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Current and novel approaches to children and young people with congenital adrenal hyperplasia and adrenal insufficiency

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Congenital adrenal hyperplasia (CAH) represents a group of autosomal recessive conditions leading to glucocorticoid deficiency. CAH is the most common cause of adrenal insufficiency (AI) in the paediatric population. The majority of the other forms of primary and secondary adrenal insufficiency are rare conditions. It is critical to establish the underlying aetiology of each specific condition as a wide range of additional health problems specific to the underlying disorder can be found. Following the introduction of life-saving glucocorticoid replacement sixty years ago, steroid hormone replacement regimes have been refined leading to significant reductions in glucocorticoid doses over the last two decades. These adjustments are made with the aim both of improving the current management of children and young persons and of reducing future health problems in adult life. However despite optimisation of existing glucocorticoid replacement regimens fail to mimic the physiologic circadian rhythm of glucocorticoid secretion, current efforts therefore focus on optimising replacement strategies. In addition, in recent years novel experimental therapies have been developed which target adrenal sex steroid synthesis in patients

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with CAH aiming to reduce co-morbidities associated with sex steroid excess. These developments will hopefully improve the health status and long-term outcomes in patients with congenital adrenal hyperplasia and adrenal insufficiency.

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Adrenal steroidogenesis

The cells forming the adrenal cortex originate from the intermediate mesoderm and differentiate under the influence of various transcription factors during pregnancy and postnatal life. During foetal life and up to 12 months of age, two distinct zones are evident, an inner prominent foetal zone and an outer definitive zone that differentiates into the adult adrenal gland. After birth, the foetal zone regresses and the definitive zone, which contains an inner zona fasciculata and an outer zona glomerulosa, proliferates. The innermost zone, the zona reticularis, becomes evident after 2 years of life. These form three major functionally distinct parts of the adrenal cortex: the outer zona glomerulosa synthesizes mineralocorticoids, the middle zona fasciculata produces glucocorticoids, and the inner zona reticularis synthesises the androgen precursors dehydroepiandrosterone (DHEA) and androstenedione.

Glucocorticoid synthesis is negatively controlled by a feedback loop via the hypothalamus-pituitary-adrenal axis. A variety of central stimuli lead to the circadian and stress related secretion of corticotropin-releasing hormone stimulating the cleavage of polypeptide proopiomelanocortin (POMC) by prohormone convertase. This results in adrenocorticotropic hormone (ACTH) release from corticotroph cells of the anterior pituitary. ACTH is the key regulator of cortisol synthesis and has additional short-term effects on mineralocorticoid and adrenal androgen synthesis [1].

ACTH binds to its adrenal receptor (melanocortin receptor 2, MC2R) and stimulates the rapid import of cholesterol into the mitochondrion by steroidogenic acute regulatory protein (StAR). In parallel, the transcription of steroidogenic genes (*CYP11A1, HSD3B2, CYP17A1, CYP21A2, CYP11B1*) and co-factors relevant to glucocorticoid synthesis increases. Corticotropin-releasing hormone and subsequently ACTH are released in a pulsatile fashion. Following the pattern of ACTH secretion, adrenal cortisol secretion exhibits a distinct circadian rhythm, with peak concentrations in the morning and low concentrations in the late evening hours [2].

Mineralocorticoid synthesis is mainly controlled by the renin-angiotensin-system and a potassium feedback loop. Renin secretion from the renal juxtaglomerular cells are stimulated by a variety of factors with renal arterial perfusion (closely correlating with renal arterial pressure) being the most important regulator. Non-endocrine conditions affecting renal blood flow have significant pathophysiologic consequences on the renin-angiotensin-system. The rate limiting step of the renin-angiotensin-system is the secretion of renin. Angiotensinogen is converted by renin to angiotensin I, which itself is converted by angiotensin converting enzyme to Angiotensin II, a potent stimulator of aldosterone synthesis and secretion [2].

The distinct regulation of glucocorticoid and mineralocorticoid biosynthesis has important clinical consequences for the differential diagnosis and management of adrenal insufficiency (AI). Secondary AI manifests with isolated glucocorticoid deficiency, whereas most classic forms of primary adrenal insufficiency (PAI) have signs and symptoms of combined glucocorticoid and mineralocorticoid deficiency. Classic familial glucocorticoid deficiency characterised by unresponsiveness of the adrenal to ACTH leading to isolated glucocorticoid deficiency represents an exception.

Clinical presentation

The epidemiology of AI in children and adolescents is different to the situation during adulthood. The majority of cases in paediatrics are either due to genetic causes, most commonly due to congenital adrenal hyperplasia (CAH), a group of recessively inherited disorders of adrenal steroid biosynthesis

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leading to variable degree of glucocorticoid deficiency or caused by iatrogenic treatment. Secondary AI is most frequently due to discontinuation of glucocorticoids or to stress during treatment with suppressive doses of glucocorticoids for a variety of disorders. Autoimmune adrenalitis as commonly seen in adults is rare in childhood, with the prevalence only increasing during the second half of the second decade of life [3].

The clinical presentation of AI is non-specific often leading to a delay in establishing the diagnosis. The onset and severity of AI is variable and age dependent according to the underlying diagnosis. Clinical signs and symptoms of primary AI are characterised by the loss of both glucocorticoid and mineralocorticoid synthesis whereas secondary AI manifests with isolated glucocorticoid deficiency as the adrenal itself is intact and mineralocorticoid synthesis and regulation is therefore unaffected (Table 1).

The main cause of primary AI in childhood is CAH, which occurs with an incidence of about 1:10,000 to 1:15,000 live births in most populations [4]. Depending on the deficiency within the steroidogenic pathway different constellations of additional steroid hormone deficiencies and excess can be observed (Table 2). Variants of CAH in which androgen excess is a key feature, include 21-hydroxylase (CYP21A2), 11β-hydroxylase (CYP11B1) and 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) deficiencies. Types of CAH associated with sex steroid deficiency and AI, include deficiencies of steroidogenic acute regulatory protein (StaR), P450 side-chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), 17α-hydroxylase (CYP17A1), and P450 oxidoreductase (POR). When making the diagnosis of CAH knowing the genetic aetiology enables the physician to tailor treatment accordingly. The most common CAH form is (21OHD) caused by mutations in the *CYP21A2* gene. Thus, the principle focus of this review is therefore the management of patients with 21OHD.

Steroid 21-hydroxylase facilitates the conversion of 17-hydroxyprogesterone to 11-deoxycortisol, and progesterone to deoxycorticosterone, respective precursors for cortisol and aldosterone [5]. Approximately 75% of cases of 21OHD are unable to synthesize sufficient aldosterone and suffer from clinically apparent renal salt loss [6]. Impaired cortisol biosynthesis leads to reduced negative feedback towards the hypothalamus and pituitary and results in increased corticotropin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) secretion. Elevated CRH and ACTH concentrations stimulate adrenal hyperplasia and a rise in adrenal androgen production [6]. The clinical consequences of CAH therefore result from cortisol and aldosterone insufficiency and from sex steroid excess. Medical treatment aims to replace the deficient hormones and to limit exposure to androgen excess. Individuals affected by CAH require lifelong care. During childhood the aims of treatment are to prevent adrenal crisis, support the family with decisions regarding gender assignment, optimise linear growth, body composition, cardiovascular and bone health and ensure normal progression through puberty.

