Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

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Objective: To update the congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency clinical practice guideline published by the Endocrine Society in 2010.

Conclusions: The writing committee presents updated best practice guidelines for the clinical management of congenital adrenal hyperplasia based on published evidence and expert opinion with added considerations for patient safety, quality of life, cost, and utilization. **(*J Clin Endocrinol Metab* 103: 4043–4088, 2018)**

List of Recommendations

Newborn screening

Cost-effectiveness

1.1 We recommend that all newborn screening programs incorporate screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency. (1|⊕⊕⊕◯)

1.2 We recommend that first-tier screens use 17-hydroxyprogesterone assays standardized to a common technology with norms stratified by gestational age. (1|⊕⊕⊕◯)

Technical remark: Clinicians should be aware that immunoassays are still in use and remain a source of false-positive results. Specificity may be improved with organic extraction to remove cross-reacting substances.

1.3 We recommend that screening laboratories employ a second-tier screen by liquid chromatography–tandem mass spectrometry in preference to all other

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Abbreviations: 17OHP, 17-hydroxyprogesterone; 21OHD, 21-hydroxylase deficiency; BMI, body mass index; BMD, bone mineral density; CAH, congenital adrenal hyperplasia (both classic and nonclassic); Dex, dexamethasone; DSD, disorders of sex development; GC, glucocorticoid; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MC, mineralocorticoid; NCCAH, nonclassic congenital adrenal hyperplasia; PRA, plasma renin activity; QOL, quality of life; SDS, SD score; TART, testicular adrenal rest tumor.

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methods (*e.g.*, genotyping) to improve the positive predictive value of congenital adrenal hyperplasia screening. (1|⊕⊕◯◯)

Technical remark: Laboratories utilizing liquid chromatography–tandem mass spectrometry should participate in an appropriate quality assurance program. Additionally, clinicians should realize that immunoassays lead to more false-positive results. Thus, if laboratory resources do not include liquid chromatography–tandem mass spectrometry, a cosyntropin stimulation test should be performed to confirm diagnosis prior to initiation of corticosteroid treatment.

Prenatal treatment of congenital adrenal hyperplasia

2.1 We advise that clinicians continue to regard prenatal therapy as experimental. Thus, we do not recommend specific treatment protocols. (Ungraded Good Practice Statement)

2.2 In pregnant women at risk for carrying a fetus affected with congenital adrenal hyperplasia and who are considering prenatal treatment we recommend obtaining prenatal therapy only through protocols approved by Institutional Review Boards at centers capable of collecting outcomes from a sufficiently large number of patients, so that risks and benefits can be defined more precisely. (1|⊕⊕⊕◯)

2.3 We advise that research protocols for prenatal therapy include genetic screening for Y-chromosomal DNA in maternal blood to exclude male fetuses from potential treatment groups. (Ungraded Good Practice Statement)

Diagnosis of congenital adrenal hyperplasia

3.1 In infants with positive newborn screens for congenital adrenal hyperplasia we recommend referral to pediatric endocrinologists (if regionally available) and evaluation by cosyntropin stimulation testing as needed. (1|⊕⊕⊕◯)

3.2 In symptomatic individuals past infancy, we recommend screening with an early-morning (before 8 AM) baseline serum 17-hydroxyprogesterone measurement by liquid chromatography–tandem mass spectrometry. (1|⊕⊕⊕◯)

3.3 In individuals with borderline 17-hydroxyprogesterone levels, we recommend obtaining a complete adrenocortical profile after a cosyntropin stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects. (1|⊕⊕⊕◯)

3.4 In individuals with congenital adrenal hyperplasia, we suggest genotyping only when results of the adrenocortical profile after a cosyntropin stimulation test are equivocal, or cosyntropin stimulation cannot be accurately performed (*i.e.*, patient receiving glucocorticoid), or for purposes of genetic counseling. (2|⊕⊕⊕◯)

Technical remark: Genotyping at least one parent aids in the interpretation of genetic test results because of the complexity of the *CYP21A2* locus.

Treatment of classic congenital adrenal hyperplasia

4.1 In growing individuals with classic congenital adrenal hyperplasia, we recommend maintenance therapy with hydrocortisone. (1|⊕⊕⊕◯)

4.2 In growing individuals with congenital adrenal hyperplasia, we recommend against the use of oral hydrocortisone suspension and against the chronic use of long-acting potent glucocorticoids. (1|⊕⊕⊕◯)

4.3 In the newborn and in early infancy, we recommend using fludrocortisone and sodium chloride supplements to the treatment regimen. (1|⊕⊕⊕◯)

4.4 In adults with classic congenital adrenal hyperplasia, we recommend using daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids, as clinically indicated. (1|⊕⊕⊕◯)

4.5 In all individuals with classic congenital adrenal hyperplasia, we recommend monitoring for signs of glucocorticoid excess, as well as for signs of inadequate androgen normalization, to optimize the adrenal steroid treatment profile. (1|⊕⊕⊕◯)

4.6 In all individuals with classic congenital adrenal hyperplasia, we recommend monitoring for signs of mineralocorticoid deficiency or excess. (1|⊕⊕⊕◯)

Stress dosing

4.7 In all patients with congenital adrenal hyperplasia who require glucocorticoid treatment, for situations such as febrile illness (>38.5°C), gastroenteritis with dehydration, major surgery accompanied by general anesthesia, and major trauma we recommend increasing the glucocorticoid dosage. (1|⊕⊕⊕◯)

4.8 In patients with congenital adrenal hyperplasia under everyday mental and emotional stress and minor illness and/or before routine physical exercise we recommend against the use of increased glucocorticoid doses. (1|⊕⊕◯◯)

4.9 In patients with congenital adrenal hyperplasia who require treatment, we recommend always wearing or carrying medical identification indicating that they have adrenal insufficiency. (1|⊕⊕⊕◯)

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4.10 In patients with congenital adrenal hyperplasia, we recommend educating patients and their guardians and close contacts on adrenal crisis prevention and increasing the dose of glucocorticoid (but not mineralocorticoid) during intercurrent illness. (1|⊕⊕⊕◯)

4.11 We recommend equipping every patient with congenital adrenal hyperplasia with a glucocorticoid injection kit for emergency use and providing education on parenteral self-administration (young adult and older) or lay administration (parent or guardian) of emergency glucocorticoids. (1|⊕⊕⊕◯)

Monitoring therapy

4.12 In patients ≤18 months with congenital adrenal hyperplasia, we recommend close monitoring in the first 3 months of life and every 3 months thereafter. After 18 months, we recommend evaluation every 4 months. (1|⊕⊕◯◯)

4.13 In pediatric patients with congenital adrenal hyperplasia, we recommend conducting regular assessments of growth velocity, weight, blood pressure, as well as physical examinations in addition to obtaining biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid. (1|⊕⊕◯◯)

4.14 In pediatric patients with congenital adrenal hyperplasia under the age of 2 years, we advise annual bone age assessment until near-adult height is attained. (Ungraded Good Practice Statement)

4.15 In adults with congenital adrenal hyperplasia, we recommend annual physical examinations, which include assessments of blood pressure, body mass index, and Cushingoid features in addition to obtaining biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid replacement. (1|⊕⊕◯◯)

4.16 In adults with congenital adrenal hyperplasia, we recommend monitoring treatment through consistently timed hormone measurements relative to medication schedule and time of day. (1|⊕⊕◯◯)

4.17 In adults with congenital adrenal hyperplasia, we recommend that clinicians do not completely suppress endogenous adrenal steroid secretion to prevent adverse effects of over treatment. (1|⊕⊕⊕◯)

Treatment of nonclassic congenital adrenal hyperplasia

5.1 In children and adolescents with inappropriately early onset and rapid progression of pubarche or bone age and in adolescent patients with overt virilization we suggest glucocorticoid treatment of nonclassic congenital adrenal hyperplasia. (2|⊕⊕◯◯)

Technical remark: Risks and benefits of glucocorticoid therapy should be considered and discussed with the patient's family.

5.2 In asymptomatic nonpregnant individuals with nonclassic congenital adrenal hyperplasia we recommend against glucocorticoid treatment. (1|⊕⊕⊕◯)

5.3 In previously treated patients with nonclassic congenital adrenal hyperplasia we suggest giving the option of discontinuing therapy when adult height is attained or other symptoms resolve. (2|⊕⊕⊕◯)

5.4 In adult women with nonclassic congenital adrenal hyperplasia who also have patient-important hyperandrogenism or infertility we suggest glucocorticoid treatment. (2|⊕⊕◯◯)

5.5 In most adult males with nonclassic congenital adrenal hyperplasia, we suggest that clinicians generally not prescribe daily glucocorticoid therapy. (2|⊕◯◯◯)

Technical remark: Exceptions include infertility, testicular adrenal rest tumors or adrenal tumors, and phenotypes that are intermediate between classic and nonclassic phenotypes.

5.6 In patients with nonclassic congenital adrenal hyperplasia, we suggest hydrocortisone stress dosing for major surgery, trauma, or childbirth only if a patient has a suboptimal (<14 to 18 μg/dL, <400 to 500 nmol/L) cortisol response to cosyntropin or iatrogenic adrenal suppression. (2|⊕◯◯◯)

Technical remark: A range is given for cortisol cut points due to greater specificity of newer cortisol assays (see below).

Long-term management of patients with congenital adrenal hyperplasia

Transition to adult care

6.1 In adolescent patients with congenital adrenal hyperplasia, we suggest that the transition to adult care begins several years prior to dismissal from pediatric endocrinology. (2|⊕◯◯◯)

Technical remark: We advise the use of joint clinics comprised of pediatric, reproductive, and adult endocrinologists and urologist during this transition.

6.2 In adolescent females with congenital adrenal hyperplasia, we suggest a gynecological history and examination to ensure functional female anatomy without vaginal stenosis or abnormalities in menstruation. (2|⊕⊕◯◯)

Genetic counseling

6.3 In children with congenital adrenal hyperplasia, adolescents transitioning to adult care, adults with

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nonclassic congenital adrenal hyperplasia upon diagnosis, and partners of patients with congenital adrenal hyperplasia who are planning a pregnancy, we recommend that medical professionals familiar with congenital adrenal hyperplasia provide genetic counseling. (1|⊕⊕◯◯)

Fertility counseling

6.4 In individuals with congenital adrenal hyperplasia and impaired fertility we suggest referral to a reproductive endocrinologist and/or fertility specialist. (2|⊕⊕◯◯)

Management of congenital adrenal hyperplasia and nonclassic congenital adrenal hyperplasia during pregnancy

6.5 In women with nonclassic congenital adrenal hyperplasia who are infertile or have a history of prior miscarriage, we recommend treatment with a glucocorticoid that does not traverse the placenta. (1|⊕⊕◯◯)

6.6 In women with congenital adrenal hyperplasia who are pregnant, we advise management by an endocrinologist familiar with congenital adrenal hyperplasia. (Ungraded Good Practice Statement)

6.7 In women with congenital adrenal hyperplasia who become pregnant we recommend continued prepregnancy doses of hydrocortisone/prednisolone and fludrocortisone therapy, with dosage adjustments if symptoms and signs of glucocorticoid insufficiency occur. (1|⊕⊕◯◯)
Technical remark: Clinicians should evaluate the need for an increase in glucocorticoid during the second or third trimester and administer stress doses of glucocorticoids during labor and delivery.

6.8 In women with congenital adrenal hyperplasia who are pregnant, or trying to become pregnant, we recommend against using glucocorticoids that traverse the placenta, such as dexamethasone. (1|⊕⊕◯◯)

6.9 In women with congenital adrenal hyperplasia who are pregnant, we advise that the birthing plan includes an obstetric specialist. (Ungraded Good Practice Statement)

Surveillance for long-term complications of congenital adrenal hyperplasia and its treatment

6.10 For patients with congenital adrenal hyperplasia, we suggest introducing counseling regarding healthy lifestyle choices at an early age to maintain body mass index within the normal range to avoid metabolic syndrome and related sequelae. (2|⊕◯◯◯)

6.11 In adult patients with congenital adrenal hyperplasia, we suggest screening of bone mineral density in anyone subjected to a prolonged period of higher-than-average glucocorticoid dosing, or who has suffered a nontraumatic fracture. (2|⊕◯◯◯)

6.12 In adults with classic congenital adrenal hyperplasia, we recommend against routine adrenal imaging. (1|⊕◯◯◯)
Technical remark: Reserve adrenal imaging for individuals with classic congenital adrenal hyperplasia who have clinical evidence of an adrenal mass, poor disease control, a lapse in treatment of several years, or lack of response to intensified therapy.

6.13 In males with classic congenital adrenal hyperplasia, we recommend periodic testicular ultrasound to assess for the development of testicular adrenal rest tumors. (1|⊕⊕◯◯)

6.14 In patients with congenital adrenal hyperplasia, we recommend against routine evaluation for cardiac and metabolic disease beyond that recommended for the general population. (1|⊕⊕◯◯)
Technical remark: Clinicians should use their own judgment for the above procedures.

Restoring functional anatomy by surgery in individuals with congenital adrenal hyperplasia

7.1 In all pediatric patients with congenital adrenal hyperplasia, particularly minimally virilized girls, we advise that parents be informed about surgical options, including delaying surgery and/or observation until the child is older. (Ungraded Good Practice Statement)
Technical remark: Surgeries should be performed only in centers with experienced pediatric surgeons/urologists, pediatric endocrinologists, pediatric anesthesiologists, behavioral/mental health professionals, and social work services. Extensive discussions regarding risks and benefits, shared decision-making, review of potential complications, and fully informed consent need to occur prior to surgery. The option to forgo surgery should be considered.

7.2 In severely virilized females, we advise discussion about early surgery to repair the urogenital sinus. (Ungraded Good Practice Statement)

7.3 In the treatment of minors with congenital adrenal hyperplasia, we advise that all surgical decisions remain the prerogative of families (*i.e.*, parents

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and assent from older children) in joint decision-making with experienced surgical consultants. (Ungraded Good Practice Statement)

7.4 In female patients with congenital adrenal hyperplasia for whom surgery is chosen, we suggest vaginoplasty using urogenital mobilization and, when chosen, neurovascular-sparing clitoroplasty for severe clitoromegaly. (2|⊕○○○)

Experimental therapies and future directions

General considerations and unmet clinical needs

8.1 In patients with congenital adrenal hyperplasia, we advise against using experimental treatment approaches outside of formally approved clinical trials. (Ungraded Good Practice Statement)

Adrenalectomy

8.2 In patients with congenital adrenal hyperplasia, we suggest that bilateral adrenalectomy not be performed. (2|⊕○○○)

Mental health

9.1 For individuals with congenital adrenal hyperplasia and their parents, we recommend behavioral/mental health consultation and evaluation to address any concerns related to congenital adrenal hyperplasia. (1|⊕⊕○○)

Technical remark: Clinicians should be aware that individuals with congenital adrenal hyperplasia may be at risk for developing mental health problems and should have a low threshold for referral to psychological or psychiatric treatment. Mental health practitioners should have specialized expertise in assessing and managing congenital adrenal hyperplasia–related psychosocial problems.

Introduction

Summary of changes in 2018 congenital adrenal hyperplasia guidelines

Since the publication of the 2010 Endocrine Society clinical practice guideline for congenital adrenal hyperplasia [CAH (1)], there have been several changes. Neonatal diagnosis methods have been refined to use gestational age in addition to birth weight for cut-point interpretation or to employ liquid chromatography–tandem mass spectrometry (LC-MS/MS) as a secondary screening test. The standard for confirming a diagnosis of CAH continues to be serum 17-hydroxyprogesterone (17OHP) measurements, most often with cosyntropin stimulation. The advent of commercially available serum 21-deoxycortisol measurements may simplify identification of CAH carriers. The use of this analyte, or of steroid profiling to monitor treatment, has yet to be tested.

New human and animal data convey further concerns regarding prenatal dexamethasone (Dex) treatment. No international registry has yet been established for long-term outcomes of individuals treated prenatally with Dex. Although noninvasive prenatal diagnosis of fetal sex is now commonly performed, CAH genotype has been reported only in a proof-of-concept study and is not routinely available. This guideline now includes more detailed protocols for adults, especially pregnant women. We suggest more moderate use of stress dosing during minor illness or minor surgery in patients with CAH.

Over time, the approach to genital reconstructive surgery has changed, incorporating more shared decision-making among parents, patients, surgeons, endocrinologists, mental health providers, and support groups. A systematic review and meta-analysis of published literature on surgery for females with CAH through early 2017 could not identify enough scientifically rigorous studies delineating a favorable benefit-to-risk ratio for either early or late elective genital reconstructive surgery for females with CAH. We maintain that CAH should not be equated with other, rarer 46,XX or XY disorders of sex development (DSD) in formulating treatment guidelines and policies. Our goals have been consistently directed at preserving functional anatomy and fertility.

