Corticosteroids in Pediatric Endocrinology

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Introduction

Glucocorticoids, the end products of the hypothalamic–pituitary–adrenal axis, are human steroid hormones secreted by the zona fasciculata of the adrenal cortex (Fig. 1). This class of steroids is essential for the physiological and daily maintenance and regulation of the balance between basal and stress-related homeostasis [22, 52]. Several biologic processes in virtually all physiological organ systems are mediated and influenced by this class of molecules [22, 52]. Glucocorticoids are also essential for the proper functioning of almost all organs and tissues of the organism, including the central nervous and cardiovascular systems and metabolic organs, such as the liver and adipose tissue, as well as the immune/inflammatory response [22, 52]. In addition, glucocorticoids at "pharmacologic" or "stress-related" doses are irreplaceable therapeutic means for many allergic, inflammatory, autoimmune, and lymphoproliferative diseases [90]. Moreover, glucocorticoids are used for the treatment of a wide spectrum of disorders in childhood. In particular, glucocorticoid replacement remains the cornerstone of treatment for life-threatening endocrinopathies in childhood, such as congenital adrenal hyperplasia, Addison disease, and steroid replacement therapy for subjects with secondary hypothalamic–pituitary–adrenal axis deficit. The normal physiology of cortisol secretion and metabolism has been the focus of much research, the results and limitations of which are relevant to the consideration of optimal glucocorticoid replacement therapy in childhood. They challenge assumptions about the dose and pattern of glucocorticoid replacement, the choice of which glucocorticoid to use, and the use of reference ranges or targets in assessing glucocorticoid replacement therapy in patients with hypocortisolemia. Therefore, in-depth knowledge of the physiological

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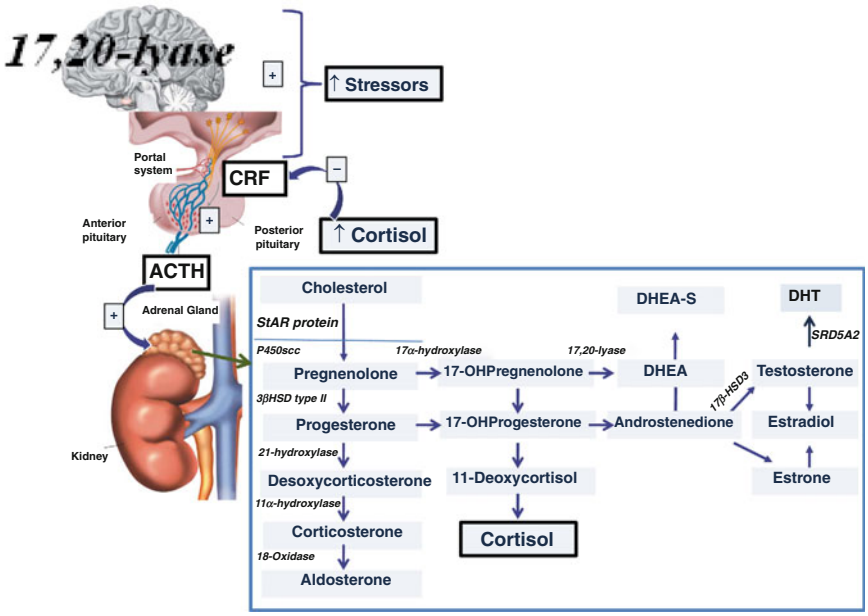

Fig. 1 Regulation of the hypothalamic–pituitary–adrenal axis. Adrenal cortisol production and secretion are regulated by the hypothalamic–pituitary–adrenal axis. Basal diurnal rhythm (regulated by internal clock genes) and various stress factors prompt the release of corticotropin-releasing hormone (*CRH*), which stimulates production and secretion of adrenocorticotropin (*ACTH*) from the pituitary gland. ACTH then stimulates cortisol (and androgen) production and release from the zona fasciculata and the zona reticularis. Positive feed-forward regulation pathways are highlighted. Negative feedback control to the hypothalamus and the pituitary gland works directly through cortisol

pattern of cortisol production and action as well as of the therapeutic opportunity can be challenging for physicians, pediatricians, and pediatric endocrinologists. In this chapter the physiology of the hypothalamic–pituitary–adrenal axis and of glucocorticoids is described. In addition, glucocorticoid replacement therapy in the main clinical disorders in youths (i.e., congenital adrenal hyperplasia, Addison disease, and Cushing disease) is elucidated.

Adrenal Gland: Embryology and Physiology

The adrenal gland was first described in 1552 by Bartolomeu Estaquio as the "glandulae renis incumbents" in *Opuscula Anatômica* [42], although its function remained a mystery for centuries. The mystery began to be solved in 1885, however, when Thomas Addison described the clinical features of 11 patients with primary adrenal insufficiency [57]. In 1949, the synthesis of cortisone

facilitated the treatment of this condition [50]. The adrenal gland is made of two tissue types, namely, the adrenal medulla and the adrenal cortex, which have different embryonic origins. By 4–5 weeks of gestation, cells from the mesoderm aggregate to form a primitive cortex between the posterior part of the dorsal mesentery and the gonadal ridge [7]. Shortly thereafter, this primitive cortex becomes surrounded by a narrow band of cells termed the permanent cortex. By 7–8 weeks of fetal life, the primitive cortex is invaded by chromaffin cells that develop rapidly and eventually replace most of the primitive cortex, forming the medulla. At this time the adrenal gland is close to the cranial part of the primitive kidney and not far from the genital ridge. The adrenal medulla, which originates from ectodermal cells, has an entirely different function from the mesodermal adrenal cortex.

In mammals, the adrenal cortex is made of three zones. The first region is the outer zone, the zona glomerulosa, which is responsible for the production and secretion of the mineralocorticoid aldosterone. The inner region is divided into the zona fasciculata and the zona reticularis and is responsible for synthesis and production of glucocorticoids (cortisol, corticosterone, and adrenal androgens). We first focus our discussion on the physiological function and regulation of cortisol production. Then we consider the more common disorders related to primary or secondary hypocortisolism, their potential therapeutic approach, and therapy-related complications in childhood.

