REVIEW ARTICLE

CURRENT CONCEPTS

Predisposing Factors for Adrenal Insufficiency

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Adrenal insufficiency — the clinical manifestation of deficient production or action of glucocorticoids — is a life-threatening disorder that may result from either primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis.[1,2] This article focuses on providing the practicing clinician with new insights into predisposing factors for adrenal insufficiency. When and during what situations should a clinician suspect adrenal insufficiency? What genetic disorders, infections, and medications should be considered? What are the current views on the underlying mechanisms?

The cardinal clinical symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855,[3] include weakness, fatigue, anorexia, and abdominal pain, with orthostatic hypotension, salt craving, and characteristic hyperpigmentation of the skin occurring with primary adrenal failure. The acute syndrome constitutes a medical emergency since it may result in a severe hypotensive crisis and clouded sensorium, together with pain in the muscles, joints, or abdomen and fever.[1,2]

In the diagnostic workup for the disorder, the capacity of the adrenal cortex to respond to corticotropin is tested with the use of the standard short corticotropin test, which measures the serum cortisol level before and 30 or 60 minutes after an intravenous or intramuscular injection of 250 μg of corticotropin.[4] An increase in the serum cortisol level to peak concentrations above 500 nmol per liter (18 μg per deciliter) indicates a normal response. The adrenal responsiveness to an exogenous corticotropin challenge is impaired in most cases of secondary adrenal disease. With mild secondary adrenal insufficiency, however, the hypothalamic–pituitary–adrenal axis may appear intact, with a normal response to a corticotropin challenge. Recent evidence suggests that the 1-μg corticotropin stimulation test is more sensitive than the 250-μg corticotropin test for establishing the diagnosis of secondary adrenal insufficiency.[5]

Once adrenal insufficiency is diagnosed, glucocorticoid replacement is initiated in two or three daily doses; one half to two thirds of the daily dose (15 to 25 mg of hydrocortisone) is given in the morning, in line with the physiologic cortisol-secretion pattern. Mineralocorticoid replacement (0.05 to 0.2 mg of fludrocortisone daily as a morning dose) is required only in the case of primary adrenal insufficiency, and dehydroepiandrosterone replacement (25 to 50 mg) remains an optional treatment.[1,2]

Management of an acute adrenal crisis consists of immediate intravenous administration of 100 mg of hydrocortisone, followed by 100 to 200 mg of hydrocortisone every 24 hours and a continuous infusion of larger volumes of physiologic saline solution (initially 1 liter per hour) under continuous cardiac monitoring. Timely diagnosis and clinical management of this condition are critical, and physicians in all areas of medicine should be aware of the causes, signs, and symptoms that herald adrenal insufficiency.

HEREDITARY DISORDERS ASSOCIATED WITH ADRENAL INSUFFICIENCY

Hereditary factors are increasingly recognized as playing a critical role in the regulation of the hypothalamic–pituitary–adrenal axis.[6] Genes that have been identified as having such a role include those that encode receptors, transcription factors, and enzymes involved in hormone synthesis or in the regulation of pituitary-gland, adrenal-gland, or target-cell function (Table 1). In addition, certain forms of autoimmune adrenalitis have hereditary components, either with an autosomal recessive pattern of inheritance (autoimmune polyglandular syndrome 1) or with an autosomal dominant pattern involving incomplete penetrance (autoimmune polyglandular syndrome 2).

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency[7] is one of the more common causes of hereditary adrenal disorders, with the classic form having an overall incidence of 1 case in 15,000 live births. The carrier frequency of classic congenital adrenal hyperplasia is approximately 1 in 60 persons. Patients with classic congenital adrenal hyperplasia usually present in early childhood with a moderate form known as simple-virilizing congenital adrenal hyperplasia or with a severe form that causes salt wasting and virilization. Nonclassic congenital adrenal hyperplasia occurs in adolescent girls and women, who present with hirsutism and infertility.

Although congenital adrenal hyperplasia is a common disorder, pitfalls in coping with stressful situations and preventing an adrenal crisis are infrequently considered in routine clinical practice[7,8]; in addition, the importance of educating parents about the management of the disorder can be underappreciated. Clinicians should take time to explain to the child and his or her family that the daily glucocorticoid regimen must not be interrupted by illness. Missed doses during a minor malaise such as a viral infection, particularly one that causes vomiting or diarrhea, can lead to shock and death. To prevent this, patients should be instructed to increase the doses of glucocorticoids during illness, surgery, or other forms of severe stress.