Table 1
Signs and symptoms of adrenal insufficiency.

Glucocorticoid deficiency	Mineralocorticoid deficiency (only PAI)
Conjugated jaundice	Poor feeding
Fatigue, lack of energy	Vomiting, nausea, abdominal pain
Weight loss, anorexia	Failure to thrive
Myalgia, joint pain	Dehydration
Fever	Dizziness, postural hypotension
Anaemia, lymphocytosis, eosinophilia	Salt craving
Slightly increased TSH	Low blood pressure, postural hypotension
Hypoglycaemia	Increased serum creatinine (volume depletion)
Increased Insulin sensitivity	Hyponatraemia, hyperkalaemia
Low blood pressure, postural hypotension	Urinary salt loss
Hyponatraemia (loss of feedback inhibition of AVP release)	Hypovolaemic shock
Apnoe	

Hyperpigmentation occurs in PAI only and is caused by excess of proopiomelanocortin (POMC)-derived peptides.
Alabaster-coloured pale skin occurs in secondary AI only caused by deficiency of POMC-derived peptides; rare in children.
Decreased pubic and axillary due to adrenal androgen deficiency in females.

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Table 2
Differential diagnosis and clinical presentation of different forms of steroidogenic adrenal insufficiency.

Enzyme	DSD	Affected organ	Deficiency	Excess
CYP21A2	46,XX	Adrenal	MC, GC	SexH
CYP11B1	46,XX	Adrenal	GC	MC, SexH
CYP17A1	46,XY	Adrenal, gonad	GC, SexH	MC
HSD3B2	46,XY (46XX)	Adrenal, gonad	MC, GC, SexH	
POR	46,XY + 46,XX	Adrenal, gonad, liver	GC, SexH	(MC)
StAR	46,XY	Adrenal, gonad	MC, GC, SexH	
CYP11A1	46,XY	Adrenal, gonad	MC, GC, SexH	
CYP11B2	–	Adrenal	MC	

CYP21A2: 21-hydroxylase, CYP11B1: 11β-hydroxylase, CYP17A1: 17α-hydroxylase, HSD3B2: 3β-hydroxysteroid dehydrogenase type 2, POR: P450 oxidoreductase, StAR: steroidogenic acute regulatory protein, CYP11A1: P450 side chain cleavage enzyme, CYP11B2: aldosterone synthase. DSD: disorder of sex development, MC: mineralocorticoid, GC: glucocorticoid, SexH: sex steroid hormone.

Diagnosis

The most appropriate diagnostic workup in a child presenting with symptoms suggestive of a diagnosis of AI in childhood will be dictated by the age of the child and their clinical presentation. CAH is the commonest form of primary adrenal insufficiency in infants and children, being identified most commonly in the neonatal period. From school age onwards AI due to X-linked adrenoleukodystrophy becomes more common with autoimmune adrenalitis presenting towards the end of the second decade of life. There is, however, no clear age limit and non-classic and late-onset forms of congenital conditions might have to be considered throughout life in unexplained cases. A thorough clinical assessment is required in all children and adolescents presenting with signs and symptoms suggestive of AI, as other endocrine systems including the hypothalamus, pituitary and gonad as well as other organ systems might be affected. It is important to recognize that AI represents one component of a specific condition, the underlying aetiology of which is important to identify as it can be associated with other significant health problems. It is key in the diagnostic work-up to establish if the adrenal insufficiency is of primary (Table 3) or secondary origin (Table 4).

Congenital adrenal hyperplasia diagnostic pathway

A wide range of clinical manifestations of 21-hydroxylase deficiency exists and these can be described as a disease continuum. About two-thirds of patients with 21OHD have clinically significant aldosterone deficiency leading to renal salt loss in addition to cortisol deficiency. In utero cortisol deficiency stimulates ACTH production, which leads to accumulation of steroid precursors and adrenal androgens. Whilst female infants with a severe enzymatic defect therefore frequently present early in the neonatal period with ambiguous genitalia, male infants appear normal and are thus more difficult to diagnose. Many countries have therefore implemented newborn screening programs aiming to reduce the morbidity and mortality associated with a delayed diagnosis of CAH. Screening programs measure 17-hydroxyprogesterone (17OHP) in filter paper blood spots obtained by a heel puncture between 2 and 4 days after birth [7]. However due to concerns regarding the high false positive rate associated with the existing screening test not all countries have added 17OHP into their screening programs, and in these regions the diagnosis needs to be pursued in all infants in whom there are clinical concerns.

The diagnostic pathway for virilised females, most commonly identified soon after birth before life-threatening salt-loss manifests, is outlined in the Chicago consensus statement [8]. In all children presenting with ambiguous genitalia aged less than 3 days of life rapid fluorescence *in-situ* hybridisation for sex-determining region of the Y chromosome (SRY) should be performed. The diagnosis in boys is usually only established once the patient clinically presents with salt-loss. Salt-wasting should be suspected in infants presenting with poor feeding, vomiting, failure to thrive, lethargy and sepsis like symptoms. The crisis can quickly deteriorate and lead to life-threatening hypovolaemic shock and consequently death. In all children presenting clinically with features suggestive of a diagnosis of CAH

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Table 3
Aetiologies of primary adrenal insufficiency in children.