Biosynthesis of Cortisol

Cortisol is the principal glucocorticoid hormone produced by the adrenal cortex in humans. The production of cortisol is the result of a series of reactions that involve the concerted action of several enzymes within the adrenals. In this complex process of steroidogenesis, the uptake of cholesterol to the mitochondria represents the first and critical step that is facilitated by the action of a regulatory protein called the steroidogenic acute regulatory protein [75]. The biosynthetic pathway of the adrenal steroids is shown in Fig. 1. Thus, during steroidogenesis, cholesterol is the precursor of a number of steroid hormones of both gonadal and adrenocortical origin. Although they share similar chemical formulae, small differences in their molecular structure characterize each steroid hormone and give them specific functions [86]. The pathway from cholesterol to the end steroid products requires five cytochrome P450 enzymes [cholesterol side-chain cleavage enzyme (20-hydroxylase, 22-hydroxylase, 20,22-lyase, CYP11A), 3β-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase and 17,20-lyase (CYP17), 21-hydroxylase (CYP21), 11β-hydroxylase (CYP11B1), aldosterone synthetase (11β-hydroxylation, 18-hydroxylation, 18-oxidation, CYP11B)]. Cholesterol is stored in the adrenal cell as cholesterol esters [75, 86]. Under the influence of an esterase, cholesterol becomes available and is transported to the mitochondria, where it is converted into pregnenolone [75, 86]. This steroid then moves into the endoplasmic reticulum,

where 3β-hydroxysteroid dehydrogenase, 21-hydroxylase, and 17-3β-hydroxylase enzymes are located. The resulting steroids include 11-deoxycorticosterone (DOC) and 11-deoxycortisol as well as two C-19 carbon steroids, androstenedione and dehydroepiandrosterone. At this point, DOC and 11-deoxycortisol return to the mitochondria, where they are converted into corticosterone and cortisol, respectively. This is the end of the biosynthetic process in the cells of the fasciculata. In the cells of the zona glomerulosa in the mitochondria, DOC is transformed into corticosterone, 18-hydroxycorticosterone, and aldosterone [75, 86].

Control of Corticosteroid Secretion

Synthesis and secretion of cortisol are regulated by the pituitary hormone adrenocorticotropin (ACTH), which in turn is regulated by hypothalamic corticotropin-releasing hormone (CRH) with the synergistic action of arginine vasopressin (AVP). These hormones comprise the hypothalamic–pituitary–adrenal axis that is directly related to a complex closed-loop system. Indeed, CRH is synthesized in the hypothalamus and carried to the anterior pituitary, where it stimulates ACTH release. Finally, ACTH stimulates the adrenal cortex to secrete cortisol. Cortisol inhibits the synthesis and secretion of both CRH and ACTH in a negative feedback regulation system [64, 67, 85, 109].

CRH is a 41-amino acid straight-chain peptide secreted mainly by the median eminence into the portal vessels. Via specific receptors (CRH-R1), CRH activates the formation of cyclic adenosine monophosphate, which then activates a series of protein kinases, resulting in increased transcription of the pro-opiomelanocortin gene and in ACTH formation [12, 64, 67, 85, 109]. ACTH has a half-life in blood of a few minutes and like other hormones binds specific receptors on the adrenal cortex, type 2 melanocortin receptors (MC2-R), and increases cyclic adenosine monophosphate formation to initiate the synthesis of cortisol, which is released immediately into the systemic circulation by diffusion [12, 64, 67, 85, 109]. ACTH stimulation of cortisol on the adrenal includes both an immediate and a chronic phase. Acutely, over a few minutes, steroidogenesis is stimulated through a steroidogenic acute regulatory protein (STAR-)-mediated increase in cholesterol delivery to the CYP11A1 enzyme in the inner mitochondrial membrane [14]. In the more chronic phase, over 24–26 h of exposure, ACTH leads to an increase in the synthesis of all steroidogenic CYP enzymes (CYP11A1, CYP17, CYP21A2, CYP11B1) in addition to adrenodoxin, and these effects are mediated at the transcriptional level. Additional effects of ACTH include: (a) increased synthesis of the low-density lipoprotein and high-density lipoprotein receptors, and possibly also HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase, the rate-limiting step in cholesterol biosynthesis; (b) increased adrenal weight by inducing both hyperplasia and hypertrophy [12, 14, 64, 67, 85, 109].

Glucocorticoid synthesis is mostly affected by two variables: the secretion patterns and the secretion rate. The former is related to three main physiological mech-

anisms affecting the secretion of cortisol: pulsative secretion and diurnal variation, stress, and negative feedback. The normal pattern of glucocorticoid secretion includes both a diurnal rhythm and a pulsatile ultradian rhythm. In fact, the natural cortisol peak in humans occurs early, before awakening, and falls progressively during the day, reaching low levels in the evening [9, 112]. The circadian rhythm of glucocorticoid secretion is accompanied by a pulsatile ultradian rhythm throughout the 24-h cycle [20]. As documented by automated frequent blood-sampling techniques, the pulses vary in amplitude throughout the day, with the amplitude generally decreasing during the diurnal trough. Of note, the two components are separable secretory modes. Thus the "pulsatile" and "circadian" rhythms are independently regulated [118]. Ultradian rhythmicity has been shown in rats [116], monkeys [94], and humans [9, 38, 46, 112]. Among the most relevant practical consequences [118] of the pulsatility is that the underlying pattern of spontaneous pulses might not be detected if sampling is infrequent and/or conducted over a short period. This might also have an additional effect on the tissue specificity. In fact, the two glucocorticoid-related tissue receptors have different affinities. Therefore, according to the circulating level of ligands, the receptors will be differentially occupied and activated [118], especially affecting the occupancy of the lower-affinity glucocorticoids receptors [118]. Prolonged versus intermittent exposure seems to also affect steroid-responsive hepatic enzymes. Studies have documented that short exposure to glucocorticoids may have different effects on tyrosine aminotransferase, an enzyme involved in the catalysis of the first step in tyrosine catabolism [88, 107]. Finally, prolonged exposure to glucocorticoids has been shown to downregulate glucocorticoids receptors [88].

This complex regulation system is further characterized by the ability of the adrenal glands to secrete steroids in a stress-related way [37]. Surgical stress such as trauma and tissue destruction, medical stress such as acute illness, fever, and hypoglycemia, and emotional stress related to psychological upset result in a significant increase in cortisol secretion in most cases. The hypothalamic–pituitary–adrenal axis in conjunction with the sympathetic system connects the brain with the periphery of the body. Of note, the body responses to a stressor – physical or emotional – that disrupts the homeostatic balance of the organism are mainly related to the hypothalamic–pituitary–adrenal axis activity [37, 93]. All the complex activities characterizing the individual's adaptive response to excessive stress are stereotypical and usually defined as the "general adaptation syndrome" [37, 93]. This physiological response involves interactions between hormones and the central nervous system. Glucocorticoids along with catecholamines (the end product of sympathetic nervous system activation) secreted by the adrenal medulla and sympathetic nerves orchestrate the "fight or flight" response, which is the first stage of the general adaptation syndrome [69]. The fight or flight response refers to different factors including: a quick mobilization of energy from storage to different systems, such as the heart, muscles, and the brain; a prompt transport of nutrients and oxygen to relevant tissues facilitated by accelerated cardiac output and breathing rate; and increased blood pressure [23]. According to the theory of Munck and colleagues [77], the physiological function of stress-induced increase in glucocorticoid levels is to

