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Adrenal Insufficiency

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ABSTRACT

Adrenal insufficiency is a serious pathologic condition characterized by decreased production or action of glucocorticoids and/or mineralocorticoids and adrenal androgens. This life-threatening disorder may be classified as primary, secondary or tertiary, resulting from diseases affecting the adrenal cortex, the anterior pituitary gland or the hypothalamus, respectively. The clinical manifestations of adrenal insufficiency include anorexia, abdominal pain, weakness, weight loss, fatigue, hypotension, salt craving and hyperpigmentation of the skin in case of primary adrenal insufficiency. The diagnosis of adrenal insufficiency can be confirmed by demonstrating inappropriately low cortisol secretion, determining whether the cortisol deficiency is secondary or primary, and defining the cause of the disorder. Treatment with glucocorticoid and/or mineralocorticoid replacement should be initiated when glucocorticoid and or mineralocorticoid deficiency is suspected. This chapter will provide an overview of the epidemiology, etiology, pathophysiology, clinical manifestations, diagnosis and treatment of adrenal insufficiency. Finally, special conditions of adrenal insufficiency, including critical illness, pregnancy, infancy and childhood will also be discussed. For complete coverage of this and related areas of Endocrinology, please visit our free online textbook, WWW.ENDOTEXT.ORG.

INTRODUCTION

Adrenal insufficiency is a disorder first described by Thomas Addison in 1855, which is characterized by deficient production or action of glucocorticoids and/or mineralocorticoids and adrenal androgens. This life-threatening disease may result from disorders affecting the adrenal cortex (primary), the anterior pituitary gland (secondary), or the hypothalamus (tertiary) (**Figure 1**) (**1-3**). The clinical symptoms of adrenal insufficiency include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, salt craving, and characteristic hyperpigmentation of the skin occurring with primary adrenocortical failure (**4, 5**). Regardless of etiology, adrenal insufficiency was an invariably fatal disorder, until the synthesis of cortisone by Kendall, Sarett, and Reichstein (**6-9**) in 1949, and the introduction of substitution therapy with life-saving synthetic glucocorticoids subsequently. However, despite this progress, there are still numerous challenges regarding the diagnosis and treatment of patients with adrenal insufficiency.

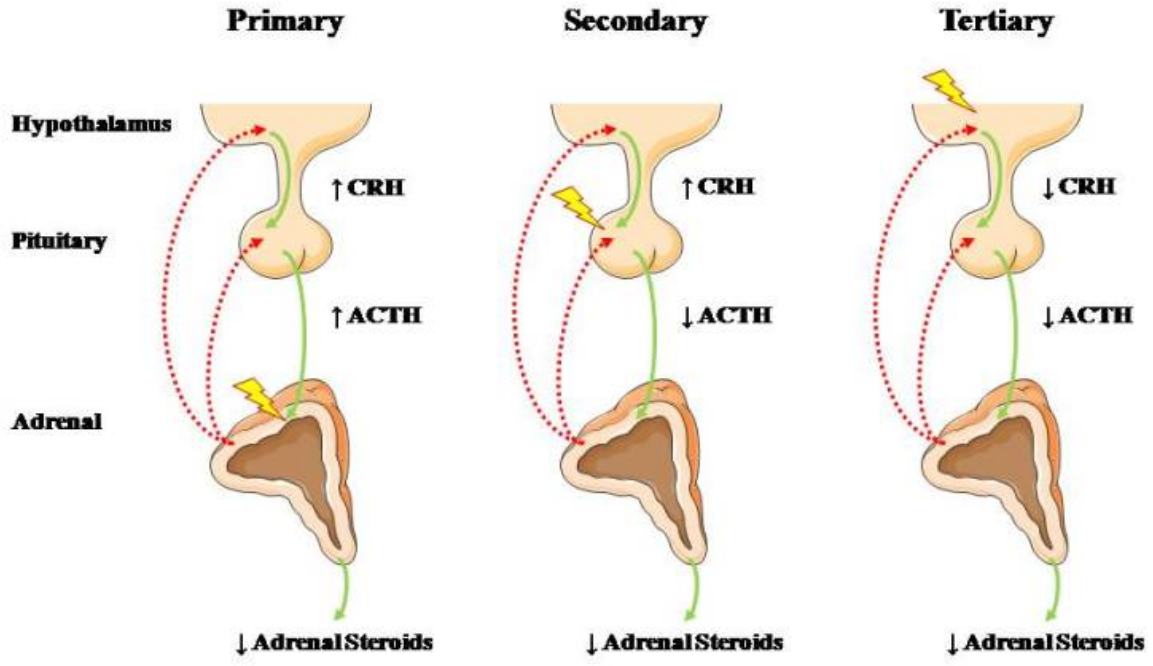

Figure 1

Types of adrenal insufficiency. CRH: corticotropin-releasing hormone, ACTH: adrenocorticotropic hormone.

EPIDEMIOLOGY

The prevalence of chronic primary adrenal insufficiency in Europe has been doubled from 40–70 cases per million population in the 1960s (**10, 11**) to 93–144 cases per million population by the end of the last century and in recent years (**12-16**). The currently estimated incidence of this disorder is 4.4–6 new cases per million population per year (**15**). Primary adrenal insufficiency affects more frequently women, and clinical manifestations can present at any age, although most often between 30 and 50 years (**12**).