In another new meta-analysis, investigators found no direct well-controlled evidence of cardiovascular or metabolic morbidity and mortality associated with CAH. Thus, we recommend that individuals with CAH should be monitored according to conventional guidelines for monitoring CAH-unaffected children, adolescents, and adults. Retaining patients with CAH after "graduation" from pediatric care is an important goal, and we have stressed the need for improved mental health monitoring. Finally, in this guideline, we discuss potential new therapies and future ways to improve quality of life (QOL) for individuals with CAH.

Definition, pathophysiology, and morbidities of CAH

CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. Based on neonatal screening and national case registries, the worldwide incidence in most studies ranges from ~1:14,000 to 1:18,000 births, but the condition is more

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prevalent in small, genetically isolated groups with a smaller gene pool, particularly in remote geographic regions [*e.g.*, Alaskan Yupiks, among others; Table 1 (2–23)]. CAH is caused in ~95% of cases by mutations in *CYP21A2*, the gene encoding adrenal steroid 21-hydroxylase (P450c21) (24, 25). This enzyme converts 17OHP to 11-deoxycortisol and progesterone to deoxycorticosterone, with these products being precursors for cortisol and aldosterone. The blockage of cortisol synthesis leads to corticotropin stimulation of the adrenal cortex, with accumulation of cortisol precursors that are diverted to sex hormone biosynthesis (Fig. 1). A cardinal feature of classic or severe virilizing CAH in newborn females is abnormal development of the external genitalia with variable extent of virilization. Evaluation for CAH needs to be considered for infants found to have bilateral nonpalpable gonads. In 75% of cases with severe enzyme deficiency, inadequate aldosterone production causes salt wasting, failure to thrive, and potentially fatal hypovolemia and shock. Distinctions between various CAH phenotypes are detailed in White and Speiser (27). Newborn screening, now universal in the United States (28) and in many other developed countries (19), can mitigate these complications. Missed diagnosis of salt-losing CAH is associated with increased risk for early neonatal morbidity and mortality. If simple virilizing CAH is not recognized and treated, both girls and boys may undergo rapid postnatal growth and virilization.

In addition to the "classic salt-wasting" and "simple virilizing" forms of CAH diagnosed in infancy, there is also a mild or "nonclassic" form, which features variable degrees of postnatal androgen excess but is sometimes asymptomatic (29). The mild subclinical impairment of cortisol synthesis in nonclassic CAH (NCCAH) generally does not lead to Addisonian crises. Based on haplotype association studies, nonclassic forms of CAH were estimated to have a prevalence of 1:500 to 1:1000 in the general white population but up to 1:50 to 1:100 among populations with high rates of consanguineous marriages (30). More recent *CYP21A2* genotype analysis indicates that NCCAH has an overall frequency of ~1:200 (95% confidence level, 1:100 to 1:280) in the US population (31).

Disease severity correlates with *CYP21A2* allelic variation. Genotyping individuals with CAH is fraught with error due to the complexity of gene duplications, deletions, and rearrangements within chromosome 6p21.3 (32). Almost 300 *CYP21A2* mutations are known (33), but large deletions and a splicing mutation (intron 2, IVS-13 A/C→G, −13 nucleotides from the splice acceptor site) that ablate enzyme activity comprise

Table 1. Comparative Incidence of Classic CAH in Different Populations

Country	Complete National Data?	Sample Size	1/Incidence	PPV % (Term Infants or Overall)	Reference
Argentina (Buenos Aires)	No	80,436	8937	50	(2)
Australia (Western Australia)[a]	No	550,153	14,869	N/A	(3)
Australia (New South Wales)	No	185,854	15,488	1.8	(4)
Australia[a]	Yes		18,034	N/A	(4)
Brazil	No	748,350	14,967		(5)
Brazil (state of Goias)	No	82,603	10,325	28.6	(6)
Brazil (state of Minas Gerais)	No	159,415	19,927	2.1	(7)
Brazil (state of Rio Grande do Sul)	No	108,409	13,551	1.6	(8)
China	No	30,000	6084		(9)
Croatia	Yes	532,942	14,403		(10)
Cuba	Yes	621,303	15,931	0.3	(11)
Czech Republic	Yes	545,026	11,848	1.6	(12)
France	Yes	6,012,798	15,699	2.3	(13)
Germany (Bavaria)	No	1,420,102	12,457	5	(14)
India	No	55,627	6334		(15)
Japan (Sapporo)	No	498,147	20,756	8	(16)
Japan (Tokyo)	No	2,105,108	21,264	25.8	(17)
New Zealand	Yes	1,175,988	26,727		(18)
Sweden	Yes	2,737,932	14,260	25.1	(19)
United Kingdom[a]	Yes		18,248	N/A	(20)
United Arab Emirates	Yes	750,365	9030		(21)
Uruguay	Yes	190,053	15,800		(22)

Data are from newborn screening except those designated as coming from national case registries. Data are from studies published in 2008 and later. Earlier studies are summarized by van der Kamp and Wit 2004 (23) and Gidlof *et al.* 2014 (19).

Abbreviations: N/A, not available; PPV, positive predictive value (for newborn screening; see section 1).

[a]Data are from national case registries.

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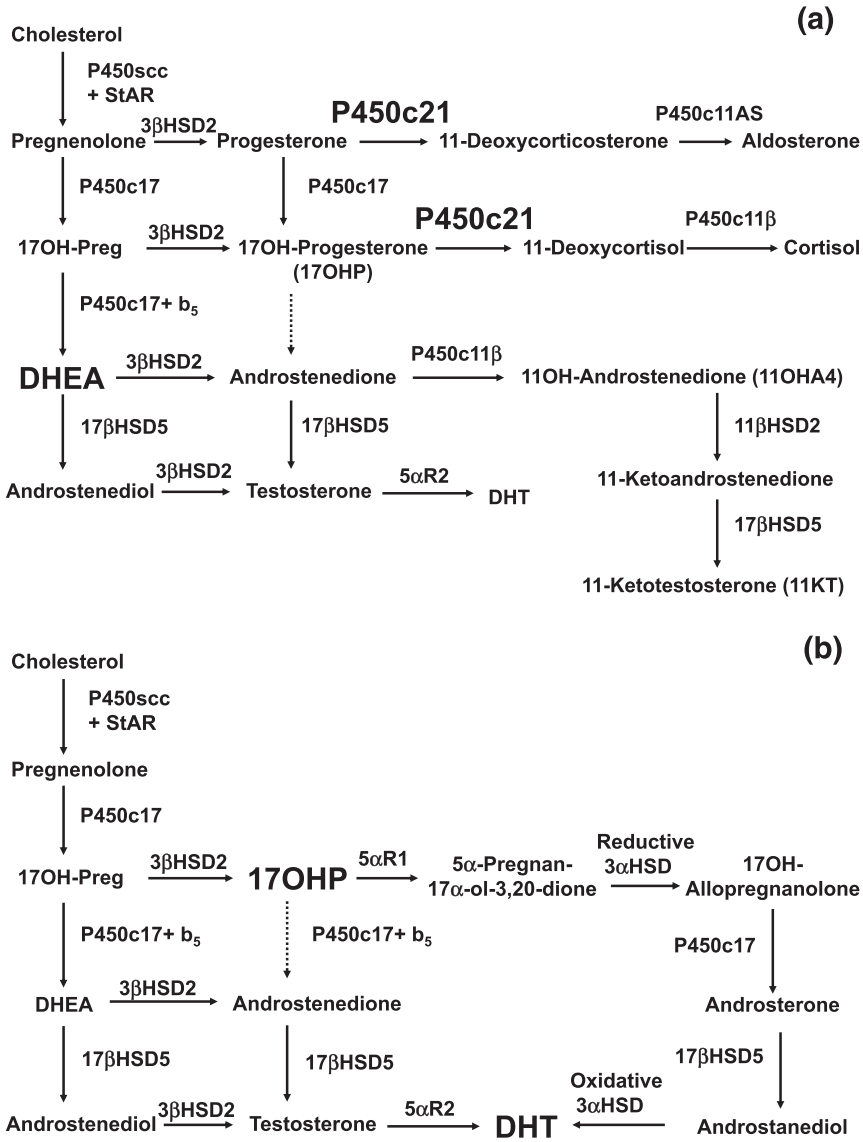

Figure 1. (a) Normal fetal adrenal steroidogenesis. Because the fetal adrenal has low levels of 3β-hydroxysteroid dehydrogenase, most steroidogenesis is directed toward dehydroepiandrosterone (DHEA) and thence to DHEA sulfate, but small amounts of steroids enter the pathways toward aldosterone and cortisol. The adrenal 21-hydroxylase P450c21 is essential in both pathways. The adrenal can synthesize small amounts of testosterone via 17βHSD5 (AKR1C3). Included to the lower right is the 11-oxyandrogen pathway, in which androstenedione is converted in the adrenal to 11β-hydroxyandrostenedione (11OHA4) and then in the adrenal and/or peripheral tissues to 11-ketoandrostenedione and ultimately 11-ketotestosterone (11KT). The production of 11OHA4 and 11KT is an important pathway in postnatal life and may also occur in the fetal adrenal. (b) In the absence of the 21-hydroxylase activity of P450c21, three pathways lead to androgens. First, the pathway from cholesterol to DHEA remains intact. Although much DHEA is inactivated to DHEA sulfate, the increased production of DHEA will lead to some DHEA being converted to testosterone and dihydrotestosterone (DHT). Second, although minimal amounts of 17OHP are converted to androstenedione in the normal adrenal, the massive amounts of 17OHP produced in CAH permit some 17OHP to be converted to androstenedione and then to testosterone. Third, the alternative pathway depends on the 5α and 3α reduction of 17OHP to 17OH-allopregnanolone. This steroid is readily converted to androstanediol, which can then be oxidized to DHT by an oxidative 3α-hydroxysteroid dehydrogenase (3αHSD) enzyme. The role of the alternative pathway in CAH is evidenced by increased levels of metabolites of its unique steroidal intermediates in the urine of infants, children, and adults with CAH (26).

~50% of classic CAH alleles (34–36). Approximately 5% to 10% of patients with salt-wasting CAH have the hypermobility form of Ehlers-Danlos syndrome due to haploinsufficiency of tenascin-X, encoded by the *TNXB* gene, which overlaps *CYP21A2* (37).

A nonconservative amino substitution in exon 4 (p.Ile172Asn) that preserves ~1% to 2% of enzyme function is associated with simple virilizing classic CAH (38). A point mutation in exon 7 (p.Val281Leu) that preserves 20% to 50% of enzyme function (38) accounts for most NCCAH alleles (31, 39, 40). Because many compound heterozygous patients carry more than one mutation on either or both *CYP21A2* alleles, there is a wide spectrum of phenotypes (35).

Commissioned Systematic Review

The writing committee commissioned two systematic reviews: one concerning the cardiac and metabolic morbidities associated with CAH (41), and the second to determine whether and when clinicians should perform genital surgery (42).

The first review (41) summarized 20 observational studies and demonstrated small but significant increases in systolic and diastolic blood pressure, insulin resistance, and carotid intima thickness in individuals with CAH compared with non-CAH controls. The quality of evidence (*i.e.*, certainty in these estimates) was low due to the observational nature of the evidence, risk of bias, and heterogeneity. Furthermore, population-based studies found higher prevalence of hypertension, hyperlipidemia, and type 2 diabetes in adults with CAH than in non-CAH controls.

The second review (42) summarized 29 observational studies evaluating patients who had undergone surgery at a mean age of 3 years. The studies evaluated various surgical techniques and reported good overall patient and surgeon satisfaction with cosmetic and functional outcomes. The review also provided estimates of surgical complication rates and sexual function. Such evidence was also of low quality and carried a high risk of bias.

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1. Newborn Screening

Cost-effectiveness

1.1 We recommend that all newborn screening programs incorporate screening for CAH due to 21-hydroxylase deficiency (21OHD). (1|⊕⊕⊕◯)

Evidence

Early recognition and treatment of CAH can prevent serious morbidity and mortality. Currently, all 50 states in the United States, 35 other countries, and portions of 17 additional countries screen for CAH. According to screening results, the incidence of classic CAH in most populations is ~1:14,000 to 1:18,000. Table 1 summarizes data from 2008 onward; data collected from 1997 to 2007 are similar (23, 43, 44).

Screening markedly reduces the time to diagnosis of infants with CAH (45–48), consequently reducing morbidity and mortality. A retrospective analysis of neonatal dried blood samples that were not screened for CAH from cases of sudden infant death in the Czech Republic and Austria identified three genotypically confirmed cases of classic CAH among 242 samples screened (49). In contrast, a large population-based study in the Manchester area of the United Kingdom found no CAH cases among 1198 dried blood samples from infants who had died between 5 days and 6 months of age (50). Males with salt-wasting CAH are more likely than females to suffer from delayed or incorrect diagnosis, as there is no genital ambiguity. Thus, a relative paucity of salt-wasting males in a patient population may be taken as indirect evidence of unreported deaths from salt-wasting crises. In fact, females outnumber males in some (10, 51–53), although not all (50, 54), retrospective studies in which CAH is clinically diagnosed, and this preponderance of females vanishes when newborn screening is introduced (54). Some researchers have reported a death rate of ~10% among infants with salt-wasting CAH in the absence of screening (55), but recent estimates from advanced economies are lower, at 0% to 4% (56).

In regard to morbidity, infants diagnosed through screening have less severe hyponatremia (48) and tend to have shorter hospitalizations (46, 48, 50, 57) than infants diagnosed later. Learning disabilities may occur in patients who have had salt-wasting crises (58). Although salt-wasting males would seem to derive the greatest benefit from screening programs, the delay before correct sex assignment of severely virilized females is also reduced (43, 48). Moreover, males with simple virilizing disease may otherwise not be diagnosed until rapid growth and accelerated skeletal maturation are observed in later childhood, leading to compromised adult stature.

Several recent reviews have attempted cost-benefit analysis of newborn screening for CAH. Such estimates generally assume that the only adverse outcome of late diagnosis of CAH is death. It is conventionally assumed that screening for a particular disease is cost-effective at <$50,000 per life-year per quality-adjusted life year (59). Recent estimates have ranged widely from $20,000 (59) to $250,000 to $300,000 (60) per quality-adjusted life year.

Initial screening methodology

1.2 We recommend that first-tier screens use 17OHP assays standardized to a common technology with norms stratified by gestational age. (1|⊕⊕⊕◯)
Technical remarks: Clinicians should be aware that immunoassays are still in use and remain a source of false-positive results. Specificity may be improved with organic extraction to remove cross-reacting substances.

Evidence

First-tier screens for CAH employ immunoassays to measure 17OHP in dried blood spots on the same filter paper ("Guthrie") cards used for other newborn screening tests (46, 59, 61). The automated time-resolved dissociation-enhanced lanthanide fluoroimmunoassay (62) has almost completely supplanted the original radioimmunoassay (63) and other types of assays.

Several technical factors limit the accuracy of these tests. First, 17OHP levels are normally high at birth and decrease rapidly during the first few postnatal days in healthy infants. In contrast, 17OHP levels increase with time in infants affected with CAH. Thus, diagnostic accuracy is poor in the first 2 days unless robust mechanisms exist to obtain follow-up samples. Second, female infants have lower mean 17OHP levels than do males, slightly reducing the sensitivity of newborn screening in some reports (64). This reduced sensitivity is generally not a major problem because almost all females with salt-wasting CAH are virilized, and thus are brought to prompt medical attention. Third, premature, sick, or stressed infants have higher levels of 17OHP than do term infants, generating many false positives. For example, in 26 years of operation of the Swedish screening program, the positive predictive value was 25% for full-term infants but only 1.4% for preterm infants, and the predictive value correlated very strongly with gestational age (19). Finally, immunoassays may lack specificity. There are no universally accepted standards for stratifying infants, but most laboratories use a series of birth weight–adjusted cut-offs (65–67).

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Screening a second sample several days later also improves both sensitivity and positive predictive value (47, 61, 68). A recent study suggested that preterm infants should have additional samples rescreened at 2 and 4 weeks of age, which is practical in hospitalized patients (67). Similarly, Brazilian investigators used 99.8 percentile 17OHP values, adjusted for birth weight, to achieve 5.6% and 14.1% positive predictive value at two sampling time points (48 to <72 hours and ≥72 hours, respectively) (69). Moreover, a comparison of one-screen vs two-screen state programs found a higher incidence of CAH when a second screen was employed (1:17,500 vs 1:9500) (70).