defend the body against the normal defense reactions that are activated by stress and not against the stress itself. According to this theory, glucocorticoids accomplish this function by turning off these defense reactions, thus preventing them from overshooting and threatening homeostasis. Therefore, it is now commonly accepted that glucocorticoid secretion in a stress situation plays a double and complementary function: a permissive and suppressive effect, the former preparing or priming defense mechanisms for action and the latter limiting these actions [78]. CRH and AVP neurons of the hypothalamic paraventricular nuclei and the noradrenergic neurons of the locus coeruleus/norepinephrine–central sympathetic systems in the brain stem represent the main apparatus of the stress system. In addition, the peripheral branches of this system consist of the hypothalamic–pituitary–adrenal axis and the systemic sympathetic and adrenomedullary nervous system [21]. Both central components of the stress system are stimulated by cholinergic and serotonergic neurotransmitters and inhibited by γ-aminobutyric acid, benzodiazepine, and arcuate nucleus pro-opiomelanocortin peptides [19, 31]. Activation of the central stress system results in the secretion of CRH and AVP into the hypophyseal portal circulation, thus inducing glucocorticoid secretion by the hypothalamic–pituitary–adrenal axis. In this complex event the systemic sympathetic and adrenomedullary nervous systems are also activated as a direct consequence of central stress system stimulation, which in turn results in a peripheral secretion of catecholamines and several neuropeptides. At rest the stress system is still active, assisting the body in responding to various distinct signals, for example, circadian, neurosensory, blood-borne, and limbic [22]. The activation of the stress system has thus several effects: it increases arousal, accelerates motor reflexes, improves attention and cognitive function, decreases appetite and sexual arousal, and also increases the tolerance of pain [23]. Although these types of stress are well known to affect cortisol production, research is still ongoing to define all the regulatory mechanisms involved. Among the reported results, studies of the immune system have shown that leukocytes may play a relevant regulatory action by secreting a series of interleukins able to significantly affect the adrenal axis [110].

The negative feedback represents a relevant feedback control able to constantly equilibrate the secretion rate of both ACTH and cortisol. When plasma concentrations of cortisol increase markedly, a negative feedback effect on the secretion of CRH and ACTH is induced [64, 67, 85, 109].

The secretion rate and cortisol metabolism represent an additional variable that needs to be considered in defining glucocorticoid synthesis in the young. The daily cortisol production rate ranges between 5 and 10 mg/m^2 body surface area [16, 28, 51, 55]. Circulating cortisol in humans is about 90 % plasma protein bound, mostly to cortisol-binding globulin and less to albumin, while only 5–10 % circulates unbound as a free active hormone [64, 67, 85, 109]. The free cortisol concentration ranges from approximately 1 nmol/l at the diurnal trough to approximately 100 nmol/l at the diurnal peak [96]. Estimations of the circulating half-life of cortisol vary between 70 and 120 min. Cortisol is cleared through several distinct pathways, including A-ring reduction to form tetrahydrocortisol and its 5α-isomer, allotetrahydrocortisol, hydroxylation to yield 6-β-hydroxycortisol, and the reduction

of the 20-oxo group to produce cortisol [34]. Cortisone is an inactive steroid that circulates at concentrations of around 60 nmol/l, largely unbound to plasma proteins and without marked diurnal variation. The main source of cortisone is 11-β-hydroxysteroid dehydrogenase-type 2 (11-β-HSD-2) in the kidney [96, 108], which gates glucocorticoid access to nuclear receptors by a prereceptor mechanism. 11-β-HSD-1 converts cortisone to cortisol, amplifying the steroid signal in target cells [97]. Additionally, cortisol derives from circulating cortisone via conversion in peripheral tissues expressing the enzyme 11-β-HSD-1. The cortisol secretion rate in children also shows some peculiarities. Several studies in children have shown that in normal children and adolescents, the cortisol secretion rate is directly related to body size [28, 51, 74]. Migeon et al. showed that when the values are corrected for body surface area, the rates are similar at various ages; in fact, the average ± standard deviation was 12 ± 2 with a range of 8–16 mg/m^2/24 h [74]. Using stable isotope dilution/mass spectroscopy, Esteban et al. showed that the cortisol secretion rate for 12 normal subjects was lower, accounting for 5.7 ± 1.5 mg/m^2/24 h [74]. Kerrigan et al. also investigated the daily cortisol production and clearance rates in a group of 18 normal unstressed pubertal male subjects by applying deconvolution analysis to serum cortisol concentrations obtained every 20 min for 24 h [51] and found similar results to Esteban's data. In addition, they showed that the estimated cortisol production rate for the early puberty group was indistinguishable from that of the late puberty subjects [51]. No difference was observed between the two pubertal groups in the secretory burst frequency and half-duration, mass of cortisol released per secretory episode, average maximal rate of hormone secretion, and serum cortisol half-life [51]. A significant diurnal pattern of cortisol secretion was observed for all subjects, manifested by nyctohemeral variations in the frequency of adrenocortical secretory bursts, the amplitude (maximal rate of cortisol secretion) and the mass of cortisol released per secretory episode. In this age group, maximum serum hormone concentrations occurred between 07:06 and 11:14 h [51]. Similar results were also reported by Linder et al., who evaluated the cortisol production rate in 33 normal children and adolescents, using a stable isotope-dilution technique with high-performance liquid chromatography-mass spectrometry [61].

Effects of Cortisol

Glucocorticoids are essential for the maintenance of homeostasis and enable the organism to prepare for, respond to, and manage physical or emotional stress. These hormones affect nearly every organ and tissue in the body and have diverse life-sustaining effects throughout the life span. Glucocorticoid access to nuclear receptors is gated by the 11-β-HSD enzymes. Corticosteroids are highly lipophilic and are thought to diffuse readily across biological membranes to access their intracellular receptors [41, 81]. At the cellular level, the myriad effects of corticosteroids are largely a consequence of transcriptional actions mediated via binding to two types of intracellular receptors: the high-affinity mineralocorticoid receptor and the

lower-affinity glucocorticoid receptors [32, 70]. On binding ligand, glucocorticoid receptors and mineralocorticoid receptors dissociate from complexes with chaperone proteins, translocate to the nucleus, and bind directly or indirectly to the regulatory regions of target genes: ≈2 % of the human genome is regulated by glucocorticoids [89], although few, any genes are exclusively controlled by corticosteroids. Rapid glucocorticoid signaling via membrane binding has also been postulated [18].

Cortisol is involved in peripheral glucose uptake and utilization (gluconeogenesis and glycogenolysis). Cortisol also affects the maintenance of proper cardiovascular tone, endothelial integrity, and the distribution of fluids within the vascular compartment. Moreover, cortisol potentiates the vasoconstrictor action of catecholamines and decreases the production of nitric oxide [25, 36]. Therefore, cortisol deficiency results in hypoglycemia, hypotension, lethargy, decreased appetite, absolute leukocytosis, eosinophilia, and anemia. Cortisol influences the activity and direction of the reactions underlying intermediary metabolism and many functions of the central nervous system, including arousal, cognition, mood, and sleep. Physiological amounts of glucocorticoids are also essential for normal renal tubular function and thus for water and electrolyte homeostasis. Studies have shown that 15–20 % of the human leukocyte transcriptome is influenced by glucocorticoids [24, 33], and almost two thirds of them are induced, whereas the rest are suppressed. Through their genomic actions, glucocorticoids regulate cellular metabolism primarily through catabolic actions in the liver, muscle, and adipose tissue [24, 33]. Finally, multiple components regulating the quantity and quality of immune/inflammatory responses are well-recognized glucocorticoid targets, providing the basis for the wide use of glucocorticoids as potent anti-inflammatory/immunosuppressive drugs in the treatment of inflammatory diseases and cancer [90].