Secondary adrenal insufficiency occurs more frequently than primary adrenal insufficiency (**1**). Its estimated prevalence is 150–280 per million and is more common in women than men (**14, 17-20**). Affected patients are mostly diagnosed in the sixth decade of life (**18, 19**).

The most common cause of tertiary adrenal insufficiency is chronic exogenous administration of synthetic glucocorticoids, which causes prolonged suppression of hypothalamic corticotropin-releasing hormone (CRH) secretion through negative feedback mechanisms (**21**).

CAUSES OF ADRENAL INSUFFICIENCY

Causes of Primary Adrenal Insufficiency

The etiology of primary adrenal insufficiency has changed over time. Prior to 1920, the most common cause of primary adrenal insufficiency was tuberculosis, while since 1950, the majority of cases (80-90%) have been ascribed to autoimmune adrenalitis, which can be isolated (40%) or in the context of an autoimmune polyendocrinopathy syndrome (60%) (**1, 2, 22-24**).

***Autoimmune adrenalitis (Addison's disease)*:** This condition is characterized by destruction of the adrenal cortex by cell-mediated immune mechanisms. Antibodies that react against steroid 21-hydroxylase are detected in approximately 90% of patients with autoimmune Addison's disease (**16**), but only rarely in patients with other causes of adrenal insufficiency or normal subjects (**25**).

Considerable progress has been made in identifying genetic factors that predispose to the development of autoimmune adrenal insufficiency (**2**). In addition to the major histocompatibility complex (MHC) haplotypes DR3-DQ2 and DR4-DQ8, other genetic factors, such as protein tyrosine phosphatase non-receptor type 22 (PTPN22), cytotoxic T lymphocyte antigen 4 (CTLA-4), and the major histocompatibility complex class II transactivator (CIITA) have been associated with this condition (**23-29**).

Primary adrenal insufficiency may also present as part of autoimmune polyendocrinopathy syndromes. Patients with autoimmune polyendocrinopathy syndrome type 1 (APS1) or APECED (Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy) syndrome may present with chronic mucocutaneous candidiasis, adrenal insufficiency, hypoparathyroidism, hypoplasia of the dental enamel and nail dystrophy, while type 1 Diabetes Mellitus (T1DM) or pernicious anemia, may develop later in life (**30, 31**). Clinical manifestations of autoimmune polyendocrinopathy syndrome type 2 (APS2) include autoimmune adrenal insufficiency, autoimmune thyroid disease and/or T1DM, whereas autoimmune polyendocrinopathy syndrome type 4 (APS4) is characterized by autoimmune adrenal insufficiency and one or more other autoimmune diseases, such as atrophic gastritis, hypogonadism, pernicious anemia, celiac disease, myasthenia gravis, vitiligo, alopecia and hypophysitis, but without any autoimmune disorders of APS1 or APS2 (**23, 24, 26, 31-33**).

***Adrenoleukodystrophy*:** This is an X-linked recessive disorder affecting 1 in 20.000 males (**2**). The molecular basis of this condition has been ascribed to mutations in the ABCD1 gene, which result in defective beta oxidation of very long chain fatty acids (VLCFAs) within peroxisomes. The abnormally high concentrations of VLCFAs in affected organs, including the adrenal cortex, result in the clinical manifestations of this disorder, which include neurological impairment due to white-matter demyelination and primary adrenal insufficiency, with the latter presenting in infancy or childhood (**1-3, 34**).

Hemorrhagic infarction: Bilateral adrenal infarction caused by hemorrhage or adrenal vein thrombosis may also lead to adrenal insufficiency (**35, 36**). The diagnosis is usually made in critically ill patients in whom a computed tomography (CT) scan of the abdomen shows bilateral adrenal enlargement. Several coagulopathies and the heparin-induced thrombocytopenia syndrome have been associated with adrenal vein thrombosis and hemorrhage, while the primary antiphospholipid syndrome has been recognized as a major cause of adrenal hemorrhage (**37**). Adrenal hemorrhage has been mostly associated with meningococcemia (Waterhouse-Friderichsen syndrome) and Pseudomonas aeruginosa infection (**38**).

***Infectious adrenalitis*:** Many infectious agents may attack the adrenal gland and result in adrenal insufficiency, including tuberculosis (tuberculous adrenalitis), disseminated fungal infections and HIV-associated infections, such as adrenalitis due to cytomegalovirus and mycobacterium avium complex (**39-41**).

***Drug-induced adrenal insufficiency* :** Drugs that may cause adrenal insufficiency by inhibiting cortisol biosynthesis, particularly in individuals with limited pituitary and/or adrenal reserve, include aminoglutethimide (antiepileptic), etomidate (anesthetic-sedative) (**42, 43**), ketoconazole (antimycotic) (**44**) and metyrapone (**45**). Drugs that accelerate the metabolism of cortisol and most synthetic glucocorticoids by inducing hepatic mixed-function oxygenase enzymes, such as phenytoin, barbiturates, and rifampicin can also cause adrenal insufficiency in patients with limited pituitary or adrenal reserve, as well as those who are on replacement therapy with glucocorticoids (**46**). Furthermore, some of novel tyrosine kinase-targeting drugs (e.g. sunitinib) have been shown in animal studies to cause adrenal dysfunction and hemorrhage (**47**).

