Adrenal insufficiency

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Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens. It is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis. Prompt diagnosis and management are essential. The clinical manifestations of primary adrenal insufficiency result from deficiency of all adrenocortical hormones, but they can also include signs of other concurrent autoimmune conditions. In secondary or tertiary adrenal insufficiency, the clinical picture results from glucocorticoid deficiency only, but manifestations of the primary pathological disorder can also be present. The diagnostic investigation, although well established, can be challenging, especially in patients with secondary or tertiary adrenal insufficiency. We summarise knowledge at this time on the epidemiology, causal mechanisms, pathophysiology, clinical manifestations, diagnosis, and management of this disorder.

Introduction

Adrenal insufficiency is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis.[1–3] It is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens. The cardinal clinical symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855, include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure.[4,5] Whatever the cause, adrenal insufficiency was invariably fatal until 1949, when cortisone was first synthesised,[6–9] and glucocorticoid-replacement treatment became available. However, despite this breakthrough, the diagnosis and treatment of patients with the disorder remain challenging.

Search strategy and selection criteria

We searched PubMed and the Cochrane Library for original articles and reviews related to adrenal insufficiency, which were published in English between 1966 and April, 2013. We used the search terms "adrenal insufficiency", in combination with the terms "incidence", "prevalence", "cause", "origin", "diagnosis", "function test", "imaging", "hydrocortisone", "glucocorticoid", "mineralocorticoid", "dehydroepiandrosterone", "management", "treatment", "therapy", "replacement", "surveillance", "crisis", "bone mineral density", "quality of life", "well being", "pregnancy", "prognosis", "morbidity", and "mortality". We largely chose publications from the past 5 years, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. The reference list was modified during the peer-review process on the basis of comments from reviewers.

Epidemiology

According to the underlying mechanism, adrenal insufficiency is classed as primary, secondary, or tertiary. Primary adrenal insufficiency results from disease intrinsic to the adrenal cortex. Central adrenal insufficiency, the collective name for the secondary and tertiary types, is caused by impaired production or action of corticotropin. Secondary adrenal insufficiency results from pituitary disease that hampers the release of corticotropin or from a lack of responsiveness of the adrenal glands to this hormone. Tertiary adrenal insufficiency results from the impaired synthesis or action of corticotropin-releasing hormone, arginine vasopressin, or both, from the hypothalamus, which in turn inhibits secretion of corticotropin.

In Europe, the prevalence of chronic primary adrenal insufficiency has increased from 40–70 cases per million people in the 1960s[10,11] to 93–144 cases per million by the end of the 20th century,[12–16] with an estimated incidence now of 4·4–6·0 new cases per million population per year.[15] Tuberculosis was the most common cause of primary adrenal insufficiency during the first half of the 20th century,[17] but lately autoimmune adrenal insufficiency has become the most common form.[16] The increase in the frequency of primary adrenal insufficiency over the past few decades, associated with a decline in the prevalence of tuberculosis, is indicative of the rising proportion of cases of autoimmune adrenal insufficiency.[18] In a series of 615 patients with Addison's disease, studied between 1969 and 2009, the autoimmune form was diagnosed in 82% of cases, the tuberculosis-related form in 9%, and other causes in about 8% of cases.[19] Primary adrenal insufficiency occurs more frequently in women than in men, and can present at any age, although most often appears between the ages of 30 and 50 years.[12]

The frequency of the various forms of primary adrenal insufficiency in children differs substantially from that in the adult population; the genetic forms are more common. In a series of 103 children with Addison's disease seen over 20 years (1981–2001), the most frequent cause was congenital adrenal hyperplasia (72%), and

other genetic causes accounted for another 6%; autoimmune disease was diagnosed in only 13%.[20]

Secondary adrenal insufficiency is more common than primary adrenal insufficiency.[1] It has an estimated prevalence of 150–280 per million and affects women more frequently than men.[14,21–24] The age at diagnosis peaks in the sixth decade of life.[22,23] A systematic review and meta-analysis of reported prevalences of hypopituitarism in adult patients who had received cranial irradiation for non-pituitary tumours showed that the point prevalence of any degree of hypopituitarism was 0·66 (95% CI 0·55–0·76) and the prevalence of corticotropin deficiency was 0·22 (0·15–0·30).[25] The most common cause of tertiary adrenal insufficiency is long-term administration of exogenous glucocorticoids, which leads to prolonged suppression of hypothalamic secretion of corticotropin-releasing hormone.[26]

Causal mechanisms

Primary adrenal insufficiency

The causes of primary adrenal insufficiency are listed in table 1. In developed countries, 80–90% of cases of primary adrenal insufficiency are caused by autoimmune adrenalitis, which can be isolated (40%) or part of an autoimmune polyendocrinopathy syndrome (60%).[1,2,19,32–34] Autoimmune Addison's disease is characterised by destruction of the adrenal cortex by cell-mediated immune mechanisms. Antibodies against steroid 21-hydroxylase are detected in about 85% of patients with idiopathic primary adrenal insufficiency,[16] but only rarely in patients with other causes of adrenal insufficiency.[35] In addition, other autoantigens, including steroid 17α-hydroxylase and the cholesterol side-chain cleavage enzyme, have been identified in patients with autoimmune Addison's disease, as well as patients with

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
Autoimmune adrenalitis		
Isolated	Associations with HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA-4, PTPN22, CIITA, CLEC16A, vitamin D receptor	None
APS type 1 (APECED)	*AIRE* gene mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Associations with HLA-DR3, HLA-DR4, CTLA-4	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Associations with HLA-DR3, CTLA-4	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
Infectious adrenalitis		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Syphilis	*Treponema pallidum*	Other syphilis-associated organ involvement
African trypanosomiasis[27]	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
Bilateral adrenal haemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Disease-associated clinical manifestations
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, haemochromatosis	Disease-associated clinical manifestations
Bilateral adrenalectomy	Unresolved Cushing's syndrome, bilateral adrenal masses, bilateral phaeochromocytoma	Symptoms and signs of underlying disease
Drug-induced adrenal insufficiency		
Anticoagulants (heparin, warfarin), tyrosine-kinase inhibitors (sunitinib)	Haemorrhage	None, unless related to drug
Aminoglutethimide	Inhibition of P450 aromatase (CYP19A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Ketoconazole, fluconazole, etomidate	Inhibition of mitochondrial cytochrome P450-dependent enzymes (eg, CYP11A1, CYP11B1)	None, unless related to drug
Phenobarbital	Induction of P450-cytochrome enzymes (CYP2B1, CYP2B2), which increase cortisol metabolism	None, unless related to drug
Phenytoin, rifampicin, troglitazone	Induction of P450-cytochrome enzymes (mainly CYP3A4), which increase cortisol metabolism	None, unless related to drug
Genetic disorders		
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* and *ABCD2* gene mutations	Weakness, spasticity, dementia, blindness, quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression

(Table 1 continues on next page)

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
(Continued from previous page)		
Congenital adrenal hyperplasia		
21-hydroxylase deficiency	*CYP21A2* gene mutations	Hyperandrogenism
11β-hydroxylase deficiency	*CYP11B1* gene mutations	Hyperandrogenism, hypertension
3β-hydroxysteroid dehydrogenase type 2 deficiency	Mutations in 3β-*HSD2* gene	Ambiguous genitalia in boys, postnatal virilisation in girls
17α-hydroxylase deficiency	*CYP17A1* gene mutations	Pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	Mutations in gene for P450 oxidoreductase	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* gene mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*StAR* gene mutations	XY sex reversal
Smith-Lemli-Opitz syndrome	*DHCR7* gene mutations	Craniofacial malformations, mental retardation, growth failure, hyponatraemia, hyperkalaemia, cholesterol deficiency
Adrenal hypoplasia congenita		
X-linked	*NR0B1* gene mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* gene mutations	XY sex reversal
IMAGe syndrome	*CDKN1C* gene mutations	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita and genital abnormalities
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Wolman's disease	*LIPA* gene mutations	Bilateral adrenal calcification, hepatosplenomegaly
Sitosterolaemia (also known as phytosterolaemia)	*ABCG5* and *ABCG8* gene mutations	Xanthomata, arthritis, premature coronary artery disease, short stature, gonadal and adrenal failure
Familial glucocorticoid deficiency or corticotropin insensitivity syndromes		
Type 1	*MC2R* gene mutations	Hyperpigmentation, tall stature, characteristic facial features, such as hypertelorism and frontal bossing, lethargy and muscle weakness but normal blood pressure
Type 2	*MRAP* gene mutations	Hyperpigmentation, normal height, hypoglycaemia, lethargy, and muscle weakness, but normal blood pressure
Variant of familial glucocorticoid deficiency	*MCM4* gene mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Primary generalised glucocorticoid resistance or Chrousos syndrome[28–31]	Generalised, partial, target-tissue insensitivity to glucocorticoids	Fatigue, hypoglycaemia, hypertension, hyperandrogenism
Triple A syndrome (Allgrove's syndrome)	*AAAS* gene mutations	Achalasia, alacrima, deafness, mental retardation, hyperkeratosis

APS=autoimmune polyendocrinopathy syndrome. CTLA-4=cytotoxic T-lymphocyte antigen 4. ABCD=ATP-binding cassette, subfamily D. StAR=steroidogenic acute regulatory protein. DHCR7=7-dehydrocholesterol reductase. ABCG5=ATP-binding cassette, subfamily G, member 5. ABCG8=ATP-binding cassette, subfamily G, member 8. MC2R=melanocortin 2 receptor. MRAP=melanocortin 2 receptor accessory protein. MCM4=minichromosome maintenance complex component 4. AAAS=achalasia, adrenocortical insufficiency, alacrima syndrome.