Stratifying subjects by actual gestational age rather than birth weight might also improve the specificity of newborn screening, as 17OHP levels are much better correlated with the former variable than with the latter (71). In the Netherlands, adopting gestational age criteria improved the positive predictive value of screening from 4.5% to 16% (57).

With regard to assays, elevated levels of adrenal steroids are not due solely to cross-reaction in immunoassays. Steroid profiles in preterm infants suggest a functional deficiency of several adrenal steroidogenic enzymes with a nadir at 29 weeks gestation (72). However, immunoassays are still in use but may be a source of false-positive results due to cross-reactivity with other steroids, for example, 17-OH-pregnenolone sulfate (73). Immunoassay specificity may be improved with organic extraction to remove cross-reacting substances, such as steroid sulfates.

The dissociation-enhanced lanthanide fluoroimmunoassay was reformulated in late 2009 to reduce its sensitivity to cross-reacting compounds in premature infants (74). This change improved the positive predictive value from 0.4% to 3.7% for the first screen alone (61).

Finally, antenatal corticosteroids may reduce 17OHP levels, potentially increasing the likelihood of false-negative screens. Studies have reported inconsistent effects of antenatal corticosteroid administration in practice (75, 76). As previously noted, testing of later samples would minimize this problem.

Second-tier screening

1.3 We recommend that screening laboratories employ a second-tier screen by LC-MS/MS in preference to all other methods (*e.g.,* genotyping) to improve the positive predictive value of CAH screening. (1|⊕⊕◯◯)

Technical remark: Laboratories utilizing LC-MS/MS should participate in an appropriate quality assurance program. Additionally, clinicians should realize that immunoassays lead to more false-positive results. Thus, if laboratory resources do not include LC-MS/MS, a cosyntropin stimulation test should be performed to confirm diagnosis prior to initiation of corticosteroid treatment.

Evidence

Decreasing cut-off levels may increase sensitivity, but at a cost of a decreasing positive predictive value. In the United States, the cut-off levels for 17OHP are typically set low enough that clinicians report ~1% of all tests as positive, with the aim of identifying all children with salt-wasting disease and almost all simple virilizing disease. Because CAH is a rare disease, the positive predictive value is very low, although the specificity and sensitivity are very high (77). In contrast, cut-off values that still identified all infants with salt-wasting CAH but only ~80% of cases of simple virilizing CAH yielded a positive predictive value of 25% in term infants (19). We could avoid much of the expense and parental anxiety of following up positive newborn screening tests with a specific and sensitive second-level screen. Both biochemical and molecular genetic approaches can be used.

Biochemical second screens. Limitations of immunoassays for 17OHP include true elevation of levels in premature infants or those who are sick or stressed, and lack of antibody specificity. Organic solvent extraction to increase immunoassay specificity is currently mandated as a second screen in several US states.

However, direct biochemical analysis of steroids using LC-MS/MS is more effective than immunoassays in addressing these issues (78, 79). The run times for individual samples in such assays are 6 to 12 minutes, impractical for screening large numbers of samples, but suitable for the smaller numbers subjected to a second-tier screen using the original dried blood samples (78, 80). It is noteworthy that ~40% of samples that are positive in first-tier screens with immunoassays actually have normal 17OHP levels as measured by LC-MS/MS, consistent with suboptimal antibody specificity. Measuring steroid ratios may further improve the screening specificity of LC-MS/MS. One approach has examined a ratio defined as the sum of 17OHP and androstenedione levels divided by the cortisol level (81). This strategy was used in actual practice as the second-tier screen in Minnesota for 3 years (204,000 births) and improved the positive predictive value of the CAH screen (82), but subsequent reports from the same center suggested that this approach was inferior to testing a second sample by routine immunoassay (67, 68). However, others have reported markedly superior results with LC-MS/MS

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(83, 84). The consistency of results might be improved by mandating participation in national proficiency testing programs (85).

Measuring additional analytes or ratios of analytes can also improve screening outcomes. For instance, 21-deoxycortisol (produced by 11β-hydroxylation of 17OHP) is normally not secreted in large amounts (even in preterm infants), and thus elevated levels are highly specific for 21OHD. A modified LC-MS/MS protocol used a ratio defined as the sum of 17OHP and 21-deoxycortisol levels divided by the cortisol level, and this parameter correctly identified all affected children with no false positives, for a positive predictive value of 100% (80). The ratio of the urinary metabolites pregnanetriolone and 6α-hydroxytetrahydrocortisone, measured by gas chromatography and tandem mass spectrometry, also gave excellent specificity, even in preterm infants (86).

Molecular genetic second screens. *CYP21A2* mutations can be detected in DNA extracted from the same dried blood spots used for hormonal screening. Detection methods include dot-blotting protocols (87), ligation detection assays (88, 89), real-time quantitative PCR (90, 91), full sequencing (92), and minisequencing (93). Because >90% of mutant alleles carry one or more of a discrete number of mutations, if no mutations are detected, one can assume that the individual is unaffected. If at least one mutation is detected, the patient requires additional evaluation. The carrier rate for classic CAH in the general population is ~2%; if this rate were not increased among infants with a positive first screen (90), and 1% of all first screens were positive, then 0.02% (1/5000) of all infants would have a positive second screen by this strategy. Because the actual frequency of CAH is ~0.006% (~1/16,000), the positive predictive value of this approach should be ~30%. There are two reasons why we cannot use the analysis of a single sample to actually diagnose CAH. First, a heterozygous carrier of a known mutation for classic 21OHD could have an undetected novel mutation in the other allele. Second, many CAH alleles carry more than one deleterious mutation, making it impossible to set phase (*i.e.*, to determine whether two mutations are on different alleles or the same allele) without genotyping at least one parent.

Several studies on the genotyping of samples from screening programs have suggested that this approach is a potentially useful adjunct to hormonal measurements (6, 87, 88, 90, 92, 94), but to the best of our knowledge there has been no large-scale study of its efficacy as a second-tier screen in actual use.

Genotyping remains more costly and time-consuming than LC-MS/MS on a per-sample basis. Although the equipment for LC-MS/MS is expensive, many screening programs already have it available for other tests.

Balance of benefits and harms

The writing committee placed a higher value on the benefits of complete ascertainment of infants affected with classic CAH and minimizing the consequences of neonatal salt-wasting crises than on the additional expense of following up false-positive screens.

2. Prenatal Treatment of CAH

2.1 We advise that clinicians continue to regard prenatal therapy as experimental. Thus, we do not recommend specific treatment protocols. (Ungraded Good Practice Statement)

2.2 In pregnant women at risk for carrying a fetus affected with CAH and who are considering prenatal treatment, we recommend obtaining prenatal therapy only through protocols approved by Institutional Review Boards at centers capable of collecting outcomes from a sufficiently large number of patients, so that risks and benefits can be defined more precisely. (1|⊕⊕⊕◯)

2.3 We advise that research protocols for prenatal therapy include genetic screening for Y-chromosomal DNA in maternal blood to exclude male fetuses from potential treatment groups. (Ungraded Good Practice Statement)

Evidence

The Endocrine Society's 2010 CAH guidelines summarized the physiology of prenatal treatment of CAH and the results of studies published through the end of 2009 (1). Prenatal treatment with Dex aims to reduce female genital virilization and its associated risk of social stigma (95), the need for reconstructive surgery, and the emotional distress associated with the birth of a child with atypical sexual development. Prenatal treatment is inappropriate for male fetuses, as this form of CAH does not disrupt the development of male genitalia. Prenatal treatment does not change the need for lifelong hormonal replacement therapy, the need for careful medical monitoring, or the risk of life-threatening salt-losing crises if therapy is interrupted. Some researchers have suggested that prenatal Dex may reduce potential androgenization of the fetal female brain, but such effects are difficult to measure and have not been studied systematically. The following paragraphs describe relevant considerations regarding prenatal Dex treatment.

Prenatal treatment has been suggested for women who have previously delivered a child with CAH and are pregnant again via the same partner. The fetus will have a

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1:4 chance of having CAH and a 1:2 chance of being female; thus, there is a 1:8 chance that the fetus will be female and have CAH. Because the period during which fetal genitalia may become virilized begins ~6 weeks after conception, treatment must be started by 6 to 7 weeks. Because genetic diagnosis by chorionic villous biopsy cannot be performed until 10 to 12 weeks, all pregnancies at risk for CAH would need to be treated, although the treatment is directed at only one in eight fetuses.

Specialized laboratories can perform sex determination from fetal Y-chromosome DNA in maternal blood with 99% accuracy (96), which could improve the probability of treating an affected female fetus from 1:8 to 1:4. In a study of prenatal treatment in 258 fetuses at risk for CAH from 2002 to 2011, testing for Y-chromosome DNA prevented treatment with Dex in only 68% of male fetuses, although the percentage rose during the course of the study (97). We suggest that prenatal sex determination be incorporated into all prenatal treatment research protocols; however, prenatal sex determination is illegal in some countries to prevent female feticide (98). We think that prenatal diagnosis and treatment research should not be performed in such countries. By using blood from both parents and an affected proband and applying massively parallel DNA sequencing coupled with extensive analysis of single nucleotide polymorphisms near the *CYP21A2* gene, it was possible to determine the *CYP21A2* genotype in 14 of 14 at-risk fetuses within 3 weeks of obtaining fetal DNA in maternal blood samples (99). This approach currently requires expensive equipment and very skillful personnel that are found only in advanced research centers, but the approach holds promise for the future.

In contrast to cortisol and prednisolone, Dex is not inactivated by placental 11βHSD2 and readily reaches the fetus. Therefore, virtually all reports of prenatal treatment use Dex, typically at doses of 20 μg/kg prepregnancy maternal body weight, to a maximum of 1.5 mg/d. In normal, untreated pregnancies, fetal cortisol levels are low in very early gestation and rise during weeks 8 to 12, while the external genitalia are differentiating (100); fetal cortisol is only ~10% of maternal levels during midgestation (101) and then increases during the third trimester. If Dex freely traverses the placenta, a dose of 20 μg/kg maternal body weight could achieve effective glucocorticoid (GC) levels that exceed typical midgestation fetal levels by ~60-fold (102). No studies have systematically tested reducing the dose in late gestation.

Efficacy. Available evidence regarding fetal outcomes and maternal sequelae of prenatal Dex treatment is of low or very low quality due to methodological limitations and small sample sizes. A systematic review and meta-analysis of reports of prenatal treatment published through August 2009 found only four studies that included a control group and provided sufficient data to analyze (103). Among 325 pregnancies treated with Dex, affected female fetuses had a weighted mean difference of −2.33 (95% CI, −3.38 to −1.27) on the Prader scale. Data concerning stillbirths, spontaneous abortions, fetal malformations, and neuropsychological outcomes were sparse, and long-term follow-up data were not reported. Aside from individual case reports, only two series of prenatal treatment of CAH have appeared since August 2009. An update of an ongoing practice in New York reported 63 treated female fetuses with classic CAH, of whom 15 had normal female genitalia, 26 had mild (Prader stages 1 to 2) virilization, and 17 had severe (Prader stages 3 to 5) virilization (mean score, 1.7) (104). In a 10-year French study, among 112 treated female fetuses, 14 had 21-hydroxylase–deficient CAH and three had 11-hydroxylase–deficient CAH; of these 17 girls, 12 had normal female genitalia at birth and 3 had moderate virilization, whereas 2 who were treated late were severely virilized (97). Thus, prenatal Dex is effective in reducing genital virilization of affected female fetuses. Poor results are typically ascribed to delayed treatment or noncompliance (105).

Maternal safety. Some studies have reported increased pregnancy-associated weight gain, striae, edema, gastric distress, and mood swings but minimal hypertension and gestational diabetes (94, 103). Some women reported Cushingoid features and increased appetite, and many women indicated that they would decline prenatal treatment of a subsequent pregnancy. Thus, prenatal treatment is associated with modest but manageable maternal complications that do not appear to pose a major risk to the mother.

Fetal safety. The US Food and Drug Administration classifies Dex as a category C drug whose safety in pregnancy is not established: according to the US Food and Drug Administration, "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks" (106). The Endocrine Society's 2010 CAH guideline reviewed earlier studies concerning the safety of prenatal Dex and other transplacental GCs (1); only the most important are reiterated here. Recent studies address four areas of concern: potential teratogenicity, birth weight, brain/behavior, and potential long-term effects.

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Teratogenicity. Consistent with animal data that Dex can cause cleft palate, the National Birth Defects Prevention Study reviewed 1769 infants with cleft lip with/without cleft palate born to women who received GCs during the first trimester, finding statistically increased risks of orofacial clefts compared with 4143 controls (107). A recent case report cited the first known instance of an orofacial cleft in a girl affected with CAH treated prenatally with Dex (108). Acute encephalopathy was reported in two infants who had received prenatal Dex, but it is not clear whether this condition was related to prenatal steroid exposure (109). Teratogenic effects of Dex observed in animal models include renal dysgenesis, reduced pancreatic β cell numbers, impaired glucose tolerance, and increased systolic and diastolic blood pressure, all discussed previously (1). Evidence continues to accumulate implicating Dex in numerous developmental defects: exposing fetal rats to Dex altered hepatic programming and increased lipid accumulation (110). Impaired thyroid development with reduced numbers of follicular cells and C cells was observed in another study (111). Incubation of 8- to 11-week-postfertilization human fetal ovaries with Dex doses corresponding to prenatal CAH treatment reduced germ cell density by increasing apoptosis in oogonia (112). Only ~800 fetuses receiving Dex in the first trimester have been reported to date, and potential teratogenicity was not evaluated in all fetuses.

Birth weight and sequelae. Multiple doses of antenatal betamethasone can improve pulmonary outcome in preterm infants but are associated with decreased newborn weight, length, and head circumference (113–116). Similarly, newborns prenatally treated with Dex for potential CAH have nominally normal birth weights but nevertheless weigh ~400 g less than controls (117). Reduced birth weight increases adult risk for chronic disorders, including hypertension, type 2 diabetes, and cardiovascular disease (118); one study associated fetal malnutrition with exposure to GCs (119). Young adults exposed to antenatal GCs have increased aortic stiffness (120). Human placental chorionic plate arteries abundantly express GC receptors; chronic GC exposure *in vitro* alters vasoreactivity, increasing vascular resistance and potentially contributing to hypertension (121). These observations concerning the developmental origins of adult disease have raised concerns about potential prenatal "programming" by fetal exposure to Dex (119, 122–124).

Brain and behavior. Adverse effects of GCs on brain development have been reported in human and animal studies (125–127). In rodents, Dex inhibits hippocampal neuronal maturation *in vitro* (128) and *in vivo* (129–131), and Dex limits proliferation of neural progenitor cells in cultured embryonic mouse neurospheres (132).

A small, well-designed Swedish study found no differences in intelligence, learning, or long-term memory between children who were prenatally exposed to Dex and those who were not, but the former group had reduced verbal working memory, reduced self-perception of scholastic competence, and increased self-rated social anxiety (133); in contrast, their parents described them as being more sociable than controls (134). Prenatally treated boys had reduced masculine and increased neutral behavior, suggesting unexpected effects on gender-role behavior (135). A follow-up study by the Swedish group found that the negative effects of Dex were sex-specific. Unaffected Dex-treated girls scored lower than did control girls on the Wechsler Intelligence Test for Children III and in visual–spatial working memory. In contrast, boys showed no cognitive impairment (136). The basis for a putative sex-specific effect of Dex is unknown.

Systematic review and meta-analysis of several studies did not detect significant differences in behavior or temperament depending on prenatal Dex exposure (103, 137, 138). Another study did not find effects on working memory in short-term exposed unaffected children or short-term exposed boys with CAH, but girls with CAH treated throughout pregnancy had slower mental processing than did controls by several assessments (139). A very small study from Poland reported improved neurocognitive function among girls with CAH who had received prenatal Dex, although the unaffected, Dex-treated girls had reduced visual perception and visual memory (140). Differences among studies may reflect inadequate sample size, inappropriate controls, or the effects of postnatal infant–mother bonding, which can partially ameliorate the effects of fetal exposure to GCs (141). Although data are inconclusive, any adverse effects of Dex on brain development would be unacceptable.