Most genetic disorders associated with adrenal insufficiency have characteristic clinical features that become evident early in life[1,2,9-11] (Table 1). However, persons with some genetic disorders may present with late-onset adrenal insufficiency.[12-14] Congenital adrenal hypoplasia is usually manifested in early childhood but may not be apparent until adolescence or early adulthood.[14]

Adrenoleukodystrophy and adrenomyeloneuropathy are two phenotypes of an X-linked recessive disorder that affects 1 in 20,000 males. This disorder is characterized by spastic paralysis as well as adrenal insufficiency.[1,2,15] Adrenoleukodystrophy begins in infancy or childhood, whereas adrenomyeloneuropathy usually begins in adolescence or early adulthood and has a milder and slower progression. It is important to realize, however, that adrenal insufficiency may be the only sign of the disorder; the diagnosis may be confirmed by measurement of very-long-chain fatty acids. This disorder accounts for up to 10% of all cases of adrenal insufficiency.

Like hereditary disorders of the adrenal gland, most genetic defects affecting the pituitary gland cause symptoms early in life; however, once again, clinicians should be aware that the signs and symptoms of some of these disorders have a late onset. For example, mutations in the gene encoding the pituitary transcription factor paired-like homeobox 1 (*PROP1*) cause a progressive deterioration of anterior pituitary function, including adrenal insufficiency, which necessitates replacement therapy with hydrocortisone in affected patients at a mean age of 18 years.[13] Furthermore, secondary adrenal insufficiency has been noted in up to 60% of patients with the Prader–Willi syndrome.[16] The Prader–Willi syndrome is the most common cause of obesity related to a syndrome (with a prevalence of 1 case in 10,000 to 20,000 obese persons) and is associated with a very high rate of sudden death (3%). Hydrocortisone treatment during the acute illness has been recommended in patients with this syndrome unless adrenal insufficiency can be ruled out.[16]

It has been suggested that numerous other genes play critical roles in the development and function of the adrenal and pituitary glands in animal models. Putative genes include morphogens such as wingless and sonic hedgehog,[17] growth factors, toll-like receptors, and scavenger molecules involved in cholesterol transport and oxidative stress.[18,19] The adrenal stress response is impaired in mice with toll-like receptor 2 or 4 deficiency.[19] Polymorphisms in the same receptors occur in humans at rates of up to 10%.[20]

Table 1. Genetic Defects Associated with Adrenal Insufficiency.

Primary Adrenal Insufficiency	Gene No.*	Disorder	Clinical Characteristics
Enzymes in steroidogenesis and cholesterol metabolism			
21-Hydroxylase (*CYP21A2*)	1589	Congenital adrenal hyperplasia	Ambiguous genitalia, hirsutism, presence or absence of salt wasting
3 Beta-hydroxysteroid dehydrogenase type II (*HSD3B2*)	3284	Congenital adrenal hyperplasia	Ambiguous genitalia, premature pubarche, hirsutism, presence or absence of salt wasting
Steroid 11-beta-hydroxylase (*CYP11B1*)	1584	Congenital adrenal hyperplasia	Virilization, impaired cortisol synthesis, hypertension due to high deoxycorticosterone level
Steroid 17-alpha-hydroxylase (*CYP17A1*)	1586	Congenital adrenal hyperplasia	Hypertension, primary amenorrhea, sexual infantilism
P-450 (cytochrome) oxidoreductase (*POR*)	5447	Congenital adrenal hyperplasia	Abnormal genitalia, skeletal malformation (the Antley–Bixler syndrome), impaired steroidogenesis
Steroidogenic acute regulatory protein (*STAR*)	6770	Congenital lipoid adrenal hyperplasia	Severe glucocorticoid and mineralocorticoid deficiency, growth failure
P-450 (cytochrome) side-chain cleavage (*CYP11A1*)	1583	P450 side-chain–cleavage deficiency	Clitoromegaly, early-onset or late-onset adrenal insufficiency without adrenal hyperplasia
7-Dehydrocholesterol reductase (*DHCR7*)	1717	Smith–Lemli–Opitz syndrome	Hyponatremia, hyperkalemia, cholesterol deficiency
Transcription factors			
Nuclear receptor subfamily 0, group B, member 1 (*NR0B1*)	190	Congenital adrenal hypoplasia	Hypogonadotropic hypogonadism in males
Nuclear receptor subfamily 5, group A, member 1 (steroidogenic factor 1) (*NR5A1*)	2516	Congenital adrenal hypoplasia	46, XY karyotype in females, with gonadal dysgenesis
Gene unknown, but located on chromosome X	64589	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital abnormalities (IMAGE) syndrome	Intrauterine growth retardation, metaphyseal dysplasia, adrenal insufficiency, gonadal anomalies
Mitochondrial abnormality (gene unknown)		Kearns–Sayre syndrome	External ophthalmoplegia, retinal degeneration, and cardiac conduction defects; other endocrine disorders
Storage disease — lipase A, lysosomal acid, cholesterol esterase (*LIPA*)	3988	Wolman's disease	Bilateral adrenal calcification, hepatosplenomegaly
Sterol secretion			
ATP-binding cassette, subfamily G (WHITE), member 5 (*ABCG5*)	64240	Sitosterolemia (also known as phytosterolemia)	Xanthomata, premature coronary artery disease, arthritis, short stature, gonadal and adrenal failure
ATP-binding cassette, subfamily G (WHITE), member 8 (*ABCG8*)	64241	Sitosterolemia (also known as phytosterolemia)	Xanthomata, premature coronary artery disease, arthritis, short stature, gonadal and adrenal failure