Table 1: **Causes of primary adrenal insufficiency**

primary ovarian failure.[32,36] T cells and cellular immunity also have important roles in the pathogenesis of autoimmune Addison's disease, and the generation of autoantibodies can be secondary to tissue destruction (figure 1).[37,38] Furthermore, several genes that confer susceptibility to autoimmune Addison's disease have been identified. In addition to the MHC haplotypes DR3-DQ2 and DR4-DQ8, cytotoxic T-lymphocyte antigen 4, protein tyrosine-phosphatase non-receptor type 22, and the MHC class II transactivator have been associated with the condition.[32–35,39–41] Now that large genome-wide screening projects are feasible, new susceptibility genes are likely to be identified in the near future.[32–35]

Primary adrenal insufficiency can also present in the context of autoimmune polyendocrinopathy syndromes. Autoimmune polyendocrinopathy syndrome type 1, which is also known as APECED (autoimmune polyendocrinopathy, candidosis, ectodermal dystrophy) syndrome, is a rare, autosomal recessive disorder caused by mutations in the autoimmune regulator (*AIRE*) gene.[32,42] It is most common among particular population groups—people from Sardinia and Finland and Iranian Jews—and is characterised by chronic mucocutaneous candidosis, adrenocortical insufficiency, hypoparathyroidism, hypoplasia of the dental enamel, and nail dystrophy; other autoimmune disorders, such as type 1 diabetes and pernicious anaemia, can develop later in life.[42,43] Antibodies against interferon-ω and interferon-α are both sensitive and specific for type 1 autoimmune polyendocrinopathy syndrome, and mutational analysis of the *AIRE* gene confirms the diagnosis in more than 95% of cases.[44] Type 2 autoimmune polyendocrinopathy syndrome is

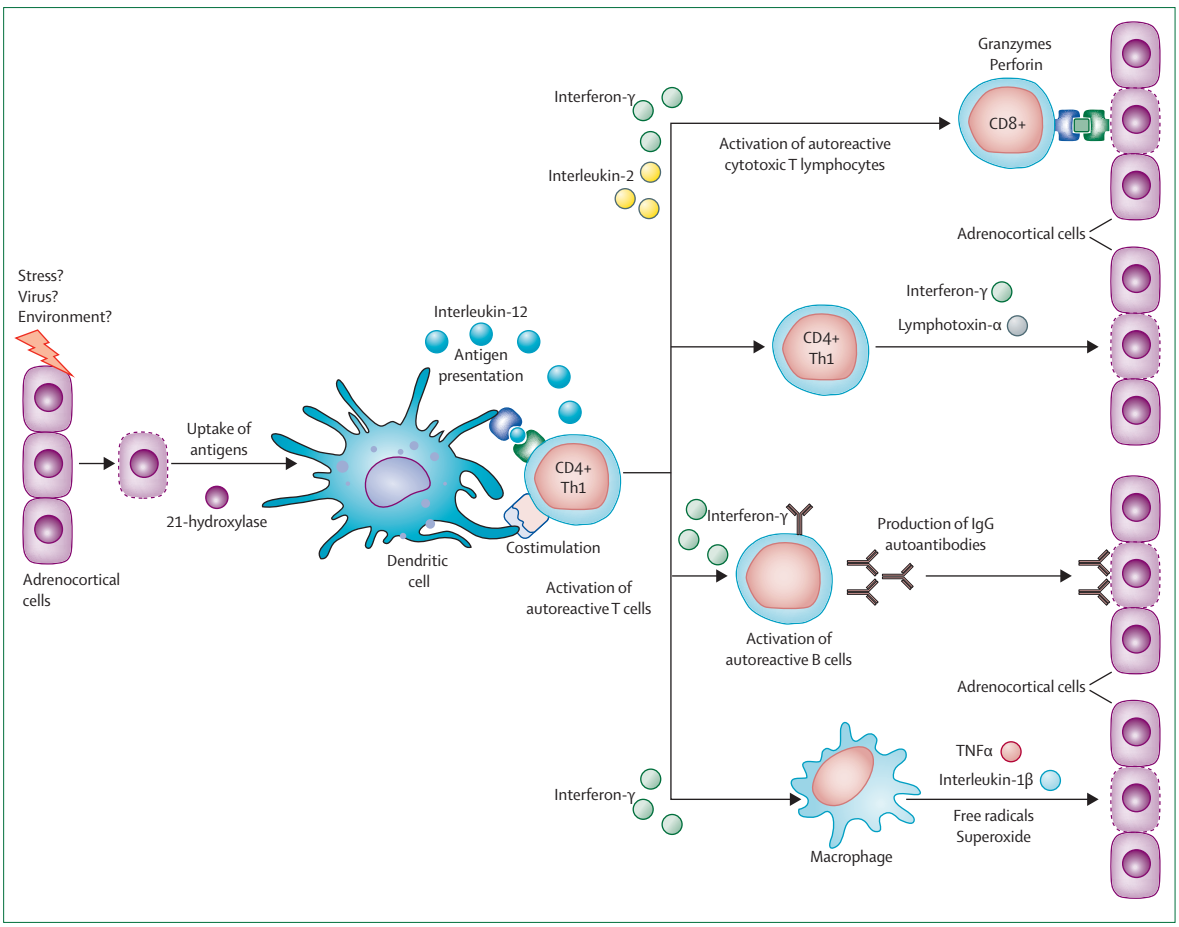

Figure 1: **Molecular immunopathogenesis of primary adrenal insufficiency**
A persistent subclinical viral infection or an aberrant response to inflammatory stressors could cause adrenocortical cell apoptosis or necrosis, leading to dendritic-cell activation by cellular components, including peptides derived from 21-hydroxylase. After activation, dendritic cells transport and present adrenocortical antigens to CD4-positive T-helper-1 (Th1) cells within the local draining lymph node. Activated specific CD4-positive Th1 cells could provide help for the activation and clonal expansion of cytotoxic lymphocytes and autoreactive B cells producing anti-21-hydroxylase and other antibodies. The continuing progressive destruction of adrenal cortex is mediated by several different mechanisms: direct cytotoxicity by apoptosis-inducing cytotoxic lymphocytes via perforin and granzyme B or by the FasL-Fas pathway; direct cytotoxicity by interferon-γ and lymphotoxin-α secreted by CD4-positive Th1 cells; autoantibody-induced activation of the complement system or antibody dependent cellular cytotoxicity; cytotoxic effects of inflammatory cytokines (tumour necrosis factor-α [TNFα], interleukin-1β) and free radicals (nitric oxide, superoxide) released by monocytes and macrophages or by the adrenocortical cells themselves.

characterised by autoimmune adrenal insufficiency and autoimmune thyroid disease, with or without type 1 diabetes; it is more prevalent than the type 1 form. It is often associated with other autoimmune conditions, affects women more commonly than men, and generally presents in the fourth decade of life.[32–34,43,45,46] Autoimmune polyendocrinopathy syndrome type 4 is a rare syndrome characterised by the association of autoimmune Addison's disease with one or more minor component autoimmune diseases (eg, hypogonadism, atrophic gastritis, pernicious anaemia, coeliac disease, myasthenia gravis, vitiligo, alopecia, and hypophysitis) but excluding the major component disease characteristics of types 1 and 2 (chronic candidosis, hypoparathyroidism, thyroid autoimmune diseases, type 1 diabetes).[45]

Table 1 lists several infectious, drug-induced, and other causes of primary adrenal insufficiency, then genetic disorders. Of the genetic causes, adrenoleukodystrophy, is an X-linked recessive disorder that affects one in 20 000 men and boys and is caused by mutations in the ATP-binding cassette, subfamily D, member 1 (*ABCD1*) gene. These mutations prevent normal transport of very-long-chain fatty acids into peroxisomes, thereby preventing their β-oxidation and breakdown. Accumulation of abnormal amounts of these fatty acids in affected organs (CNS, Leydig cells of the testes, adrenal cortex) is thought to be the underlying pathological process. The clinical features include neurological impairment resulting from white-matter demyelination and primary adrenal insufficiency, which presents in infancy or childhood. The two major forms of adrenoleukodystrophy are the cerebral form (50% of cases; early childhood manifestation with rapid progression) and adrenomyeloneuropathy (35% of cases;

onset in early adulthood with slow progression) in which demyelination is restricted to the spinal cord and peripheral nerves. Since adrenal insufficiency can be the initial clinical manifestation, adrenoleukodystrophy should be considered in young male patients with adrenal insufficiency and confirmed biochemically by measurement of plasma concentrations of very-long-chain fatty acids.[1–3,47]

Primary adrenal insufficiency occasionally presents acutely as a consequence of bilateral adrenal haemorrhage in patients with antiphospholipid syndrome. It is characterised by recurrent arterial and venous thrombosis, complications during pregnancy, and the presence of autoantibodies to phospholipids. The condition can be isolated or manifest in the context of connective tissue disorders or malignant disorders.[48,49]

In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia, a group of autosomal recessive disorders resulting from deficiency of one of the enzymes needed for synthesis of cortisol in the adrenal cortex. The most common form is classic 21-hydroxylase deficiency, a condition characterised by low synthesis of glucocorticoids and, in many cases, mineralocorticoids, adrenal hyperandrogenism, and impaired development and function of the adrenal medulla.[50–52] More rare forms are caused by deficiency of 11β-hydroxylase, 17α-hydroxylase, 17,20-lyase, 3β-hydroxysteroid dehydrogenase, or P450 oxidoreductase.