Condition/deficiency	Gene	OMIM	Associated clinical signs and symptoms
Impaired steroidogenesis			
Impaired cholesterol transport			
Steroidogenic acute regulatory protein (Congenital lipoid adrenal hyperplasia; CLAH)	*StAR*	201710	46,XY DSD, gonadal insufficiency
Steroidogenic enzyme/co-factor deficiency causing Congenital adrenal hyperplasia (CAH)			
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2*	201810	46,XX and 46,XY DSD, gonadal insufficiency
21-hydroxylase	*CYP21A2*	201910	46,XX DSD, hyperandrogenism
11β-hydroxylase	*CYP11B1*	202010	46,XX DSD, arterial hypertension
CYP17A1 deficiency	*CYP17A1*	202110	46,XY DSD, arterial hypertension, gonadal insufficiency
P450 oxidoreductase	*POR*	201750	46,XX and 46,XY DSD, gonadal insufficiency, bone malformation, affects all endoplasmic CYP450 enzymes
Steroidogenic enzyme deficiency (non CAH)			
P450 side-chain cleavage enzyme	*CYP11A1*	118485	46,XY DSD, gonadal insufficiency
Aldosterone synthase	*CYP11B2*	124080	Isolated mineralocorticoid deficiency
Defects of cholesterol synthesis/metabolism			
Wolman disease (lysosomal acid lipase deficiency, cholesterol ester storage disease)	*LIPA*	278000	Diffuse punctate adrenal calcification, xanthomatous changes in liver, adrenal, spleen, lymph nodes, bone marrow, small intestine, lungs and thymus, and slight changes in skin, retina, and central nervous system, hypercholesterolaemia, steatorrhoea, poor prognosis
Smith-Lemli Opitz disease	*DHCR7*	270400	Mental retardation, craniofacial malformations, limb abnormalities, growth failure
Abeta-lipoproteinaemia	*MTP*	200100	Ataxia, retinopathy, acanthocytosis, fat malabsorption
Familial hypercholesterolaemia	*LDLR*	143890	Tendinous xanthomas, xanthelesma, corneal arcus
Adrenal dysgenesis			
Without syndromic features			
X-linked adrenal hypoplasia congenital (AHC)	*NROB1* (DAX1)	300200	Combined primary and secondary hypogonadism, DMD in contiguous gene syndrome
Adrenal hypoplasia steroidogenic factor-1 deficiency	*NR5A1* (SF1)	184757	46,XY DSD, gonadal insufficiency
With syndromic features			
IMAGe syndrome	*CDKN1C*	300290	Intrauterine growth retardation, metaphyseal dysplasia, adrenal insufficiency, genital anomalies
Pallister-Hall syndrome	*GLI3*	165240	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly
Meckel syndrome	*MKS1*	249000	Central nervous system malformation, polycystic kidneys with fibrotic liver changes, polydactyly
Pena-Shokeir syndrome 1	*DOK7* *RAPSN*	208150	Arthrogryposis, foetal akinesia, IUGR, cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, pterygia of the limbs
Pseudotrisomy 13		264480	Holoprosencephaly, severe facial anomalies, postaxial polydactyly, various other congenital defects, and normal chromosomes
Hydrolethalus syndrome	*HYLS1*	236680	Severe prenatal onset hydrocephalus, polydactyly
Galloway-Mowat syndrome		251300	Early-onset severe encephalopathy, intractable epilepsy, nephrotic syndrome, microcephaly, hiatal hernia
ACTH resistance			
Familial glucocorticoid deficiency (FGD) Type 1	*MC2R*	202200	Tall stature, isolated deficiency of glucocorticoids, generally normal aldosterone production
Familial glucocorticoid deficiency (FGD) Type 2	*MRAP*	607398	Isolated deficiency of glucocorticoids, generally normal aldosterone production
Impaired redox homeostasis			
Triple A syndrome (Allgrove syndrome)	*AAAS*	231550	Alacrimia, achalasia; neurologic impairment, deafness, mental retardation, hyperkeratosis
Mitochondrial deficiency of free radical detoxification	*NNT*	614736	

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Table 3 (*continued*)

Condition/deficiency	Gene	OMIM	Associated clinical signs and symptoms
	TRXR2	606448	Isolated deficiency of glucocorticoids
	GPX1, PRDX3		Digenic inheritance has been shown in one patient with isolated glucocorticoid deficiency
Miscellaneous			
DNA repair defects	*MCM4*	609981	NK cell deficiency, growth failure, increased chromosomal breakage
Bioinactive ACTH	*POMC*	201400	
Adrenal destruction			
Inherited aetiologies			
Autoimmune adrenalitis			
Isolated autoimmune adrenalitis	Associated with HLA-DR3, CTLA-4		
Autoimmune polyglandular syndromes (APS)			
APS Type 1	*AIRE*	240300	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphomas
APS Type 2	Associated with HLA-DR3, CTLA-4	269200	Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anaemia
APS Type 4	Associated with HLA-DR3, CTLA-4		Other autoimmune diseases, excluding thyroid disease or diabetes (unusual in children)
Peroxisomal defects			
X-linked Adrenoleukodystrophy (X-ALD)	*ABCD1*	300100	Progressive neurodegeneration, behavioural changes, cognitive decline, loss of speech, hearing and vision, dementia, spasticity, seizures
Refsum disease	*PEX7*	266500	Least severe form of peroxisome biosynthesis defects
Neonatal adrenoleukodystrophy (Autosomal recessive)	*PEX1*	601539	Craniofacial abnormalities, and liver dysfunction, and biochemically by the absence of peroxisomes
Zellweger syndrome	*PEX1*	214100	Craniofacial abnormalities, hepatomegaly, severe mental retardation and growth failure, hypotonia, deafness, blindness, genitourinary abnormalities, stippled epiphyses
Kearns-Sayre syndrome	Mitochon-drial DNA deletions	530000	External ophthalmoplegia, retinal degeneration, and cardiac conduction defects; other endocrinopathies
Acquired aetiologies			
Haemorrhage			Bilateral adrenal haemorrhage of the newborn, Primary antiphospholipid syndrome, Anticoagulation
Trauma/surgery			Bilateral adrenalectomy
Infection			Septic shock, Meningococcal sepsis (Waterhouse-Frederichsen syndrome), Tuberculosis, Fungal infections (histoplasmosis, cryptococcosis, coccidiomycosis, blastomycosis), Cytomegalovirus, HIV-1
Infiltration			Metastatic cancers, Primary adrenal lymphoma, Amyloidosis, Sarcoidosis, Haemochromatosis
Drugs			Ketoconazole, Rifampicin, Phenytoin, Phenobarbital, Aminoglutethimide, Mitotane, Abiraterone, Etomidate, Suramine, Mifepristone

after day 3 of life plasma 17OHP, 11-deoxycortisol, and androstenedione concentrations should be measured [9]. Urinary steroid profile analysis is also an extremely helpful non-invasive test. A urine steroid profile can be performed on a spot urine sample and provides additional diagnostic evidence for CAH and helps to differentiate between the different forms of CAH [10,11]. Children without significant salt-loss may present later in life with signs of precocious pseudo-puberty including premature adrenarche/pubarche, acne, genital hyperpigmentation, growth acceleration, and advanced bone age. Most males have a testicular volume in the pre-pubertal range. However, CAH should be ruled out during the baseline assessment of patients with larger testicular volumes as secondary central

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Table 4
Aetiologies of secondary adrenal insufficiency in children.

Condition/deficiency	Gene	OMIM	Associated clinical signs and symptoms
Hypothalamic disorders			
Congenital aetiologies			
Septo-optic dysplasia (de Morsier Syndrome)	*HESX1*	182230	Combined pituitary hormone deficiency, optic-nerve hypoplasia, and midline brain defects
CRH deficiency			
Acquired aetiologies			
Steroid withdrawal syndrome			
Inflammatory disorders			Abscess, meningitis, encephalitis
Trauma			
Radiation therapy			Craniospinal irradiation in leukaemia, irradiation for tumours outside the hypothalamic–pituitary axis
Surgery			
Tumour			Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, and intrasellar or suprasellar metastases
Infiltrative diseases			Sarcoidosis, Histiocytosis X, haemochromatosis
Pituitary disorders			
Congenital aetiologies			
Aplasia/hypoplasia			
Multiple pituitary hormone deficiencies			
Prophet of PIT1	*PROP1*	262600	Additional deficiency of GH, PRL, TSH, LH/FSH
Lim homeobox gene 4	*LHX4*	262700	Additional deficiency of Growth hormone, TSH
SRY-box 3	*SOX3*	312000	
Isolated ACTH deficiency			
T-box factor 19 (*TPIT*)	*TBX19*	201400	Severe neonatal-onset adrenal insufficiency
Proopiomelanocortin	*POMC*	609734	Adrenal insufficiency, early-onset obesity, red hair pigmentation
Proprotein convertase 1	*PCSK1*	600955	Hypoglycemia, malabsorption, hypogonadotrophic hypogonadism
Acquired aetiologies			
Steroid withdrawal syndrome			Endogenous glucocorticoid hypersecretion due to Cushing syndrome, exogenous glucocorticoid administration for >2 wk
Tumour			Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, and intrasellar or suprasellar metastases, adenoma, carcinoma
Trauma			Pituitary stalk lesions, battering, shaken baby, vehicular
Pituitary apoplexy (Sheehan's syndrome)			High blood loss or hypotension
Radiation therapy			Craniospinal irradiation in leukaemia, irradiation for tumours outside the hypothalamic–pituitary axis, irradiation of pituitary tumours
Infiltration			Tuberculosis, actinomycosis, sarcoidosis, Wegener granulomatosis
Lymphocytic hypophysitis			Isolated or as a part of APS