The long-term effects of fetal GC exposure have been studied in infants whose mothers received Dex or betamethasone to promote fetal lung maturation (142). In this setting, prenatal GC exposure alters the hypothalamic–pituitary–adrenal axis, augmenting the cortisol response to stress (143) with adverse mental health sequelae in childhood and adolescence (144). Long-term effects of postnatal GC on the human brain include decreased memory and hippocampal volume (145), decreased cerebellar cortical volume (146), diminished cognitive function (147–149), increased psychopathology, and reduced QOL (148, 150)

Two confounding factors should be considered in future studies of side effects. First, individuals with CAH

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who were not prenatally exposed to Dex may have reduced working memory or short-term memory (137, 138). Second, women with CAH had reduced test scores for working memory, processing speed, digit span, and matrix reasoning compared with controls (151). Brain MRI showed effects on the white matter, hippocampus, thalamus, cerebellum and brainstem; magnetic resonance spectroscopy also showed reduced choline content in the temporal lobe. Patients treated with higher GC doses had greater abnormalities (151).

Potential long-term effects. Long-term effects of fetal exposure to GCs are well described (116). A retrospective epidemiological study found that antenatal Dex used to induce late-gestation pulmonary maturation was an independent risk factor for development of asthma at 3 to 6 years (152). Among 24 prematurely born children who received prenatal Dex for pulmonary maturation, the incidence of asthma and allergic disorders was higher at ages 2 to 5 than among 16 matched controls (153). Studies in rats receiving Dex during gestation showed decreased GC responsiveness and receptor expression (154), as well as suppression of innate cytokines with induction of adaptive cytokines (155).

Individuals who had received antenatal betamethasone 30 years earlier had increased insulin resistance, and 7% had elevated basal cortisol (156). Antenatal synthetic GCs alter fetal rodent DNA methylation, permanently affecting the expression of genes involved in carbohydrate homeostasis and the programming of the hypothalamic–pituitary–adrenal axis (157). Brief maternal exposure to Dex reduced adrenal expression of steroidogenic enzymes during adulthood in mice (158). Altered DNA methylation apparently underlies the long-term effects of both GCs and maternal stress on the fetus (129–131). Effects on subsequent generations may reflect effects on precursor germ cells in the developing gonad (112). Whether and to what extent the alterations observed in the rodent model of prenatal Dex exposure occur in humans cannot be readily determined.

Balance of benefits and harms

Antenatal treatment with CAH remains controversial and poses unresolved ethical questions. Consequently, the 2010 Endocrine Society practice guidelines recommended that "prenatal therapy continue to be regarded as experimental" (1). Since then, the group studying prenatal treatment in Sweden has discontinued this treatment because of "possible adverse side effects" (159). The German Society of Pediatric Endocrinology and Diabetology in conjunction with five other German medical societies concluded that "Prenatal CAH therapy is still an experimental therapy" (160). A "Clinical Opinion" in the American Journal of Obstetrics and Gynecology concluded that the "risks outweigh the benefits" (102). Risk-benefit analysis must consider the need to treat multiple unaffected fetuses, however briefly, without direct benefit to treat one affected female; accumulating data suggesting potential long-term risks from fetal Dex therapy render this approach problematic. Therefore, in validating earlier expert opinion, this writing committee placed a higher value on preventing unnecessary prenatal exposure of the fetus and mother to Dex and avoiding potential harms associated with this exposure than on minimizing the emotional toll of atypical external genital development on parents and patients. Preimplantation genetic diagnosis and other evolving assisted reproductive technologies are additional options (161, 162) but carry their own risk and ethical controversies (163), but this is beyond the context of this guideline.

3. Diagnosis of CAH

3.1 In infants with positive newborn screens for CAH we recommend referral to pediatric endocrinologists (if regionally available) and evaluation by cosyntropin stimulation testing as needed. (1l⊕⊕⊕◯)

3.2 In symptomatic individuals past infancy, we recommend screening with an early morning (before 8 AM) baseline serum 17OHP measurement by LC-MS/MS. (1l⊕⊕⊕◯)

3.3 In individuals with borderline 17OHP levels, we recommend obtaining a complete adrenocortical profile (defined below) after a cosyntropin stimulation test to differentiate 21OHD from other enzyme defects. (1l⊕⊕⊕◯)

3.4 In individuals with CAH, we suggest genotyping only when results of the adrenocortical profile after a cosyntropin stimulation test are equivocal, or cosyntropin stimulation cannot be accurately performed (*i.e.*, patient receiving GC), or for purposes of genetic counseling. (2l⊕⊕⊕◯)
Technical remark: Genotyping at least one parent aids in the interpretation of genetic test results because of the complexity of the *CYP21A2* locus.

Evidence

In neonates with a positive screen, the decision of whether to inform only the infant's primary physician or a pediatric endocrinologist depends on the availability of subspecialists (47). Usually, the primary care provider follows up moderately elevated 17OHP with a repeat filter paper specimen and evaluates higher values with serum electrolytes and 17OHP levels. If these measurements are abnormal, the clinician refers the infant to a pediatric endocrinologist.

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Second-tier screening with LC-MS/MS can efficiently measure a panel of steroids and permit diagnosis of other forms of CAH, as has been shown for 11β-hydroxylase deficiency (164, 165). If basal serum or filter paper results are not fully informative, it is necessary to evaluate the patient with a cosyntropin stimulation test (166). Extant norms are for tests employing a pharmacological dose of 0.25 mg given intravenously (in infants with very low birth weight, the dose may be reduced to 0.125 mg) of cosyntropin (ACTH [1–24]), which maximally stimulates the adrenal cortex. This diagnostic test is distinguished from the low-dose ACTH stimulation test used to evaluate the integrity of the hypothalamic–pituitary–adrenal axis (167). Samples should be obtained at baseline and 60 minutes after administering cosyntropin. At minimum, cortisol and 17OHP should be measured, but 17OHP may be elevated in the presence of other enzymatic defects, particularly 11β-hydroxylase deficiency and, more rarely, 3β-hydroxysteroid dehydrogenase deficiency or P450 oxidoreductase deficiency. To fully differentiate the various enzymatic defects potentially causing CAH, clinicians should ideally send samples to an endocrine reference laboratory for measurement of 17OHP, cortisol, 11-deoxycorticosterone, 11-deoxycortisol, 17-OH-pregnenolone, dehydroepiandrosterone, and androstenedione by LC-MS/MS. If blood volume or venous access are at issue in small infants, a sample can be collected only at 60 minutes following intravenous or intramuscular cosyntropin administration. Product ratios are particularly useful in distinguishing enzymatic defects (164, 165). As an alternative to blood sampling, urine samples can be analyzed at a few special centers using gas chromatography–mass spectrometry or LC-MS/MS; this approach provides a similarly accurate biochemical diagnosis (168).

Cosyntropin stimulation tests should be deferred until after the first 24 to 48 hours of life. There is a high incidence of both false-positive and false-negative results when clinicians obtain samples immediately after birth. Other steroids whose levels are usually elevated in 21OHD include 21-deoxycortisol, androstenedione, and testosterone.

In symptomatic individuals past infancy, LC-MS/MS on serum samples obtained prior to 8 AM should be used to screen for CAH. In menstruating females, we recommend sampling in the early follicular phase. Figure 2 contains a sample diagnostic strategy (169–172). Cosyntropin stimulation is needed for patients with indeterminate baseline 17OHP levels. For patients with nondiagnostic stimulated 17OHP values, particularly those receiving GC therapy, genotyping (171, 176, 177) may confirm the diagnosis.

Hormonal phenotypes correlate quite well with *CYP21A2* genotypes; however, genotyping cannot detect salt wasting. For example, genotyping may reveal the

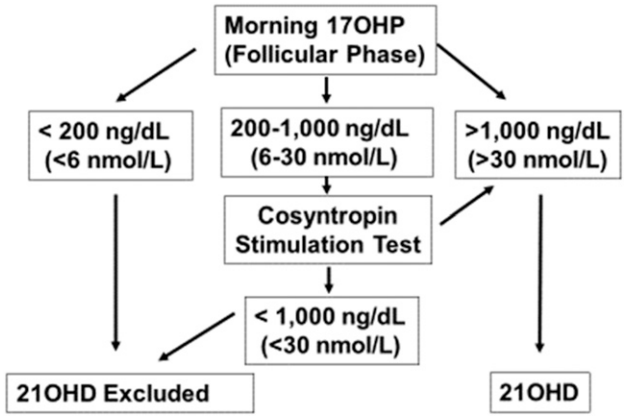

Figure 2. Diagnosis of 21OHD. Reference standards for hormonal diagnosis were derived from Refs. (170, 171, 173, 174). These diagnostic thresholds appear similar for LC-MS/MS assays from limited data (175). Note that randomly measured 17OHP levels can be normal in NCCAH; hence, 17OHP levels should be screened in the early morning (before 8 AM). For menstruating females, steroid measurements should be obtained in the follicular phase and may differ depending on the assay employed. Individuals with classic CAH, including both salt-wasting and simple virilizing forms of 21OHD, typically have unstimulated 17OHP values of several thousand. Note that it is sometimes difficult to distinguish clinically between non–salt-wasting classic and nonclassic forms of CAH.

IVS2 the salt-wasting and simple virilizing forms (35, 178, 179). Heterozygotes have slightly elevated 17OHP after ACTH stimulation, but there is overlap with unaffected subjects (173). Other analytes have been used as markers of heterozygosity (180, 181), but genotyping is a superior method of heterozygote detection. Heterozygotes do not require medical treatment but should have genetic counseling (see section 6.3).

4. Treatment of Classic CAH

4.1 In growing individuals with classic CAH, we recommend maintenance therapy with hydrocortisone (HC). (1|⊕⊕⊕◯)

4.2 In growing individuals with CAH, we recommend against the use of oral HC suspension and against the chronic use of long-acting potent GCs. (1|⊕⊕⊕◯)

4.3 In the newborn and in early infancy, we recommend using fludrocortisone and sodium chloride supplements to the treatment regimen. (1|⊕⊕⊕◯)

4.4 In adults with classic CAH, we recommend using daily HC and/or long-acting GCs plus mineralocorticoids (MCs), as clinically indicated. (1|⊕⊕⊕◯)

4.5 In all individuals with classic CAH, we recommend monitoring for signs of GC excess, as well as for signs of inadequate androgen normalization, to optimize the adrenal steroid treatment profile. (1|⊕⊕⊕◯)

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4.6 In all individuals with classic CAH, we recommend monitoring for signs of MC deficiency or excess. (1l⊕⊕⊕◯)

Evidence

Proper treatment with GCs prevents adrenal crisis and virilization, allowing nearly normal growth and development during childhood. Management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism. For infant patients, clinicians may exceed the recommended GC doses to reduce markedly elevated adrenal hormone levels, but it is important to rapidly reduce the dose when target levels are achieved. Frequent reassessment is needed. Attempts to completely normalize 17OHP levels typically result in overtreatment with features of Cushing syndrome. Infants with classic 21OHD require GCs in addition to MC treatment and supplemental sodium chloride. The requirement for sodium in normally growing infants is ~1 mmol/kg per day, the amount provided by human milk. However, in patients with salt-wasting CAH, this amount is insufficient, and sodium chloride supplements are recommended (182). Ideally, a standardized salt solution prepared by a pharmacy or standard sodium chloride tablets should be used for salt supplementation. Sodium chloride supplementation may not be needed if high-dose fludrocortisone is used (183); however, it is particularly important to monitor blood pressure in infants who require treatment with high doses of MC, owing to the variable capacity of the immature renal tubules to reabsorb sodium. Clinicians should reassess MC and sodium doses periodically based on blood pressure, serum sodium, potassium, and plasma renin activity (PRA).

Although the defect in aldosterone biosynthesis is clinically apparent only in the salt-wasting form, subclinical aldosterone deficiency is present in all forms of 21OHD (184, 185) and is best evaluated by the aldosterone-to-PRA ratio (184). Consequently, all individuals with classic CAH benefit from fludrocortisone therapy and adequate dietary sodium beginning in infancy. Maintaining sodium balance is essential for euvolemia and for reducing vasopressin and ACTH, allowing reduced GC doses and thus leading to better growth (186).

During childhood, the preferred GC is HC because its short half-life minimizes the adverse side effects typical of longer-acting, more potent GCs, especially growth suppression (Table 2) (187). In one trial, the estimated growth-suppressive effect of prednisolone was ~15-fold more potent than that of HC (188); Dex may be up to 70- to 80-fold more potent than HC (189). Although free-alcohol HC suspensions achieve cortisol levels comparable to those achieved by HC tablets (190), HC cypionate oral suspensions were inadequate to control CAH in children (191) due to uneven distribution in liquid form. Good control can be achieved by orally administering crushed, weighed HC tablets mixed with a small volume of liquid, if needed, immediately before administration. Compounding pharmacies should be chosen for reliability in preparing very small doses or special drug formulations, as there have been reports of variable dose accuracy in compounded preparations (192–194).

Insufficient data exist to recommend fractional distribution of doses throughout the day or empiric dosing in the very early morning hours (195). When doses exceed 20 mg/m^2 per day in infants or 15 to 17 mg/m^2 per day in adolescents, there is a decrease in height standard deviation score (SDS), leading to a decreased adult height SDS (196–199).

Table 2 provides suggested dosing guidelines. Differences in HC absorption and half-life occur, which may influence HC dosing requirements (200). Although prednisolone and Dex treatments are effective in suppressing adrenal androgens in children with CAH, these more potent drugs are more likely than HC to impede statural growth and cannot be routinely recommended. During puberty, even if replacement therapy and compliance are adequate, control may be suboptimal because of increased cortisol clearance (201). The adult height of patients with CAH correlates negatively with the dose of GC administered in early puberty; patients treated with <20 mg of HC/m^2 per day at the start of puberty are significantly taller than those given higher HC doses (187). Therefore, as with younger patients, it is important during puberty to treat with the lowest effective dose to achieve treatment goals.

At or near completion of growth, long-acting GCs may be administered (Table 3), although HC remains the

Table 2. Maintenance Therapy in Growing Patients with CAH

Drugs	Total Daily Dose	Daily Distribution
GCs: HC tablets	10–15 mg/m^2·d	3 times·d
MCs: fludrocortisone tablets	0.05–0.2 mg/d	1–2 times/d·d
Sodium chloride supplements	1–2 g/d (17–34 mEq/d) in infancy	Divided into several feedings

These doses and schedules are meant as examples and should not be construed as a restrictive menu of choices for the individual patient.

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Table 3. Maintenance Therapy Suggested in Fully Grown Patients

Type of Long-Acting Corticosteroid	Suggested Dose (mg/d)	Daily Doses
HC	15–25	2–3
Prednisone	5–7.5	2
Prednisolone[a]	4–6	2
Methylprednisolone	4–6	2
Dex[a]	0.25–0.5	1
Fludrocortisone	0.05–0.2	1–2

[a] Suspension or elixir may permit improved dose titration for these drugs.

preferred treatment. There are no randomized controlled studies featuring long-term follow-up of adults receiving different modes of treatment of classic CAH, and practice varies (202, 203).

The optimal dose of fludrocortisone substitution in adults (as in infants and children) has not been critically studied. The need for MCs decreases with age, as serum aldosterone is high and renal MC receptor mRNA is low at birth (204), and the salt content in most diets is high. Most nonhypertensive adults with classic CAH benefit from continued fludrocortisone treatment. The requirement for MC replacement should be reassessed during the transition from pediatric to adult care.

Control of hyperandrogenic symptoms in young women may require treatment in addition to GC and MC, such as androgen-receptor antagonists. Oral contraceptives containing drospirenone effectively reduce both adrenal and ovarian androgen synthesis, although not affecting cortisol (205), blood pressure, PRA, or serum potassium levels (206). Oral contraceptives, however, cannot replace GC and MC treatment in classic CAH, although some symptomatic women with NCCAH may prefer such treatment. Spironolactone is relatively contraindicated as an androgen antagonist in salt-wasting CAH, as it is also an MC antagonist and can cause volume depletion. Treatment of hirsutism is beyond the scope of this guideline and has been discussed separately in another Endocrine Society guideline (207).

Balance of benefits and harms

The proposed GC choice places higher value on reducing the negative effects on growing children than on convenience.