Central adrenal insufficiency

Secondary adrenal insufficiency results from any process that involves the pituitary gland and interferes with corticotropin secretion (table 2). The corticotropin deficiency can be isolated or can occur in association with deficiencies of other pituitary hormones. Isolated corticotropin deficiency generally results from an autoimmune process, as shown by the frequent association with other autoimmune endocrine disorders (thyroiditis, type 1 diabetes).[53,54] Genetic causes of corticotropin deficiency include loss-of-function mutations in the genes encoding pro-opiomelanocortin gene and proprotein convertase subtilisin or kexin type 1 inhibitor, which also result in early-onset severe obesity,[53,55] as well as mutations in TPIT, a T-box factor that controls transcription of the pro-opiomelanocortin gene in corticotrophs only.[53,56]

Tertiary adrenal insufficiency results from processes that involve the hypothalamus and interfere with secretion of corticotropin-releasing hormone, arginine vasopressin, or both (table 3). Suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term administration of high doses of glucocorticoids is the most common cause. Therefore, in most cases, slow withdrawal of glucocorticoid treatment over 9–12 months is needed for full recovery of the HPA axis.[26,57–59] Tertiary adrenal insufficiency also occurs in patients cured of Cushing's syndrome, since the persistently high serum cortisol concentrations before treatment suppress the HPA axis in the same way as high exogenous doses of glucocorticoids.[60–63] Finally, drugs such as mifepristone, a glucocorticoid receptor antagonist, antipsychotics, and antidepressants cause target-tissue resistance to glucocorticoids through impairment of glucocorticoid signal transduction.[60]

Pathophysiology and clinical presentation

The adrenal cortex has three distinct zones, which secrete the various hormones under the direct control of well understood feedback mechanisms. Aldosterone is synthesised in the outermost zone, the zona glomerulosa. Its secretion is predominantly regulated by the renin–angiotensin system and extracellular potassium concentrations; therefore, it is not impaired in secondary and tertiary adrenal insufficiency. Cortisol secretion from the zona fasciculata is primarily regulated by corticotropin, which is released from the anterior pituitary in response to the hypothalamic neuropeptides corticotropin-releasing hormone and arginine vasopressin.[50,60,64] In healthy people, cortisol secretion is pulsatile, and circulating cortisol concentrations fluctuate naturally in a circadian fashion, highest in the early morning (0600–0800 h) and lowest around midnight.[60,64–67] The adrenal androgens, androstenedione, dehydroepiandrosterone, and the sulphate ester of dehydroepiandrosterone, are synthesised in the innermost zona reticularis.[50] Dehydroepiandrosterone and its sulphate show a characteristic, age-associated pattern, with very high concentrations in the neonatal period, a decline to very low concentrations during the first few months of life, and a continuous increase starting between age 6 and 10 years, termed adrenarche. Peak concentrations of these two hormones are achieved during the third decade of life; they then decline steadily from the fifth decade (adrenopause) with concentrations decreasing to 10–20% of the maximum at around age 70 years. The age-related decline in dehydroepiandrosterone sulphate does not reflect a general loss of adrenocortical output because cortisol concentrations are maintained and even slightly rise with age.[50,68]

The clinical manifestations of primary adrenal insufficiency (table 4) result from deficiency of all adrenocortical hormones (aldosterone, cortisol, androgens); they can also include signs of other concurrent autoimmune conditions. Most of the symptoms are non-specific and can delay diagnosis and treatment of the condition. Hypoglycaemia can be the presenting sign in children with adrenal insufficiency, and it can lead to deterioration of glycaemic control and the need for reduction of the total daily insulin doses in patients with type 1 diabetes. A specific sign of chronic, but not acute, primary adrenal insufficiency is hyperpigmentation, which predominantly affects areas of skin subjected to pressure (elbows, knuckles, palmar creases,

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
Space-occupying lesions or trauma		
Pituitary tumours (adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas) or trauma (pituitary stalk lesions)	Low corticotropin secretion	Anterior or posterior pituitary hormone deficiencies, or both, and associated symptoms
Pituitary surgery or irradiation for pituitary tumours, tumours outside the HPA axis or leukaemia	Low corticotropin secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Infections or infiltrative processes (lymphocytic hypophysitis, haemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener's granulomatosis)	Low corticotropin secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Pituitary apoplexy	Low corticotropin secretion	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Sheehan's syndrome (peripartum pituitary apoplexy and necrosis)	Low corticotropin secretion	Peripartum abrupt onset of severe headache, visual disturbance, nausea, and vomiting; anterior or posterior pituitary hormone deficiencies or both, and primary disease-associated symptoms
Genetic disorders		
Transcription factors involved in pituitary development		
HESX homeobox 1	*HESX1* gene mutations	Panhypopituitarism; short stature, delayed puberty, cognitive changes, septo-optic dysplasia
Orthodentical homeobox 2	Mutations in gene for orthodentical homeobox 2	Panhypopituitarism; neonatal hypoglycaemia, pituitary hypoplasia, ectopic posterior pituitary gland
LIM homeobox 4	Mutations in gene for LIM homeobox 4	Panhypopituitarism; growth hormone, thyrotropin, and corticotropin deficiencies
PROP paired-like homeobox 1	Mutations in gene for PROP paired-like homeobox 1	Panhypopituitarism; late-onset corticotropin deficiency, occasionally enlarged sella turcica
SRY (sex-determining region Y)		
Box 3	Mutations in gene for SRY (sex-determining region Y) box 3	Panhypopituitarism; infundibular hypoplasia, hypopituitarism, mental retardation
T-box 19	Mutations in gene for T-box 19	Congenital isolated corticotropin deficiency
Congenital pro-opiomelanocortin deficiency	Mutations in gene for pro-opiomelanocortin	Early-onset severe obesity, hyperphagia, red hair
Prader-Willi syndrome	Deletion or silencing of genes in imprinting centre for the syndrome	Hypotonia, obesity, mental retardation, hypogonadism

***Table 2*: Causes of secondary adrenal insufficiency**

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
Space-occupying lesions or trauma		
Hypothalamic tumours (craniopharyngiomas or metastasis from lung or breast cancer)	Low CRH secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Hypothalamic surgery or irradiation for CNS or nasopharyngeal tumours	Low CRH secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Infections or infiltrative processes (lymphocytic hypophysitis, haemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener's granulomatosis)	Low CRH secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Trauma, injury (fracture of skull base)	Low CRH secretion	Anterior or posterior pituitary hormone deficiencies, or both, and primary disease-associated symptoms
Drug-induced adrenal insufficiency		
Glucocorticoid therapy (systemic or topical) or endogenous glucocorticoid hypersecretion (Cushing's syndrome)	Low CRH and corticotropin secretion	Primary disease-associated symptoms
Mifepristone	Tissue resistance to glucocorticoids through impairment of glucocorticoid signal transduction	If excessive it can cause severe glucocorticoid deficiency; no other symptoms, unless related to drug
Antipsychotics (chlorpromazine), antidepressants (imipramine)	Inhibition of glucocorticoid-induced gene transcription	None, unless related to drug

HPA=hypothalamic–pituitary–adrenal. CRH=corticotropin-releasing hormone.

***Table 3*: Causes of tertiary adrenal insufficiency**

lips, buccal mucosa). It is caused by stimulation of the melanocortin-1 receptor in the skin by the high circulating corticotropin concentrations.[1–5] The preclinical time course of adrenal insufficiency can span many years after detection of early metabolic changes by screening, even in the presence of high specific autoantibody titres and significantly raised corticotropin concentrations.[69] In autoimmune adrenal insufficiency, the first zone affected by immune-mediated destruction is generally the zona glomerulosa, possibly because it is thinner than the other two, or is more vulnerable to autoimmune attack. This feature might explain the first step of adrenal failure, which is characterised by high plasma renin activity and low aldosterone concentrations, followed by a phase of progressive glucocorticoid deficiency, initially with inadequate response to stressful stimuli and then by a phase of overt failure with low basal cortisol concentrations.[45,70]

	Pathophysiological mechanism	Prevalence (%)
Symptoms		
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency	100
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency	100
Gastric pain, nausea, vomiting (most common in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency	92
Myalgia, joint pain	Glucocorticoid deficiency	6–13
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency	12
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	16
Dry and itchy skin (in women)	Adrenal androgen deficiency	..
Loss or impairment of libido (in women)	Adrenal androgen deficiency	..
Signs		
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocortin-derived peptides	94
Alabaster-coloured pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin-derived peptides	..
Fever	Glucocorticoid deficiency	..
Low blood pressure, postural hypotension, dehydration (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency	88–94
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency	..
Biochemical findings		
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency	..
Hyponatraemia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to SIADH)	88
Hyperkalaemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	64
Anaemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency	..
Increased thyrotropin (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)	..
Hypercalcaemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)	6
Hypoglycaemia	Glucocorticoid deficiency	..

If prevalence is not given, data are not available. SIADH=syndrome of inappropriate antidiuretic hormone secretion.

Table 4: **Clinical manifestations and biochemical findings in adrenal insufficiency**

The clinical manifestations of secondary or tertiary adrenal insufficiency result from glucocorticoid deficiency only (secretion of aldosterone and adrenal androgens is preserved); however, they can also include signs of the primary underlying disorder. Hyperpigmentation is not present because corticotropin secretion is not increased, and hyponatraemia and volume expansion can occur secondary to a so-called inappropriate increase in arginine vasopressin secretion. There might also be symptoms and signs of deficiency of other anterior pituitary hormones.

A life-threatening adrenal crisis can be the first presentation of adrenal insufficiency. Clinical features include vomiting, abdominal pain, myalgia, joint pains, severe hypotension, and hypovolaemic shock. The acute presentation can be precipitated by a physiological stress, such as surgery, trauma, or an intercurrent infection.

Diagnosis of adrenal insufficiency

There are three main aims in the diagnosis of adrenal insufficiency (table 5): to confirm inappropriately low cortisol secretion; to find out whether the adrenal insufficiency is primary or central; and to delineate the underlying pathological process.[1–3]

Whatever the cause, the diagnosis of adrenal insufficiency depends entirely on the demonstration that cortisol secretion is inappropriately low. All current stimulation tests measure total cortisol concentration, which is related closely to the biologically active free cortisol in most, but possibly not all, situations.[72] High concentrations of cortisol-binding globulin in patients receiving oral oestrogens or in pregnancy can lead to falsely normal results.[73] Conversely, in patients with cirrhosis, concentrations of cortisol-binding globulin are low and can lead to falsely abnormal results.[74] Measurement of serum free cortisol concentrations can offer additional information, although the assay is not generally available; salivary cortisol concentration might be a useful alternative.[75]

In healthy people, serum cortisol concentrations are highest in the early morning, at 275–555 nmol/L (100–200 µg/L). A low serum cortisol concentration (<80 nmol/L [30 µg/L]) in a blood sample taken in the early morning strongly suggests adrenal insufficiency.[76,77] By contrast, a morning serum cortisol concentration of more than 415 nmol/L (150 µg/L) predicts a normal serum cortisol response to insulin-induced hypoglycaemia or a short corticotropin test in almost all patients.[78,79] Simultaneous measurements of cortisol and corticotropin concentrations identify most cases of primary adrenal insufficiency.