precocious puberty might have already developed. In later life acne, hirsutism, amenorrhoea, oligomenorrhea and infertility are frequent features. Non-classic 21OHD is the most common specific cause in women presenting with androgen excess [12]. The percentage of undiagnosed patients, in particular males, remains unknown and individuals are regularly diagnosed during family studies. A short synacthen test can be helpful to identify patients non-classic with borderline 17OHP concentrations. As some patients with non-classic CAH are at risk to have partial glucocorticoid deficiency the SST is useful to assess the stress response in patients with non-classic CAH [13].

Once a biochemical diagnosis of CAH has been established this should be confirmed by molecular genetic analysis in a certified laboratory. As the data regarding genotype–phenotype correlations increases [14] the argument that genotyping should be performed early as part of routine clinical care strengthens. This provides information on severity of clinical disease expression and aids possible subsequent discussion on future antenatal diagnosis, treatment and family planning [15]. Remarkably, in adults with CAH health outcomes might not be associated with the genotype suggesting that potential health problems are acquired rather than genetically determined [16].

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Psychology support is often required to help the family adjust to the diagnosis. Input from paediatric urologists and/or gynaecologists experienced in the management of patients with CAH may also be required in cases where there is significant virilisation of the external genitalia. Decision making around surgical procedures and their timing should be between the multi-disciplinary team and the family [17]. Gender assignment is not regarded a common issue in patients with CAH.

Primary adrenal insufficiency due to other causes: diagnostic pathway

Primary AI due to autoimmune adrenalitis or Addison's disease usually presents later in childhood in children with nonspecific symptoms including; fatigue, weight loss and hypotension. Importantly whilst 80% of patients with primary AI are hyponatraemic at diagnosis only 40% might have hyperkalaemia. Hyperpigmentation is also not consistently associated with a diagnosis of Addisons disease in children [18]. Other rarer syndromes associated with primary adrenal failure in children include adrenoleukodystrophy, Wolman disease, Triple A syndrome and Zellweger disease [19]. In children the short synacthen test is used to diagnose glucocorticoid deficiency, with random cortisol measurements being of little value. Whilst the exact cut-off is dependent on the local cortisol assay used, most centres use a cut-off for failure as below 500–550 nmol/L (18–20 μg/dL) 30–60 min after $_{1-24}$ACTH stimulation [3]. The measurement of ACTH and renin enables differentiation between primary and secondary adrenal failure. If the clinical situation permits bloods for all these parameters should be taken before initiation of replacement therapy. In addition, we advocate storage of spot urine and plasma/serum samples to allow establishing a specific differential diagnosis. Adrenal autoantibodies and very long chain fatty acids (VLCFA) need to be included in the diagnostic work-up. With improved technologies for molecular genetic analysis using next generation sequencing approaches and the increasing evidence of non-classic presentations of various forms of adrenal insufficiency, we predict an increasing use of these tests as part of the diagnostic pathway.

Treatment

Once the diagnosis of adrenal insufficiency has been established hydrocortisone is the recommended therapy for glucocorticoid replacement in childhood. During the first 6 months of life infants with a diagnosis of adrenal insufficiency need to have growth and development monitored 6-weekly. This age group is at particularly high risk of inter-current infections, and mortality, in the main, due to inadequate increases in hydrocortisone therapy during episodes of inter-current illness. Limited data on mortality suggest that mortality in the first 6 months of life in children with AI is 19 times that expected [20]. After 6-months of age reviews should be performed at 3-monthly intervals until transition to adult care. Particular care to the dosing regimen is required during puberty to keep pace with changes in glucocorticoid needs [9,21]. In CAH the initiation of medication and the protocol for monitoring to detect early salt loss are outlined below.

Multi-disciplinary team

Adrenal insufficiency is a chronic life-long illness, which requires not only hormone replacement but also ongoing support to the patient and their family supporting them to engage with and manage their condition. Education and training about AI is an integral part of clinical care and the patient and the family benefits from a multi-disciplinary team around the patient and the child. This team should be tailored to the underlying aetiology and is commonly composed of paediatric endocrinologists, specialist nurses, paediatric urologists, psychologists, clinical geneticists and biochemists [22].

Mineralocorticoid replacement

The renin-angiotensin-aldosterone system is active by 16 weeks of gestational age [23]. Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex under the regulation of serum potassium and angiotensin II, with ACTH having only a short-term effect [24]. Mineralocorticoids in children with adrenal insufficiency are replaced as fludrocortisone. In infancy there is a relative aldosterone

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resistance with the immature kidney tubular system being unable to adequately respond to aldosterone action to regulate water and sodium homoeostasis [25]. During the neonatal period and early infancy a higher dose of fludrocortisone is therefore required [25]. Fludrocortisone doses during first year of life are commonly 150 μg/m^2/day. Sodium supplementation is also required as milk-feeds (both formula and breast) only provide maintenance sodium requirements of 2 mmol/kg/day, which is not adequate to replace the sodium losses present in AI. Sodium supplements of 5–8 mmol/kg/day are usually adequate, although some children may require doses of up to 10–12 mmol/kg per day. If hyponatraemia persists on a standard dose of fludrocortisone, (150 μg/m^2/day), the dose of fludrocortisone should only be increased further after 10–12 mmol/kg/day of sodium supplements have failed to normalize serum sodium [26]. If higher fludrocortisone doses are necessary, close monitoring of blood pressure and renin is indicated to avoid iatrogenic hypertension. Commonly, sodium supplementation can safely be discontinued when salt intake is sufficient via food. This can be initiated from usually 8 months of age and should be approached on an individualised basis taking growth, development and compliance into account. Some centres have abandoned the use of NaCl supplementation and titrate fludrocortisone according to renin concentrations and blood pressure. Clinical studies comparing the outcome of these two strategies have a high clinical research priority.