Stress dosing

4.7 In all patients with CAH who require GC treatment, for situations such as febrile illness (>38.5°C), gastroenteritis with dehydration, major surgery accompanied by general anesthesia, and major trauma we recommend increasing the GC dosage. (1|⊕⊕⊕◯)

4.8 In patients with CAH under everyday mental and emotional stress and minor illness and/or before routine physical exercise we recommend against the use of increased GC doses. (1|⊕⊕◯◯)

4.9 In patients with CAH who require treatment we recommend always wearing or carrying medical identification indicating that they have adrenal insufficiency. (1|⊕⊕⊕◯)

4.10 In patients with CAH, we recommend educating patients and their guardians and close contacts on adrenal crisis prevention and increasing the dose of GC (but not MC) during intercurrent illness. (1|⊕⊕⊕◯)

4.11 We recommend equipping every patient with CAH with a GC injection kit for emergency use and providing education on parenteral self-administration (young adult and older) or lay administration (parent or guardian) of emergency GCs. (1|⊕⊕⊕◯)

Evidence

Patients with severe forms of 21OHD are unable to produce sufficient cortisol in response to stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma, and therefore require increased doses of GC during such episodes (Table 4). In contrast to maintenance treatment given three times daily, we suggest that stress dosing be given every 6 hours (208). In studies of adrenally intact children undergoing anesthesia and minor surgery, serum cortisol does not exceed 10 μg/dL (276 nmol/L) (209). Therefore, the need for stress dosing for minor procedures should be assessed on an individualized basis.

In a questionnaire-based study of 122 adults with classic CAH, the most common precipitating causes of adrenal crisis were respiratory and gastrointestinal infections (210). In a population-based prospective study of 102 Bavarian children with classic CAH, 27.5% experienced an adrenal crisis or hypoglycemia, mostly during the first 4 years of life, primarily in those with the salt-wasting form of CAH (211). A link to an instructional video for emergency intramuscular injection of HC is provided in the Appendix.

Table 4. Suggested Stress Doses of GC for Adrenal Crisis

Patients' Age	Initial Parenteral HC Dose
Infants and preschool children	25 mg
School-age children	50 mg
Adults	100 mg

Successive IV HC may be administered as one-quarter of the initial parenteral HC dose (above) given every 6 h.

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When stress doses of HC are administered, MCs are not needed because HC can activate MC receptors (212). Patients should resume maintenance HC doses when stable and avoid fasting during acute illnesses. Owing to the risk of hypoglycemia and electrolyte imbalance, parents should be instructed to give oral glucose and electrolyte supplementation to young children. Inability to tolerate oral fluids or medication warrants immediate medical attention and parental administration of GCs and isotonic fluids to prevent adrenal crisis. Parenteral GCs are not always carried by emergency service personnel; we recommend that patients be supplied with vials of injectable HC and be taught to administer the drug intramuscularly. Routine exercise and psychological stress (*e.g.*, anxiety and academic examinations) do not require increased GC dosing (213). There is no evidence supporting the use of additional GCs for prolonged extended exercise training.

Adults with classic CAH should continue to carry medical alert identification and injectable HCs for emergencies, as 20% of adrenal crises in patients with CAH occur during adulthood, most commonly during gastrointestinal illnesses (210). A register of 588 individuals with CAH showed a hazard ratio for death of 2.3 (CI, 1.2 to 4.3), equating to a 6.5-year mean reduction in life expectancy (214) attributed to adrenal crises. Separate detailed guidelines are available in a previous Endocrine Society guideline on primary adrenal insufficiency (215).

Monitoring therapy

4.12 In patients ≤18 months with CAH, we recommend close monitoring in the first 3 months of life and every 3 months thereafter. After 18 months, we recommend evaluation every 4 months. (1|⊕⊕◯◯)

4.13 In pediatric patients with CAH, we recommend conducting regular assessments of growth velocity, weight, blood pressure, as well as physical examinations in addition to obtaining biochemical measurements to assess the adequacy of GC and MC. (1|⊕⊕◯◯)

4.14 In pediatric patients with CAH under the age of 2 years, we advise annual bone age assessment until near-adult height is attained. (Ungraded Good Practice Statement)

4.15 In adults with CAH, we recommend annual physical examinations, which include assessments of blood pressure, body mass index (BMI), and Cushingoid features in addition to obtaining biochemical measurements to assess the adequacy of GC and MC replacement. (1|⊕⊕◯◯)

4.16 In adults with CAH, we recommend monitoring treatment through consistently timed hormone measurements relative to medication schedule and time of day. (1|⊕⊕◯◯)

4.17 In adults with CAH, we recommend that clinicians do not completely suppress endogenous adrenal steroid secretion to prevent adverse effects of over treatment. (1|⊕⊕⊕◯)

Evidence

Adjusting medications for CAH is difficult. The challenge in infancy is to find the appropriate fludrocortisone dose without causing hypertension, as MC sensitivity naturally increases in the first year of life. In a prospective study of 33 individuals with classic CAH diagnosed by newborn screening, more than half experienced hypertension in the first 18 months of life (216). In a population-based study of children (n = 716; age range, 3 to 18 years), the dose of fludrocortisone was associated with blood pressure, and children with regularly measured PRA had lower blood pressure than did those without PRA documentation (217).

Pertinent features of the medical history include the age of pubic hair onset, unexpected phallic or body growth, development of adult apocrine odor, and symptoms of salt craving or adrenal crisis. The examination should identify potential accelerated height velocity, signs of virilization, and advanced bone maturation that occur after protracted undertreatment. In contrast, reduced height velocity, accelerated weight gain, and high blood pressure occur after protracted overtreatment. Laboratory data should indicate the need for dose adjustment before changes in growth, bone age, and physical features occur. Bone age is a lagging indicator of past inadequate adrenal suppression and should therefore be used judiciously. Bone age x-rays are not helpful before the age of 2 years; excessive radiation exposure should be avoided. If bone age advances to a pubertal level at an inappropriately early age, testing for secondary central/GnRH-dependent precocious puberty is warranted.

Serum 17OHP and androstenedione are traditional indicators of the adequacy of GC treatment in CAH. More recently, it has been found that metabolites such as 21-deoxycortisol and 11-oxysteroids may provide more direct evidence of adrenal androgen precursor production in CAH (218, 219). Steroids can be measured in blood, saliva (220), urine (86), or dried filter-paper blood samples (221, 222). LC-MS/MS is the gold standard for blood and saliva measurement, whereas gas chromatography–mass spectrometry is the recommended method for urinary measurements of hormones. Circadian rhythm and the timing of GC intake influence steroid measurements (223). Thus, monitoring treatment by consistently timed hormone measurements is

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recommended. Complete suppression of serum 17OHP level is not a treatment goal but instead indicates overtreatment. Androstenedione levels should be referenced to age- and sex-specific norms. ACTH measurements are not useful in patients with CAH. Acceptably treated patients with CAH generally have upper normal to mildly elevated 17OHP and androstenedione levels when measured in a consistent manner. Clinicians should adjust doses in the context of the overall clinical picture and not solely based on a single laboratory assessment. We do not provide specific target levels for adrenal steroid measurement, because laboratory reference ranges vary, sample timing varies, and one must consider the whole clinical picture.

The prevalence of testicular adrenal rest tumors (TARTs) is variable, increasing after 10 years of age (203, 224). Screening by testicular ultrasound assessments should begin in adolescence. There are no data to suggest how often this should be done, but expert opinion would suggest about every 1 to 2 years in asymptomatic males, or more often in symptomatic patients. Optimization of GC treatment can shrink early stage TARTs and prevent progressive enlargement, resulting in infertility (see also the section on fertility).

The principles of monitoring GC treatment in adult patients with CAH differ somewhat from those employed in children, with attention shifting to reproductive function and chronic complications rather than skeletal maturation. There are neither established optimal biomarkers nor target values, and clinicians should adjust GC doses primarily using clinical indicators. For women, androstenedione and testosterone are good parameters of disease control (202), but additional tests should be considered in the context of menstrual irregularity and signs of androgen excess. For women who experience a delay in conception, GC treatment should aim to achieve a follicular-phase progesterone level <0.6 ng/mL (2 nmol/L), a much tighter control than for women not attempting to conceive, often requiring a bedtime dose of prednisolone (225). The dose of fludrocortisone and/or salt supplementation should be titrated to standing blood pressure, PRA appropriate for age, and serum potassium measurements. For men, suppressed gonadotropins are a reliable sign of infertility, and elevated FSH indicates sustained testicular damage in men with TARTs (226). Men with large TARTs may also have low morning testosterone, indicating poor Leydig cell function (227). The ratio of androstenedione to testosterone is <0.5 in eugonadal men; values >2 indicate poor CAH control with a significant fraction of testosterone of adrenal origin (228). The presence of TARTs does not correlate strictly with the degree of control (229). Table 5 illustrates the use of various analytes in the management of adults with classic CAH. The issue of TARTs is discussed further below (see section 6 on long-term management).

5. Treatment of NCCAH

5.1 In children and adolescents with inappropriately early onset and rapid progression of pubarche or bone age and in adolescent patients with overt virilization we suggest GC treatment of NCCAH. (2|⊕⊕◯◯)

Technical remark: Risks and benefits of GC therapy should be considered and discussed with the patient's family.

5.2 In asymptomatic nonpregnant individuals with NCCAH we recommend against GC treatment. (1|⊕⊕⊕◯)

5.3 In previously treated patients with NCCAH we suggest giving the option of discontinuing therapy when adult height is attained or other symptoms resolve. (2|⊕⊕⊕◯)

5.4 In adult women with NCCAH who also have patient-important hyperandrogenism or infertility we suggest GC treatment. (2|⊕⊕◯◯)

5.5 In most adult males with NCCAH, we suggest that clinicians generally not prescribe daily GC therapy. (2|⊕◯◯◯)

Technical remark: Exceptions include infertility, TARTs, or adrenal tumors and phenotypes that are intermediate between classic and nonclassic phenotypes.

5.6 In patients with NCCAH, we suggest HC stress dosing for major surgery, trauma, or childbirth only if a patient has a suboptimal ($<$14 to 18 μg/dL, $<$400 to 500 nmol/L) cortisol response to cosyntropin or iatrogenic adrenal suppression. (2|⊕◯◯◯)

Technical remark: A range is given for cortisol cut points due to greater specificity of newer cortisol assays (see below).

Evidence

Expert opinion suggests that individuals with asymptomatic NCCAH do not warrant therapy (230, 231). The writing committee suggests that children should be treated for inappropriately early onset of body hair and odor only when bone maturation is sufficiently accelerated to adversely affect future height. In the presence of premature pubarche without advanced bone age, clinicians can withhold treatment with careful monitoring. In adolescents with irregular menses and acne, symptoms are usually reversed within 3 months of GC treatment, whereas hirsutism remission is more difficult with GC monotherapy. As in other androgenic

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Table 5. Utility of Various Analytes for Monitoring CAH Treatment

Patients	Analyte	Physiology	Goals and Comments
All ages	Plasma renin	Volume status	Low to normal unless hypertensive
	Potassium	MC replacement	Goal is normal
	Sodium	GC and MC replacement	Goal is normal
	Testosterone	Total androgens	Goal is at or near normal
	Androstenedione	Mostly adrenal origin	Goal is at or near normal
	Sex hormone–binding globulin	Testosterone-binding protein	For calculation of free and bioavailable testosterone
	17OHP	Variable	Normal values indicate overtreatment
Men	Testosterone	Adrenal or gonadal origin	Interpret abnormal values in context of gonadotropins and androstenedione levels
	Gonadotropins	Gonadal axis status	Low indicates poor control
	Androstenedione	Mainly adrenal	Goal is <0.5× testosterone
	Semen analysis	Fertility	Goal is normal
Women	Follicular-phase progesterone	Mainly adrenal origin when elevated	Goal is <0.6 ng/mL (<2 nmol/L) for women trying to conceive

disorders, an oral contraceptive with or without antiandrogens is likely the best approach for treating hirsutism in women with NCCAH (171, 207, 232, 233). For patients treated in childhood or adolescence, it may be reasonable to consider tapering and discontinuing GC treatment once near-adult height has been reached.

If a woman affected with NCCAH becomes pregnant in the absence of GC treatment, she need not be treated during pregnancy. Two retrospective studies of pregnancies among women with NCCAH found that the majority of pregnancies occurred prior to the mother's diagnosis of NCCAH (234, 235). GC treatment was given to induce fertility in 23% (234) and 42% (235) of cases. Both studies reported elevated miscarriage rates of ~25% in those not receiving GC and 6% in those exposed to GC. A third report found no difference in miscarriage rate between GC-treated and untreated women, but the former group had a shorter time to conception (236). Thus, women with subfertility may benefit from GC treatment to conceive and maintain pregnancy.

Available data indicate that TARTs in men with NCCAH are extremely rare (237); consequently, prophylactic GCs do not seem to be warranted in these men. There is no evidence of clinically significant cortisol deficiency or adrenal crisis in NCCAH, and we do not suggest substitution therapy in previously untreated individuals with NCCAH during severe stress unless they have demonstrated a subnormal cortisol response during diagnostic cosyntropin stimulation. Some individuals with NCCAH (60% in one small study) showed an inadequate response to cosyntropin stimulation, but none had frank episodes of adrenal insufficiency (171, 238, 239). A cortisol cut-off range is given as 14 to 18 μg/dL in part due to CBG variability, but also because newer assays with greater specificity run lower (240).

Individuals with the P30L/null genotypes and some *de novo* mutations comprise a problematic population, as their biochemical and clinical phenotypes straddle the classic/nonclassic boundary. Some of these patients benefit from chronic low-dose HC therapy.

6. Long-Term Management of Patients With CAH

Transition to adult care

6.1 In adolescent patients with CAH, we suggest that the transition to adult care begins several years prior to dismissal from pediatric endocrinology. (2|⊕○○○)

Technical remark: We advise the use of joint clinics comprised of pediatric, reproductive, and adult endocrinologists and urologist during this transition.

6.2 In adolescent females with CAH, we suggest a gynecological history and examination to ensure functional female anatomy without vaginal stenosis or abnormalities in menstruation. (2|⊕⊕○○)

Evidence

Several reviews, but no controlled studies, describe how to transfer patients with CAH from pediatric to adult care. Our suggestions are based on clinical experience (241–244). Adult women with CAH often remember childhood visits to their physician as highly intrusive. Therefore, after follow-up from the initial surgery, clinicians should avoid gynecological examinations unless and until the patient experiences delayed or painful menses, planned sexual activity, or pregnancy.

Adolescent girls with virilizing CAH should be referred to a gynecologist and/or a pediatric surgeon/urologist for a genitourinary examination with sedation or anesthesia when appropriate. The patient and, if appropriate, her family, should discuss whether surgery should be considered. At the appropriate time, the

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medical/surgical team, ideally including a reproductive endocrinologist, should discuss issues of sexual activity, contraception, and fertility. Obstetricians should be aware that despite an apparent normal pregnancy rate of ~90%, women with classic CAH have low fecundity (0.25 live births per woman *vs* 1.8 in the general population) (225). In NCCAH, 72% of pregnancies result in live births (236).

A gradual transition of adolescents to adult care would ideally allow the patient's relationship with the adult physician to be consolidated before the patient terminates his or her relationship with the pediatric endocrinologist, typically after age 18. At this juncture, patients should be reminded of the importance of continued GC treatment. Poor medical adherence among adults with CAH contributes to depression and increased mortality (245). A baseline bone mineral density (BMD) measurement and, in males, a testicular ultrasound should be considered. Young men should be advised regarding the risk of noncancerous testicular masses (see section 6.5).

Genetic counseling

6.3 In children with CAH, adolescents transitioning to adult care, adults with NCCAH upon diagnosis, and partners of patients with CAH who are planning a pregnancy, we recommend that medical professionals familiar with CAH provide genetic counseling. (1|⊕⊕◯◯)

Evidence

CAH genotype and phenotype correlate well; siblings with CAH generally, but not always, have similar symptoms and degrees of female virilization. For this autosomal recessive disorder, there is a 25% probability that each subsequent sibling of the index case will have CAH and a 50% probability that each will be an asymptomatic carrier. Based on a classic CAH incidence of 1:10,000 to 1:20,000 (23, 43, 44, 52), 1:50 to 1:71 people in the general population are heterozygotes. Using a median value of 1:60 (~2%), a patient with classic CAH would have a 1:120 probability of having a child with classic CAH. For NCCAH, almost 70% of diagnosed patients are compound heterozygotes, carrying one allele that causes classic CAH and one that causes NCCAH (171, 246). The milder mutation determines the phenotype, meaning that the patient has NCCAH, but the patient's offspring have a 50% chance of inheriting the classic CAH allele. Theoretically, and without genotyping, a NCCAH parent has an ~1:250 risk of having a child with classic CAH [$(0.7 \times 0.5) \times (0.02 \times 0.5) = 0.4\%$]. However, in two retrospective analyses of children born to women with NCCAH, the risk was higher, at 1.5% to 2.5% (234, 235). Similar risks were found in a mixed group of men with CAH and NCCAH (247). To refine the risk, *CYP21A2* genotyping is recommended prior to pregnancy planning.

