therapy with rituximab and depot tetracosactide. *J Clin Endocrinol Metab* 2020; **105**: e1250–59.
- 152 Bhake RC, Kluckner V, Stassen H, et al. Continuous free cortisol profiles-circadian rhythms in healthy men. *J Clin Endocrinol Metab* 2019; **104**: 5935–47.
- 153 Debono M, Ghobadi C, Rostami-Hodjegan A, et al. Modified-release hydrocortisone to provide circadian cortisol profiles. *J Clin Endocrinol Metab* 2009; **94**: 1548–54.

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