In all forms of CAH a degree and spectrum of aldosterone deficiency and salt-loss is present [27,28]. Therefore the traditional labelling of patients with CAH as “salt wasting” or “simple virilising” is misleading as in reality a continuous spectrum exists between severe and mild disease [29]. Thus, in our clinical practice we have abandoned using these terms. The majority of patients with CAH and aldosterone deficiency present during weeks two to three of life with salt loss, which can be life threatening if not recognized and treated early. In girls where ambiguous genitalia have been identified at birth daily monitoring of serum electrolytes should be performed in the neonatal period until the diagnosis is confirmed. Bloods should be drawn for measurement of aldosterone and plasma renin. The ratio of aldosterone to plasma renin activity is reduced with increasing disease severity and has been suggested to represent a better marker of disease severity than measurement of renin or aldosterone alone [26]. Aldosterone, however, remains a challenging analyte in the low concentration range even by employing liquid chromatography tandem mass spectrometry methods. All patients with an elevated PRA or aldosterone to PRA ratio require fludrocortisone therapy and adequate dietary sodium, which includes almost all children with classic CAH. Since the physiologic mineralocorticoid resistance improves with age, the requirement for continuing fludrocortisone replacement should be regularly reassessed by measuring blood pressure and renin concentrations.

Monitoring fludrocortisone replacement

Sensitivity to mineralocorticoid increases with age. Thus blood pressure, plasma electrolytes and plasma renin activity should be monitored every 2–3 months during the first 18 months of life, using age, sex and height-adjusted references, to avoid over treatment, which presents with hypertension and hypokalaemia [26]. Suppressed plasma renin concentrations indicate over treatment. The challenge in infancy is in determining the appropriate fludrocortisone dose to avoid life-threatening salt-wasting crises, whilst, limiting overexposure to fludrocortisone. A recent study identified a high prevalence of transient fludrocortisone induced hypertension in young children aged 0–4 years with classic CAH [30] despite following the Endocrine Society guidelines on CAH [31]. They highlighted the 12–18 month age group as being particularly at risk and recommend close monitoring of BP in association with reductions in fludrocortisone dosage between 12 and 18 months of life to avoid potential harm to the renal and cardiovascular systems from fludrocortisone induced hypertension. After infancy the relative fludrocortisone dose in relation to body surface area decreases and this trend continues throughout childhood and adolescence. After 18 months of life monitoring of treatment adequacy can be performed 3 monthly. Fludrocortisone doses of 100 μg/m^2/day after the first two years of life are commonly sufficient to maintain a normal blood pressure and renin concentration. However, these requirements have to be individualised as occasionally patients require significantly higher doses. Commonly, this requirement drops further with adolescents and adults are usually sufficiently supplemented with a total daily dose of 100–200 μg (50–100 μg/m^2 per day) [9]. Fludrocortisone is usually administered once daily, although twice daily therapy with two equally divided doses can be

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helpful. For example, in a situation of increased physiological fluid and electrolyte loss, such as a hot climate the patient may benefit from higher more frequent doses of fludrocortisone [32].

At present it remains unclear as to whether additional mineralocorticoid replacement is required during stress and for elective surgical procedures. Where oral intake is possible fludrocortisone should be administered. If oral intake is not possible, recommended replacement doses of intravenous hydrocortisone (Table 5) circumvent the need for fludrocortisone as 40 mg hydrocortisone exerts equivalent mineralocorticoid activity to 100 μg fludrocortisone. Of note, prednisolone has only reduced and dexamethasone has no mineralocorticoid activity [33]. During stressful circumstances, e.g. febrile illness (>38.5 °C) and gastroenteritis associated with inability to tolerate oral fluids, major trauma and surgery for which general anaesthesia is required, regular measurement of serum and urine electrolytes should be performed, and sufficient replacement of sodium administered intravenously.

Glucocorticoid replacement

The aims of therapy in adrenal insufficiency are to prevent adrenal crisis and additionally in children with CAH to minimise androgen secretion and consequent virilisation, enabling normal growth and development. Current recommended treatment regimes, consist of hormone replacement with oral hydrocortisone tablets in growing patients and fludrocortisone therapy [15]. Prednisolone and dexamethasone are not recommended for use in replacement regimens during childhood as they are associated with growth suppression and significant weight gain [34]. Liquid preparations of hydrocortisone are not recommended due to the uneven distribution of the drug in the liquid [35]. As food intake prior to hydrocortisone ingestion prolongs its absorption half-life doses are currently recommended to be taken prior to food, although some experts have argued that administration with food may prolong the half-life of hydrocortisone facilitating the production of a more physiological cortisol profile [36]. It has been suggested that fludrocortisone has not only mineralocorticoid but also potent glucocorticoid activity [9]. This is of particular relevance in newborns and infants to avoid glucocorticoid over-exposure.

The average daily hydrocortisone replacement dose in AI is aligned to the daily physiological cortisol production, which is approximately 8 mg/m^2/day (measured using stable isotopic methodology [37]) and enterohepatic cortisol circulation, together yielding an average hydrocortisone replacement dose of 8–10 mg/m^2/day [9]. In CAH where suppression of the HPA-axis is required to control androgen excess a higher dose of up to 15 mg/m^2/day is recommended [9,31]. Importantly, doses of more than 17 mg/m^2/day during puberty have a significant deleterious effect on growth velocity and final height [38]. In infancy there is evidence to suggest that androgen excess is not associated with increased height velocity and that lower hydrocortisone replacement doses can therefore be used (8–10 mg/m^2/day) [39].

In our clinical practice, we aim to replace half to two-thirds of the daily hydrocortisone dose as early as possible in the morning (ideally 3–5 am). This is based on circadian pattern of normal adrenocortical secretion, with concentrations being lowest at 00.00, rising between 0200 and 0400 h, reaching their peak at approximately 0800 h, and then falling throughout the day [40]. Despite these efforts, current glucocorticoid replacement regimes struggle to mimic the physiological profile of cortisol production over 24 h. Bioavailability of orally administered hydrocortisone high at close to 95%, but the half-life is short, between 60 and 120 min [41,42]. The serum cortisol profile following hydrocortisone administration therefore exhibits steep peaks followed by a rapid fall to trough concentrations with the

Table 5
Intravenous glucocorticoid doses during critical illness, major surgery or adrenal crisis.

Age		Bolus (single dose)[a]	Maintenance[a]
≤3 years	Hydrocortisone	25 mg IV	25–30 mg IV per day
>3 years and <12 years	Hydrocortisone	50 mg IV	50–60 mg IV per day
≥12 years	Hydrocortisone	100 mg IV	100 mg IV per day
Adults	Hydrocortisone	100 mg IV	100–200 mg IV per day

[a] Dose for bolus and maintenance approximately equals 100 mg/m^2.

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resultant pattern not paralleling physiological cortisol production [43]. There is limited evidence to suggest that changing the timing of hydrocortisone doses in adults with AI to try to better replicate physiological cortisol production reduces the total daily dose of hydrocortisone required, potentially reducing the prevalence of associated metabolic complications [43]. One small paediatric study in children with CAH, conducted over a four week period, found that whether the higher hydrocortisone dose was administered in the morning or the evening found no effect on disease control, measured using basal 17OHP, DHEAS, androstenedione, and testosterone concentrations and concluded to follow a replacement regime with a high-morning dose rather than a reverse circadian rhythm [44].

Although there is significant variability in the number and timing of hydrocortisone dose administration internationally hydrocortisone is most commonly administered in a thrice daily regimen [45], aiming to mimic the circadian rhythm of cortisol secretion [31]. Debate is ongoing whether dosing should be increased four times a day as the duration of hydrocortisone in the circulation is about 6 h. We do, however, advice against a large late evening dose as this will create a high cortisol concentrations during the physiological nadir and due to the half-life of hydrocortisone still fail to sufficiently suppress the early morning ACTH surge.