Similarly, a salivary cortisol concentration at 0800 h of more than 16 nmol/L (5·8 µg/L) excludes adrenal insufficiency, whereas a value of less than 5 nmol/L (1·8 µg/L) indicates a high probability of adrenal insufficiency. This test has been used to screen for adrenal insufficiency, but it has not been fully validated as the only diagnostic test.

	Normal range*	Interpretation
Primary adrenal insufficiency		
0800 h basal serum cortisol	165–680 nmol/L	Serum cortisol <165 nmol/L, definite adrenal insufficiency; serum cortisol <300 nmol/L, adrenal insufficiency not excluded; serum cortisol >550 nmol/L generally excludes primary adrenal insufficiency
0800 h basal plasma corticotropin	4·5–12 pmol/L	Plasma corticotropin >22 pmol/L, definite adrenal insufficiency; plasma corticotropin >45 pmol/L in most cases
24 h urinary free cortisol	11–84 µg/24 h (men); 10–34 µg/24 h (women)	Not helpful in the diagnosis of adrenal insufficiency
Standard-dose corticotropin test	Peak cortisol >550 nmol/L (sensitivity 90%, specificity 100%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; in most cases there is no cortisol increase because endogenous corticotropin stimulation is already at peak
Secondary and tertiary adrenal insufficiency		
0800 h basal serum cortisol	165–680 nmol/L	Serum cortisol <100 nmol/L, definite adrenal insufficiency; serum cortisol 100–500 nmol/L, adrenal insufficiency not excluded; serum cortisol >500 nmol/L excludes secondary adrenal insufficiency
0800 h basal plasma corticotropin	4·5–12 pmol/L	Plasma corticotropin <12 pmol/L, adrenal insufficiency not excluded
Standard-dose corticotropin test	Peak cortisol >500 nmol/L (sensitivity 90%, specificity 100%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <600 nmol/L, adrenal insufficiency not excluded; peak cortisol <400 nmol/L suggests central adrenal insufficiency
Low-dose corticotropin test	Peak cortisol >500 nmol/L (sensitivity 90%, specificity 90%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <600 nmol/L, adrenal insufficiency not excluded; peak cortisol <400 nmol/L suggests central adrenal insufficiency
Prolonged corticotropin test	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L, definite adrenal insufficiency
Insulin tolerance test	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <550 nmol/L, adrenal insufficiency not excluded
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency		
Standard-dose corticotropin test	Cortisol at 30 min >500 nmol/L; peak 17-hydroxyprogesterone <50 nmol/L	Peak 17-hydroxyprogesterone >300 nmol/L, classic disease; peak 17-hydroxyprogesterone 31–300 nmol/L, non-classic disease; peak 17-hydroxyprogesterone <50 nmol/L, likely unaffected or heterozygote

CAH=congenital adrenal hyperplasia. *For serum cortisol concentrations, multiply by 0·363 to convert nmol/L to µg/L. For plasma corticotropin concentrations, multiply by 4·5 to convert pmol/L to ng/L. For serum 17-hydroxyprogesterone concentrations, multiply by 0·331 to convert pmol/L to ng/dL. Sensitivity and specificity for the standard-dose and low-dose corticotropin tests are given in comparison with the insulin-induced hypoglycaemia test, which is regarded as the gold-standard.[71]

***Table 5*: Diagnostic tests for adrenal insufficiency**

Measurement of urinary free cortisol concentrations is not helpful in the diagnosis of adrenal insufficiency mainly because the lower levels of the range are not contributory.[1–5]

Measurement of the basal plasma corticotropin concentration can generally distinguish between primary and central adrenal insufficiency. With simultaneous measurement of basal serum cortisol concentration, measurement of plasma corticotropin can both confirm the diagnosis of adrenal insufficiency and establish its cause.[79] In healthy people, corticotropin concentrations at 0800 h are 4·5–12·0 pmol/L (20–52 ng/L) in a two-site chemiluminescent assay. In primary adrenal insufficiency, the 0800 h plasma corticotropin concentration is high, and is associated with high plasma renin concentration or activity, low aldosterone concentrations, hyponatraemia, and hyperkalaemia. By contrast, plasma corticotropin concentrations are low or low normal in secondary or tertiary adrenal insufficiency. Plasma concentrations of renin and aldosterone are generally unaffected in secondary or tertiary adrenal insufficiency, but mineralocorticoid deficiency can occur after a very long duration of corticotropin deficiency.[80] In autoimmune adrenal insufficiency, plasma renin concentrations are usually the first to increase, followed by an increase in corticotropin and decrease in aldosterone concentrations.[45,70]

Adrenal insufficiency is characterised by adrenal androgen deficiency. Serum concentrations of dehydroepiandrosterone and its sulphate are low in patients with primary or central adrenal insufficiency, but these characteristics facilitate diagnosis only in patients younger than 40 years, because of the physiological, age-related decline in adrenal androgen secretion.

Adrenal insufficiency is generally diagnosed by the standard-dose corticotropin test, which is safe, reliable and accurate.[81–85] The test entails stimulation of the adrenal glands by pharmacological doses (250 µg) of exogenous corticotropin 1–24, which has the full biological potency of native 39-aminoacid corticotropin.[1–39] It is administered intravenously or intramuscularly, and serum cortisol concentrations are measured at baseline then 30 min and 60 min after stimulation. A peak cortisol concentration is defined as normal if more than 500 nmol/L (180 µg/L). The standard-dose corticotropin test should not be used during the first 4–6 weeks after a hypothalamic or pituitary insult, because the adrenal cortex might still respond to exogenous corticotropin administration adequately, and the result could be falsely normal.[83–85]

Since some patients with adrenal insufficiency show a normal cortisol response in the standard-dose corticotropin test because the pharmacological dose of corticotropin is sufficent to elicit a response,[1–24] studies have explored the use of a low-dose test (1 µg or 500 ng/1·73 m²) to increase the sensitivity.[84,85] This test

can be more sensitive and specific than the standard test,[86–89] but technical details can influence its accuracy.[90] Therefore, it should be reserved for patients with mild primary adrenal insufficiency or central adrenal insufficiency of recent origin (4–6 weeks duration).[85–89]

Prolonged stimulation with exogenous corticotropin is used to differentiate between primary and secondary or tertiary adrenal insufficiency. In primary adrenal insufficiency, the adrenal glands do not respond to corticotropin, whereas in secondary or tertiary insufficiency, they respond after longer periods of stimulation with corticotropin. In the test, 250 µg corticotropin is given intravenously as an infusion over 8 h or over 24 h on 2 or 3 consecutive days; serum cortisol concentration and 24 h urinary cortisol and 17-hydroxycorticoid concentrations are measured before and after the infusion.[91]

When secondary adrenal insufficiency is suspected, the insulin tolerance test is another choice for confirmation of the diagnosis, particularly in patients with suspected corticotropin deficiency of recent origin. This test investigates the integrity of the HPA axis and is widely regarded as the gold standard. In addition, it has the advantage of assessing growth hormone reserve. However, it should not be done in patients with cardiovascular disease or a history of seizures, and a high degree of supervision is necessary. Insulin (0·10–0·15 U/kg) is given to induce hypoglycaemia, and cortisol concentrations are measured every 30 min for at least 120 min.[84,85]

The corticotropin-releasing hormone test assesses pituitary corticotropin reserve. This test can be useful in distinguishing secondary from tertiary adrenal insufficiency, although this distinction is seldom important in terms of treatment. It entails intravenous administration of corticotropin-releasing hormone at a dose of 1 µg/kg (up to a maximum of 100 µg) and measurement of serum cortisol and plasma corticotropin concentrations at baseline, every 15 min to 1 h, then every 30 min to 2 h after stimulation. In patients with secondary adrenal insufficiency, there is little or no corticotropin response, whereas in those with tertiary disease, there is an exaggerated and long-lasting corticotropin response.[84]

We emphasise that none of these dynamic tests, including the insulin tolerance test, correctly classifies all patients with adrenal insufficiency. Mild secondary adrenal insufficiency can be missed, and healthy individuals can show slightly abnormal responses. Therefore, clinical judgment should prevail, and patients with persisting symptoms suggesting adrenal insufficiency should be reassessed.