Other causes of primary adrenal insufficiency are listed in **Table 1**.

Table 1 Causes of Primary Adrenal Insufficiency

Disease	Pathogenetic Mechanism
Autoimmune adrenalitis	
Isolated	Associations with HLA-DR3-DQ2, HLADR4-DQ8, MICA, CTLA-4, PTPN22, CIITA, CLEC16A, Vitamin D receptor
APS type 1 (APECED)	*AIRE* gene mutations
APS type 2	Associations with HLA-DR3, HLA-DR4, CTLA-4
APS type 4	Associations with HLA-DR3, CTLA-4
Infectious adrenalitis	
Tuberculous adrenalitis	Tuberculosis
AIDS	HIV-1, cytomegalovirus

Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidiodomycosis
Syphilis	Treponema pallidum
African Trypanosomiasis	Trypanosoma brucei
Bilateral adrenal hemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome
Bilateral adrenal metastases	Primarily lung, stomach, breast and colon cancer
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, haemochromatosis
Bilateral adrenalectomy	Unresolved Cushing's syndrome, bilateral adrenal masses, bilateral pheochromocytoma
Drug-induced adrenal insufficiency	
Anticoagulants (heparin, warfarin), tyrosine kinase inhibitors (sunitinib)	Hemorrhage
Aminoglutethimide	Inhibition of P450 aromatase (CYP19A1)
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2)
Ketoconazole, fluconazole, etomidate	Inhibition of mitochondrial cytochrome P450-dependent enzymes (e.g. CYP11A1, CYP11B1)
Phenobarbital	Induction of P450-cytochrome enzymes (CYP2B1, CYP2B2), which enhance cortisol metabolism
Phenytoin, rifampin, troglitazone	Induction of P450-cytochrome enzymes (primarily CYP3A4), which enhance cortisol metabolism
Genetic disorders	
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* and *ABCD2* gene mutations
Congenital adrenal hyperplasia	
21-Hydroxylase deficiency	*CYP21A2* gene mutations
11β-Hydroxylase deficiency	*CYP11B1* gene mutations
3β-hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2* gene mutations
17α-Hydroxylase deficiency	*CYP17A1* gene mutations
P450 Oxidoreductase deficiency	*POR* gene mutations
P450 side-chain cleavage deficiency	*CYP11A1* gene mutations
Congenital lipoid adrenal hyperplasia	*StAR* gene mutations
Smith-Lemli-Opitz syndrome	*DHCR7* gene mutations
Adrenal hypoplasia congenita	
X-linked	*NR0B1* gene mutations
Xp21 contiguous gene syndrome	Deletion of the Duchenne muscular dystrophy, glycerol kinase and *NR0B1* genes

SF-1 linked	*NR5A1* gene mutations
IMAGe syndrome	*CDKN1C* gene mutations
Kearns-Sayre syndrome	Mitochondrial DNA deletions
Wolman's disease	*LIPA* gene mutations
Sitosterolaimia (also known as phytosterolemia)	*ABCG5* and *ABCG8* gene mutations
Familial glucocorticoid deficiency (FGD, or ACTH insensitivity syndromes)	
Type 1	*MC2R* gene mutations
Type 2	*MRAP* gene mutations
Variant of FGD	*MCM4* gene mutations
FGC - Deficiency of mitochondrial ROS detoxification	*NNT*, *TXNRD2*, *GPX1*, *PRDX3* gene mutations
Primary Generalized Glucocorticoid Resistance or Chrousos syndrome	*NR3C1* gene mutations
Sphingosine-1-phosphate lyase 1 deficiency	*SPGL1* gene mutations
Infantile Refsum disease	*PHYH, PEX7* gene mutations
Zellweger syndrome	*PEX1* and other *PEX* gene mutations
Triple A syndrome (Allgrove's syndrome)	*AAAS* gene mutations

Modified from References (**48, 49**)

Causes of Secondary and Tertiary Adrenal Insufficiency

Secondary adrenal insufficiency may be caused by any disease process that affects the anterior pituitary and interferes with ACTH secretion. The ACTH deficiency may be isolated or occur in association with other pituitary hormone deficits.

Tertiary adrenal insufficiency can be caused by any process that involves the hypothalamus and interferes with CRH secretion. The most common cause of tertiary adrenal insufficiency is chronic administration of synthetic glucocorticoids that suppress the hypothalamic-pituitary-adrenal (HPA) axis (**50**).

Other causes of secondary and tertiary adrenal insufficiency are listed in **Tables 2 and 3** respectively.

Table 2 Causes of Secondary Adrenal Insufficiency.