An important consideration with regard to hydrocortisone dosing are patients taking medication that accelerates cortisol metabolism. This is mainly happening by enzyme induction of cytochrome P450 3A4. Thus, patient treated with drugs such as anticonvulsant or antiretroviral medication may require increased hydrocortisone doses to ensure adequate cortisol replacement [46].

Stress treatment

Adrenal crisis due to impaired cortisol response to physical stress is a serious threat in adrenal insufficiency. Studies in adults during febrile illness (>38.5 C), trauma and surgery studies have shown that metabolites of ACTH, cortisol, urinary cortisol and urinary cortisol metabolites increase [47,48]. During mild/moderate inter-current illness where fluids are tolerated steroid doses should be increased to 30 mg/m^2/day divided in four 6-hourly equal doses. The high oral bioavailability of hydrocortisone means that if absorption from the gastrointestinal tract is not impaired the oral route is nearly as effective as the intravenous route [41]. However, patients with diarrhoea and vomiting, who are unable to take their medication require IM hydrocortisone (100 mg/m^2 per dose) and immediate review by a medical professional. On review blood pressure, blood glucose, urea and electrolyte concentrations should be measured. If any of these are abnormal the child should be admitted. Patients with severe illness or major surgery require ongoing IV hydrocortisone replacement (Table 5). To avoid peaks and troughs this is ideally given as continuous IV infusions rather than IV or IM bolus injections [49]. Increased glucocorticoid doses should be avoided in mental and emotional stress, minor illness, and before physical exercise, as this would greatly increase the frequency of supra-physiologic dosing.

Sodium chloride IV replacement if required during adrenal crisis, needs to be carefully monitored, to avoid rapid sodium chloride shifts. Fludrocortisone adjustment is commonly not required. In patients presenting with hyponatraemia sodium should initially be corrected to 120–125 mmol/L at a rate of 0.5 mmol/L/h, thereafter correction to normal values should continue over 48 h.

Patients with CAH are at increased risk of hypoglycaemia due to impaired adrenomedullary function. In patients with CAH the adrenal medulla does not develop normally and they have significantly lower plasma and urinary epinephrine, and plasma total and free metanephrine concentrations than healthy controls [50]. The degree of adrenomedullary dysfunction correlates with the severity of the enzyme impairment [51]. The combination of cortisol and adrenaline insufficiency results in dysregulation of glucose, insulin and leptin metabolism [52,53]. Although the clinical consequences of adrenal medullary insufficiency remain speculative, it is hypothesized to play a role in hypoglycaemia during intercurrent illnesses in children with CAH and to be a risk factor in the development of insulin insensitivity [54]. If there is loss of consciousness and/or circulatory collapse blood glucose should be measured hourly until normalized and stable. Hypoglycaemia should be managed appropriately according to local guidelines.

All patients are advised to carry a steroid emergency card or Medic Alert Bracelet emphasising the diagnosis “adrenal insufficiency” emphasising the urgent requirement of hydrocortisone stress cover

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during critical illness. Patients and parents should have an emergency glucocorticoid injection kit and meticulous self-injection training.

Major surgery

Elective surgery should be carefully planned in conjunction with the anaesthetic team. The patient should ideally be first on the surgical list in the morning. The night prior to surgery the normal evening dose of hydrocortisone should be administered. At 06:00 a dextrose-saline infusion should be started and continued until oral fluids can be tolerated post-surgery. The required hydrocortisone morning medication can be given as IV hydrocortisone in the same dose as the oral medication. If the patient is on the afternoon surgical list they should receive their standard morning hydrocortisone dose.

At induction an intravenous dose of hydrocortisone should be administered followed by a continuous hydrocortisone infusion according to the recommendation of stress dosing (Table 5). Consideration should be taken of the surgical procedure being performed. For example, in children undergoing neurosurgical procedures in whom the mineralocorticoid water retentive effect of hydrocortisone may be a disadvantage, dexamethasone should be used. Whilst there is limited data on cortisol production in healthy children in response to minor surgical procedure our knowledge on endogeneous cortisol production in response to major surgical procedures remains limited [55].

Minimally invasive surgical procedures

Minimally invasive procedures do not result in activation of the hypothalamo–pituitary axis in children [55]. The current advice for hydrocortisone replacement in children with AI undergoing minimally invasive procedures is therefore no more than three times physiological replacement (10 mg/m^2/day orally) in the 24 h perioperative period. The daily hydrocortisone dose following minimally invasive procedures should be about 30 mg/m^2/day ideally divided into four equal 6-hourly doses. Recent evidence suggests these guidelines for stress dosing in AI substantially exceed physiological requirements during minimally invasive procedures, however further research in this area is required before amendments are made [55]. The increase in hydrocortisone dose should follow the surgical procedure as in the majority of healthy patients the increased cortisol production in response to minor procedures occurs at the time of recovery and not during the surgical procedure [56].

Puberty

Puberty is associated with changes in the metabolism of cortisol, with cortisol clearance being increased, especially in females [57]. The half-life of cortisol during puberty can therefore be as low as 40 min, compared to 80 min in pre- or post-puberty [58]. Increased growth hormone production increases glomerular filtration and cortisol clearance, and oestradiol increases cortisol binding globulin concentrations. In addition, reduced activity of 11-beta-hydroxysteroid dehydrogenase type 1 during the pubertal growth spurt leads to decreased reactivation of cortisone to cortisol and, effectively, hypocortisolism [59]. Thus, the concentrations of circulating cortisol are significantly reduced during puberty, with glucocorticoid dosing requiring regular assessment and amendment to maintain control of the hypothalamo–pituitary axis. During puberty a more frequent dosing schedule of four times daily is frequently required [57].

Monitoring glucocorticoid replacement

Long-term health problems in patients with adrenal insufficiency are increasingly a concern. They can arise from the disease process itself, for example excess androgen exposure in CAH, as well as from under-treatment or over-treatment, which leads to deficient or excess glucocorticoids. There are no clear guidelines around screening for co-morbidities in children and adolescents with AI, although it has been suggested that an annual review process could be helpful [9].

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Growth

A dose-dependent negative effect of glucocorticoids of linear growth has been identified during infancy, childhood and adolescence [60]. Exposure to glucocorticoid doses above 15 mg/m^2/day [38,61], or treatment with long-acting, high-potency glucocorticoids impacts negatively on growth [34]. Infancy is the time of most rapid linear growth acquisition, and impaired linear growth due to excess glucocorticoid therapy during this period cannot be recovered [62]. Glucocorticoid exposure should therefore be limited by using the minimum effective dose [33]. Children receiving lower doses of hydrocortisone, should be monitored 3 monthly to optimise the dose, with treatment aiming to keep height, BMI, blood pressure and bone age within normal limits are able to achieve a normal target height [63]. Several small studies have assessed the potential of growth hormone in isolation, and growth hormone in combination with a GnRH to enhance growth in children with classic CAH [64,65]. However, as normal final height can be achieved by carefully titrating hydrocortisone the additional use of expensive and experimental therapies with potential side effects does not seem justified.