Fertility counseling

6.4 In individuals with CAH and impaired fertility we suggest referral to a reproductive endocrinologist and/or fertility specialist. (2|⊕⊕◯◯)

Evidence

Fertility in males with CAH is often impaired (226, 237, 248–250). Common factors contributing to male infertility include the presence of TARTs, suppression of gonadotropins, and testicular failure. In one study, males with CAH born after the introduction of neonatal screening had normal fertility (247).

The prevalence of TARTs in boys aged 2 to 18 years who have classic CAH varies from 21% to 28% (227, 251); there have been few studies describing TARTs in males with NCCAH. The prevalence of TARTs increases with age but is highly variable in men with classic CAH. These tumors often regress with intensification of GC therapy if detected early (see section 6.13) (252). The presence of TARTs is a predictor of infertility (226, 248, 253). The prevalence of these tumors varies between 0% and 94%, depending on the study population (254, 255). TARTs are usually small and bilateral, not palpable, but easily detectable by ultrasound (227, 251). TARTs have no malignant features but can lead to obstructive azoospermia and infertility (248). When tumors are unresponsive to intensified GC therapy, testicular sperm extraction can be performed (256). Suppression of gonadotropin secretion by high levels of adrenal androgens also impairs fertility; this is evident when the androstenedione-to-testosterone ratio is >2. Sperm banking may be an option to maintain fertility. One study reported that fewer men with CAH had stable heterosexual relationships than did age-matched controls (255), whereas more recent data showed no such differences in relationships but a reduction in sexual activity among men with CAH (247).

Several studies have shown that, for a variety of reasons, only a minority of women with classic CAH try to conceive (225, 257). Those who wish to conceive can achieve nearly normal pregnancy rates with adequate suppression of follicular-phase progesterone (<0.6 ng/mL = 2 nmol/L, Table 5) (225) by optimizing GC and MC treatments. Factors beyond CAH, such as tubular obstruction and endometriosis, can contribute to infertility and must be excluded. Ovarian adrenal rest tumors are

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relatively rarely detected compared with TARTs (258). Fertility in the context of NCCAH is discussed in section 5. Ovulation induction and *in vitro* fertilization, along with other assisted reproductive technologies, may be considered for women in whom these measures prove insufficient.

Management of CAH and NCCAH during pregnancy

6.5 In women with NCCAH who are infertile or have history of prior miscarriage, we recommend treatment with a GC that does not traverse the placenta. (1|⊕⊕◯◯)

6.6 In women with CAH who are pregnant, we advise management by an endocrinologist familiar with CAH. (Ungraded Good Practice Statement)

6.7 In women with CAH who become pregnant we recommend continued prepregnancy doses of HC/prednisolone and fludrocortisone therapy, with dosage adjustments if symptoms and signs of GC insufficiency occur. (1|⊕⊕◯◯)

Technical remark: Clinicians should evaluate the need for an increase in GC during the second or third trimester and administer stress doses of GCs during labor and delivery.

6.8 In women with CAH who are pregnant, or trying to become pregnant, we recommend against using GCs that traverse the placenta, such as Dex. (1|⊕⊕◯◯)

6.9 In women with CAH who are pregnant, we advise that the birthing plan includes an obstetric specialist. (Ungraded Good Practice Statement)

Evidence

Androgen and cortisol levels increase gradually during pregnancy due to increases in sex hormone–binding globulin and corticosteroid-binding globulin. Placental aromatization typically protects the fetus from the potential virilizing effects of maternal androgens (259). Maternal 17OHP is elevated in normal pregnancy and hence cannot be used to monitor GC treatment. High progesterone levels during pregnancy may compete for the MC receptor, theoretically necessitating increased fludrocortisone doses, but this possibility has not been studied. Clinicians should not use Dex, or other steroids that are not inactivated by placental 11β-HSD2, to treat pregnant women affected by CAH. There are no data and no widely accepted recommendations for managing GC doses in pregnancy. Nonspecific symptoms of adrenal insufficiency, including postural hypotension and fatigue, may develop in pregnancy but are not unique to women with classic CAH. GC and/or fludrocortisone doses may be increased if such signs and symptoms occur. In such cases, a GC dosage increase of 20% to 40% from the 24th week onward is often beneficial (215). During labor and delivery, stress doses of GCs should be administered, but there are no controlled studies regarding optimal dosing. Women with CAH may be at increased risk for gestational diabetes (257, 260). Thus, clinicians should monitor glucose tolerance as clinical judgment indicates throughout pregnancy. Treatment should be individualized for pregnant patients with CAH. Caesarean section is the most common method of delivery due to the high prevalence of previous vaginal surgery and cephalopelvic disproportion, although vaginal delivery has been reported in 16% to 42% of women, nearly all of whom had a non–salt-wasting phenotype (225, 257). It is difficult to draw definitive conclusions about the need for GC therapy in women with NCCAH based on limited data (234–236); however, treatment may benefit infertile women with NCCAH or those with a history of miscarriage. Similar principles of pregnancy management apply to women with NCCAH requiring GC treatment during pregnancy.

Surveillance for long-term complications of CAH and its treatment

6.10 For patients with CAH, we suggest introducing counseling regarding healthy lifestyle choices at an early age to maintain BMI within the normal range to avoid metabolic syndrome and related sequelae. (2|⊕◯◯◯)

6.11 In adult patients with CAH, we suggest screening of BMD in anyone subjected to a prolonged period of higher-than-average GC dosing, or who has suffered a nontraumatic fracture. (2|⊕◯◯◯)

6.12 In adults with classic CAH, we recommend against routine adrenal imaging. (1|⊕◯◯◯)

Technical remark: Reserve adrenal imaging for individuals with classic CAH who have clinical evidence of an adrenal mass, poor disease control, a lapse in treatment of several years, or lack of response to intensified therapy.

6.13 In males with classic CAH, we recommend periodic testicular ultrasound to assess for the development of TARTs (see section 6.4). (1|⊕⊕◯◯)

6.14 In patients with CAH, we recommend against routine evaluation for cardiac and metabolic disease in patients with CAH beyond that recommended for the general population. (1|⊕⊕◯◯)

Technical remark: Clinicians should use their own judgment for the above procedures.

Evidence

Children and adolescents on standard GC therapy for CAH have no evidence of decreased BMD when assessed

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by dual-energy x-ray absorptiometry normalized for height, irrespective of duration of treatment, type of GC used, and 17OHP or androgen levels (261–263). The standard of care for good bone health includes age-appropriate vitamin D and calcium intake along with weight-bearing exercise.

In contrast, a retrospective study of 62 adult women with CAH reported that chronic exposure to pharmacological GC doses may lead to bone loss accompanied by an increased incidence of fractures relative to healthy controls (264). Two studies of large cohorts of adults with CAH reported a high prevalence of osteopenia (BMD T-scores, −1.0 to −2.5 SD) and a modestly increased prevalence of osteoporosis (202, 203). No increase in fracture incidence has been observed (265). The occurrence and severity of bone loss did not correlate with CAH genotype or phenotype but appeared to be related to GC exposure. Chakhtoura *et al.* (266) showed a negative correlation between the cumulative lifetime GC dose and BMD. These data underscore the need to avoid excessive GC exposure.

Adrenal masses affect 1% to 4% of normal men and women (267), and their prevalence increases with age (268). One study using CT imaging in adults with CAH reported a high prevalence of benign adrenal masses, especially among those on inadequate GC therapy (269). Adrenal carcinomas are rarely found in persons with CAH (270), and only a single pediatric case has been reported (271). Massive adrenal myelolipomas have developed in several adults with CAH, requiring surgical removal for mass effects (272). Insufficient data exist to recommend routine screening for adrenal masses.

Children with CAH have a higher BMI than do controls due to increased fat mass (273). Approximately half of pediatric patients are overweight, and 16% to 25% are obese (273–275). The commissioned systematic review included a meta-analysis of 14 observational studies, ranging widely in age (14 months to 63 years, ~70% <18 years old). The 437 patients with CAH in those 14 studies had mildly increased systolic and diastolic blood pressures (respective mean differences, +4.4 and +2.4 mm Hg), homeostatic model assessment of insulin resistance (+0.5), and carotid intima thickness (+0.08 mm) compared with controls without CAH (41). No statistically significant difference was noted in fasting blood glucose, insulin level, glucose or insulin level 2 hours after a glucose load, or serum lipids. Data on cardiac events were sparse, and most of the literature focused on surrogate outcomes. The commissioned systematic review also summarized evidence from other observational studies that presented data not amenable to meta-analysis, including cohorts from Sweden, the United Kingdom, Germany, and Brazil. These studies suggested that individuals with CAH may have higher frequency of hypertension, hyperlipidemia, atrial fibrillation, venous thromboembolism, obesity, and diabetes. A moderate to high risk of bias was noted among the studies included in the systematic review (41). In view of increased body fat and the potential for cardiac and metabolic consequences, we suggest beginning lifestyle counseling early to counteract these trends.

Women with CAH are often overweight (202, 203, 260), but patients with CAH >30 years of age had similar fat mass to age-matched controls. Few had hypertension, cardiovascular disease, or diabetes. The most significant metabolic abnormality was a 20% prevalence of gestational diabetes, somewhat higher than the prevalence for the general population, which is estimated at 7% to 10% but ranges from 1% to 25% (276).

7. Restoring Functional Anatomy by Surgery in Individuals With CAH

7.1 In all pediatric patients with CAH, particularly minimally virilized girls, we advise that parents be informed about surgical options, including delaying surgery and/or observation until the child is older (Ungraded Good Practice Statement).
Technical remark: Surgeries should be performed only in centers with experienced pediatric surgeons/urologists, pediatric endocrinologists, pediatric anesthesiologists, behavioral/mental health professionals, and social work services. Extensive discussions regarding risks and benefits, shared decision-making, review of potential complications, and fully informed consent need to occur prior to surgery. The option to forgo surgery should be considered.

7.2 In severely virilized females (single urogenital opening, Fig. 3), we advise discussion about early surgery to repair the urogenital sinus (Fig. 4). (Ungraded Good Practice Statement)

7.3 In the treatment of minors with CAH, we advise that all surgical decisions remain the prerogative of families (*i.e.*, parents and assent from older children) in joint decision-making with experienced surgical consultants. (Ungraded Good Practice Statement)

Evidence

There are no randomized controlled studies of either the best age or the best methods for restoring functional female anatomy with a separate urethra and vaginal opening in individuals with CAH. Published literature to date has relied on evaluations in late adolescence or adulthood, often 20 years or more after the initial surgery.

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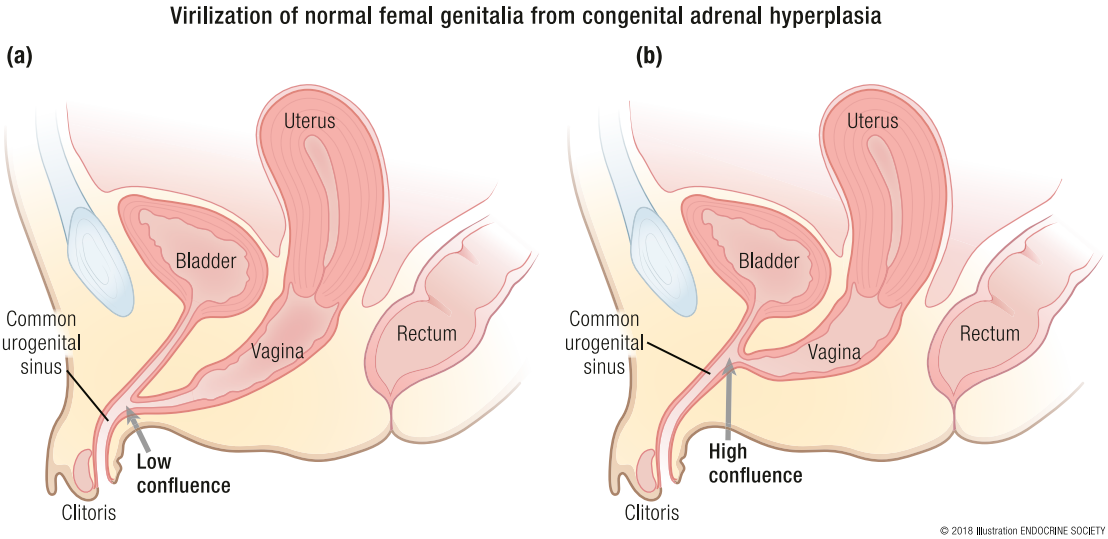

Figure 3. Lower urogenital anatomy of mild and severe CAH. (a and b) The lower urogenital anatomy of mild and severe CAH is shown. Note the low confluence in (a), where the vagina and urethra meet close to the skin, in contrast to (b), where the confluence of the vagina and urethra is close to the bladder neck. [Illustration ENDOCRINE SOCIETY]

During that time, methods for separating the urogenital sinus, bringing the vaginal opening to the perineum, introitoplasty, and treating clitoromegaly have evolved.

Based on present outcome data, we suggest that, for patients with a low urogenital confluence of the vagina and urethra (Fig. 3), experienced surgeons perform complete surgical repair at an early age (separating the urogenital sinus, bringing the vaginal opening to the perineum, introitoplasty, and, if chosen, clitoroplasty) (277–281). For individuals with a high confluence (Fig. 3), the timing is less certain, although retrospective studies report that early surgery has good long-term success in respect to sexual function compared with normal controls (277–281). The unproven surgical advantage of delayed reconstruction is that the risk of vaginal stenosis and the need for subsequent vaginal dilation may be diminished. If clinicians are considering treating infants with severe virilization for clitoromegaly, the advantages of early complete reconstruction is the ability to use the excess common urogenital sinus tissue to reconstruct the anterior vaginal wall (282). One should avoid premenarchal vaginal dilation for stenosis.

In the female patient with CAH with severe virilization in whom no surgery has been performed, there is an ongoing need for observation in regard to possible urinary tract infections and obstruction of menstrual flow at puberty, because the vagina opens into the common urogenital sinus.

In the rare patients with 46,XX CAH and complete virilization (Prader 5/normally formed "penis" with the urethral meatus within the glans) controversy exists with respect to the optimal gender assignment (see section 9 on mental health). Surgical feminization with a female gender identity is especially challenging secondary to extreme virilization. Future fertility is possible as a female. If the same patient is raised as male from infancy or early childhood, surgery to remove the uterus and ovaries prior to puberty, or drugs to suppress pubertal hormones, may be required to avoid gender-incongruent body development. The pros and cons of female vs male gender assignment and the fertility implications must be openly and completely discussed. Lifelong medical treatment with GCs and MCs would still be required, and supplemental testosterone may be required to support male secondary sexual characteristics. Height outcomes for male patients would be short compared with mid-parent height.

Complications following urogenital reconstruction in individuals with CAH may include vaginal stenosis, labial or introital scarring, loss of sexual function, urethra–vaginal fistulae, and urinary incontinence (283). One retrospective study documented a relative decrease in clitoral sensitivity after clitoral surgery, yet other studies have not documented any impairment in sexual function compared with that of age-matched healthy controls (280, 284–286). An enlarged clitoris observed in the newborn may decrease in prominence over time with standard medical treatment. No data exist regarding long-term outcomes for individuals who have not had surgery to separate the urogenital sinus and bring the vagina to the perineum, or those who have not undergone clitoral reduction. Surveys of surgical practice in the United States (287, 288) and internationally (279) also report a preference for early surgery for CAH. Clinicians should share with parents all available information on the timing, risks, benefits, and complications of surgery

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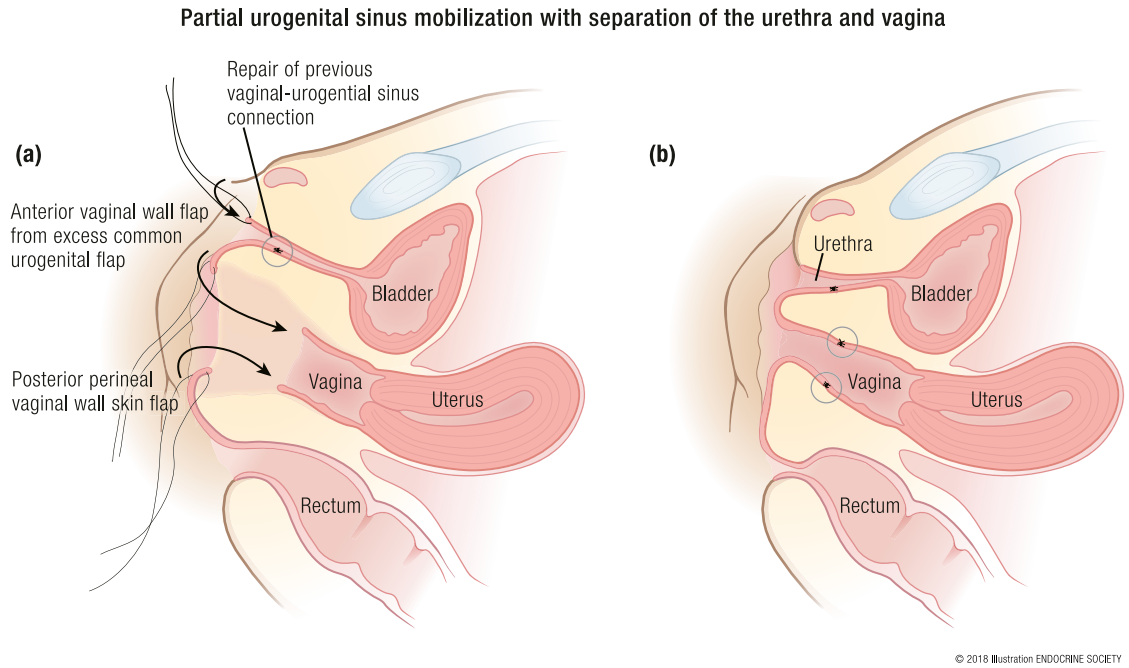

Figure 4. Partial urogenital mobilization with separation of the urethra and vagina. (a and b) Schematic of partial urogenital sinus mobilization where normal female anatomy is restored. Note the separation in (a) of the vagina and urethra with preparation of the excess common urogenital sinus to form the anterior vaginal wall by anastomosis to the normal anterior vaginal wall (b) and preparation of the posterior perineal skin flap (a) to form the posterior vaginal wall (b). [Illustration ENDOCRINE SOCIETY]

and counsel them that deferring or forgoing surgery is an option. It is also important to discuss, both with the parents at the time of diagnosis and with the patients as they mature, what is known about the long-term prognosis for sexual and reproductive function. There is no objective evidence at this time as to whether early, late, or no surgery best preserves overall QOL or sexual function.