Disease	**Pathogenetic Mechanism**
Space occupying lesions or trauma	
Pituitary tumors (adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas) or trauma (pituitary stalk lesions)	Decreased ACTH secretion
Pituitary surgery or irradiation for pituitary tumors, tumors outside the HPA axis or leukemia	Decreased ACTH secretion
Infections or Infiltrative processes (lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener's granulomatosis)	Decreased ACTH secretion
Pituitary apoplexy	Decreased ACTH secretion

Sheehan's syndrome (peripartum pituitary apoplexy and necrosis)	Decreased ACTH secretion
Genetic disorders	
Transcription factors involved in pituitary development	
HESX homeobox 1	HESX1 gene mutations
Orthodentical homeobox 2	OTX2 gene mutations
LIM homeobox 4	LHX4 gene mutations
PROP paired-like homeobox 1	PROP1 gene mutations
SRY (sex-determining region Y) – box 3	SOX3 gene mutations
T-box 19	TBX19 gene mutations
Congenital Proopiomelanocortin (POMC) deficiency	POMC gene mutations
Prader-Willi Syndrome (PWS)	Deletion or silencing of genes in the imprinting center for PWS

Modified from Reference (**48**)

Table 3 Causes of Tertiary Adrenal Insufficiency.

Disease	**Pathogenetic Mechanism**
Space occupying lesions or trauma	
Hypothalamic tumors (craniopharyngiomas or metastasis from lung, breast cancer)	Decreased CRH secretion
Hypothalamic surgery or irradiation for central nervous system or nasopharyngeal tumors	Decreased CRH secretion
Infections or Infiltrative processes (lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener's granulomatosis)	Decreased CRH secretion
Trauma, injury (fracture of skull base)	Decreased CRH secretion
Drug-induced adrenal insufficiency	
Glucocorticoid therapy (systemic or topical) or endogenous glucocorticoid hypersecretion (Cushing's syndrome)	Decreased CRH and ACTH secretion
Mifepristone	Tissue resistance to glucocorticoids through impairment of glucocorticoid signal transduction
Antipsychotics (chlorpromazine), antidepressants (imipramine)	Inhibition of glucocorticoid-induced gene transcription

Modified from Reference (**48**)

PATHOPHYSIOLOGIC MECHANISMS OF ADRENAL INSUFFICIENCY

Pathophysiology of Primary Adrenal Insufficiency

In primary adrenal insufficiency, although the above mentioned causes lead to gradual destruction of the adrenal cortex, the symptoms

and signs of the disease appear when the loss of adrenocortical tissue is higher than 90% (**37**). At the molecular and cellular level, a viral infection, even subclinical, or an excessive tissue response to inflammatory signals may potentially lead to apoptosis or necrosis of adrenocortical cells. Cellular components, such as 21OH-derived peptides, trigger the activation of local dendritic cells, which then transport and present these antigens to CD4+ Th1 cells. Upon activation, CD4+ Th1 cells help the committed clonal expansion of cytotoxic lymphocytes and autoreactive B cells releasing antibodies against 21-hydroxylase and possibly other antibodies. The gradual destruction of adrenocortical tissue seems to be mediated by four distinct and complementary molecular mechanisms: (a) direct cytotoxicity by lymphocytes that induce apoptosis; (b) direct cytotoxic actions by IFN-γ and lymphotoxin-α released by activated CD4+ Th1 cells; (c) cellular cytotoxicity by autoantibodies or by autoantibody-mediated activation of the complement system; and (d) cytotoxic effects of inflammatory cytokines (IL-1β, TNF-α) and free radicals (superoxide, NO) secreted by monocytes/macrophages or by the adrenal cells (**51**).

In the initial phase of chronic gradual destruction, the adrenal reserve is decreased and although the basal steroid secretion is normal, the secretion in response to stress is suboptimal. Consequently, any major or even minor stressor can precipitate an acute adrenal crisis. With further loss of adrenocortical tissue, even basal steroid secretion is decreased, leading to the clinical manifestations of the disease. Low plasma cortisol concentrations result in the increase of production and secretion of ACTH due to decreased negative feedback inhibition (**37**). The elevated plasma ACTH concentrations are responsible for the well-recognized hyperpigmentation observed in these patients.

Pathophysiology of Secondary and Tertiary Adrenal Insufficiency

In secondary or tertiary adrenal insufficiency, the resultant ACTH deficiency leads to decreased secretion of cortisol and adrenal androgens, while mineralocorticoid production remains normal. In the early stages, basal ACTH secretion is normal, while stress-induced ACTH secretion is impaired (**37**). With further loss of basal ACTH secretion, there is atrophy of *zonae fasciculata* and *reticularis* of the adrenal cortex. Therefore, basal cortisol secretion is decreased, but aldosterone secretion by the *zona glomerulosa* is preserved.

CLINICAL MANIFESTATIONS OF ADRENAL INSUFFICIENCY

The clinical manifestations of adrenal insufficiency depend upon the extent of loss of adrenal function and whether mineralocorticoid production is preserved. The onset of adrenal insufficiency is often gradual and may go undetected until an illness or other stress precipitates an adrenal crisis (**50, 52**).

***Adrenal Crisis*:** Adrenal crisis or acute adrenal insufficiency may complicate the course of chronic primary adrenal insufficiency, and may be precipitated by a serious infection, acute stress, bilateral adrenal infarction or hemorrhage. It is rare in patients with secondary or tertiary adrenal insufficiency. The main clinical manifestation of adrenal crisis is shock, but patients may also have nonspecific symptoms, such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, confusion or coma. Hypoglycemia is rare in acute adrenal insufficiency, but more common in secondary adrenal insufficiency.