Reproductive health

Females with CAH usually enter puberty at the normal time. However menarche can be delayed in individuals with poor control and increased exposure to androgens, with an irregular menstrual cycle also being associated with poor overall disease control [66]. It is thought that females with CAH are at increased risk of a polycystic ovarian-like syndrome, presenting clinically with oligomenorrhoea and infertility due to excess androgen exposure during episodes of poor control [67]. However different studies have identified a variable association between CAH and polycystic ovaries. Studies in adult females with CAH have identified the prevalence of polycystic ovaries on pelvic ultrasound to be the same as the general population or as high as 83% [68,69]. Findings from adolescent studies report similarly conflicting results [68,70]. Abiraterone acetate, a prodrug which is metabolized to abiraterone, is a potent site-directed inhibitor of CYP17A1. A recently published phase 1 study in adult females with CAH reported that abiraterone acetate therapy administered alongside hydrocortisone replacement doses of 8 mg/m^2/day enabled normalisation of measures of androgen excess with the potential to be used as adjunct therapy [71].

Males with CAH are at risk of developing testicular adrenal rest tumours (TART), an important cause of primary gonadal failure and infertility [72]. The prevalence of TARTs in childhood ranges from 18 to 29%, with the youngest affected patient being four years of age [73–75]. The prevalence of TARTs increases post-puberty with some studies reporting a prevalence as high as 94% in adulthood [76]. These benign testicular tumours compress the seminiferous tubules leading to obstructive azoospermia, damage to the surrounding testicular tissue ultimately resulting in infertility. TARTs are hypothesized to originate from aberrant adrenal cells descending during embryogenesis with testicular cells [77]. The aetiology of TARTs remains incompletely understood, although they appear to be more prevalent in individuals with poor metabolic control [73]. Interestingly in a recent paediatric study some of these early stage tumours were found to disappear in response to high dose glucocorticoid therapy (30 mg/m^2/day) [73]. Since the identification of tumours less than 2 cm in diameter is not possible by palpation due to their location in the rete testis ultrasound screening for TART has been recommended every 2 years in early childhood and annually in the peri-pubertal period [72,73].

Quality of life and cognition

Lifelong medication and regular clinic visits are an inevitable consequence of being diagnosed with adrenal insufficiency. Chronic illness impacts negatively on psychosocial development. More specifically in CAH androgen excess may affect normal psychosocial development and there is evidence to suggest that excess exposure to corticosteroids also impacts negatively on brain development and function [78]. Some studies investigating quality of life and subjective health status in adults with CAH have identified impaired quality of life (QoL) and a tendency to

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psychological problems in affected individuals, whilst others report normal health related QoL [79]. Studies to clarify these discrepancies are needed [33]. A number of different cognitive changes have also been described in CAH patients including reduced intelligence, learning difficulties, impaired attention, reduced verbal fluency and memory [80]. Whilst some cognitive effects during acute brain damage may be transient, others such as repeated exposure to excess glucocorticoids or androgens are likely to become permanent [81]. Assessment of quality of life and cognitive function do not form a routine part of clinical care in children and adolescents with CAH at present. However it has been suggested that screening for psychological difficulties should be incorporated the care pathway with those found to have abnormal screening results offered further psychological evaluation and intervention [82]. This appears to be of major importance as the impact of intrinsic factors versus external factors including health care provision on overall health related QoL in CAH remains unclear [33].

Cardiovascular and metabolic health

Children and adolescents with CAH have increased BMI and blood pressure compared to healthy controls, with BMI correlating positively with glucocorticoid dose [83,84]. Children with CAH are also at risk of developing impaired insulin sensitivity, with unfavourable changes in HOMA-IR being associated with raised fasting insulin concentrations [85,86]. More recently a retrospective cross-sectional study of 107 individuals (mean age 9.2 years, range 0.4–20.5 years) reported that individuals managed with lower doses of hydrocortisone replacement therapy (13.3 $mg/m^2/day$) have lower HOMA IR than historical controls [87]. Overall, altered insulin sensitivity appears to be therapy-related with both over and under-treatment potentially leading to impaired insulin sensitivity [33]. Carotid intima thickness, a surrogate marker for atherosclerosis, has been shown to be increased in a study of 19 young adults with CAH [88]. This finding was independent of hormonal control, glucocorticoid dose or metabolic parameters including lipid status, glucose or insulin concentrations. The relevance of these structural changes to future cardiovascular health in patients with CAH remains unclear. However, two studies reported that these changes can be already detected in children and young persons [89,90]. There is no evidence to suggest that children with CAH are at risk of dyslipidaemia, with the majority of studies describing normal lipid profiles in children and adolescents with CAH [33]. The current guidelines in children recommend that BP should be assessed at every clinic visit and that BP should be maintained within the normal range for age and sex to minimise the risk of long-term cardiovascular complications. Investigations into insulin sensitivity should be considered in individuals who present clinically with signs of insulin insensitivity.

Bone health

Long-term glucocorticoid therapy suppresses osteoblast activity and increases bone resorption by osteoclasts. Patients with CAH exposed to supraphysiological hydrocortisone doses are therefore at risk of developing bone health abnormalities. To date studies in adolescents and young adults with CAH have not identified any bone mineral density abnormalities [33]. However, data on bone mineral density in adults aged over 30 years and in postmenopausal women with CAH suggest there is an increased prevalence of osteopaenia and osteoporosis compared to healthy controls [79,91,92]. In children and adolescents it is therefore advised to limit cumulative hydrocortisone overexposure to optimise bone health and to maintain serum androgen concentrations in the upper normal range. There are currently no recommendations for regular monitoring of bone mineral density in children and adolescents with CAH.

Monitoring of treatment

Assessment of treatment efficacy in children with CAH involves monitoring for signs of glucocorticoid excess in addition to signs of inadequate control of sex steroid excess [31]. Classically disease control has been measured by monitoring growth velocity, bone age (annually after 4 years of age) and

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serum concentrations of androgen precursors [31,93]. However there is ongoing debate amongst clinicians both regarding the specific analytes that should be measured to assess control and what the number and timing of these measurements should be. Measurements of cortisol concentrations are not useful to monitor quality of glucocorticoid replacement in adrenal insufficiency [94]. Treatment of CAH should aim to normalise sex-hormones. The optimal glucocorticoid dose fails to suppress 17OHP and its metabolites and maintains sex hormone concentrations in the age and sex-specific normal range.

Glucocorticoid metabolism varies with age and between individuals, it has therefore been suggested that doses should be titrated against 24 h serum cortisol profiles [95]. After hydrocortisone administration approximately 95% of the drug is absorbed into the circulation. Peak concentrations of cortisol are reached after two hours with the duration of action being 4–6 h (half-life average 80 min) [41]. Hourly cortisol profiles over a 24 h period enable assessment of whether there are times when the patient is either over or under exposed to cortisol and whether the doses are been administered frequently enough at the right times of day. Thus, the assessment of cortisol kinetics and dynamic profiles might improve glucocorticoid replacement with respect to finding a more individualised dose and better timings. The possibility of using saliva to monitor 24 h cortisol profiles has also being explored. Salivary cortisol can be collected in a painless way and offers a measure of bioactive free hormone [96]. Dried blood spots have also been assessed as a means of 24 h steroid profiling using liquid chromatography tandem mass spectrometry [97]. However, different monitoring strategies have not been compared in clinical studies and no evidence base exists therefore in relation to outcomes.