Recent cohort studies have shown no change in neurocognitive outcomes in children undergoing a single use of anesthesia under the age of 36 months (289). However, animal evidence and retrospective human studies have raised concerns that prolonged or repeated general anesthesia may impair brain development in early life, specifically impairing long-term language abilities and cognition (290).

Balance of benefits and harms

Presumed values in seeking early surgery for virilized females with CAH are restoring female anatomy, preventing urinary tract infection and hydrometrocolpos, reducing parental anxiety regarding the child's congenital anomaly, avoiding stigmatization of a girl with masculinized genitals, and avoiding the psychological trauma of genital surgery during childhood and adolescence (291, 292). The presumed benefit of late surgery is patient autonomy regarding surgery with a better understanding of the individual's own preferences (a shared decision-making process as opposed to parental choices) regarding gender identity, risks, benefits, alternatives, and complications.

Genital reconstructive surgery requires the level of surgical experience and endocrine, anesthesiologic, nursing, and psychosocial support that is only found at centers that perform this procedure regularly. Surgical expertise has been defined in one group's opinion as having performed at least 10 genitoplasties in the preceding 8 years (293).

7.4 In female patients with CAH for whom surgery is chosen, we suggest vaginoplasty using urogenital mobilization and, when chosen, neurovascular-sparing clitoroplasty for severe clitoromegaly. (2|⊕○○○)

Evidence

Total urogenital mobilization (294) signaled a significant advance in the surgical management of CAH. This technique has evolved into the present technique of partial urogenital mobilization, where, instead of a 360° dissection, surgery is avoided superior to the urethra under the pubic bone, a nerve-rich zone that contains the sphincteric musculature necessary for urinary continence (279, 282, 295, 296). Urinary incontinence and vaginal stenosis requiring dilation or reoperation remain as postoperative concerns (297–300). Long-term follow-up studies are now confirming that urinary incontinence is rare, but that a minority of patients will require

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additional vagina surgery after puberty (277, 282, 301–304). Nerve-sparing clitoroplasty (305) is an optional procedure and should be explained as such.

Balance of benefits and harms

The writing committee shares the stated preference of most patients and clinicians and places a high value on the outcomes of early complete repair performed by surgeons experienced with urogenital mobilization, on the reduced need for complex secondary procedures in adolescence or adulthood, and on maintaining normal perineal and clitoral sensation. Additionally, expert opinion states that, for patients with 46,XX CAH living as females, potential fertility should be preserved to the extent possible. In those living as males, potential options of preservation of ovarian tissues should be discussed with parents (and patients when practical) prior to ovarectomy.

8. Experimental Therapies and Future Directions

General considerations and unmet clinical needs

8.1 In patients with CAH we advise against using experimental treatment approaches outside of formally approved clinical trials. (Ungraded Good Practice Statement)

Evidence

As reviewed in the sections above, despite life-saving GC and fludrocortisone acetate therapies, many children and adults with CAH commonly experience adverse outcomes (202, 203). Therefore, further study of alternative treatment approaches should consider growth, metabolic, reproductive, and neuropsychiatric endpoints.

Improved GC delivery methods

We advocate the development of new treatment approaches that minimize the daily GC dose with the goals of achieving physiological cortisol replacement and preventing excessive androgen secretion. Normal adrenocortical secretion has a circadian rhythm (306, 307). Programmed infusion of HC delivered in a circadian fashion to poorly controlled patients with CAH resulted in nearly normal ACTH and 17OHP (308, 309). In a phase 2 study, eight adults with classic CAH and multiple comorbidities experienced significant reduction in adrenal androgens and significant improvement in QOL parameters and fatigue following 6 months of subcutaneous HC infusion aimed at mimicking physiologic cortisol secretion (310). Although conceptually appealing, parenteral HC hemisuccinate preparations are not designed or approved for subcutaneous administration; infusion site reactions occur, and pump management is complex. Nevertheless, this approach may have value for motivated patients, particularly those who demonstrate rapid HC metabolism.

Once-daily modified-release oral HC in adults with classic CAH afforded serum cortisol concentrations typical of a classic diurnal rhythm; however, serum 17OHP and androstenedione rose to higher levels late in the day than with conventional thrice-daily HC administration (311). A newer version of this product (multiparticulate capsules) was studied in a phase 2 open-label trial of 16 adults with classic CAH (312). Compared with various forms of conventional therapy prior to entry, this approach yielded decreased 17OHP and androstenedione values throughout the day, despite a reduced HC dose equivalent (28 ± 11.8 vs 25.9 ± 7.1 mg/d). A phase 3, parallel-arm, randomized, open-label study is in progress to determine whether this approach improves short-term clinical outcomes (NCT 02716818).

Currently, the lowest dose HC tablet is a 5-mg tablet that is excessive for infants and young children. Availability of pediatric dose formulations would eliminate concerns about improper compounding of HC from tablets (192–194). Another clinical trial examined utility of very low–dose HC granules for treatment of infants with CAH (313).

Androgen/estrogen antagonists and synthesis inhibitors

An alternative approach to optimizing GC exposure is to combine a roughly physiological replacement dose of GC with a second therapy that directly inhibits androgen and estrogen production and/or action, and we think that such approaches deserve further study. The first example of this approach was a four-drug regimen that combined the androgen antagonist flutamide and the aromatase inhibitor testolactone with a reduced dosage of HC (8 mg/m^2 per day) and fludrocortisone. Compared with conventional treatment with HC and fludrocortisone, this regimen decreased growth rate, weight velocity, and bone maturation in a crossover study of 12 children (314). In a 2-year randomized parallel study of 28 children, patients receiving the experimental four-drug regimen had normal growth and bone maturation, despite elevated adrenal steroids (315).

All pathways to androgens and estrogens require the enzyme 17-hydroxylase/17,20-lyase (P450c17, CYP17A1) (Fig. 1). Abiraterone acetate is an orally active prodrug of abiraterone, a potent P450c17 inhibitor (316) indicated for treatment of castration-resistant prostate cancer (317, 318). A phase 1, open-label, multiple-dose study of

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abiraterone acetate enrolled six adult women with classic CAH and high serum androstenedione concentrations (>345 ng/dL or >12 nmol/L) (319). At 250 mg/d, abiraterone acetate normalized the predose androstenedione on day 7 in all participants. Because abiraterone acetate also inhibits gonadal steroid production, this study was limited to adult women taking oral contraceptives. Consequently, abiraterone acetate use in CAH may be limited to prepubertal children and to adults taking gonadal replacement. A phase 1/2 trial of abiraterone acetate in prepubertal children with CAH is in progress (NCT 02574910). Implicit in these new treatment approaches is the goal of normalizing growth and development in children with CAH by reducing GC exposure.

Growth hormone and growth-promoting drugs

A systematic review and meta-analysis of adult height in individuals with classic CAH diagnosed before the age of 5 years was prepared in conjunction with the previous version of these guidelines (186). Of 1016 published reports, only 35 met the eligibility criteria for inclusion in the analysis. All were observational studies with methodological limitations and very low–quality evidence. Again, most patients were diagnosed before the era of newborn screening, fewer than half reported a mean age of diagnosis under 1 year, and most did not give details of GC doses. The pooled data indicated a corrected adult height SDS of −1.05. Subgroup analysis revealed that the addition of MC treatment was associated with increased height outcome.

Individuals with NCCAH can also have compromised adult height, but the height deficit is less severe than with classic CAH. However, there is limited evidence that initiation of GC treatment before puberty may improve adult height (320, 321). A 1- to 2-year nonrandomized study of children with CAH showed improved growth rate and height *z* score for bone age for growth hormone used alone (n = 12) or in combination with GnRH agonist (n = 8; $P < 0.0001$) (322). Fourteen patients treated with growth hormone and GnRH plus conventional therapy for ~4 years had improved adult height (+1.1 SDS) (323) compared with historical controls with CAH treated with conventional therapy alone (SDS of −0.4 vs −1.4, $P = 0.01$). GnRH analog treatment increases adult height in children with CAH who develop central precocious puberty (324). No randomized study has investigated the effect of a GnRH agonist alone or aromatase inhibitors on adult height in children with CAH and normally timed puberty.

In summary, individuals with CAH can achieve normal adult height through judicious use of standard GC and MC therapies, and height-enhancing drugs are to be considered only for individuals whose heights are, or are expected to be, significantly shorter than those of peers, defined as a height of at least −2.25 SDS. We advocate further prospective, randomized, and carefully controlled studies to determine whether the use of growth-promoting drugs increases adult height in individuals with CAH.

Other medical strategies

An alternative strategy to decrease the adrenal androgen excess is to reduce ACTH production. A single-blind, placebo-controlled, fixed-sequence, single-dose trial of eight women with classic CAH explored the addition of a selective corticotropin-releasing hormone receptor type 1 antagonist, NBI-77860, to conventional therapy (325). The study drug reduced the mean morning increase in ACTH by >40% and that of 17OHP by up to 27% with variable reductions of androstenedione and testosterone.

Another study administered mitotane, a drug that has an adrenolytic effect (used for adrenocortical cancer and Cushing syndrome), to a man with classic CAH and TARTs who was infertile for 2 years (326). Adrenal-derived androgen precursors declined, and TARTs regressed, despite a rise in ACTH. Ultimately, sperm count increased, and paternity was achieved. Mitotane cannot be recommended as routine treatment outside of approved research studies due to its significant toxicities, potential teratogenicity (pregnancy category D), and profound induction of CYP3A4, which markedly increases GC metabolism. A phase 1 trial of ATR-101 (NCT 02804178), which shares some mechanisms with mitotane (327–329), has been completed in adults with classic CAH but is not yet published.

Adrenalectomy

8.2 In patients with CAH we suggest that bilateral adrenaletomy not be performed. (2|⊕○○○)

Evidence

Bilateral adrenalectomy reduces the risk of virilization in females and allows for decreased GC doses. Objections to adrenalectomy are based on surgical risk, possible increased risk of adrenal crisis due to loss of residual adrenal function, and possible loss of hormones that may have beneficial effects.

Among 18 individuals with CAH who underwent bilateral adrenalectomy, 5 patients had one or more adrenal crises, and 2 of the younger patients experienced severe hypoglycemia with illness during ~5 years of follow-up (330). All patients reported subjective benefits after surgery, including weight loss, a reduced need for frequent monitoring, and reduced signs and symptoms of androgen excess. Eight patients (44%) had elevated steroid precursors postoperatively while on a reduced HC dose, presumably from adrenal rests, which required

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increased HC doses. However, GC doses were lower after adrenalectomy than before.

Five adult female patients with salt-wasting CAH underwent bilateral adrenalectomy with a mean follow-up time of 4.2 years (331). Two patients underwent adrenalectomy for infertility and became pregnant within 2 years. Three patients underwent adrenalectomy for unsuppressible hyperandrogenism and worsening obesity. All three patients lost weight; however, they all also experienced pigmentation and adrenal crises during follow-up. Adrenalectomy may not totally remove hyperandrogenemia owing to the potential development of adrenal rest tumors in the testes (330), ovaries (332), or retroperitoneum (333). For these reasons, the initial enthusiasm from short-term success has been tempered by long-term complications. Owing to the high risk for significant morbidity and mortality after operation, individuals with a prior history of medical nonadherence are poor candidates for elective adrenalectomy.

Balance of benefits and harms

In recommending further research on experimental therapies in adults, the goal is to improve QOL by maintaining a near-physiological hormone balance. For children, the writing committee placed high value on reducing the impact of GC excess on growth, BMI, and cardiometabolic complications.

Investigation into epinephrine deficiency

We advocate for additional research concerning epinephrine deficiency in the stress response. Individuals with classic CAH have adrenomedullary insufficiency because GCs play essential roles in the development and regulation of the adrenal medulla (334). Combined cortisol and epinephrine deficiency results in glucose, insulin, and leptin dysregulation, shown during short-term high-intensity exercise (335, 336) and long-term moderate-intensity exercise (337). The clinical implications of epinephrine deficiency are not fully known, but it likely contributes to the risk for hypoglycemia during febrile illnesses, especially in young children (211, 338). Epinephrine replacement or supplementation has not been studied.

Preclinical research

Gene therapy temporarily restored adrenal steroidogenesis in 21-hydroxylase–deficient mice (339). The ability to correct the genetic mutations causing CAH by applying gene therapy to an individual's own adrenal stem cells would theoretically cure CAH and avoid the need for adrenal replacement therapy. Cell-based therapies and gene-editing technology may present novel options for disease remediation or cure in the future (340, 341).

9. Mental Health

9.1 For individuals with CAH and their parents, we recommend behavioral/mental health consultation and evaluation to address any concerns related to CAH. (1l⊕⊕◯◯)

Technical remark: Clinicians should be aware that individuals with CAH may be at risk for developing mental health problems and should have a low threshold for referral to psychological or psychiatric treatment. Additionally, mental health practitioners should have specialized expertise in assessing and managing CAH-related psychosocial problems.

Evidence

Classic CAH, with the associated risks of potentially fatal electrolyte crises and the effects of hyperandrogenization on the body, brain, and gender-related behavior, may generate anxiety and present challenges to parents and affected individuals (342). In 46,XX newborns with marked genital masculinization, gender assignment is initially in doubt, and parents experience shock. Severely virilized newborns may inadvertently be assigned as males, especially where tradition strongly favors males (343, 344). Once such assignment has been made, it may be difficult to reverse (345). In view of the documentation of good adjustment of male-raised patients with 46,XX CAH with highly masculinized genitalia and the potential risks of feminizing surgery for cosmesis and sexual functioning (see section 7), some experts advise considering deliberate male rearing of newborns with 46,XX CAH with highly masculinized genitalia (346), despite the implied loss of fertility and necessity of lifelong androgen treatment. This argument is supported by the masculinizing effects of prenatal androgen excess in female-raised children with 46,XX CAH on diverse domains of gender-role behaviors (347–351), which may lead to gender questioning and variable transgender identification (352). Nevertheless, most female-raised adolescents and adults with 46,XX CAH end up with a female core gender identity and social role. Of 250 individuals with 46,XX CAH raised female, only 5.2% had serious gender-identity problems (353).

Case reports, but not systematic studies, have documented other psychosocial consequences of atypical genital development (354). These consequences include awareness of the incongruence between the patient's genital appearance and assigned gender; conflicted gender typing by family members; increased curiosity about the patient's genitals and increased stigmatization by others; and impaired genital self-image, which may

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contribute to an overall impaired bodily self-image associated with short stature, increased weight, and hirsutism. Such experiences may result in social withdrawal, especially from situations involving nudity (team sports or medical examinations), and avoidance of romantic interactions and sexual involvement. To prevent adverse psychosocial consequences, clinical management recommendations have typically included corrective genital surgery in early infancy (feminizing or masculinizing, depending on the gender assignment of the child, as discussed in section 7). In view of the potential complications and mixed cosmetic and functional outcomes of such surgery (see section 7), several intersex activist groups, ethicists, and service providers have severely criticized all such surgeries (355–357) or advocated for postponing them until the patient can give informed consent (358–361). Some advocates have called for a moratorium on such surgeries until better empirical evidence of the risks and benefits is available (362). The critics also point out that no controlled observational studies are available to document whether genital surgery prevents the adverse psychosocial consequences of genital ambiguity.