The major factor precipitating an adrenal crisis is mineralocorticoid deficiency and the main clinical problem is hypotension. Adrenal crisis can occur in patients receiving appropriate doses of glucocorticoid if their mineralocorticoid requirements are not met (**53**), whereas patients with secondary adrenal insufficiency and normal aldosterone secretion rarely present in adrenal crisis. However, glucocorticoid deficiency may also contribute to hypotension by decreasing vascular responsiveness to angiotensin II, norepinephrine and other vasoconstrictive hormones, reducing the synthesis of renin substrate, and increasing the production and effects of prostacyclin and other vasodilatory hormones (**54, 55**).

***Chronic Primary Adrenal Insufficiency*:** The clinical manifestations of chronic primary adrenal insufficiency are owing to deficient concentrations of all adrenocortical hormones (mineralocorticoids, glucocorticoids, adrenal androgens) and include general malaise, fatigue, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain or diarrhea, which may alternate with constipation, hypotension, electrolyte abnormalities (hyponatremia, hyperkalemia, metabolic acidosis), hyperpigmentation, autoimmune manifestations (vitiligo), decreased axillary and pubic hair, and loss of libido and amenorrhea in women (**50, 52**). The onset of chronic adrenal insufficiency is often insidious and the diagnosis may be difficult in the early stages of the disease.

***Secondary or Tertiary Adrenal Insufficiency*:** The clinical features of secondary or tertiary adrenal insufficiency are similar to those of primary adrenal insufficiency. However, hyperpigmentation of the skin does not occur, because the secretion of ACTH is not increased. Also, since the production of mineralocorticoids by the *zona glomerulosa* is mostly preserved, dehydration and hyperkalemia are not present, and hypotension is less prominent. Hyponatremia and increased intravascular volume may be the result of "inappropriate" increase in vasopressin secretion. Hypoglycemia is more common in secondary adrenal insufficiency possibly due to concomitant growth hormone insufficiency and in isolated ACTH deficiency. Clinical manifestations of a pituitary or hypothalamic tumor, such as symptoms and signs of deficiency of other anterior pituitary hormones, headache or visual field defects, may also be present (**50, 52**).

DIAGNOSIS OF ADRENAL INSUFFICIENCY

The clinical diagnosis of adrenal insufficiency can be confirmed by demonstrating inappropriately low cortisol secretion, determining whether the cortisol deficiency is secondary or primary and, hence, dependent or independent of ACTH deficiency, and detecting the cause of the disorder (**50, 52**).

***Basal morning serum cortisol concentrations*:** The diagnosis of adrenal insufficiency depends upon the demonstration of inappropriately low cortisol secretion. Serum cortisol concentrations are normally highest in the early morning hours (06:00h – 08:00h), ranging between 10 – 20 mcg/dL (275 – 555 nmol/L) than at other times of the day. Serum cortisol concentrations determined at 08:00h of less than 3 µg/dL (80 nmol/L) are strongly suggestive of adrenal insufficiency (**56**), while values below 10 µg/dL (275 nmol/L) make the diagnosis likely. Simultaneous measurements of cortisol and ACTH concentrations confirm in most cases the diagnosis of primary adrenal insufficiency.

***Morning salivary cortisol concentrations*:** Adrenal insufficiency is excluded when salivary cortisol concentration at 08:00h is higher than 5.8 ng/mL (16 nmol/L), whereas the diagnosis is more possible for values lower than 1.8 ng/mL (5 nmol/L).

***Urinary free Cortisol (UFC)*:** Basal urinary cortisol and 17-hydroxycorticosteroid excretion is low in patients with severe adrenal insufficiency, but may be low-normal in patients with partial adrenal insufficiency. Generally, baseline urinary measurements are not recommended for the diagnosis of adrenal insufficiency.

***Basal plasma ACTH, renin and aldosterone concentrations*:** Basal plasma ACTH concentration at 08:00h, when determined simultaneously with the measurement of basal serum cortisol concentration, may both confirm the diagnosis of adrenal insufficiency and establish the cause (**57**). The normal values of basal 08:00h plasma ACTH concentrations range between 20-52 pg/mL (4.5-12 pmol/L). In primary adrenal insufficiency, the 08:00h plasma ACTH concentration is elevated, and is coupled with increased concentration or activity of plasma renin, low aldosterone concentrations, hyperkalemia and hyponatremia. In the cases of secondary or tertiary adrenal insufficiency, plasma ACTH concentrations are low or low normal, associated with normal values of plasma concentrations of renin and aldosterone.

***Standard dose ACTH stimulation test*:** Adrenal insufficiency is usually diagnosed by the standard-dose ACTH test, which determines the ability of the adrenal glands to respond to 250 mcg intravenous or intramuscular administration of ACTH(1-24) by measurement of serum cortisol concentrations at 0, 30 and 60 min following stimulation. The test is defined as normal if peak cortisol concentration is higher than 18–20 mcg/dL (500–550 nmol/L), thereby excluding the diagnosis of primary adrenal insufficiency and almost all cases of secondary adrenal insufficiency. However, if secondary adrenal insufficiency is of recent onset, the adrenal glands will have not yet atrophied, and will still be capable of responding to ACTH stimulation normally. In these cases, a low-dose ACTH stimulation test or an insulin-induced hypoglycemia test may be required to confirm the diagnosis (**58-60**).