Even with careful optimisation current replacement regimens with hydrocortisone tablets do not parallel the physiological pattern of cortisol production with the dose of hydrocortisone required to maintain a safe background cortisol concentration resulting in supraphysiological cortisol concentrations 1–2 h after administration [41]. Exposure to high concentrations of glucocorticoids suppresses growth, increases blood pressure and can cause osteoporosis and iatrogenic Cushing's syndrome [34,83,84,91,98]. Despite significant reductions in glucocorticoid doses over the last decade CAH continues to be associated with significant morbidity and mortality. Children with CAH have reduced final height compared to their mid-parental target height despite treatment optimization. They also have an increased prevalence of cardiovascular risk factors including obesity and hypertension [87] and are at increased risk of infertility in adulthood [33]. However, further dose reductions would place patients at an increased risk of adrenal crisis, with under-treatment also leading to increased adrenal androgen production. Novel approaches to treatment are therefore being explored.

Novel approaches to glucocorticoid replacement

Hormone replacement in CAH remains challenging as the pharmaco-kinetics and dynamics of immediate release hydrocortisone make it almost impossible to replicate physiological cortisol profiles [87]. Due to the lack of low dose hydrocortisone preparations a variety of unlicensed hydrocortisone preparations at doses of between 0.5 and 5 mg are currently used in paediatric practice [45]. Such preparations bear the risk of significant dose variations [99]. A recent innovation of multilayered multiparticulate hydrocortisone granules (Infacort®), might overcome these problems in the foreseeable future. A dose of 10 mg Infacort® has been shown to be bioequivalent to 10 mg hydrocortisone and unit doses of 0.5, 1, 2 and 5 mg have been tested in a recent phase 1 study [45]. The efficiency of this formulation needs to be tested in infants and children and will have the potential to optimise glucocorticoid replacement in this age group.

Continuous subcutaneous hydrocortisone infusions

In individuals with persistent poor control studies of cortisol clearance might provide important information. Where plasma cortisol profile (hourly samples) identifies a rapid clearance of hydrocortisone initially a more frequent regiment of hydrocortisone replacement should be trialled. If good control remains elusive these individuals may benefit from continuous subcutaneous

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hydrocortisone infusion therapy administered via an insulin pump, which has been adapted to deliver hydrocortisone [58]. Several small, uncontrolled studies have now demonstrated that subcutaneous hydrocortisone infusions can accurately mimic the circadian cortisol profile, improving hydrocortisone replacement and resulting in near normal ACTH and 17OHP concentrations in previously poorly controlled subjects [100,101]. In published studies improved control of adrenal androgen has been achieved with decreased glucocorticoid doses. Pump therapy is also a helpful option in children who are unable to tolerate oral steroids e.g. severe gastritis and in patients with obesity or hypertension secondary to high dose glucocorticoid therapy [58]. Whilst pump therapy offers many benefits, including improved management of stress and inter-current illness the risk of site and pump failures and the need for injections in combination with being attached to a medical device limit their use in general clinical practice.

Sustained release hydrocortisone preparations

The development of modified release hydrocortisone preparations which aim to provide a more physiological cortisol profile is ongoing [40]. Chronocort®, a modified-release formulation of hydrocortisone aims to replicate cortisol circadian rhythm and to suppress the overnight ACTH surge which drives excess androgen production in CAH [102]. The recently published phase 2 study for Chronocort® demonstrated a decrease in equivalent hydrocortisone dose required, lower 24-h and afternoon androstenedione area under the curve and lower 24 h and morning 17-hydroxyprogesterone area under the curve [103]. A further dual-release hydrocortisone preparation, Plenadren™ (Duocort/ViroPharma, Helsingborg, Sweden), has been trialled in patients with adrenal insufficiency as once-daily dosing, compared to thrice-daily dosing [104,105]. However is does not address the overnight rise in ACTH and the suitability of the use this glucocorticoid preparation in patients with CAH requires further research.

Experimental therapies

Inhibition of corticotropin releasing hormone

Corticotropin Releasing Hormone (CRH) stimulates ACTH production and release from pituitary corticotrophs. Inhibition of CRH and/or ACTH production would enable administration of lower HC replacement doses, reducing the side effects from supraphysiological hydrocortisone doses. A recent single-blind, placebo-controlled, single centre study explored the use of a selective corticotropin-releasing factor type 1 receptor antagonist in adult females with 21OHD aged 18–58 years. The authors reported a meaningful reduction of 17OHP and ACTH in combination with variable concentrations of androstenedione and testosterone [106]. Future clinical studies are required to determine the clinical relevance of these promising efforts reducing the ACTH drive, which has the potential to reduce glucocorticoid doses in the future.

Blocking androgen synthesis and androgen action

The androgen-receptor blocker, flutamide, has been used in conjunction with the aromatase inhibitor testolactone, low dose hydrocortisone replacement therapy (8 mg/m^2/day) and fludrocortisone replacement. This four-drug regimen normalalised linear growth and bone maturation, despite elevated adrenal androgens as compared with conventional therapy in a 2-year randomized study [107]. More potent antiandrogens are now available, currently in use for the treatment of prostate cancer. Bicalutamide has a half-life of one week and reduced hepatoxicity when compared to flutamide [108].

A novel potentially very interesting alternative is abiraterone acetate which blocks the enzymatic function of CYP17A1. The recently published phase 1 study reported that low dose abiraterone acetate therapy administered alongside hydrocortisone replacement doses of 8 mg/m^2/day enabled normalisation of measures of androgen excess [71]. However, the long term safety of these therapies, and their role in the management of CAH warrants future clinical studies.

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Practice points

- Hydrocortisone divided into three or four doses is the drug of first choice until final height is achieved.
- The timing of hydrocortisone replacement is of significant importance with 50–66% of the daily dose to be administered as early as possible in the morning.
- Adequate glucocorticoid replacement commonly fails to suppress or normalise 17-hydroxyprogesterone concentrations, but normalises androstenedione and testosterone into the age and sex specific normal range.
- The relative mineralocorticoid dose per body surface area declines with increasing age and decreasing mineralocorticoid resistance.
- Replacement doses are monitored assessing renin concentrations (target upper normal range) and blood pressure (normal age and sex specific, ideally height adapted range).
- Glucocorticoid over-exposure appears to be a key factor associated with long-term health problems; thus patients at all ages should be treated with the absolute minimal required glucocorticoid dose.

Research agenda

- It appears vital to establish large scale clinical research networks to assess the current and future health status in patients with CAH and adrenal insufficiency.
- Oral hydrocortisone replacement regimes have been optimised over the last decade, future research needs to address the optimum method of steroid hormone delivery and monitoring of hormone replacement.
- The development of novel adjunct treatments minimising cumulative hydrocortisone exposure appear useful; however, the wider clinical indication and use in clinical practice will require a broader evidence base.
- Replacement strategies aiming to mimic physiological glucocorticoid replacement are required in all age groups.

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