Cortisol Replacement Therapy: Relevance in Pediatric Endocrinology

The first treatment for adrenal insufficiency was introduced in the 1930s when lipid extracts from adrenal glands were tested, leading to a drastic and rapid drop of the mortality rate from 100 % to a seemingly normal life expectancy. In 1937 and 1949, the synthesis of 11-deoxycortisone (11-DOC) and cortisone, respectively, represented major improvements in therapy. Since the first published report of the efficacy of cortisone in the treatment of rheumatoid arthritis in 1949 [92], patients with adrenal insufficiency have been treated with glucocorticoid replacement, and after the introduction of fludrocortisone in the 1950s replacement therapy has remained virtually unchanged [66]. Hydrocortisone is now used in many centers around the world.

As mentioned, following the first report of the efficacy of cortisone in treating rheumatoid arthritis, glucocorticoids have been used widely in several autoimmune diseases and in the treatment of a spectrum of disorders in childhood. In particular, glucocorticoid replacement remains the cornerstone of treatment for certain

life-threatening endocrinopathies in childhood, such as congenital adrenal hyperplasia, Addison disease, and as replacement therapy for those subjects with secondary hypothalamic–pituitary–adrenal axis deficit. In the next sections, a short description of these main disorders in childhood is provided, evidencing the role of glucocorticoids in their treatment.

Adrenal Insufficiency

Adrenal insufficiency is a clinical condition characterized by a state of failure of the adrenal cortex to provide sufficient amounts of steroid hormones, in particular glucocorticoids. Several causes might be responsible for the development of adrenal insufficiency in childhood. According to the localization of its underlying cause, adrenal insufficiency in childhood can be essentially categorized into two major groups: primary and secondary. The most frequent causes of primary and secondary adrenal insufficiency are summarized in Table 1.

The group of primary adrenal insufficiency includes: autoimmune adrenalitis (Addison disease, which can arise in isolation or as part of an autoimmune polyglandular syndrome), infections (tuberculosis, cryptococcosis, mycosis, AIDS), congenital conditions (adrenoleukodystrophy, adrenomyeloneuropathy, congenital adrenal hyperplasia), bilateral adrenalectomy, bilateral adrenal hemorrhage, metastases and surgery, and drug-induced adrenal insufficiency (treatment with mitotane, etomidate, ketoconazole, aminoglutethimide). Secondary adrenal insufficiency results from hypothalamic–pituitary impairment, with consecutive lack of CRH and/or ACTH. Thus, this group mainly includes: pituitary tumors or other tumors of the hypothalamic–pituitary region often associated with panhypopituitarism (caused

Table 1 Most frequent causes of primary and secondary adrenal insufficiency

Primary	Autoimmune adrenalitis (isolated or related to an autoimmune polyglandular syndrome)
	Infections (tuberculosis, cryptococcosis, mycosis, AIDS)
	Congenital (congenital adrenal hyperplasia, adrenoleukodystrophy, adrenomyeloneuropathy)
	Bilateral adrenalectomy
	Bilateral adrenal hemorrhage
	Metastases and surgery
	Drug-induced adrenal insufficiency (treatment with mitotane, etomidate, ketoconazole, aminoglutethimide)
Secondary	Pituitary tumors or other tumors of the hypothalamic–pituitary axis (secondary adrenal insufficiency as a consequences of tumor growth and treatment, i.e., surgery, radiation
	Exogenous chronic glucocorticoid treatment
	Head trauma
	Pituitary infiltration (tuberculosis, sarcoidosis, Wegener's granulomatosis)

by tumor growth or treatment with surgery or irradiation), exogenous glucocorticoids leading to suppression of CRH/ACTH release, head trauma, and pituitary infiltration.

Although most of these conditions rarely occur in childhood, adrenal insufficiency related to congenital adrenal hyperplasia, Addison disease, and Cushing's syndrome are not uncommon, thus requiring clinicians, health-care planners, and patients to understand these life-threatening disorders and the proper management of adrenal insufficiency in the various clinical settings. While etiological aspects characterize the different causes of adrenal insufficiency, glucocorticoids traditionally represent the main therapeutic option in all forms of adrenal insufficiency, including acute and chronic states.

Acute adrenal insufficiency is a life-threatening disease that involves severe hypotension or hypovolemia, acute abdominal pain, nausea and vomiting, lack of stamina, and weight loss [4]. Anorexia, fever, weakness, fatigue, lethargy, and confusion may also be associated with this condition. Dizziness, irritability, and postural hypotension are frequent complaints; these symptoms can be triggered by several predisposing factors such as trauma, surgery, and infections, which suddenly increase the need for corticosteroids. Acute adrenal insufficiency-related shock is often unresponsive to volume replacement and vasoconstrictor agents [54, 84, 111]. Hyperpigmentation and salt-craving are also often detected. According to the underlying cause, the onset of the disease can be insidious, taking years to diagnose, or can lead to the development of an acute crisis following an intercurrent illness [54, 84].

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by the deficiency of an enzyme involved in steroidogenesis within the adrenal cortex [72, 115]. Although several enzymatic defects have been described, the most common is cytochrome P450 21-hydroxylase (CYP21) deficiency. The defect accounts for approximately 95 % of cases and results from mutations [5, 44, 56, 103] of the *CYP21A2* gene located on chromosome 6p21.3. The enzyme adrenal insufficiency converts 17-hydroxyprogesterone into 11-deoxycortisol and progesterone into 11-deoxycortisone, which are precursors for cortisol and aldosterone, respectively (Fig. 1). Therefore, defects of the enzymatic activity result in an impaired adrenal synthesis of cortisol often associated with aldosterone deficiency, which in turn leads to increased ACTH secretion by the pituitary gland. The impaired cortisol/aldosterone synthesis and the increased ACTH production directly induce: severe salt wasting (SW) and Addisonian crisis, related to cortisol and aldosterone deficiency; adrenal gland hyperplasia, related to ACTH oversecretion; and accumulation of steroid precursors, inducing a variable degree of virilization as a direct consequence of adrenal androgen overproduction [115].

According to the degree of the enzyme deficiency, different clinical phenotypes can be defined including: classic SW, classic simple virilizing (SV), and nonclassic (NC) CAH. The classic SW form is the most severe form of enzymatic activity deficiency, resulting from a residual activity of less than 1 %. In this form, severe cortisol deficiency and decreased aldosterone synthesis are detected. Female patients are virilized prenatally owing to adrenal androgen excess. Neonates (boys and girls) also suffer from life-threatening Addisonian crisis. In those forms characterized by a residual enzyme activity of 1–2 % (simple virilizing) CAH, the residual activity is enough for sufficient aldosterone production, thus preventing SW. By contrast, cortisol synthesis is impaired and this results in the development of genital ambiguity in affected female patients due to prenatal virilization. In those forms with a residual enzymatic activity around 20–50 % (nonclassic), cortisol and aldosterone production are normal. In these subjects a mild androgen excess may be detected and may induce premature pubarche, cystic acne, hirsutism, and menstrual disorders in some subjects in childhood/adolescence, or may even be asymptomatic. Some patients present first in adulthood with fertility problems.