***Low-Dose ACTH stimulation test*:** This test theoretically provides a more sensitive index of adrenocortical responsiveness because it results in physiologic plasma ACTH concentrations. This test should be performed at 14:00h, when the endogenous secretion of ACTH is at its lowest. The results might not be valid if it is performed at another time. At 14:00h, a blood sample is collected for determination of basal cortisol concentrations. The low dose of ACTH(1-24) (500 nanograms ACTH(1-24)/1.73 m^2) is then administered as an intravenous bolus. In normal subjects, this dose results in a peak plasma ACTH concentration about twice that of insulin-induced hypoglycemia (**60**). Subsequently, blood samples are collected at +10 min, +15 min, +20 min, +25 min, +30 min, +35 min, +40 min and +45 min after stimulation for determination of serum cortisol concentrations (**51**). A value of 18 µg/dL (500 nmol/L) or more at any time during the test is indicative of normal adrenal function. The advantage of this test is that it can detect partial adrenal insufficiency that may be missed by the standard-dose test (**58-62**). The low-dose test is also preferred in patients with secondary or tertiary adrenal insufficiency (**63-66**).

***Prolonged ACTH Stimulation Tests*:** Prolonged stimulation with exogenous administration of ACTH helps differentiate between primary and secondary or tertiary adrenal insufficiency. In secondary or tertiary adrenal insufficiency, the adrenal glands display cortisol secretory capacity following prolonged stimulation with ACTH, whereas in primary adrenal insufficiency, the adrenal glands are partially or completely destroyed and do not respond to ACTH. The prolonged ACTH test consists of the intravenous administration of 250 µg of ACTH as an infusion over eight hours (8-hour test) or over 24 hours on two (or three) consecutive days (two-day test), and the measurement of serum cortisol, and 24-hour urinary cortisol and 17-hydroxycorticoid (17-OHCS) concentrations before and after the infusion (**67**).

***Insulin-induced hypoglycemia test*:** This test provides an alternative choice for confirmation of the diagnosis when secondary adrenal insufficiency is suspected. The insulin tolerance test helps in the investigation of the integrity of the HPA axis and has the ability to assess growth hormone reserve. Insulin, at a dose of 0.1-0.15 U/kg, is administered to induce hypoglycemia, and measurements of cortisol concentrations are determined at 30 min intervals for at least 120 min (**68, 69**). This test is contraindicated in patients with cardiovascular disease or a history of seizures, and requires a high degree of supervision.

***Corticotropin-releasing hormone (CRH) test*:** This test is used to differentiate between secondary and tertiary adrenal insufficiency. It consists of intravenous administration of CRH (1 mcg/kg up to a maximum of 100 mcg) and determination of serum cortisol and plasma ACTH concentrations at 0, 15, 30, 45, 60, 90 and 120 min following stimulation. Patients with secondary adrenal insufficiency demonstrate little or no ACTH response, whereas patients with tertiary adrenal insufficiency show an exaggerated and prolonged response of ACTH to CRH stimulation, which is not followed by an appropriate cortisol response (**70, 71**).

***Autoantibody screen*:** Adrenocortical antibodies or antibodies against 21-hydroxylase can be detected in more than 90% of patients with recent onset autoimmune adrenalitis. Furthermore, antibodies that react against other enzymes involved in the steroidogenesis (P450scc, P450c17) and anti-steroid-producing cell antibodies are present in some patients (**1, 3, 22-26, 33, 72-74**).

***Very long chain fatty acids*:** To exclude adrenoleukodystrophy, plasma very long chain fatty acids should be determined in male patients with isolated Addison's disease and negative autoantibodies (**34**).

***Imaging*:** Patients without any associated autoimmune disease and negative autoantibody screen should undergo a computed tomography (CT) scan of the adrenal glands. In cases of tuberculous adrenalitis, the CT scan shows initially hyperplasia of the adrenal glands and subsequently spotty calcifications during the late stages of the disease. Bilateral adrenal lymphoma, adrenal metastases or adrenal infiltration (sarcoidosis, amyloidosis, hemochromatosis) may also be detected by CT scan. If central adrenal insufficiency is suspected, a magnetic resonance imaging (MRI) scan of the hypothalamus and pituitary gland should be performed. This may detect any potential disease process, such as craniopharyngiomas, pituitary adenomas, meningiomas, metastases and infiltration by Langerhans cell histiocytosis, sarcoidosis or other granulomatous diseases (**75, 76**). It should be noted that imaging is not required when adrenal cortex autoantibodies are detected.

TREATMENT OF ADRENAL INSUFFICIENCY

Adrenal insufficiency is one of the most life-threatening disorders. Treatment should be administered to the patients as soon as the diagnosis is established, or even sooner if an adrenal crisis occurs (**77, 78**).