Corticotropin-receptor and signaling			
Melanocortin 2 receptor (adrenocorticotropic hormone) (*MC2R*)	4158	Familial glucocorticoid deficiency 1	Hyperpigmentation, increased height, facial features, such as hypertelorism and frontal bossing, lethargy and muscle weakness but normal blood pressure
Melanocortin 2 receptor accessory protein (*MRAP*)	56246	Familial glucocorticoid deficiency 2	Hyperpigmentation, normal height, hypoglycemia, lethargy and muscle weakness but normal blood pressure
Achalasia, adrenocortical insufficiency, alacrima (Allgrove, triple-A) (*AAAS*)	8086	Triple-A syndrome	Achalasia, alacrima, adrenal insufficiency, deafness, mental retardation, hyperkeratosis
Autoimmune adrenalitis			
Autoimmune regulator (*AIRE*)	326	Polyendocrine autoimmune syndrome type 1	Adrenal insufficiency, hypoparathyroidism, chronic mucocutaneous candidiasis
Gene unknown, but appears to be associated with the CD28/CTLA4 region on chromosome 2q33		Polyendocrine autoimmune syndrome type 2	Addison's disease, thyroid disease, type 1 diabetes mellitus
Peroxisomal abnormalities			
ATP-binding cassette, subfamily D (ALD), member 1 (*ABCD1*)	215	Adrenoleukodystrophy or adrenomyeloneuropathy	Weakness, spasticity, dementia, blindness, quadriparesis; adrenal insufficiency may be the only sign of adrenoleukodystrophy
ATP-binding cassette, subfamily D (ALD), member 2 (*ABCD2*)	225	Adrenoleukodystrophy or adrenomyeloneuropathy	Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy, with slower progression
Pituitary insufficiency			
Transcription factors			
HESX homeobox 1 (*HESX1*)	8820	Panhypopituitarism	Short stature, cognitive alterations, septo-optic dysplasia, delayed puberty, other signs of pituitary failure
Orthodenticle homeobox 2 (*OTX2*)	5015	Panhypopituitarism	Neonatal hypoglycemia, pituitary hypoplasia, ectopic posterior pituitary gland
LIM homeobox 4 (*LHX4*)	89884	Panhypopituitarism	Growth hormone, thyrotropin, and corticotropin deficiencies
SRY (sex-determining region Y)-box 3 (*SOX3*)	6658	Panhypopituitarism	Infundibular hypoplasia, hypopituitarism, varying degrees of mental retardation
PROP paired-like homeobox 1 (*PROP1*)	5626	Panhypopituitarism	Late-onset corticotropin deficiency, occasionally enlarged sella turcica
T-box 19 (*TBX19*)	9095	Congenital isolated adrenocorticotrophic deficiency	Low or absent cortisol production
Corticotropin synthesis — proopiomelanocortin (*POMC*)	5443	Proopiomelanocortin (POMC) deficiency syndrome	Early-onset obesity, red hair, pigmentation
Imprinting center — imprinted in Prader–Willi syndrome (nonprotein coding) (*IPW*)	3653	Prader–Willi syndrome	Hypotonia, mental retardation, obesity, and hypogonadism

* Gene numbers are from the gene database of the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/).

Whether mutations and gene polymorphisms involving these factors predispose affected persons to adrenal insufficiency requires clarification.

DRUGS AS PREDISPOSING FACTORS FOR GLUCOCORTICOID DEFICIENCY

Drugs may cause glucocorticoid deficiency at hypothalamic, pituitary, and adrenal levels as well as at the sites of the glucocorticoid receptor, its signaling pathway, and peripheral glucocorticoid metabolism (Table 2). Suppression of the hypothalamic–pituitary–adrenal axis by exogenous glucocorticoid treatment is the most common cause of an impaired adrenal response. According to current estimates, nearly 1% of people in the general population (2.5% of those who are more than 70 years of age) are treated with long-term regimens of glucocorticoids for inflammation related to chronic disease.[21] Since the proportion of elderly persons in the population is increasing, this figure is likely to rise.