Addison Disease

Autoimmune adrenalitis, or autoimmune Addison disease (AAD), is a rare condition in childhood. Both humoral and cellular immunity play a role in AAD pathogenesis, with presence of adrenal cortex autoantibodies in the serum of patients [3]. These adrenal cortex autoantibodies are of the immunoglobulin subclasses IgG1, IgG2, and IgG4 and are directed against the steroidogenic enzymes, with steroidogenic 21-hydroxylase being the most prevalent [100, 117]. Although the presence of adrenal cortex autoantibodies is a main feature of the disease, their role in the pathogenesis of autoimmune Addison disease is still debated. Studies have shown that the destruction of adrenocortical cells is mainly mediated by T-lymphocytes. Thus the secondary release of peptides may result in the production of antibodies [13]. Autoimmune adrenalitis may present in 60 % of cases as part of an autoimmune polyendocrine syndrome, while in the remaining 40 % it is isolated [4]. During the first two decades of life, isolated AAD is predominantly observed in male subjects (70 %); however, after the third decade of life, there is a substantial female preponderance (81 %) [102]. Spontaneous recovery of adrenal function has been described but is rare. Addison disease is the final result of AAD; the initial phase is subclinical, and after at least 90 % of the adrenal gland has been destroyed, symptoms of adrenal failure occur [11]. This condition can easily be misdiagnosed in childhood, thus negatively affecting data on its true prevalence; autoimmune adrenalitis is the main cause of adrenal insufficiency after the introduction of antituberculosis therapy, and is responsible for 68–94 % of the cases in European and North American reports [10, 29, 79]. Determination of inappropriately low cortisol production associated with the presence of high titers of adrenal cortex autoantibodies is strongly suggestive of autoimmune adrenalitis. The diagnosis is confirmed by excluding

other causes of adrenal failure, using other tests as necessary. Treatment is based on corticosteroid replacement, and the prognosis following treatment is the same as for the normal population. Thus the standard initial therapy is corticosteroid replacement.

Cushing's Syndrome in Children: Role of Glucocorticoid Therapy

Cushing's syndrome refers to a large group of clinical conditions characterized by the presence of signs and symptoms associated with prolonged exposure to inappropriate levels of the hormone cortisol [67]. In children with Cushing's syndrome, the hypothalamic–pituitary–adrenal axis has lost its ability for self-regulation. Thus, the impaired hypothalamic–pituitary–adrenal axis function may result from an excessive secretion of either ACTH or cortisol and from the loss of the negative feedback function [67].

Cushing's syndrome is a rare entity; its overall incidence is approximately two to five new cases per million people per year. Characteristically, in older children, a female predominance has been described that decreases with younger age and seems to switch to a male predominance in infants and young toddlers [67, 85, 109].

Although both exogenous and endogenous causes can induce Cushing's syndrome, the former are certainly more common in children. In particular, exogenous or iatrogenic causes might result from chronic administration of glucocorticoids or ACTH (such as in the treatment of many nonendocrine diseases including neoplastic, hematologic, pulmonary, autoimmune, epileptic, and dermatologic disorders). Among the endogenous causes of Cushing's syndrome in children, ACTH overproduction from the pituitary (called Cushing's disease) is the most common, and results from an ACTH-secreting pituitary microadenoma or, rarely, a macroadenoma. Cushing's disease is more common in children older than 7 years of age, accounting for approximately 75 % of all cases of Cushing's syndrome in this age group. By contrast, in children younger than 7 years adrenal causes of Cushing's syndrome (adenoma, carcinoma, or bilateral hyperplasia) are the most frequent. Ectopic ACTH/CRH production occurs rarely in young children and adolescents, and for some forms they have never been described in young children [85, 104, 105, 109]. A few additional rare diseases, such as primary pigmented adrenocortical nodular disease (PPNAD), massive macronodular adrenal hyperplasia (MMAD), McCune–Albright syndrome, might be related to Cushing's syndrome in childhood. PPNAD is a genetic disorder and the majority of cases are associated with Carney complex, a syndrome of multiple endocrine abnormalities in addition to lentigo and myxomas. Periodic, cyclical, or otherwise atypical Cushing's syndrome is often documented in children and adolescents with PPNAD. MMAD is another rare bilateral disease that leads to Cushing's syndrome [105]. In children with MMAD, the adrenal glands are massively enlarged, with multiple huge nodules that are typical yellow-to-brown cortisol-producing adenomas. Data have shown that in some

patients with MMAD, cortisol levels seem to increase with food ingestion (food-dependent Cushing's syndrome), which might result from an aberrant expression of the gastric inhibitory polypeptide receptor in the adrenal glands. In the majority of patients with MMAD, however, the disease does not appear to be gastric inhibitory polypeptide receptor dependent.

In children with McCune–Albright syndrome, adrenal adenomas or, more frequently, bilateral macronodular adrenal hyperplasia can also be seen [30, 53]. In this syndrome, there is a somatic mutation of the *GNAS1* gene leading to constitutive activation of the Gsα protein and continuous, non-ACTH-dependent activation of steroidogenesis by the adrenal cortex.

The treatment of choice varies according to the underlying cause [49, 85, 104, 105, 109]. Transsphenoidal surgery (TSS) with or without irradiation of the pituitary gland represents the treatment of choice for almost all patients with ACTH-secreting pituitary adenomas (Cushing's disease). Surgical resection with or without radiotherapy is also the treatment of choice for benign adrenal tumors. The treatment of choice in bilateral micronodular or macronodular adrenal disease, such as PPNAD and MMAD, is usually bilateral total adrenalectomy. In addition, in subjects with Cushing's disease or ectopic ACTH-dependent Cushing's syndrome in whom surgery or radiotherapy has failed, or in whom the tumor has not been localized, adrenalectomy is a potential treatment. Finally, pharmacotherapy is also an option if surgery fails for Cushing's disease or in ectopic ACTH secretion where the source cannot be identified. Several molecules can be used, such as mitotane, aminoglutethimide, metyrapone, trilostane, and ketoconazole, which may act by: inhibiting the biosynthesis of corticosteroids by blocking the action of 11-β-hydroxylase and cholesterol side chain cleavage enzymes; destroying adrenocortical cells that secrete cortisol; blocking the conversion of cholesterol to pregnenolone in the adrenal cortex; inhibiting the synthesis of cortisol, aldosterone, and androgens; preventing the conversion of 11-deoxycortisol to cortisol; inhibiting the conversion of pregnenolone to progesterone; or blocking adrenal steroidogenesis.