The diagnosis of autoimmune adrenal insufficiency is based on the presence of autoantibodies to the adrenal cortex, radiological evidence of non-enlarged (normal or small) adrenal glands, the presence of other autoimmune diseases, and the exclusion of other known causes of adrenal insufficiency. Autoantibodies to the adrenal cortex or 21-hydroxylase are present in more than 90% of patients with autoimmune adrenalitis of recent onset. Furthermore, autoantibodies against other steroidogenic enzymes (P450scc, P450c17) and antibodies to steroid-producing cells are present in some patients and can be predictive markers of primary ovarian failure.[1,3,19,32–36,45,92,93]

In male patients with isolated Addison's disease and no autoantibodies present, plasma concentrations of very-long-chain fatty acids (chain length of ≥24 carbon atoms; C26, C26/C22, and C24/C22 ratios) should be measured to exclude X-linked adrenoleukodystrophy.[47]

Patients with no associated autoimmune disease and no autoantibodies present should undergo CT of the adrenal glands. In tuberculous adrenalitis, which should be part of the differential diagnosis in developing countries and immigrant populations, CT shows hyperplasia of the adrenal glands in the early stages and spotty calcifications in the late stages of the disease. Rarer causes of adrenal insufficiency that can be detected by adrenal CT include bilateral adrenal lymphoma, adrenal metastases, or adrenal infiltration (sarcoidosis, amyloidosis, haemochromatosis).[1,3,32–35,94] If central adrenal insufficiency is suspected, MRI of the hypothalamic and pituitary regions should be done. It can reveal pituitary adenomas, craniopharyngiomas, meningiomas, metastases, and infiltration by sarcoidosis, Langerhans cell histiocytosis, or other granulomatous disease.[94,95] Imaging is not required if antibodies to the adrenal cortex are present.[92,93]

Treatment

Adrenal insufficiency is potentially life-threatening. Treatment should be initiated as soon as the diagnosis is confirmed, or sooner if the patient presents in adrenal crisis (panel).[1–5]

A very important part of the management of chronic adrenal insufficiency is education of the patient and his or her family. They need to understand the importance of life-long replacement therapy, the need to increase the usual glucocorticoid dose during stress, and the need to notify medical staff if the patients are to undergo any surgical procedure. In addition, they must always have supplies of hydrocortisone injections and should be taught how and when to administer them.[96,97]

Patients with adrenal insufficiency should be treated with hydrocortisone (or cortisone acetate if hydrocortisone is not available), which is the most physiological option for glucocorticoid replacement. The recommended daily hydrocortisone dose is 10–12 mg/m^2; it can be given in two to three doses, with administration of half to two-thirds of the total daily dose in the morning.[1–5,60,82,98–103] Small decreases in bone mineral density, probably from use of higher than recommended doses, as well as impaired quality of life, have been documented in patients treated with hydrocortisone.[103–105] Longer-acting synthetic glucocorticoids, such as prednisolone, prednisone, and dexamethasone, should be avoided

Panel: Prevention and therapeutic management of adrenal insufficiency

Acute adrenal insufficiency

Glucocorticoid replacement

- Rapid rehydration with physiological saline infusions under continuous cardiac monitoring; inject 100 mg hydrocortisone intravenously, followed by 100–200 mg hydrocortisone in glucose 5% by continuous intravenous infusion (or, hydrocortisone intramuscularly every 6 h at a dose of 50–100 mg depending on age and body surface area)

Mineralocorticoid replacement

- Needed only in primary adrenal insufficiency
- Not needed if hydrocortisone dose >50 mg per 24 h

Adrenal androgen replacement

- Not required

Chronic adrenal insufficiency

Glucocorticoid replacement

- Primary adrenal insufficiency—start on 20–25 mg hydrocortisone per 24 h
- Secondary adrenal insufficiency—15–20 mg hydrocortisone per 24 h; if cortisol concentrations are borderline low in response to the corticotropin test, consider 10 mg hydrocortisone daily or stress dose hydrocortisone cover only and monitor closely
- Hydrocortisone should be given in three doses with two-thirds or half of the total daily dose given early in the morning
- Educate patient and family about stress dose hydrocortisone cover
- Monitoring should include assessment of the patient for signs of glucocorticoid under-replacement (weight loss, fatigue, nausea, myalgia, lack of energy) or over-replacement (weight gain, central obesity, stretch marks, osteopenia and osteoporosis, impaired glucose tolerance, hypertension)

Mineralocorticoid replacement

- Needed only in primary adrenal insufficiency
- Not needed if the daily hydrocortisone dose exceeds 50 mg
- Start with 100 µg fludrocortisone (50–250 µg per day) as a single dose early in the morning along with the hydrocortisone
- Monitoring should include assessment of the patient for signs of mineralocorticoid under-replacement (postural drop in arterial blood pressure >20 mm Hg, weight loss, dehydration, hyponatraemia, increased plasma renin activity) or over-replacement (weight gain, increased arterial blood pressure, hypernatraemia, suppressed plasma renin activity)

Adrenal androgen replacement

- Should be considered in patients with impaired wellbeing and mood despite optimum replacement therapy with glucocorticoids and mineralocorticoids, or in women with symptoms and signs suggesting adrenal androgen insufficiency
- Start with dehydroepiandrosterone 25–50 mg as a single morning dose
- Monitoring during treatment in women should include measurement of serum testosterone and sex-hormone binding globulin (to calculate free androgen index) concentrations; in both sexes, serum dehydroepiandrosterone sulphate and androstenedione concentrations should be monitored (24 h after the last preceding dose of dehydroepiandrosterone)

Additional monitoring requirements

- Regular follow-up in outpatient endocrinology clinic every 6 months
- In primary adrenal insufficiency of autoimmune origin, ask about symptoms and signs of other autoimmune disorders and undertake relevant testing every 6–12 months
- Check emergency bracelet or steroid card and update as required
- Ensure that the patient or the family (for children) are informed about stress dose hydrocortisone cover and are provided with the hydrocortisone emergency self-injection kit
- Ask about other medications that can induce (eg, rifampicin, mitotane, anticonvulsants) or inhibit (eg, antiretroviral therapy) hepatic enzymes involved in cortisol metabolism, and adjust the hydrocortisone dose accordingly

Prevention of adrenal crises

- Patients should carry a medical alert bracelet and a card stating that they are on long-term steroid treatment
- Patients who have been on exogenous glucocorticoid treatment for longer than 2–3 weeks should not stop this treatment suddenly
- Patients should be given an emergency hydrocortisone self-injection kit and trained how and when to use it
- Patients should be advised to double or triple hydrocortisone treatment during intercurrent illnesses and seek immediate medical advice so that the cause of intercurrent illness can be identified and treatment given if necessary; to visit the nearest emergency department if vomiting persistently and unable to tolerate oral hydrocortisone treatment; and to inform medical staff about the need for early admission to hospital and parenteral hydrocortisone treatment in case of a severe illness or surgery

Modified from Arlt.[83]

because the longer duration of action can lead to signs of chronic glucocorticoid excess.[106] Hydrocortisone preparations that result in both delayed and sustained release of the hormone have been developed lately, and are under clinical investigation.[107,108] These formulations result in more stable cortisol concentrations throughout the day and reproduce the physiological cortisol rise during early morning hours after oral intake of the

preparation at bedtime. A once-daily dual-release hydrocortisone tablet has also been developed to obtain a more physiological circadian-based serum cortisol exposure-time profile. Compared with the conventional approach, treatment with this preparation improved cardiovascular risk factors, glucose metabolism, and quality of life, all of which can help to improve outcome in patients with adrenal insufficiency.[109]

In the absence of objective variables to assess the adequacy of replacement therapy, the physician has to rely primarily on symptoms and signs that suggest under-replacement or over-replacement of glucocorticoids, to titrate the glucocorticoid replacement dose appropriately, and to prevent significant morbidity.[60]

During minor illness or surgical procedures, the dose of glucocorticoid can be increased to up to three times the usual maintenance dose.[60,98–103] During major illness or surgery, doses of glucocorticoid up to ten times the daily production rate might be needed to avoid an adrenal crisis.[60,98–103]

In primary adrenal insufficiency, mineralocorticoid replacement therapy is necessary to prevent sodium loss, intravascular volume depletion, and hyperkalaemia. It is given in the form of fludrocortisone (9-α-fluorohydrocortisone) in a dose of 0·05–0·20 mg daily, in the morning. The dose of fludrocortisone is titrated individually on the basis of blood pressure, serum sodium and potassium concentrations, and plasma renin activity concentrations. The mineralocorticoid dose might have to be increased in the summer, especially if patients are exposed to temperatures higher than 29°C.[60,83,98–103] In secondary or tertiary adrenal insufficiency, mineralocorticoid replacement is not necessary, but replacement of other anterior pituitary deficits might be.

In women, the adrenal cortex is the main source of androgen production in the form of dehydroepiandrosterone and its sulphate. Treatment with dehydroepiandrosterone improves mood and general wellbeing in adult patients and in children and adolescents with adrenal insufficiency.[83,98–102,110–117] Dehydroepiandrosterone replacement should be considered in patients whose wellbeing is greatly impaired despite optimum glucocorticoid and mineralocorticoid replacement. A single oral morning dose of 25–50 mg is sufficient to maintain serum concentrations within the normal range. Treatment surveillance should include measurement of serum concentrations of dehydroepiandrosterone sulphate (aiming at the middle of the normal range for healthy young people) and female patients should be advised to report any androgenic side-effects.

The aim of treatment in classic congenital adrenal hyperplasia is not only to provide adequate glucocorticoid and mineralocorticoid replacement to prevent adrenal crises, but also to suppress the excess secretion of corticotropin from the anterior pituitary to decrease the overproduction of adrenal androgens. In childhood, satisfactory control of adrenal androgen secretion is generally achieved with 10–15 mg/m^2 hydrocortisone daily divided into three doses; higher doses might be needed in the neonatal period.[118,119] Since these doses exceed physiological cortisol secretion, patients should be monitored carefully for signs of iatrogenic Cushing's syndrome.[120] Treatment efficacy is assessed by the growth velocity, the rate of skeletal maturation, weight gain, and serum concentrations of 17-hydroxyprogesterone and androstenedione at 0800 h.[121] Mineralocorticoid replacement should be started in patients with classic congenital adrenal hyperplasia who have impaired aldosterone secretion.[118–121]

Adrenal crisis is a life-threatening emergency that occurs frequently in patients with adrenal insufficiency receiving standard replacement therapy and requires immediate management. In a postal survey of 840 patients with Addison's disease in four countries, about 8% of respondents needed hospital treatment for an adrenal crisis annually.[122] Initial management in adrenal crisis is to treat hypotension and to reverse the electrolyte abnormalities and cortisol deficiency. Treatment consists of immediate intravenous administration of 100 mg hydrocortisone and rapid rehydration with normal saline infusion under continuous cardiac monitoring, followed by 100–200 mg hydrocortisone in glucose 5% per 24 h by continuous intravenous infusion; alternatively, hydrocortisone can be given by intravenous or intramuscular injection every 6 h at a dose of 50–100 mg depending on age and body surface area.[83] With daily hydrocortisone doses of 50 mg or more, mineralocorticoid replacement in primary adrenal insufficiency can be stopped or reduced because this dose is equivalent to 0·1 mg fludrocortisone.[60] Once the patient's condition is stable, intravenous glucocorticoid treatment can be decreased over the next few days and an oral maintenance dose can be instituted.[1–3,60,83,98–103]

Special diagnostic and therapeutic conditions

Adrenal insufficiency in critically ill patients

Adrenal insufficiency is common in critically ill patients and is increasingly reported in sepsis, severe pneumonia, adult respiratory stress syndrome, trauma, HIV infection, or after treatment with etomidate.[2,123–127] It can also be associated with structural damage to the adrenal gland, pituitary gland, or hypothalamus; however, many critically ill patients develop reversible failure of the HPA axis.[2,123–126]

The underlying pathophysiological mechanisms leading to adrenal insufficiency in the course of critical illness are not clear; however, they include both decreased cortisol secretion and impaired glucocorticoid signal transduction. Proinflammatory cytokines could compete with corticotropin at its receptor[128] or induce tissue resistance to glucocorticoids[129–131] (figure 2).