To avoid an unexpected adrenal crisis in persons admitted to the hospital on an emergency basis, physicians should not only ask whether the patient has been taking glucocorticoids but should also be aware of the many obscure situations involving the use of glucocorticoids. Patients may be unaware of or reluctant to report exposure to glucocorticoids. These may include athletes, patients with cancer, patients with orthopedic conditions, and persons receiving adrenal extracts from sites on the Internet for what has been termed the "adrenal fatigue syndrome." A lack of awareness that continuous use of topical glucocorticoids can suppress adrenal function is another widespread problem in daily practice. Concomitant use of glucocorticoids with inhibitors (e.g., itraconazole, diltiazem, mibefradil, and even grapefruit juice) of CYP3A4, the most abundant drug-metabolizing cytochrome P450 enzyme, prolongs the biologic half-life of the glucocorticoid, thereby markedly enhancing its effect in suppressing adrenal function.[22] In addition to glucocorticoids, other steroid compounds such as megestrol acetate and medroxyprogesterone inhibit the hypothalamic–pituitary–adrenal axis. Consideration of the integrity of the hypothalamic–pituitary–adrenal axis will also be important when the new selective glucocorticoid-receptor activators come into common use.[23]

There has been an increased incidence of adrenal dysfunction, particularly among patients who are receiving antifungal therapies. Such therapies (e.g., ketoconazole) are known to interfere with glucocorticoid synthesis and are therefore also used, in doses of 400 to 800 mg per day, to treat hypercortisolism. Although some of the newer antifungal compounds (e.g., itraconazole and fluconazole) have fewer adrenostatic effects, adrenal insufficiency that occurs after treatment with high doses has been reported.[24] These compounds may therefore confer a predisposition to adrenal insufficiency during states of increased glucocorticoid requirement, such as severe stress in any kind of critical illness.

Etomidate, a commonly used, potent hypnotic agent, can also lower cortisol levels, even after a single injection of the drug.[25] Therefore, in the case of any critically ill patient, the clinician should specifically ask about the use of etomidate; if the patient is receiving etomidate, the clinician should consider adding glucocorticoid therapy.[26]

It is prudent to monitor adrenal function during severe stress in patients who are receiving novel tyrosine kinase–targeting drugs, since some of these compounds (e.g., sunitinib) have been shown in studies in animals to cause adrenal dysfunction and hemorrhage.[27] The underlying mechanism may be related to the fact that vascular endothelial growth factor–receptor antagonists impair endothelial integrity, which may then lead to hemorrhage in the highly vascularized adrenal gland during stress.

Finally, since growing numbers of chronically ill patients take multiple drugs, clinicians must consider the additive effect of a combination of drugs with antiglucocorticoid effects. Recent comprehensive toxicologic in vitro assays have shown that increasing numbers of environmental compounds have the capability to impair adrenal steroidogenesis. Such compounds range from endocrine disruptors (e.g., phytoestrogen flavonoids) to widely used insecticides (e.g., lindane). The effect on adrenal function in humans, however, has yet to be determined.[28]

DISEASES THE CLINICIAN SHOULD CONSIDER

Diseases that cause outright adrenal insufficiency are rare. In addition to the genetic defects men-

Table 2. Drug-Related Glucocorticoid Insufficiency.

Mechanism	Drugs
Primary adrenal insufficiency	
Hemorrhage	Anticoagulants (heparin, warfarin), tyrosine kinase inhibitors (sunitinib)
Inhibition of cortisol-synthesis enzyme	
P-450 aromatase (CYP19A1)	Aminoglutethimide
3 Beta hydroxysteroid-dehydrogenase type 2 (HSD3B2)	Trilostane
Mitochondrial cytochrome P-450–dependent enzymes (e.g., CYP11A1, CYP11B1)	Ketoconazole Fluconazole Etomidate
Activation of cortisol metabolism	
Enzyme induction of P-450 cytochromes (CYP2B1 and CYP2B2), which reduces corticosteroid levels	Phenobarbital
Induction of drug-metabolizing cytochrome P-450 enzymes (primarily CYP3A4)	Phenytoin, rifampin, troglitazone
Secondary adrenal insufficiency	
Suppression of corticotropin-releasing hormone and corticotropin synthesis	Glucocorticoid therapy (systemic or topical), fluticasone, megestrol acetate, medroxyprogesterone, ketorolac tromethamine, opiate drugs
Peripheral resistance to glucocorticoids	
Interaction with glucocorticoid receptor	Mifepristone
Inhibition of glucocorticoid-induced gene transcription	Antipsychotic drugs (chlorpromazine), antidepressant drugs (imipramine)

tioned above, pituitary tumors, hemorrhage, infections, and autoimmune disease are the most common causes of complete adrenal insufficiency.[1,2]