Although the treatment of choice varies according to the underlying cause of Cushing's syndrome or disease, the hypothalamic–pituitary–adrenal axis is often negatively affected [49, 85, 104, 105, 109]. Hypopituitarism is the most common adverse effect, and it is more frequent when surgery precedes radiotherapy. In addition, after the completion of successful TSS in Cushing's disease or excision of an autonomously functioning adrenal adenoma, there will be a period of adrenal insufficiency while the hypothalamic–pituitary–adrenal axis recovers. Therefore, in this situation glucocorticoids might be replaced. Treatment is aimed at restoring physiological changes, with a usual replacement dose of 12–15 mg/m^2/day two or three times daily [63]. In addition, in the immediate postoperative period, cortisol treatment should be started initially at stress doses of glucocorticoids and then weaning relatively rapidly to a physiological replacement dose.

According to the underlying alteration, glucocorticoid replacement might be temporarily adopted only for a short period [49, 85, 104, 105, 109]. Thereafter, patients should be closely followed up with a systematic assessment of the adrenocortical function. Clinicians might consider discontinuing glucocorticoid

treatment if normal responses to a 1-h ACTH test are documented (cortisol level over 18 μg/dl at 30 or 60 min after ACTH stimulation) [49, 85, 104, 105, 109].

In children with unilateral adrenalectomy as in patients with Cushing's disease post-TSS, a similar replacement regimen is needed for a single adrenocortical tumor. By contrast, for those who have undergone bilateral adrenalectomy, lifetime replacement with both glucocorticoids (as described previously) and mineralocorticoids (fludrocortisone 0.1–0.3 mg daily) is needed. In these patients, too, glucocorticoids at stress doses are needed immediately postoperatively, with a relatively quick weaning to physiological replacement doses. In addition, for temporary and permanent adrenal insufficiency, acute illness, trauma, or surgical procedures, stress doses must be adopted in all patients [49, 85, 104, 105, 109].

Replacement Therapy in Young Patients with Impaired Adrenal Function

The main aim of treatment of adrenal insufficiency in childhood is to restore the impaired hypothalamic–pituitary–adrenal axis, without impairing growth while allowing for normal pubertal development and fertility. In addition, in subjects with congenital adrenal hyperplasia a proper suppression of androgen production is needed to minimize the peripheral effects of hyperandrogenism secretion.

The available evidence suggests that conventional treatment of patients with hypoadrenalism may result in adverse effects on some surrogate markers of disease risk, such as a lower bone mineral density, than in age- and sex-matched controls, and in increased postprandial glucose and insulin concentrations. Although the quality of life of patients with hypoadrenalism may be impaired, there is no evidence of an improvement with higher doses of steroids, although quality of life is better if the hydrocortisone dose is split up, with the highest dose taken in the morning. Thus the evidence suggests that most patients may safely be treated with a low dose of glucocorticoids in two or three divided doses, along with education about the appropriate course of action in the event of intercurrent illnesses.

The glucocorticoid of choice in childhood is hydrocortisone, which is short acting and hence has the lowest growth-suppressing effect (Table 2) [48, 101]. During infancy, especially in subjects needing an initial reduction of markedly elevated adrenal sex hormones, up to 25 mg of hydrocortisone/m^2 may be required. This is more than the daily physiological secretion of 7–9 mg/m^2 in newborns and 6–8 mg/

Table 2 Suggested maintenance therapy for growing patients

Medication	Total dose	Daily doses
Hydrocortisone	15–25 (mg/m^2/day)	Three times per day
Fludrocortisone	0.05–0.2 (mg/m^2/day)	One to two times per day
Sodium chloride supplements	1–3 g/day (1,751 mEq/day)	Divided in several feeding

m^2 in older infants and children [48, 101]. Hydrocortisone oral suspension is not recommended [73]; divided or crushed tablets of hydrocortisone should be used in growing children. Cortisone acetate requires conversion to cortisol for bioactivity [82]; thus hydrocortisone is considered the drug of first choice. To mimic the circadian cortisol secretion, the daily hydrocortisone dose is divided into two or three doses, with administration of one half to two thirds of the total daily dose in the morning. The short elimination half-life of hydrocortisone (approximately 1.5 h) when given in traditional immediate-release preparations, however, leads to high peaks with low values in between. A twice-daily regimen with administration of the second dose 6–8 h after the morning dose is recommended. The timing of the second dose may be changed slightly according to the patient's activities. Some authors postulate that a thrice-daily administration is more beneficial [2, 6, 43, 59, 87], although there is no hard evidence available yet to support this. Whereas hydrocortisone is preferred during infancy and childhood, longer-acting glucocorticoids may be recommended at or near the completion of linear growth, such as in older adolescents or young adults (Table 3). Prednisone and prednisolone should be given twice daily [48, 101]. Prednisolone may be preferable since it is the active drug. The dose (2–4 mg/m^2/day) should be one-fifth that of hydrocortisone. The dosage of dexamethasone is 0.25–0.5 mg/m^2/day given once daily. These steroids have minimal mineralocorticoid effects compared with hydrocortisone. In children with advanced bone age, such as in boys with non-salt-losing CAH, initiation of therapy may precipitate central precocious puberty, requiring additional treatments, such as with a GnRH agonist. In some children with treatment refractory to hydrocortisone, long-acting glucocorticoids may be effective [91]. In symptomatic patients with non-classic-CAH, treatment with glucocorticoids is recommended. In these patients, chronic steroid treatment may suppress the hypothalamic–pituitary–adrenal axis, so they require stress dosing during surgery or severe illness. For asymptomatic patients with non-classic-CAH, hydrocortisone treatment is not required during stress [101]. All patients with classic CAH require mineralocorticoid replacement with fludrocortisone at a dose of 0.05–0.2 mg/day. The dose is slightly higher (up to 0.3 mg/day) in newborns and small infants because of their increased metabolism and end-organ resistance to mineralocorticoids. Such therapy will reduce vasopressin and ACTH levels and lower the dosage of glucocorticoid required. The need for continuing mineralocorticoids should be assessed based on plasma renin activity (PRA) and blood pressure [47]. Although aldosterone levels are normal in patients with NSW CAH, these patients also benefit from mineralocorticoid replacement as

Table 3 Suggested maintenance therapy for fully grown patients

Type of long-acting glucocorticoids	Suggested dose (mg/day)	Daily doses (mg/day)
Hydrocortisone	15–25	Two to three times per day
Prednisone	5–7.5	Two times per day
Prednisolone	0.25–0.5	Two times per day
Dexamethasone	5–50	Once daily
Fludrocortisone	0.05–0.2	Once daily

it helps to decrease the dose of glucocorticoid required to suppress androgens. Hence, published guidelines recommend that all children with classic CAH be treated with fludrocortisone [48, 101]. Owing to the obligatory urinary sodium loss, sodium chloride supplementation should be provided to infants. Sodium chloride supplements are often needed in infancy at 1–3 g/day (17–51 mEq/day; 1 g = 17 mEq of sodium), divided with each feed [48, 76, 101]. Older infants and children generally do not require salt supplementation.