***Treatment of Chronic Adrenal Insufficiency*:** One of the most important aspects of the management of chronic primary adrenal insufficiency is patient and family education. Patients should understand the reason for life-long replacement therapy, the need to increase the dose of glucocorticoid during minor or major stress and to inject hydrocortisone, methylprednisolone or dexamethasone in emergencies.

Emergency precautions: Patients should wear a medical alert (Medic Alert) bracelet or necklace and carry the Emergency Medical Information Card, which should provide information on the diagnosis, the medications and daily doses, and the physician involved in the patient's management. Patients should also have supplies of dexamethasone sodium phosphate and should be educated about how and when to administer them.

Glucocorticoid replacement therapy: Patients with adrenal insufficiency should be treated with hydrocortisone, the natural glucocorticoid, or cortisone acetate if hydrocortisone is not available. The hydrocortisone daily dose is 10-12 mg per meter square body surface area and can be administered in two to three divided doses with one half to two thirds of the total daily dose being given in the morning (**1-5, 77, 79-85**). Small reductions of bone mineral density (BMD) probably due to higher than recommended doses (**86**), as well as impaired quality of life (**87, 88**) were observed in patients treated with hydrocortisone. A longer-acting synthetic glucocorticoid, such as prednisone, prednisolone or dexamethasone, should be avoided because their longer duration of action may produce manifestations of chronic glucocorticoid excess, such as loss of lean body mass and bone density, and gain of visceral fat (**89**). Recently, preparations of hydrocortisone that lead to both delayed and sustained release of this compound have been developed and are under clinical investigation (**90, 91**). These formulations maintain stable cortisol concentrations during 24 hours and physiologic circadian rhythmicity with the cortisol peak occurring during the early morning after oral intake of the preparation at bed-time. Furthermore, a novel once-daily (OD) dual-release hydrocortisone tablet has been developed to maintain more physiologic circadian-based serum cortisol concentrations. Compared to the conventional treatment, the OD dual-release hydrocortisone improved glucose metabolism, cardiovascular risk factors and quality of life (**92**). Regardless of the type of the formulation used, glucocorticoid replacement should be monitored clinically, evaluating weight gain/loss, arterial blood pressure, annualized growth velocity and presence of Cushing features (**93**).

Glucocorticoid replacement during minor illness or surgery: During minor illness or surgical procedures, glucocorticoids should be given at a dosage up to three times the usual maintenance dosage for up to three days. Depending on the nature and severity of the illness, additional treatment may be required.

Glucocorticoid replacement during major illness or surgery: During major illness or surgery, high doses of glucocorticoid analogues (10 times the daily production rate) are required to avoid an adrenal crisis. A continuous infusion of 10 mg of hydrocortisone per hour or the equivalent amount of dexamethasone or prednisolone eliminates the possibility of glucocorticoid deficiency. This dose can be halved the

second postoperative day, and the maintenance dose can be resumed at the third postoperative day.

Mineralocorticoid replacement therapy: Mineralocorticoid replacement therapy is required to prevent intravascular volume depletion, hyponatremia and hyperkalemia. For these purposes, fludrocortisone (9-alpha-fluorohydrocortisone) in a dose of 0.05 - 0.2 mg daily should be taken in the morning. The dose of fludrocortisone is titrated individually based on the findings of clinical examination (mainly the body weight and arterial blood pressure) and the levels of plasma renin activity. Patients receiving prednisone or dexamethasone may require higher doses of fludrocortisone to lower their plasma renin activity to the upper normal range, while patients receiving hydrocortisone, which has some mineralocorticoid activity, may require lower doses. The mineralocorticoid dose may have to be increased in the summer, particularly if patients are exposed to temperatures above 29ºC (85ºF) (**77, 79-85**). If patients receiving mineralocorticoid replacement develop hypertension, the dose of fludrocortisone should be reduced accordingly (**93**). In case of uncontrolled blood pressure, patients should be encouraged to continue fludrocortisone and initiate antihypertensive therapy, such as angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, or dihydropyridine calcium blockers (**93, 94**).

Androgen replacement: In women, the adrenal cortex is the primary source of androgen in the form of dehydroepiandrosterone and dehydroepiandrosterone sulfate. Treatment with DHEA enhances mood and general well being both in adult patients and in children and adolescents with adrenal insufficiency (**80-85, 87, 95-101**). A single oral morning dose of DHEA of 25-50 mg may be sufficient to maintain normal serum androgen concentrations in premenopausal women with primary adrenal insufficiency, who present with decreased libido, anxiety, depression, and low energy levels (**93**). If symptoms are still present during a period of 6 months, patients are advised to discontinue DHEA replacement (**93**). Naturally, women should be encouraged to report any side effects of androgen therapy. Finally, DHEA replacement should be monitored by determining serum DHEA concentrations in the morning before patient receives her daily DHEA dose (**93**).