There is evidence that the Waterhouse–Friderichsen syndrome, a meningococcal sepsis syndrome involving bilateral adrenal hemorrhage, is not limited to meningococcal infection, but may occur after infection with staphylococci or other pathogens.[29,30] Considering the steady increase in methicillin-resistant *Staphylococcus aureus* and opportunistic infections, such causes of adrenal insufficiency should be kept in mind.

Tuberculous adrenalitis was once the most frequent cause of primary adrenal insufficiency, and this remains the case in many developing countries. In recent years, there has been a resurgence of tuberculous adrenalitis as a result of the increasing number of patients with the acquired immunodeficiency syndrome. Adrenalitis due to cytomegalovirus infection is especially common in patients with the human immunodeficiency virus infection, and apart from numerous opportunistic pathogens, antifungal therapy may further compromise adrenal function in these persons.[31]

In the Western world, glucocorticoid deficiency due to autoimmune disease accounts for up to 80% of the cases of primary adrenal failure.[1,2] Patients with autoimmune diseases, as well as some of their family members, frequently have multiple organ-specific endocrine disorders as part of an autoimmune polyglandular syndrome. Autoimmune thyroid disease is the most commonly observed organ manifestation, whereas vitiligo, primary gonadal failure, atrophic gastritis, and type 1 diabetes are less common.[1,2] Latent or subclinical forms may be more frequent than hitherto assumed.[32] Consequently, the possibility of adrenal dysregulation should be considered in all patients who have any form of autoimmune endocrine or metabolic disorder (Fig. 1).

The diagnosis of adrenal insufficiency is also frequently overlooked in inpatients with hyponatremia.[33] Up to 20% of patients with normovolemic hyponatremia have secondary adrenal insufficiency that is due in most cases to the empty sella syndrome, Sheehan's syndrome, or pituitary tumors. In these patients, plasma antidiuretic hormone levels are elevated, most likely owing to a

failure of endogenous glucocorticoid to suppress the hormone. Hydrocortisone-replacement therapy leads to rapid normalization of serum sodium levels.[33]

Another underdiagnosed clinical problem is hypopituitarism due to brain injury. Pituitary dysfunction occurs in up to 30% of patients with trauma to the brain and may not appear until months or years after the traumatic incident.[34]

GLUCOCORTICOID INSUFFICIENCY RELATED TO CRITICAL ILLNESS

Disease processes that cause a predisposition to adrenal failure during periods of increased stress appear to be more frequent than previously assumed. Terms such as "relative adrenal insufficiency" and, more accurately, "critical illness–related corticosteroid insufficiency" have been used to characterize these conditions.

Recently, expert panels and consensus conferences involving intensivists, pulmonologists, and endocrinologists have examined the clinical relevance of adrenal insufficiency and have provided recommendations for diagnosis and management.[35] The syndrome has been defined as inadequate glucocorticoid activity in relation to the severity of the patient's illness and has been most prominently investigated in cases of sepsis and septic shock.[36-39] The best test currently available for establishing the diagnosis is the 1-μg corticotropin stimulation test, in which cortisol levels are measured 30 minutes after stimulation, with a level of less than 25 μg per deciliter (690 nmol per liter) or an increment over baseline of less than 9 μg per deciliter (250 nmol per liter) representing an inadequate adrenal response. An inadequate response to corticotropin testing occurs in up to 60% of patients with sepsis[38]; however, declining cortisol-binding globulin levels in patients with sepsis may moderate the impairment of active free-cortisol production. To better define this syndrome, endocrine testing for adrenal insufficiency in patients with sepsis or other critical illnesses must be improved. Confounding factors such as variability in sampling and cortisol assays, including interfering antibodies, need to be considered. Measurement of free cortisol or widespread implementation of more accurate mass spectrometry methods might help to overcome these analytic limitations.[40,41]