Glucocorticoid Adjustment Issues

Maintenance dosing of glucocorticoids for replacement therapy is based on the need to reproduce the secretory rate of cortisol in the intact system. During severe illness and stress, the activity of the hypothalamic–pituitary–adrenal axis is significantly enhanced, resulting in a considerable rise of cortisol release from the adrenal cortex [4, 36]. Therefore, owing to the relevant changes of glucocorticoid synthesis in different clinical settings, glucocorticoid replacement doses need to be constantly adjusted accordingly. In 2008, a consensus statement for recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients was published [45, 68]. By contrast, agreement among intensive care and endocrinology specialists is low for the pediatric population, especially regarding diagnostic criteria and the prevalence of adrenal insufficiency associated with critical illness [71, 99]. Pediatric endocrinologists are often required to provide consultation regarding suspected adrenal insufficiency in critically ill children. Although acute adrenal insufficiency is rare, it is a life-threatening condition. Thus early diagnosis is key for effective and life-saving treatment of affected patients. All patients and their partners or relatives must receive crisis prevention training, including a steroid emergency card/bracelet and detailed instructions on stress-related dose adjustment to ensure that medical providers know about their underlying disorder. In addition, an emergency kit must be provided (e.g., 100 mg hydrocortisone-21-hydrogensuccinate) for traveling abroad; alternatively, prednisolone or other corticosteroid preparations can be used in emergency conditions if hydrocortisone is not readily available (Table 4).

Table 4 Recommendations for patients with chronic adrenal failure

Emergency card/bracelet
Education of patient and partner:
Rationale for dose adjustments in stress
Discussion of typical situations requiring dose adjustment (e.g., fever, surgery, trauma)
Nausea, vomiting, and diarrhea as reasons to use parenteral hydrocortisone
Signs and symptoms of emerging adrenal crisis
Provision of a hydrocortisone ampule (e.g., 100 mg hydrocortisone 21-hydrogensuccinate) to the patient for emergency use by attending physician

The cortisol secretory rate increases substantially during physiological stress. Consequently, the complex events that can occur in the setting of an adrenal crisis, mainly characterized by hypoglycemia, hypotension, and even cardiovascular collapse, need to be prevented in patients with adrenal insufficiency (primary or secondary) by adequately educating patients and parents to increase glucocorticoid doses during stress. Although this approach is universally adopted, there is controversy as to what constitutes "stress" and the need to increase glucocorticoid doses. However, the correct definition of a "stressing condition" is of paramount importance for a properly balanced glucocorticoid therapy, thus avoiding preventable episodes of adrenal insufficiency crisis or over-dosages and their associated side effects. If the children act and appear well, they might not require a stress-dose steroid regimen during mild stresses such as immunizations, uncomplicated viral illnesses, and upper respiratory tract infections with sore throat, rhinorrhea, and/or low-grade fever and otitis media. By contrast, clinical conditions such as those accompanied by fever (≥38 °C), vomiting, diarrhea, lethargy, inadequate oral intake, trauma, dental procedures, surgery, and large burns must be considered as "severe stresses," thus requiring an appropriate increase of glucocorticoid doses. In addition, physical exercise and especially moderate to extreme schedules of exercise are also considered "stress" and thus may require glucocorticoid dose increases.

A common recommendation is to treat most stresses that require increased doses with hydrocortisone 30–50 mg/m^2/day (approximately doubling or tripling the daily dose) divided into three or four daily doses [26, 48, 58, 60, 99], with higher doses to cover more severe illnesses or surgical procedures.

Parenteral glucocorticoid administration is indicated for those children who are unable to tolerate oral maintenance or stress doses during an illness. Parents need to be instructed to start at home using 50 mg/m^2 of intramuscular hydrocortisone sodium succinate, which seems to provide coverage for ≈ 6–8 h. If glucocorticoids are administered intramuscularly, a consultation with a health-care provider is recommended and emergency evaluation and treatment with intravenous hydrocortisone should be undertaken if the child's condition does not improve or if it worsens.

Although it is accepted that patients with hypoadrenalism may also adjust glucocorticoid replacement therapy during moderate to extreme physical activity, the amount of increase is still under debate. The degree to which doses should be increased is also debated, with recommendations varying between two and ten times the maintenance rate [60]. Although some authors postulate that moderate to extreme physical exercise may be facilitated by a slight increase (≈30 %) in hydrocortisone dosage 60 min before exercise [4], there is no evidence to support this. In addition, in a randomized, double-blind crossover study of nine adolescents with congenital adrenal hyperplasia, Weise et al. showed that an additional morning dose of hydrocortisone, which resulted in doubling of cortisol levels, just before short-term high-intensity exercise did not have an effect on blood levels of glucose, lactate, or free fatty acids, on exercise capacity, or on peak blood pressure response [114]. The peak heart rate was marginally (but statistically significantly) higher following the extra dose of hydrocortisone (mean 193 vs. 191 beats/min). Of the nine patients, one correctly

identified the session at which he had received the extra dose of hydrocortisone, three identified the wrong session, and five said they did not notice a difference. In their consensus statement on congenital adrenal hyperplasia, the Lawson Wilkins Pediatric Endocrine Society and European Society for Paediatric Endocrinology did not recommend increasing the glucocorticoid dose during psychological and emotional stress [48]. Therefore, although the topic is still open to discussion, it is important to state that young subjects should be advised not to take extra doses of hydrocortisone regularly (especially for day-to-day physical or psychological stressors), in order to minimize the long-term effects of chronic high-dose glucocorticoids. During hospitalization, major trauma, or surgery, intravenous hydrocortisone should be administered at a dosage of 50–100 mg/m^2/day divided into four doses (a bolus dose of 25 mg in neonates, infants, and preschool children, 50 mg in school-age children, and 100 mg in adults followed by three to four times the maintenance daily dose divided every 6 h) [101]. Hydrocortisone has mineralocorticoid activity at stress doses of 50 mg/m^2, hence mineralocorticoid supplementation is not required.

Surgical or trauma patients may receive rectal, intramuscular, or intravenous hydrocortisone. Intravenous bolus and subsequent dosage guidelines are as follows: for children younger than 3 years, 25 mg followed by 25–30 mg/day; for children 3–12 years of age, 50 mg followed by 50–60 mg/day; and for adolescents and adults, 100 mg followed by 100 mg/day [48, 101]. The most severe stresses, such as major surgery or sepsis, are often treated more aggressively, with dosages up to 100 mg/m^2 per day in divided doses every 6 h intravenously [99]. Although various glucocorticoid preparations could be used for stress dosing, hydrocortisone is the preferred agent because of its mineralocorticoid activity. Stress doses are administered for only 24–48 h unless the underlying illness is prolonged. Before general anesthesia and surgery, parenteral hydrocortisone is also recommended. A preoperative dose of 50 mg/m^2 30–60 min before induction of anesthesia can be administered intravenously or intramuscularly. A second dose of 50 mg/m^2 can then be administered as a constant infusion or as an intravenous bolus divided every 6 h over the next 24 h. Intravenous or oral stress doses may be continued until the patient has recovered [99].