In the absence of glucocorticoids, the glucocorticoid receptor is primarily in the cytoplasm as part of a complex with heat shock proteins and immunophilins. When ligands bind, the receptor undergoes conformational change, dissociates from the chaperone proteins, and moves into the nucleus, where it binds to positive or negative glucocorticoid response elements in the promoter regions of anti-inflammatory or pro-inflammatory genes. The glucocorticoid receptor can also inhibit the expression of pro-inflammatory genes independently of DNA binding by physically interacting with the transcription factor p65, a subunit of nuclear factor κB. This interaction inhibits p65–p50 heterodimer translocation into and action at the nucleus. Glucocorticoids can induce some anti-inflammatory effects through non-genomic effects. Membrane-bound glucocorticoid receptors can activate kinase pathways within minutes. The activation of the MAPK pathway results in the inhibition of cytosolic phospholipase A2α, whereas activated phosphatidylinositol 3-kinase leads to the induction of endothelial nitric oxide synthetase and the subsequent production of nitric oxide. Moreover, glucocorticoids can impair T-cell receptor signalling through non-genomic inhibition of FYN oncogene-related kinase and lymphocyte-specific protein tyrosine kinase by the glucocorticoid receptor.

In addition to sepsis itself, the medications used during its treatment can interfere with glucocorticoid synthesis and signal transduction. Furthermore, impaired blood supply to the pars distalis of the pituitary can induce pituitary ischaemia or necrosis, and the increased accumulation of nitric oxide, superoxide, or central neuropeptides or prostaglandins can contribute to a decrease in hypothalamic–pituitary hormone secretion in patients with sepsis.[2,123–126]

A multidisciplinary, multispecialty task force of experts in critical care medicine was convened to provide recommendations on the diagnosis and management of adrenal insufficiency in critically ill patients.[132] The diagnosis in this setting is confirmed by a change in total serum cortisol of less than 250 nmol/L (90 μg/L) after corticotropin (250 μg) administration or a randomly measured total cortisol of less than 275 nmol/L (100 μg/L). 200 mg hydrocortisone daily divided into four doses or as a continuous infusion of 240 mg per day (10 mg/h) for at least 7 days is recommended for septic shock. Methylprednisolone (1 mg/kg daily for at least 14 days) is recommended in patients with severe early acute respiratory distress syndrome. The role of glucocorticoid therapy in other critically ill patients has not been fully elucidated.[132]

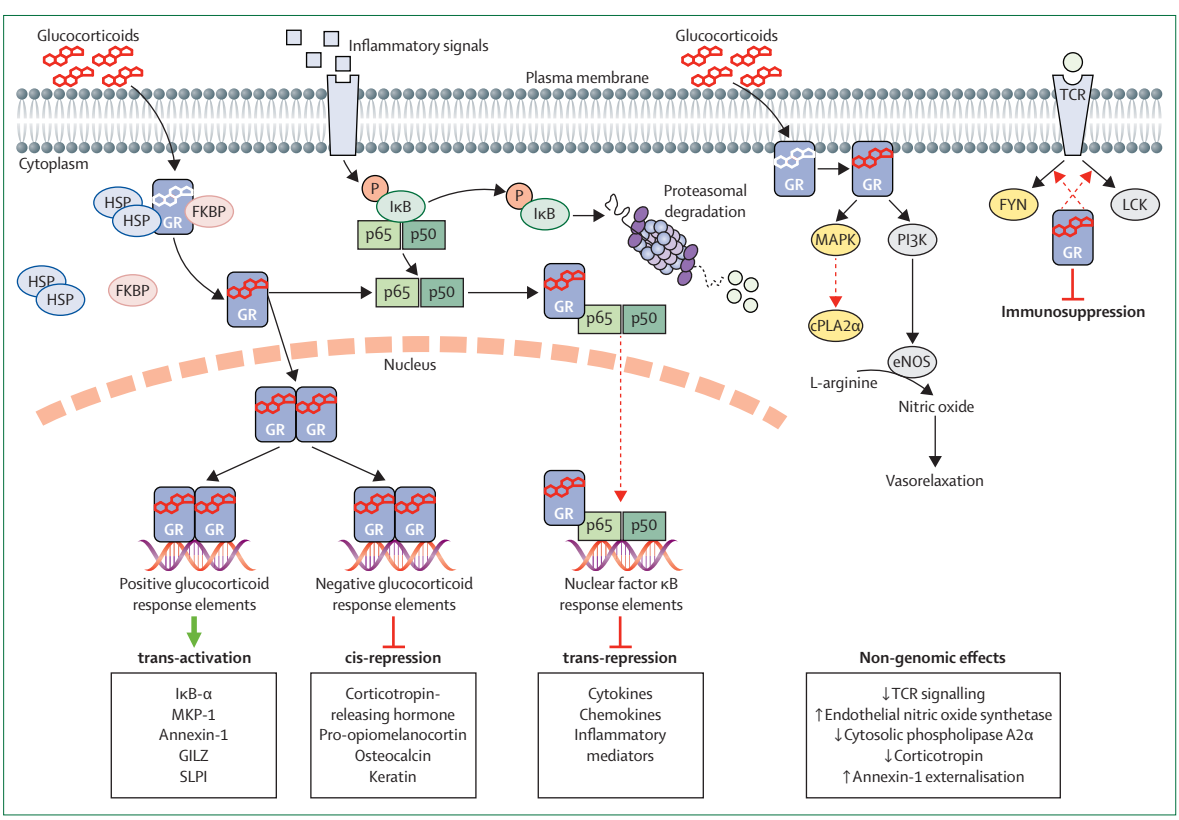

Figure 2: **Molecular mechanisms of glucocorticoid action during the inflammatory process**
GR=glucocorticoid receptor. HSP=heat shock proteins. FKBP=FK binding proteins. IκB=inhibitor of kappa B. p65=transcription factor p65. p50=transcription factor p50. MAPK=mitogen-activated protein kinases. PI3K=phosphatidylinositol 3-kinase. TCR=T-cell receptor. FYN=FYN oncogene-related kinase. LCK=lymphocyte-specific protein tyrosine kinase. MKP-1=MAPK phosphatase 1. GILZ=glucocorticoid-induced leucine zipper protein. SLPI=secretory leukoprotease inhibitor.

Thyroid dysfunction

Patients with adrenal insufficiency and untreated hyperthyroidism should receive two or three times their usual glucocorticoid replacement dose to compensate for the increased cortisol clearance owing to the hyperthyroid state.[133] In addition, to prevent adrenal crises, thyroxine replacement in patients with hypothyroidism should start after the adrenal insufficiency has been excluded or treated.

Pregnancy

Adrenal insufficiency in pregnancy is quite rare; however, it can lead to substantial morbidity and even death of both mother and fetus if not diagnosed and treated promptly. Pregnancy is a physiological state of glucocorticoid excess and is associated with high serum concentrations of cortisol-binding globulin, free cortisol, and progesterone, especially in the latter stages.[134] Patients with adrenal insufficiency in pregnancy should be treated with hydrocortisone 12–15 mg/m² daily, in three doses with the largest one given in the morning. At the onset of labour, the daily hydrocortisone dose should be doubled or tripled or a parenteral dose of 50–100 mg can be given during the second stage of labour. If the patient undergoes caesarean section, hydrocortisone should be given intravenously at a dose of 100 mg every 6 h then tapered over the next 48 h.[135,136]

Drug interactions

Anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine, stimulate cytochrome P450 3A4, thereby inducing hepatic enzymes and leading to accelerated glucocorticoid metabolism and reduced glucocorticoid effect. By contrast, antiretroviral drugs, such as ritonavir, inhibit cytochrome P3A activity, and lead to delayed glucocorticoid metabolism and increased glucocorticoid concentration (appendix).[60]

See Online for appendix

Conflicts of interest

We declare that we have no conflicts of interest.

Contributors

EC undertook the literature search and data analysis and wrote the paper. NCN undertook the literature search, participated in preparation of the tables, and prepared the figures. GPC reviewed the paper critically and offered his comments. All the authors read and approved the final version.