Mechanisms of adrenal suppression in sepsis remain largely unclear; however, cytokines such as tumor necrosis factor-α or other peptides derived from blood cells — known as corticostatins — that may compete with corticotropin on its receptor[42] influence adrenal regulation during inflammation, induce tissue resistance to glucocorticoids, or have both effects.[43] In order for an adrenocortical cell to respond adequately to the severe stress of inflammation, intraadrenal cell–cell communication needs to be intact.[42] This involves a close crosstalk of adrenocortical cells with chromaffin cells, as well as endothelial cells and intraadrenal immune cells.[42] As summarized in Figure 2, it has been suggested that neuropeptides, neurotransmitters, oxidative stress, altered adrenal blood flow, and substrate deficiency due to low lipoprotein cholesterol levels and drug interactions affect adrenal integrity.[42,44,45] Septicemia itself and medications used during its treatment (Table 2) may interfere with receptor signaling associated with the membrane microdomains, with the machinery of cholesterol transport and storage, with enzymes involved in steroidogenesis, and with the mitochondrial function that is critical for steroidogenesis.[46] Furthermore, impaired blood supply to the pars distalis may induce pituitary ischemia, necrosis, or both during septic shock, and an increased accumulation of nitric oxide, superoxide, or central neuropeptides or prostaglandins contributes to a decrease in hypothalamic–pituitary hormones in patients with sepsis (Fig. 2).

The clinical consequences of impaired adrenal function in patients with sepsis remain unclear. A recent large, multicenter, randomized, double-blind, placebo-controlled trial showed that although hydrocortisone does help to reverse septic shock, it does not improve survival.[39] Therefore, general use of glucocorticoids in patients with sepsis does not appear to be warranted. A clearer understanding of the relevant causes of adrenal insufficiency in patients with sepsis and a more refined definition of subgroups that may benefit from glucocorticoid therapy are required. Additional factors that may contribute to the conflicting results include the severity of the sepsis, the duration of therapy, and the use or nonuse of fludrocortisone[39] to treat hypoaldosteronism. It is imperative that we gain a better understanding of both the true pattern of cortisol secretion during critical illness and the pharmacokinetics of vari-

Risk groups	Congenital abnormalities	Endocrine autoimmune disorders	Trauma	Chronic inflammatory disorders	Infectious diseases	Coagulation disorders	Liver disease	Tumors	Tissue infiltration	Mental disorders, addictions
Clinical signs and patient history	Short stature Disorders of sexual differentiation Hirsutism Obesity in congenital adrenal and pituitary disorders	Hashimoto's disease Diabetes mellitus type 1 Pernicious anemia Vitiligo in autoimmune polyglandular syndromes	Head trauma Bleeding Burns Pregnancy Surgical trauma Sports	Rheumatoid arthritis Asthma Crohn's disease Allergies	HIV-1–cytomegalovirus infection Tuberculosis Candidiasis Histoplasmosis	Waterhouse–Friderichsen syndrome in sepsis Thrombocytopenia Drug-related adrenal hemorrhage (e.g., with heparin) Antiphospholipid syndrome causing adrenal hemorrhage	Hepatitis Liver failure Liver transplantation with low lipoproteins and adrenal exhaustion syndrome	Pituitary and adrenal tumors Metastases (bilateral lymphoma, renal cancer) History of hypophysectomy History of bilateral adrenalectomy or removal of incidentaloma History of irradiation	**Adrenal** Amyloidosis Hemochromatosis Sarcoidosis **Pituitary** Histiocytosis Wegener's granulomatosis Sarcoidosis	Anxiety disorders Atypical depression Antidepressants Alcohol
Additional considerations	Be aware of late onset of adrenal insufficiency	Be aware of thyroid hormone triggering adrenal crisis	Check for steroid use in elite athletes Consider pituitary apoplexy (Sheehan's syndrome) in pregnancy Check for use of perioperative etomidate	Check for intranasal, intraarticular, and topical use of steroids and novel selective glucocorticoid-receptor agonists	Check for antifungal therapies or rifampin or steroids	Be aware of nonmeningococcal infections causing Waterhouse–Friderichsen syndrome	Consider masking by immunosuppressive steroid therapy	Check for craniospinal irradiation in leukemia and other brain tumors Consider palliation of breast and endometrial cancer with megestrol acetate or use of other steroid in tumor therapy	Consider additional suppression by steroid therapy	Be aware of HPA-axis dysregulation Rule out Addison's disease in patients with anorexia nervosa

Consider nonspecific symptoms: fatigue, hypotension, malaise, vomiting, abdominal pain, fever of unknown origin, failure to thrive, hemodynamic complications in patients in critical condition (fluid resistance in shock, poor response to vasopressors)

Suspect impaired HPA-axis; initiate diagnostic workup and hydrocortisone treatment

Figure 1. Clinical Checklist for Adrenal Insufficiency.