***Treatment of adrenal crisis*:** The aim of initial management in adrenal crisis is to treat hypotension, hyponatremia and hyperkalemia, and to reverse glucocorticoid deficiency. Treatment should be started with immediate administration of 100 mg hydrocortisone i.v. and rapid rehydration with normal saline infusion under continuous cardiac monitoring, followed by 100–200 mg hydrocortisone in glucose 5% per 24-hour continuous iv infusion; alternatively, hydrocortisone could be administered iv or im at a dose of 50-100 mg every 6 hours depending on body surface area and age (**80**). With daily hydrocortisone doses of 50 mg or more, mineralocorticoids in patients with primary adrenal insufficiency can be discontinued or reduced because this dose is equivalent to 0.1 mg fludrocortisone (**79**). Once the patient's condition is stable and the diagnosis has been confirmed, parenteral glucocorticoid therapy should be tapered over 3-4 days and converted to an oral maintenance dose (**1-3, 77, 79-85**). Patients with primary adrenal insufficiency require life-long glucocorticoid and mineralocorticoid replacement therapy.

Treatment of chronic secondary and tertiary adrenal insufficiency: In chronic secondary or tertiary adrenal insufficiency, glucocorticoid replacement is similar to that in primary adrenal insufficiency, however, measurement of plasma ACTH concentrations cannot be used to titrate the optimal glucocorticoid dose. Mineralocorticoid replacement is rarely required, while replacement of other anterior pituitary deficits might be necessary.

ADRENAL INSUFFICIENCY IN CRITICALLY ILL PATIENTS

Clinical manifestations of adrenal insufficiency are common in critically ill patients, specifically in patients with severe pneumonia, adult respiratory distress syndrome, sepsis, trauma, HIV infection or after treatment with etomidate (**2, 102-106**).

The molecular pathogenetic mechanisms underlying adrenal insufficiency in critical illness have not been fully elucidated. However, it seems that both inadequate cortisol secretion and impaired glucocorticoid receptor signaling are convincingly involved. Indeed, proinflammatory cytokines may compete with ACTH on its receptor (**107**) and/or induce tissue resistance to glucocorticoids (**108-110**). Moreover, the widely used medications during the treatment of sepsis may impair both glucocorticoid production and glucocorticoid signaling. Furthermore, other neuropeptides, signaling molecules, components of oxidative stress and the impaired adrenal blood flow contribute to adrenal insufficiency.

To provide recommendations on the diagnosis and management of adrenal insufficiency in critically ill patients, the American College of Critical Care Medicine suggested that the diagnosis is best made by a delta total serum cortisol of < 9 mcg/dL following ACTH (250 microg) administration or a random total cortisol of < 10 mcg/dL. Hydrocortisone at a dose of 200 mg/day in four divided doses or as a continuous infusion at a dose of 240 mg/day (10 mg/hr) for at least 7 days is recommended for patients with septic shock. Methylprednisolone at a dose of 1 mg/kg/day for at least 14 days is recommended in patients diagnosed with severe early acute respiratory distress syndrome. The role of glucocorticoid therapy in other critically ill patients remains to be further elucidated (**111**).

ADRENAL INSUFFICIENCY DURING PREGNANCY

Although adrenal insufficiency is relatively rare in pregnancy, it may be associated with significant maternal and/or fetal morbidity and mortality if it remains undiagnosed or untreated (**112, 113**). Symptoms are usually "nonspecific", such as nausea, vomiting and fatigue,

making the diagnosis of adrenal insufficiency challenging. The current diagnostic tests are serum cortisol concentrations and the cosyntropin stimulation test (**93, 113**). However, it should be emphasized that the peak cortisol response following ACTH stimulation is higher in pregnant than in non-pregnant women during the second and third trimesters, as a result of physiologic pregnancy-associated hypercortisolism and elevations of cortisol-binding globulin (**114**). Regarding glucocorticoid replacement during pregnancy, hydrocortisone, cortisone acetate, prednisolone or prednisone can be administered; in contrast,, fluorinated glucocorticoids such as dexamethasone should be avoided because they cross the placenta at higher rates (**93**). Mineralocorticoid replacement is usually more complicated to assess during pregnancy because of the "nonspecific" symptoms often observed in physiologic pregnancy (**93**). A hydrocortisone stress dose (bolus intravascular injection of 50-100 mg hydrocortisone followed by continuous infusion of 100-200 mg hydrocortisone/24h) should be administered at the beginning of active labor (**93, 115, 116**).

ADRENAL INSUFFICIENCY IN INFANCY AND CHILDHOOD

Children with primary adrenal insufficiency should be treated with hydrocortisone phosphate at a daily dose of 10-12 mg per meter square body surface area divided into two or three doses (**93**). Alternatively, cortisone acetate can be administered with safety also as two to three daily doses. Intermediate-acting or long-acting glucocorticoid analogues, such as prednisolone/prednisolone or dexamethasone respectively, are not recommended due to undesirable chronic side effects, such as glucose intolerance or osteopenia/osteoporosis. The hydrocortisone daily dose should be adjusted according to the increasing body surface area of the child. Caution should be paid to decreased growth velocity, excessive weight gain or other clinical manifestations suggestive of iatrogenic Cushing syndrome. Children with primary adrenal insufficiency also require fludrocortisone at a daily dose of 50-300 μg (**93**). During the first 6 months, infants require supplementation of sodium chloride at a dose of 1-2 g/day administered in multiple feedings, because the infant kidney is physiologically resistant to mineralocorticoids and the infant milk (breast milk or formula) has relatively low sodium content (**93, 117**).

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