References

1 Arlt W, Allolio B. Adrenal insufficiency. *Lancet* 2003; **361:** 1881–93.
2 Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009; **360:** 2328–39.
3 Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes* 2010; **17:** 217–23.
4 Addison T. On the constitutional and local effects of disease of the supra-renal capsules. London: Samuel Highley, 1855.
5 Løvås K, Husebye ES. Addison's disease. *Lancet* 2005; **365:** 2058–61.
6 Sarett LH. Partial synthesis of pregnene-4-triol-17(β), 20(β), 21-dione-3,11 and pregnene-4-diol-17(β), 21-trione-3,11,20 monoacetate. *J Biol Chem* 1946; **162:** 601–31.
7 Kendall EC. Hormones of the adrenal cortex in health and disease. *Proc Am Philos Soc* 1953; **97:** 8–11.
8 Reichstein T. [The most important hormones of adrenal cortex]. *Acta Endocrinol (Copenh)* 1954; **17:** 375–84.
9 Hillier SG. Diamonds are forever: the cortisone legacy. *J Endocrinol* 2007; **195:** 1–6.
10 Mason AS, Meade TW, Lee JA, Morris JN. Epidemiological and clinical picture of Addison's disease. *Lancet* 1968; **2:** 744–47.
11 Nerup J. Addison's disease—clinical studies. A report of 108 cases. *Acta Endocrinol (Copenh)* 1974; **76:** 127–41.
12 Kong MF, Jeffcoate W. Eighty-six cases of Addison's disease. *Clin Endocrinol (Oxf)* 1994; **41:** 757–61.
13 Willis AC, Vince FP. The prevalence of Addison's disease in Coventry, UK. *Postgrad Med J* 1997; **73:** 286–88.
14 Laureti S, Vecchi L, Santeusanio F, Falorni A. Is the prevalence of Addison's disease underestimated? *J Clin Endocrinol Metab* 1999; **84:** 1762.
15 Løvås K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. *Clin Endocrinol (Oxf)* 2002; **56:** 787–91.
16 Erichsen MM, Løvås K, Skinningsrud 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.
17 Dunlop D. Eighty-six cases of Addison's disease. *BMJ* 1963; **2:** 887–91.
18 Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003; **2:** 119–25.
19 Betterle C, Morlin L. Autoimmune Addison's disease. *Endocr Dev* 2011; **20:** 161–72.
20 Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab* 2005; **90:** 3243–50.
21 Bates AS, Van't Hoff W, Jones PJ, Clayton RN. The effect of hypopituitarism on life expectancy. *J Clin Endocrinol Metab* 1996; **81:** 1169–72.
22 Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *J Clin Endocrinol Metab* 2000; **85:** 1420–25.
23 Regal M, Páramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)* 2001; **55:** 735–40.
24 Tomlinson JW, Holden N, Hills RK, et al, for the West Midlands Prospective Hypopituitary Study Group. Association between premature mortality and hypopituitarism. *Lancet* 2001; **357:** 425–31.
25 Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, et al. Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96:** 2330–40.
26 Gomez MT, Magiakou MA, Mastorakos G, Chrousos GP. The pituitary corticotroph is not the rate limiting step in the postoperative recovery of the hypothalamic-pituitary-adrenal axis in patients with Cushing syndrome. *J Clin Endocrinol Metab* 1993; **77:** 173–77.
27 Reincke M, Heppner C, Petzke F, et al. Impairment of adrenocortical function associated with increased plasma tumor necrosis factor-alpha and interleukin-6 concentrations in African trypanosomiasis. *Neuroimmunomodulation* 1994; **1:** 14–22.
28 Charmandari E, Kino T. Chrousos syndrome: a seminal report, a phylogenetic enigma and the clinical implications of glucocorticoid signalling changes. *Eur J Clin Invest* 2010; **40:** 932–42.
29 Charmandari E. Primary generalized glucocorticoid resistance and hypersensitivity. *Horm Res Paediatr* 2011; **76:** 145–55.
30 Charmandari E. Primary generalized glucocorticoid resistance and hypersensitivity: the end-organ involvement in the stress response. *Sci Signal* 2012; **5:** pt5.
31 Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. *Endocr Dev* 2013; **24:** 67–85.
32 Mitchell AL, Pearce SH. Autoimmune Addison disease: pathophysiology and genetic complexity. *Nat Rev Endocrinol* 2012; **8:** 306–16.
33 Napier C, Pearce SH. Autoimmune Addison's disease. *Presse Med* 2012; **41:** e626–35.
34 Husebye E, Løvås K. Pathogenesis of primary adrenal insufficiency. *Best Pract Res Clin Endocrinol Metab* 2009; **23:** 147–57.
35 Husebye ES, Løvås K. Immunology of Addison's disease and premature ovarian failure. *Endocrinol Metab Clin North Am* 2009; **38:** 389–405.

36 Reato G, Morlin L, Chen S, et al. Premature ovarian failure in patients with autoimmune Addison's disease: clinical, genetic, and immunological evaluation. *J Clin Endocrinol Metab* 2011; **96:** E1255–61.

37 Bratland E, Skinningsrud B, Undlien DE, Mozes E, Husebye ES. T cell responses to steroid cytochrome P450 21-hydroxylase in patients with autoimmune primary adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94:** 5117–24.

38 Bratland E, Husebye ES. Cellular immunity and immunopathology in autoimmune Addison's disease. *Mol Cell Endocrinol* 2011; **336:** 180–90.

39 Baker PR, Baschal EE, Fain PR, et al. Haplotype analysis discriminates genetic risk for DR3-associated endocrine autoimmunity and helps define extreme risk for Addison's disease. *J Clin Endocrinol Metab* 2010; **95:** E263–70.

40 Baker PR, Baschal EE, Fain PR, et al. Dominant suppression of Addison's disease associated with HLA-B15. *J Clin Endocrinol Metab* 2011; **96:** 2154–62.

41 Skinningsrud B, Lie BA, Lavant E, et al. Multiple loci in the HLA complex are associated with Addison's disease. *J Clin Endocrinol Metab* 2011; **96:** E1703–08.

42 Akirav EM, Ruddle NH, Herold KC. The role of AIRE in human autoimmune disease. *Nat Rev Endocrinol* 2011; **7:** 25–33.

43 Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. *Nat Rev Endocrinol* 2010; **6:** 270–77.

44 Husebye ES, Perheentupa J, Rautemaa R, Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. *J Intern Med* 2009; **265:** 514–29.

45 Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev* 2002; **23:** 327–64.

46 Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome type 2: the tip of an iceberg? *Clin Exp Immunol* 2004; **137:** 225–33.

47 Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. *Biochim Biophys Acta* 2012; **1822:** 1465–74.

48 Presotto F, Fornasini F, Betterle C, Federspil G, Rossato M. Acute adrenal failure as the heralding symptom of primary antiphospholipid syndrome: report of a case and review of the literature. *Eur J Endocrinol* 2005; **153:** 507–14.

49 Ramon I, Mathian A, Bachelot A, et al. Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in the antiphospholipid syndrome: long-term outcome of 16 patients. *J Clin Endocrinol Metab* 2013; **98:** 3179–89.

50 Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr Rev* 2011; **32:** 81–151.

51 Merke DP, Chrousos GP, Eisenhofer G, et al. Adrenomedullary dysplasia and hypofunction in patients with classic 21-hydroxylase deficiency. *N Engl J Med* 2000; **343:** 1362–68.

52 Charmandari E, Eisenhofer G, Mehlinger SL, et al. Adrenomedullary function may predict phenotype and genotype in classic 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2002; **87:** 3031–37.

53 Andrioli M, Pecori Giraldi F, Cavagnini F. Isolated corticotrophin deficiency. *Pituitary* 2006; **9:** 289–95.

54 Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. *Endocr Rev* 2005; **26:** 599–614.

55 Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* 2008; **4:** 569–77.

56 Couture C, Saveanu A, Barlier A, et al. Phenotypic homogeneity and genotypic variability in a large series of congenital isolated ACTH-deficiency patients with TPIT gene mutations. *J Clin Endocrinol Metab* 2012; **97:** E486–95.

57 Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA* 1999; **282:** 671–76.

58 Avgerinos PC, Cutler GB Jr, Tsokos GC, et al. Dissociation between cortisol and adrenal androgen secretion in patients receiving alternate day prednisone therapy. *J Clin Endocrinol Metab* 1987; **65:** 24–29.

59 Schürmeyer TH, Tsokos GC, Avgerinos PC, et al. Pituitary-adrenal responsiveness to corticotropin-releasing hormone in patients receiving chronic, alternate day glucocorticoid therapy. *J Clin Endocrinol Metab* 1985; **61:** 22–27.

60 Charmandari E, Kino T, Chrousos GP. Glucocorticoids. In Yaffe SJ, Aranda JV, eds. Neonatal and pediatric pharmacology, 4th edn. Philadelphia: Lippincott Williams and Wilkins, 2010: 760–72.

61 Gordijn MS, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. *Cochrane Database Syst Rev* 2012; **5:** CD008727.

62 Zöllner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (part 2)–the risk as determined by gold standard adrenal function tests: a systematic review. *Pediatr Allergy Immunol* 2007; **18:** 469–74.

63 Drake AJ, Howells RJ, Shield JP, Prendiville A, Ward PS, Crowne EC. Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002; **324:** 1081–82.

64 Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol* 2005; **67:** 259–84.

65 Nader N, Chrousos GP, Kino T. Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster: potential physiological implications. *FASEB J* 2009; **23:** 1572–83.

66 Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. *Trends Endocrinol Metab* 2010; **21:** 277–86.

67 Charmandari E, Chrousos GP, Lambrou GI, et al. Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man. *PLoS One* 2011; **6:** e25612.

68 Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006; **355:** 1647–59.

69 Baker PR, Nanduri P, Gottlieb PA, et al. Predicting the onset of Addison's disease: ACTH, renin, cortisol and 21-hydroxylase autoantibodies. *Clin Endocrinol (Oxf)* 2012; **76:** 617–24.

70 Betterle C, Scalici C, Presotto F, et al. The natural history of adrenal function in autoimmune patients with adrenal autoantibodies. *J Endocrinol* 1988; **117:** 467–75.

71 Weintrob N, Sprecher E, Josefsberg Z, et al. Standard and low-dose short adrenocorticotropin test compared with insulin-induced hypoglycemia for assessment of the hypothalamic-pituitary-adrenal axis in children with idiopathic multiple pituitary hormone deficiencies. *J Clin Endocrinol Metab* 1998; **83:** 88–92.

72 Christ-Crain M, Jutla S, Widmer I, et al. Measurement of serum free cortisol shows discordant responsivity to stress and dynamic evaluation. *J Clin Endocrinol Metab* 2007; **92:** 1729–35.

73 Klose M, Lange M, Rasmussen AK, et al. Factors influencing the adrenocorticotropin test: role of contemporary cortisol assays, body composition, and oral contraceptive agents. *J Clin Endocrinol Metab* 2007; **92:** 1326–33.

74 Tan T, Chang L, Woodward A, et al. Characterising adrenal function using directly measured plasma free cortisol in stable severe liver disease. *J Hepatol* 2010; **53:** 841–48.