The figure shows a practical chart for identifying adrenal insufficiency among persons in 10 major risk groups with a potential predisposition to clinical or subclinical adrenal insufficiency. The corresponding list of patient history and clinical signs should raise awareness about a possible adrenal dysfunction, particularly in the critically ill patient, and allow timely initiation of therapy. HPA denotes hypothalamic–pituitary–adrenal.

ous hydrocortisone-replacement therapies. Finally, the adverse effects of glucocorticoid replacement on insulin resistance, protein catabolism, and immunosuppression may be aggravated by high-fat parenteral nutrition in critically ill patients, since lipids have recently been shown to increase the action of glucocorticoids.[47]

On the basis of available evidence, current recommendations, and good clinical practice, and irrespective of the results of adrenal testing, moderate doses of hydrocortisone (200 to 300 mg per day) should be given soon after the onset of septic shock in patients who remain hypotensive despite adequate administration of fluids and vasopressor agents.[35,36,39] Current evidence is insufficient to recommend the replacement of other steroids that are suppressed in patients with sepsis, including mineralocorticoids and adrenal androgens.[1,48,49]

In addition to impairment of adrenal glucocorticoid regulation, hypoaldosteronism occurs frequently in critically ill patients. This condition probably does not result from a selective effect on the adrenal zona glomerulosa or aldosterone synthase; rather, it seems likely that the same mechanisms that lead to glucocorticoid insufficiency account for the hypoaldosteronism. Future studies will need to address these mechanisms. The role of mineralocorticoid supplementation in the treatment of critically ill patients is already being investigated in ongoing multicenter trials.

Several randomized studies have assessed the role of glucocorticoid treatment in patients with acute lung injury or the acute respiratory distress syndrome.[50,51] A consistent finding in these studies was that such treatment resulted in an accelerated resolution of the disorders.[35] In addition, preliminary data suggest that glucocorticoids have a beneficial effect in patients with severe pancreatitis[52] and in those who have undergone trauma with hemorrhagic shock, as well as in patients who have just undergone cardiac surgery[53] and those who are being weaned from mechanical ventilation.[54]

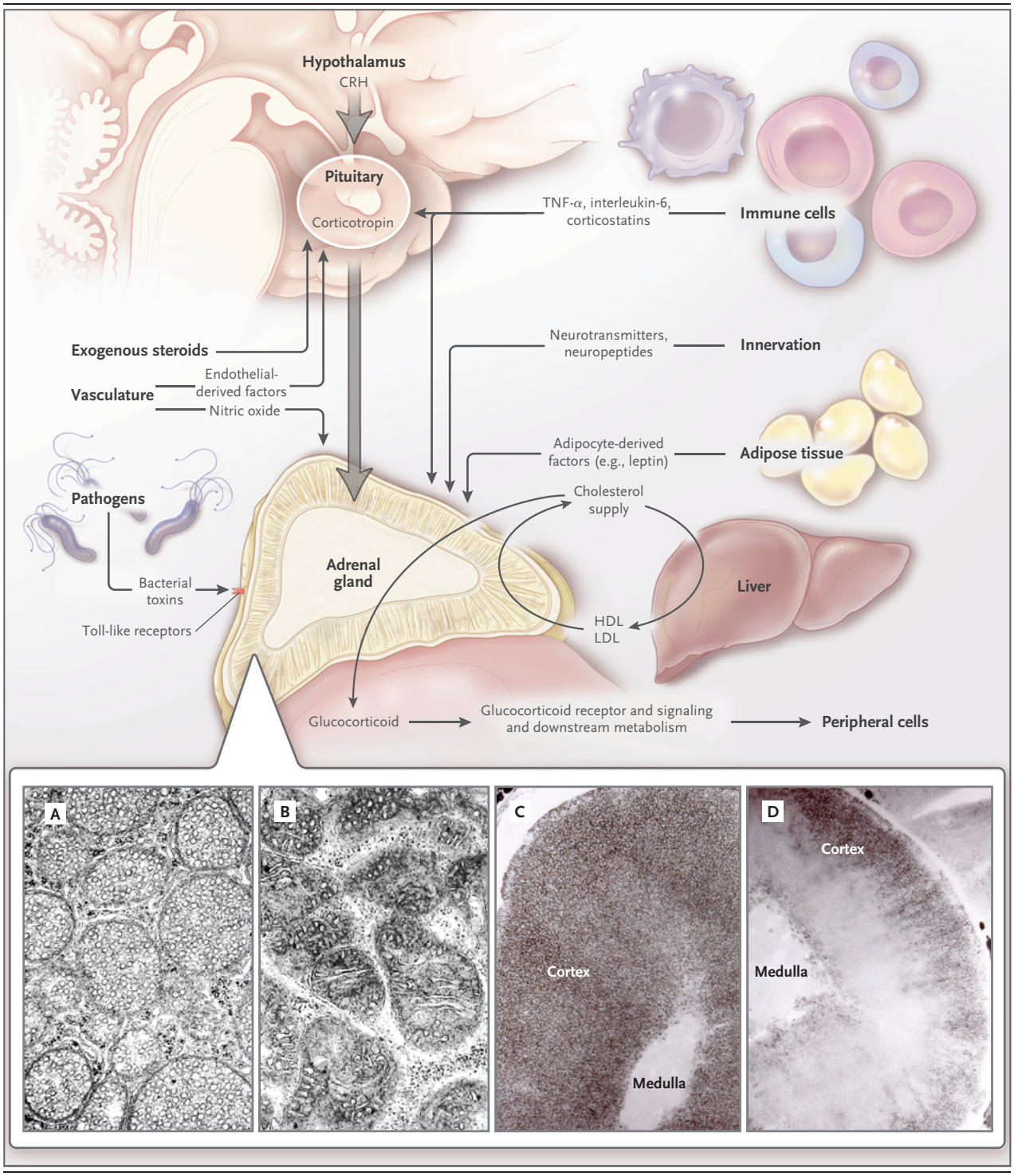
It has become evident that patients with liver diseases have adrenal disturbances. Signs of adrenal insufficiency are present in 33% of patients with acute liver failure, 65% of patients with chronic liver disease and sepsis, and 92% of patients who have undergone a liver transplantation.[45] Consequently, the term "hepato–adrenal syndrome" has been introduced. It has been suggested that immunosuppression with glucocorticoids in liver-transplant recipients has masked the syndrome. Patients with liver diseases have very low lipoprotein levels, and a substrate shortage may therefore lead to an adrenal exhaustion syndrome. However, a reduction in total cortisol may reflect a decrease in cortisol-binding globulin rather than a decrease in free cortisol. Nevertheless, patients with liver diseases should be carefully monitored for symptoms and signs of adrenal insufficiency and may benefit from glucocorticoid-replacement therapy.[55]