However, surveys of women with CAH showed that most respondents favored genital surgery before adolescence (281, 284, 363–365), as did parents of girls with CAH (281, 285, 366). Moreover, even if the patient has reached the age of consent, obtaining truly informed consent appears unrealistic if the patient is sexually inexperienced. Unfortunately, we lack systematic comparative studies of early vs late (*i.e.*, after attainment of age of consent) genital surgery, or electing to have no surgery at all, in regard to outcomes such as stigma, sexual functioning, and QOL, and we do not yet know whether improvements in surgical techniques in the last decade will yield improvements in outcomes. Parents, therefore, are likely to hear conflicting recommendations (367). In contemplating the pros and cons of early genital surgery, one must also consider that no studies have been conducted to demonstrate that potential adverse psychosocial consequences of gender-incongruent genital appearance can be ameliorated by psychological counseling or psychotherapy. Physicians should inform families of all these concerns and allow them to reach a reasoned decision with input from various sources, including patient and family support groups.

Findings on general QOL in patients with CAH compared with controls vary widely: from better (255, 368) to comparable (369–372) to impaired (202, 284, 373–375). Impaired QOL is more common in adults than in children and is, in some respects, associated with more severe forms of CAH (284, 369, 371) and with increased adiposity, insulin resistance, and use of prednisolone or Dex (376). Inconsistencies in findings are due to a variety of factors such as variations in sample composition, in hormone and surgical treatment regimens, and in assessment tools. DSD-specific tools for the assessment of QOL are yet to be developed. Specific findings on mental health and psychiatric disorders in clinic samples of individuals with CAH are similarly mixed and suffer from comparable methodological problems (342). Epidemiological national registry studies in Sweden have shown that females and males with CAH had an elevated risk of receiving any psychiatric diagnosis [OR, 1.5 (1.1 to 2.2)]. Girls and women with CAH had an increased risk of reaction to extreme stress and adjustment disorders [OR 2.1, (1.3 to 3.6)] and of alcohol abuse [OR, 2.8 (1.7 to 4.7)] compared with those without the disorder, with the highest risk among those with the most severe genotype. For boys and men, there were increased rates of reported suicides and suicide attempts [OR, 2.3 (1.1 to 5.0)] and alcohol abuse [OR, 1.9 (1.0 to 3.5)] (377, 378).

Existing clinical guidelines (379–384) recommend interdisciplinary teams that include mental health professionals with expertise in managing psychosocial problems specific to DSD. Tasks may include (1) parent/family medical education, parent/family counseling regarding psychosocial prognosis, and managing parents' distress; (2) assisting in gender assignment at birth in cases of marked genital virilization; (3) discussing the pros and cons of gender-confirming (not medically necessitated) genital surgery in infancy and early childhood; and (4) counseling regarding potential gender reassignment of patients with 46,XX CAH after infancy (353). Note that physician-recommended reassignment of inadvertently male-assigned 46,XX patients to female during infancy does not require a psychological gender evaluation, as children's use of gender labels starts at ~17 to 24 months, and consistent self-labeling by gender is not attained until ~3 years of age (385, 386).

Additional DSD-specific items for counseling patients and families include preparation for genital surgery; concerns about inappropriate curiosity or frank stigmatization by other family, peers, lovers, or even medical staff (387) in reaction to gender-atypical somatic features; gender-atypical behavior and related problems with social fit; bisexual and homosexual attractions, which are somewhat increased in women with 46,XX CAH but still limited to a minority (388, 389); sexual functioning; and the impact of the CAH condition and its treatment on QOL. Ideally, mental health staff with expertise in DSD should manage such

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problems with help from clinical guidelines (342, 379–383, 389–394), educational websites, and long-distance consultations with specialists via the Internet or phone.

Balance of benefits and harms

Because CAH implies multiple emotional stressors and coping challenges for the patients and their families with variable consequences for mental health and QOL, we think that mental health support is a valuable complement to endocrinological and surgical management.

10. Objectives for Future Research

Newborn screening

- Determine whether analytes other than 17OHP, either singly or in combination with other biochemical or genetic tests, may improve the sensitivity and specificity of newborn screening programs.

Prenatal treatment

- Establish national and international registries of prenatally treated newborns.
- Conduct long-term follow-up studies of prenatally treated newborns and control groups through reproductive age.

Diagnosis of CAH

- Determine the utility of novel adrenal steroid panels to diagnose CAH.

Treatment of CAH

- Determine optimal treatment regimens through prospective trials.
- Define the utility of new steroid biomarkers, for example, 21-deoxycortisol, 11-ketotestosterone, and pregnenolone sulfate, in monitoring therapy.
- Better delineate situations that require "stress dosing" and the minimal effective GC doses to manage these events.
- Determine how GC requirements change throughout pregnancy and delivery.

NCCAH

- Rigorously delineate the criteria for diagnosing, treating, and monitoring NCCAH.
- Demonstrate the risks and benefits of GC therapy for improving pregnancy outcomes in NCCAH.

Long-term management

- Determine the optimal modes of transition of care from pediatric to medical and reproductive endocrinologists.
- Conduct long-term studies to assess the risks of cardiovascular disease, tumor formation, infertility, and other comorbidities in adults with CAH.
- Develop and implement telemedicine procedures for proper endocrine and psychiatric care of patients and families living in remote areas.
- Characterize the long-term implications of genetic findings (*e.g.*, CAH–tenascin-X contiguous deletion) via genetic studies in association with clinical phenotyping.

Surgery

- Conduct long-term follow-up studies to assess the outcomes of various surgical approaches compared with delayed surgery or no surgery.
- In contrast to other congenital genitourinary abnormalities such as bladder exstrophy, prune belly syndrome, and posterior urethral valves, the incidence of urogenital sinus anomalies associated with CAH has not decreased. Thus, there is a continuing need to derive evidence-based guidelines for surgical treatment of CAH, including ideal timing of surgery, surgical technique, risk of incontinence, risk of additional surgery (such as repair of vaginal stenosis at puberty), risk of loss of sexual function, and extent of clitoral surgery.

Experimental therapies

- Develop new treatment approaches that minimize GC exposure.
- Further define the clinical implications of epinephrine deficiency.

Mental health

- Develop and validate additional tools for evaluating QOL in patients (and their families) to facilitate improved assessment of current and future therapies.

Methodology

Participants

The Writing Committee consisted of 10 content experts representing the following specialties: endocrinology, pediatric urology, and psychology. Two of the

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committee members brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist who led the team of comparative effectiveness researchers that conducted the systematic reviews and meta-analyses. The methodologist also supervised application of the GRADE methodological framework for each recommendation, including quality of evidence assessments and strength of recommendation designations.

Guideline development process

The Endocrine Society's guideline development process combines elements of the GRADE framework (395) with, when relevant, an approach thought to be appropriate for rare endocrine diseases where scientific evidence is limited or nonexistent. The Society applies the steps in the GRADE framework to research questions for which there is an ample body of knowledge of low quality or higher (see Table 6). In these situations, GRADE provides the methodological and statistical rigor that results in robust recommendations that are classified using quality of evidence and strength of recommendation as described in by Guyatt *et al.* (396) and also represented graphically in Table 6.

Where evidence is extremely limited and/or not systematically analyzed, we provide recommendations based on an expert review of the limited data. This process is less systematic than the GRADE methodological framework; however, these recommendations are also clearly classified using the GRADE classification system.

Some of the Society's clinical practice guidelines also include ungraded good practice statements (397). This unclassified clinical guidance can include expert opinion statements on good practice, references to recommendations made in other guidelines, and observations on preventive care and shared decision-making.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, we include technical remarks. These provide supplemental information such as timing, setting, dosing regimens, and necessary expertise. All recommendations are followed by a synopsis of the evidence that underpins it. Authors may also include short statements on patients' values and preferences, the balance of benefits and harms, and minority opinions, where relevant.

Internal and external review

Approximately 18 months into the development process, Endocrine Society clinical practice guidelines

Table 6. GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1): "We recommend…"** *Benefits clearly outweigh harms and burdens, or vice versa*	1|⊕⊕⊕⊕	1|⊕⊕⊕O	1|⊕⊕OO	1|⊕OOO
	Conditional (2): "We suggest…" *Benefits closely balanced with harms and burdens*	2|⊕⊕⊕⊕	2|⊕⊕⊕O	2|⊕⊕OO	2|⊕OOO

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undergo a Comment Review Period (CRP) of 1 month when there is an opportunity for internal and external stakeholders to review the guideline draft and provide comments. These stakeholders include Endocrine Society members, the Society's Clinical Guidelines Subcommittee (CGS), representatives of any cosponsoring organizations, a representative of Council, and an Expert Reviewer. Following revisions to the guideline manuscript in response to CRP comments, it is returned to CGS, the Council Reviewer, and the Expert Reviewer for a second review and ballot. Finally, the guideline manuscript is subject to JCEM Publisher's Review prior to publication. This review is undertaken by an individual with expertise in the topic, without relevant conflicts of interest (COIs), and external to the guideline writing committee, CGS, and Council.

COIs

The Endocrine Society's COI rules for the development of clinical practice guidelines are as follows:

1. To be considered for membership of a Writing Committee, nominees are required to disclose all relationships with industry for the 12-month period prior to guideline Writing Committee initiation. This is consistent with the reporting time frame for the National Institutes of Health and the Food and Drug Administration.
2. Potential conflicts of interest that should be declared include all relationships with commercial, noncommercial, institutional, and patient/public organizations that are (or may be) pertinent to the scope of the guideline.
3. The chair of the Clinical Guidelines Subcommittee reviews all disclosed relationships and determines whether they are relevant to the topic of the guideline and present a potentially relevant conflict of interest.
4. The chair of the Clinical Guidelines Subcommittee selects Writing Committee Chairs and Co-Chairs, based on COI information, the individuals' clinical expertise, and other skills. The Endocrine Society Council reviews and endorses the nominees or makes appropriate changes. The three Chairs then select and appoint Writing Committee members.
5. The Chair and Co-Chair of the Writing Committee must be free of any COI or other biases that could undermine the integrity or credibility of the work.
6. At least half (≥50%) of the Writing Committee members must be free of relevant COIs.
7. Following initiation of the Committee, members are asked to disclose relationships with industry at every in-person meeting and on most conference calls.
8. Writing Committee members with relevant COIs are required to declare the situation and recuse themselves from any relevant discussions, votes, and from drafting recommendations.
9. All Writing Committee members must refrain from adding new relevant industry relationships throughout the guideline development process.
10. If a member is aware of another person who might have a conflict and has not declared it for some reason, they are obliged to bring this to the Writing Committee Chair's attention.
11. Staff, Writing Committee Chairs, and members must be alert for situations that might present a potential or perceived conflict of interest.

Appendix A

Resources for newborn screening:

- http://www.babysfirsttest.org/newborn-screening/conditions/congenital-adrenal-hyperplasia

Resources for clinical trials on CAH:

- http://clinicaltrials.gov/ct2/results?term=congenital+adrenal+hyperplasia

Resources for patients and families:

- https://www.caresfoundation.org
- https://www.cc.nih.gov/ccc/patient_education/pepubs/cah.pdf

Video demonstration of emergency HC intramuscular injection:

- https://www.youtube.com/watch?v=moSz5ZoTJFE

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Appendix B. Conflict of Interest of CAH Guideline Writing Committee

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info.
Phyllis W. Speiser (Chair)	Chief, Division of Pediatrics, and Professor of Pediatric Endocrinology, Cohen Children's Medical Center of New York, Northwell Health	• American Association of Clinical Endocrinology • Pediatric Endocrine Society	None declared	• Gerson Lehman Group, consultant • Hood Law Firm, medical expert witness	None declared	None declared
Wiebke Arlt	Chair of Medicine at the College of Medical and Dental Sciences of the University of Birmingham (UK) and Centre for Endocrinology, Diabetes, and Metabolism	• Society for Endocrinology UK, Chair of Clinical Committee, Member of Council and Nomination Committee • European Network for the Study of Adrenal Tumors, Member of Steering Committee and Adrenocortical Carcinoma Working Group Committee	None declared	• Bayer Health Care Advisory Board • Janssen, Advisory Board • Diurnal Ltd, consultancy and site investigator • Patents on the use of steroid metabolomics for the diagnosis, differential diagnosis, monitoring, and prognostic prediction in steroid-related disorders	None declared	None declared
Richard J. Auchus	Professor of Internal Medicine and Pharmacology, University of Michigan	None declared	• American Association of Clinical Endocrinologists, Adrenal Scientific Committee Member and President, Michigan Chapter • *Endocrinology* Associate Editor • CARES Foundation, Medical Advisory Board	• Novartis Pharmaceuticals, contracted research support and consultant • Strongbridge Biopharma, contracted research support and consultant • Neurocrine Biosciences, contracted research support and consultant • Millendo Therapeutics, contracted research support and consultant • Quest Diagnostics, consultant • Corcept Therapeutics, consultant • Janssen Pharmaceuticals, consultant • Spruce Biosciences, contracted research support and consultant • Diurnal Ltd, consultant • Adrenas Therapeutics, consultant • Selenity Therapeutics, consultant • United States Anti-Doping Agency, consultant	None declared	None declared
Laurence Baskin	Professor of Urology and Pediatrics, University of California San Francisco	None declared	None declared	None declared	None declared	None declared
Gerard Conway	University College London Hospitals, London, UK	None declared	None declared	None declared	None declared	None declared
Deborah P. Merke[a]	Senior Investigator, Chief Pediatric Service, National Institutes of Health Clinical Center	None declared	None declared	Up-to-Date, author	• Diurnal Ltd, Principal Investigator • Millendo Therapeutics, Principal Investigator	None declared
Heino Meyer-Bahlberg	Research Scientist, New York State Psychiatric Institute, and Professor of Clinical Psychology (in Psychiatry), Vagelos College of Physicians and Surgeons of Columbia University	• Pediatric Endocrine Society (and 12 other professional nonendocrine societies) • Scientific Advisory Board of dsd-LIFE (research project in six European countries on somatic DSD funded by the European Union) • Consultant, Workgroup on Gender Dysphoria of the American Psychiatric Association	None declared	None declared	None declared	None declared

(*Continued*)

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Appendix B. Conflict of Interest of CAH Guideline Writing Committee (Continued)

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info.
		• Council on Research and Quality Care member, panel for the 10-year update of the 2005 International Consensus Conference on Intersex Management • Member, Standards of Care Revision (SOC-8) Committee of the World Professional Association for Transgender Health (chapter lead for the intersex-care chapter) • Distinguished Visiting Professor, School of Medicine, Tehran University of Medical Sciences				
Walter L. Miller	Retired; Distinguished Professor Emeritus, University of California San Francisco; and Emeritus Chief of Endocrinology, University of California San Francisco Children's Hospitals	• Pediatric Endocrine Society • Japanese Society for Pediatric Endocrinology (Honorary) • European Society for Pediatric Endocrinology • The CARES Foundation • American Association for the Advancement of Science • American Society for Biochemistry and Molecular Biology	• Chair, History Committee, Pediatric Endocrine Society • Medical Advisory Board, CARES Foundation • Associate Editor for *Hormone Research in Paediatrics*	• Spruce Biosciences, consultant • Adrenas Therapeutics, consultant • Share of royalties on patents held by the University of California concerning bovine GH	None declared	None declared
M. Hassan Murad	Professor of Medicine and Director of Evidence-Based Practice Center Mayo Clinic	None declared	None declared	None declared	None declared	None declared
Sharon E. Oberfield	Professor of Pediactrics; Director, Division of Pediatric Endocrinology, Diabetes, and Metabolism, Columbia University Medical Center	Member of Board of Directors of Androgen Excess and Polycystic Ovary Syndrome Society	• Associate Editor for *Hormone Research in Paediatrics*	None declared	National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases-B study section	None declared
Perrin White	Professor of Pediatrics, University of Texas Southwestern Medical Center	None declared	None declared	None declared	• National Institutes of Health, grantee • Janssen Pharmaceutical, receive study drug gratis	None declared

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Disclosure Summary: See Appendix B.

Disclaimer: The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgement of healthcare providers and each patient's individual circumstances.

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