75 Raff H. Utility of salivary cortisol measurements in Cushing's syndrome and adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94:** 3647–55.

76 Hägg E, Asplund K, Lithner F. Value of basal plasma cortisol assays in the assessment of pituitary-adrenal insufficiency. *Clin Endocrinol (Oxf)* 1987; **26:** 221–26.

77 Deutschbein T, Unger N, Mann K, Petersenn S. Diagnosis of secondary adrenal insufficiency: unstimulated early morning cortisol in saliva and serum in comparison with the insulin tolerance test. *Horm Metab Res* 2009; **41:** 834–39.

78 Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short synacthen test in outpatient assessment? *Ann Clin Biochem* 2002; **39:** 148–50.

79 Schmidt IL, Lahner H, Mann K, Petersenn S. Diagnosis of adrenal insufficiency: evaluation of the corticotropin-releasing hormone test and Basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. *J Clin Endocrinol Metab* 2003; **88:** 4193–98.

80 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.

81 Gleeson HK, Walker BR, Seckl JR, Padfield PL. Ten years on: safety of short synacthen tests in assessing adrenocorticotropin deficiency in clinical practice. *J Clin Endocrinol Metab* 2003; **88:** 2106–11.

82 Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM. The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab* 2006; **91:** 43–47.

83 Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94:** 1059–67.

84 Chrousos GP, Kino T, Charmandari E. Evaluation of the hypothalamic-pituitary-adrenal axis function in childhood and adolescence. *Neuroimmunomodulation* 2009; **16:** 272–83.

85 Grossman AB. Clinical Review: The diagnosis and management of central hypoadrenalism. *J Clin Endocrinol Metab* 2010; **95:** 4855–63.

86 Kazlauskaite R, Evans AT, Villabona CV, et al, for the Consortium for Evaluation of Corticotropin Test in Hypothalamic-Pituitary Adrenal Insufficiency. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab* 2008; **93:** 4245–53.

87 Kazlauskaite R, Maghnie M. Pitfalls in the diagnosis of central adrenal insufficiency in children. *Endocr Dev* 2010; **17:** 96–107.

88 Wallace I, Cunningham S, Lindsay J. The diagnosis and investigation of adrenal insufficiency in adults. *Ann Clin Biochem* 2009; **46:** 351–67.

89 Fleseriu M, Gassner M, Yedinak C, Chicea L, Delashaw JB Jr, Loriaux DL. Normal hypothalamic-pituitary-adrenal axis by high-dose cosyntropin testing in patients with abnormal response to low-dose cosyntropin stimulation: a retrospective review. *Endocr Pract* 2010; **16:** 64–70.

90 Wade M, Baid S, Calis K, Raff H, Sinaii N, Nieman L. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. *Eur J Endocrinol* 2010; **162:** 109–13.

91 Rose LI, Williams GH, Jagger PI, Lauler DP. The 48-hour adrenocorticotrophin infusion test for adrenocortical insufficiency. *Ann Intern Med* 1970; **73:** 49–54.

92 Laureti S, Aubourg P, Calcinaro F, et al. Etiological diagnosis of primary adrenal insufficiency using an original flowchart of immune and biochemical markers. *J Clin Endocrinol Metab* 1998; **83:** 3163–68.

93 Falorni A, Laureti S, De Bellis A, et al, for the SIE Addison Study Group. Italian addison network study: update of diagnostic criteria for the etiological classification of primary adrenal insufficiency. *J Clin Endocrinol Metab* 2004; **89:** 1598–604.

94 Boland GW. Adrenal imaging: from Addison to algorithms. *Radiol Clin North Am* 2011; **49:** 511–28, vii.

95 Ouyang T, Rothfus WE, Ng JM, Challinor SM. Imaging of the pituitary. *Radiol Clin North Am* 2011; **49:** 549–71.

96 Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. *BMJ* 2012; **345:** e6333.

97 Wass JAH, Howell TH, Arlt W, Pearce S. Addison's disease. Potentially life-threatening steroid dependency. Addison's Disease Self Help Group. 2011. www.addisons.org.uk/info/emergency/soscrisisletter.pdf (accessed Oct 16, 2013).

98 Løvås K, Husebye ES. Replacement therapy for Addison's disease: recent developments. *Expert Opin Investig Drugs* 2008; **17:** 497–509.

99 Hahner S, Allolio B. Therapeutic management of adrenal insufficiency. *Best Pract Res Clin Endocrinol Metab* 2009; **23:** 167–79.

100 Quinkler M, Hahner S. What is the best long-term management strategy for patients with primary adrenal insufficiency? *Clin Endocrinol (Oxf)* 2012; **76:** 21–25.

101 Falorni A, Minarelli V, Morelli S. Therapy of adrenal insufficiency: an update. *Endocrine* 2013; **43:** 514–28.

102 Reisch N, Arlt W. Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin North Am* 2009; **38:** 407–18, ix–x.

103 Løvås K, Gjesdal CG, Christensen M, et al. Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. *Eur J Endocrinol* 2009; **160:** 993–1002.

104 Bleicken B, Hahner S, Loeffler M, et al. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 2010; **72:** 297–304.

105 Bleicken B, Hahner S, Loeffler M, Ventz M, Allolio B, Quinkler M. Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. *Eur J Endocrinol* 2008; **159:** 811–17.

106 Stavreva DA, Wiench M, John S, et al. Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. *Nat Cell Biol* 2009; **11:** 1093–102.

107 Newell-Price J, Whiteman M, Rostami-Hodjegan A, et al. Modified-release hydrocortisone for circadian therapy: a proof-of-principle study in dexamethasone-suppressed normal volunteers. *Clin Endocrinol (Oxf)* 2008; **68:** 130–35.

108 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.

109 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.

110 Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341:** 1013–20.

111 Hunt PJ, Gurnell EM, Huppert FA, et al. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 2000; **85:** 4650–56.

112 Brooke AM, Kalingag LA, Miraki-Moud F, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006; **91:** 3773–79.

113 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.

114 Bhagra S, Nippoldt TB, Nair KS. Dehydroepiandrosterone in adrenal insufficiency and ageing. *Curr Opin Endocrinol Diabetes Obes* 2008; **15:** 239–43.

115 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.

116 Binder G, Weber S, Ehrismann M, et al, for the South German Working Group for Pediatric Endocrinology. Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo-controlled phase III trial. *J Clin Endocrinol Metab* 2009; **94:** 1182–90.

117 Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154:** 1–11.

118 Charmandari E, Hindmarsh PC, Johnston A, Brook CG. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: alterations in cortisol pharmacokinetics at puberty. *J Clin Endocrinol Metab* 2001; **86:** 2701–08.

119 Charmandari E, Johnston A, Brook CG, Hindmarsh PC. Bioavailability of oral hydrocortisone in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Endocrinol* 2001; **169:** 65–70.

120 Charmandari E, Chrousos GP. Metabolic syndrome manifestations in classic congenital adrenal hyperplasia: do they predispose to atherosclerotic cardiovascular disease and secondary polycystic ovary syndrome? *Ann N Y Acad Sci* 2006; **1083:** 37–53.

121 Charmandari E, Matthews DR, Johnston A, Brook CG, Hindmarsh PC. Serum cortisol and 17-hydroxyprogesterone interrelation in classic 21-hydroxylase deficiency: is current replacement therapy satisfactory? *J Clin Endocrinol Metab* 2001; **86:** 4679–85.

122 White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *Eur J Endocrinol* 2010; **162:** 115–20.

123 Fleseriu M, Loriaux DL. "Relative" adrenal insufficiency in critical illness. *Endocr Pract* 2009; **15:** 632–40.

124 Annetta M, Maviglia R, Proietti R, Antonelli M. Use of corticosteroids in critically ill septic patients: a review of mechanisms of adrenal insufficiency in sepsis and treatment. *Curr Drug Targets* 2009; **10:** 887–94.

125 Cohen J, Venkatesh B. Relative adrenal insufficiency in the intensive care population; background and critical appraisal of the evidence. *Anaesth Intensive Care* 2010; **38:** 425–36.

126 Moraes RB, Czepielewski MA, Friedman G, Borba EL. Diagnosis of adrenal failure in critically ill patients. *Arq Bras Endocrinol Metabol* 2011; **55:** 295–302.

127 Albert SG, Ariyan S, Rather A. The effect of etomidate on adrenal function in critical illness: a systematic review. *Intensive Care Med* 2011; **37:** 901–10.

128 Bornstein SR, Engeland WC, Ehrhart-Bornstein M, Herman JP. Dissociation of ACTH and glucocorticoids. *Trends Endocrinol Metab* 2008; **19:** 175–80.

129 Charmandari E, Kino T, Ichijo T, Chrousos GP. Generalized glucocorticoid resistance: clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. *J Clin Endocrinol Metab* 2008; **93:** 1563–72.

130 Nicolaides NC, Galata Z, Kino T, Chrousos GP, Charmandari E. The human glucocorticoid receptor: molecular basis of biologic function. *Steroids* 2010; **75:** 1–12.

131 Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci* 2012; **1261:** 55–63.

132 Marik PE, Pastores SM, Annane D, et al, and the American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; **36:** 1937–49.

133 Mishra SK, Gupta N, Goswami R. Plasma adrenocorticotropin (ACTH) values and cortisol response to 250 and 1 microg ACTH stimulation in patients with hyperthyroidism before and after carbimazole therapy: case-control comparative study. *J Clin Endocrinol Metab* 2007; **92:** 1693–96.

134 Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM. Diurnal salivary cortisol patterns during pregnancy and after delivery: relationship to plasma corticotrophin-releasing-hormone. *Clin Endocrinol (Oxf)* 1990; **33:** 279–89.

135 Yuen KC, Chong LE, Koch CA. Adrenal insufficiency in pregnancy: challenging issues in diagnosis and management. *Endocrine* 2013; **44:** 283–92.

136 Lekarev O, New MI. Adrenal disease in pregnancy. *Best Pract Res Clin Endocrinol Metab* 2011; **25:** 959–73.