For older adolescents and young adults, recently published guidelines [45] need to be followed during surgery, dental procedures, delivery, and invasive procedures, and are summarized in Table 5.

Role of Associated Hormonal Deficiencies or Treatment

Several studies have shown the role of multiple pituitary hormone deficiencies and especially of impaired thyroid function in defining glucocorticoid therapy. Adrenal crisis can develop after initiation of thyroid hormone replacement in subjects with hypothyroidism and with an accompanied unrecognized adrenal insufficiency. Although the underlying mechanisms are not fully understood, it has been hypothesized that patients with hypothyroidism have reduced cortisol requirements secondary to a reduced metabolic rate in the presence of untreated hypothyroidism [39,

Table 5 Treatment during surgery, dental procedures, delivery, and invasive procedures for fully grown youths and young adults (from Husebye et al.)

Procedure	Preoperative needs	Postoperative needs
Major surgery with long recovery time	100 mg hydrocortisone i.m. just before anesthesia	Continue 100 mg hydrocortisone i.m. every 6 h until able to eat and drink. Then double oral dose for 48 h, then taper to normal dose
Major surgery with rapid recovery	100 mg hydrocortisone i.m. just before anesthesia	Continue 100 mg hydrocortisone i.m. every 6 h for 24–48 h. Then double oral dose for 24–48 h, then taper to normal dose
Labor and vaginal birth	100 mg hydrocortisone i.m. at onset of labor	Double oral dose for 24–48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery	100 mg hydrocortisone i.m. just before anesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives	Hospital admission overnight with 100 mg hydrocortisone i.m. and fluid, repeat dose before start of procedure	Double oral dose for 24 h, then return to normal dose
Other invasive procedures	100 mg hydrocortisone i.m. just before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental procedure	Extra morning dose 1 h before surgery	Double oral dose for 24 h, then return to normal dose
Minor procedure	Usually not required	Extra dose (e.g., 20 mg hydrocortisone) if symptoms are present

98]. Soon after thyroid hormone replacement therapy is started, the metabolic rate and cortisol requirements increase, resulting in an adrenal crisis. Similarly, cortisol metabolism is significantly increased in subjects with hyperthyroidism, thus resulting in an increased glucocorticoid requirement. Because of elevated cortisol clearance, it is suggested to increase cortisol replacement as much as twofold in individuals with hyperthyroidism and adrenal insufficiency [4].

Studies have shown that growth hormone treatment can affect cortisol levels. By inhibiting 11-β-HDS-1 activity in the liver, growth hormone treatment can result in decreased conversion of inactive cortisone to active cortisol [35]. Therefore, in subjects with secondary adrenal insufficiency requiring growth hormone therapy, signs and symptoms of adrenal insufficiency need to be monitored and glucocorticoid therapy increased accordingly. In addition, in children with anatomic abnormalities of the pituitary or stalk on magnetic resonance imaging, or with organic causes (e.g., cranial surgery, tumors, trauma) and/or multiple anterior pituitary hormone deficiencies, the hypothalamic–pituitary–adrenal axis should be evaluated. Similar considerations apply for children with cranial radiation, septo-optic dysplasia, autoimmune hypophysitis, PROP-1 deficiency, and head trauma [8, 15, 83]. If indicated, periodic reassessment of previously normal hypothalamic–pituitary–adrenal function should be considered in patients with organic hypopituitarism.

Hypothalamic–pituitary–adrenal function needs to be evaluated in children who receive medication able to affect cortisol biosynthesis, such as drugs that accelerate (i.e., phenytoin, barbiturates, and rifampin) [4, 99] or inhibit (i.e., aminoglutethimide, etomidate, ketoconazole, metyrapone, medroxyprogesterone, and megestrol) [27, 99] cortisol metabolism.

Lastly, but no less important, the hypothalamic–pituitary–adrenal axis should be explored in children and adolescents who have discontinued long-term glucocorticoid treatment. Chronic administration of synthetic glucocorticoids leads to feedback inhibition of endogenous cortisol secretion and may eventually induce adrenal insufficiency, with weakness, fatigue, or nausea. In these subjects, signs of adrenal insufficiency might particularly occur during stress after therapy is discontinued, due to an insufficient capacity of the adrenals to respond to stress. Recovery of the hypothalamic–pituitary–adrenal axis usually occurs within weeks after short-term (up to 3 months) therapy, but may occasionally take many months [40, 80, 95].

Pregnancy

Pregnancy and especially its related hormonal and metabolic changes represent a physiological condition requiring glucocorticoid adjustment in subjects. Owing to the effects of estrogen on liver, pregnancy is physiologically associated with a gradual and pronounced increase in corticosteroid-binding globulin production, which in turns results in increased levels of free cortisol levels, particularly during the last trimester. Additional factors such as the placental synthesis and release of biologically active CRH and ACTH, increased ACTH responsiveness, pituitary desensitization to cortisol feedback, and enhanced pituitary responses to corticotropin-releasing factors [62, 106] represent determinant contributors of the progressive free cortisol rise during pregnancy, up to twofold [1, 62, 106]. Thus, during pregnancy hydrocortisone doses might be increased by 50 % [4]. However, although physiological requirements increase during pregnancy, the need for hydrocortisone replacement dose adjustment during the last trimester is still debated. In single case reports, adrenal crisis due to insufficient dose adaptation during pregnancy has been observed. Therefore, we recommend close supervision and favor an increase in the glucocorticoid replacement dose by up to 50 % during the last trimester. In addition, a recent consensus statement in subjects with primary adrenal insufficiency recommended administering 100 mg of hydrocortisone intramuscularly at onset of labor, continuing with a double oral dose for 24–48 h after delivery and followed by rapid tapering [45].

Newer Formulations of Hydrocortisone

In some subjects treated with hydrocortisone, the replacement therapy often does not fully replicate the normal circadian pattern of cortisol secretion, thus significantly affecting disease control. Therefore, during the past few decades researchers

attempted to overcome this issue by formulating new preparations of hydrocortisone, such as continuous subcutaneous infusion or modified-release hydrocortisone (MR-HC; Chronocort®), with promising preliminary results.

In a pilot study of adults, continuous subcutaneous hydrocortisone infusion was shown to properly restore the physiological circadian variation, resulting in a significant decrease of glucocorticoid daily doses [65]. Hydrocortisone infusion was not associated with major side effects and was linked to an improvement in subjective health status. Similarly, continuous subcutaneous infusion of hydrocortisone in a circadian pattern was able to achieve good disease control in a poorly controlled pubertal boy on high-dose oral treatment [17]. Results of phase II trials in the USA have shown that bedtime dosing of Chronocort® more closely mimics the physiological secretion pattern of cortisol and decreases morning 17-hydroxyprogesterone levels [113].

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