Figure 2 (facing page). Current Concepts of Immune–Endocrine and Metabolic Factors Involved in Glucocorticoid Dysregulation in Critical Illness.

Cytokines, chemokines, and adipokines derived from immune cells and fat cells and bacterial and viral toxins mediated by toll-like receptors modify pituitary–adrenal hormone synthesis and glucocorticoid tissue sensitivity and the activation of peripheral cortisol metabolism. Similarly, the function of the hypothalamic–pituitary–adrenal axis is influenced by blood flow, endothelial factors, neurotransmitters, and neuropeptides. Furthermore, synthesis of pituitary and adrenal hormones requires a large supply of vitamins, antioxidants, and cholesterol. Impairment and dysregulation of any of these pathways will disrupt the integrity of the hypothalamic–pituitary–adrenal axis and may lead to a disturbed adrenal stress response. An electron micrograph shows the vesicular mitochondria of an adrenocortical cell in a normal mouse and in a mouse with suppressed corticosterone responses due to the administration of dexamethasone (Panels A and B, respectively; uranyl acetate and lead citrate staining). The number and conformational structure of internal mitochondrial membranes correlate with the steroidogenic capacity of an adrenocortical cell. Animal models with a defect in steroid production frequently show alterations in vesicular mitochondria, with reduction and tubular transformation of internal membranes.[19,42] Staining of histologic sections of adrenal glands with Sudan black shows the storage of lipid droplets in the adrenal cortex of rats in an unstressed state and 2 hours after stimulation with corticotropin-releasing hormone (Panels C and D, respectively). Since cholesterol constitutes the substrate for steroidogenesis, there is a rapid disappearance of cholesterol-storing liposomes after activation of the hypothalamic–pituitary–adrenal axis (Panel D), illustrating the requirement of an external cholesterol supply for the adrenal gland. CRH denotes corticotropin-releasing hormone, HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and TNF tumor necrosis factor.

CONCLUSION

In 1855, Thomas Addison concluded that "my experience, though necessarily limited, leads to a belief that [adrenal insufficiency] is by no means



of very rare occurrence and that were we better acquainted with its symptoms and progress, we should probably succeed in detecting many cases, which in the present state of our knowledge may be entirely overlooked or misunderstood."[3] Today, we are better acquainted with the symptoms of this disease and better able to manage it with a simple glucocorticoid-replacement regimen; however, clinicians must be aware of the growing list of causes and predisposing factors involved in the development of this life-threatening disorder. A simplified checklist of groups that are at in-

creased risk for adrenal impairment may help to raise awareness among clinicians (Fig. 1). This information is important, since timely and adequate hydrocortisone replacement in patients with acute adrenal insufficiency represents a lifesaving and effective solution in medical emergencies.

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