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CARES Connections

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SPRING 2025
VOL. 28

IN THIS ISSUE

Research & Treatment
1, 3–8, 13–20

Executive Director's Message
2

25th Anniversary Everyone CARES Gala
9

Events
10–11

A Personal Story
11

Annual Patient Education Conference – Indianapolis
12

Education & The Dr. Is In
20 & 21

Support
22

Fundraising
23 & 24

CARES Shop
24

VISIT OUR WEBSITE

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Glucocorticoid therapy in classic congenital adrenal hyperplasia: traditional and new treatment paradigms

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ABSTRACT

Introduction: Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is a rare genetic condition characterized by cortisol deficiency and excess adrenal androgens. CAH treatment is a lifelong balancing act between the need to reduce excess androgens, typically with supraphysiologic glucocorticoid (GC) doses, and concerns about potentially serious GC-related adverse events. Tradeoffs between the consequences of excess androgens versus GCs must be constantly reassessed throughout each patient's lifetime, based on current clinical needs and treatment goals. Adding to this burden are limited treatment options and the need for new CAH medications.

Areas covered: This narrative review describes the current challenges of CAH treatment, the potential of new non-GC therapies to reduce excess androgens and thereby allow for lower GC doses, and the potential implications of decreasing GC doses to a more physiologic range (i.e. sufficient to replace missing cortisol, but without the need to reduce androgens).

Expert opinion: Even with non-GC therapies, patients' needs will continue to shift throughout their lifetimes. Treatment will therefore always require joint decision-making between physicians and patients. However, over the lifetimes of patients with CAH, any reduction in GC daily dose may have a large cumulative impact in decreasing the GC-related burden of this disease.

ARTICLE HISTORY
Received 31 October 2024
Accepted 3 January 2025

KEYWORDS
Androgen; congenital adrenal hyperplasia; glucocorticoid; glucocorticoid replacement dose; physiologic glucocorticoid dose; treatment challenges

1. Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition caused by pathogenic variants in genes that are involved in steroidogenesis [1,2]. These pathogenetic variants are associated with a continuum of CAH phenotypes, ranging from a mild (or sometimes non-symptomatic) non-classic form to the more severe and rarer classic form, which occurs in ~1:15,000 live births [1–3].

Approximately 95% of all CAH cases are caused by a deficiency in 21-hydroxylase, an adrenal enzyme required for producing cortisol and aldosterone [3-7]. Cortisol deficiency results in a loss of negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, leading to an over-secretion of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) and the excess production of adrenal androgens (hereafter, generally referred to as 'androgens' for simplicity) (Figure 1). In patients showing clinical signs of aldosterone deficiency (e.g. hypotension, hyponatremia, hyperkalemia, and dehydration), treatment with a mineralocorticoid is required; those with elevated renin levels (without corresponding clinical findings) may also benefit from mineralocorticoid replacement.

In patients with classic CAH due to 21-hydroxylase deficiency (hereafter simply referred to as CAH), addressing androgen excess is challenging. Glucocorticoid (GC) therapy serves two functions in these patients [1,2]. First, GC medications replace missing cortisol, which is essential given the critical role that cortisol plays in regulating cardiovascular, metabolic, and neurologic function. Second, GCs are used to reduce excess ACTH and androgens, which result from the lack of negative feedback of endogenous cortisol to the hypothalamus and pituitary (Figure 1). In CAH, supraphysiologic doses of GCs (i.e. higher than needed to simply replace missing cortisol [8,9]) are typically needed to adequately control excess ACTH and androgens; in contrast, androgens are not elevated in Addison's disease or other forms of adrenal insufficiency (AI) and patients therefore typically require lower GC doses (i.e. for cortisol replacement alone) [10].

Since lifelong exposure to supraphysiologic GC doses can lead to serious cardiovascular, metabolic, and skeletal complications and can negatively impact a patient's mental health and quality of life [4,11–25], there is a pressing need for novel CAH therapies that might allow for GC dose reductions to a more physiologic range. Several non-GC drugs that target the HPA axis have been shown in clinical trials to reduce ACTH, androgens, and/or androgen precursors [26–31]. These promising results offer the possibility of a new treatment paradigm in which non-GC therapies reduce ACTH-mediated excess androgen production, thereby allowing GC to be

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A Message from the Executive Director

Dear Friend,

I am delighted to welcome you to the Spring Edition of CARES Connections, especially as we celebrate a truly momentous occasion for the CARES Foundation—our 25th anniversary! It's hard to believe that 25 years ago, we embarked on this journey with a simple yet powerful mission: to support individuals and families impacted by congenital adrenal hyperplasia (CAH). Today, we look back with pride at the incredible progress we've made in serving the CAH community, both here in the U.S. and around the world.

Over the past quarter-century, we've had the privilege of supporting families in more than 80 countries, advocating for essential changes, and collaborating with medical professionals to enhance the lives of those affected by CAH. Among our most significant achievements are the nationwide implementation of newborn screening for CAH, which has led to early diagnoses and lives saved, and the establishment of EMS protocols to ensure emergency responders have the tools and knowledge to provide the best care during critical situations. We've also played a key role in the creation of the PACE app, which equips patients and caregivers with valuable information to manage adrenal crises and navigate illness, stress, or emergencies.

Our dedication to research and support remains unwavering. We continue to offer a wide range of resources, including both in-person and virtual support group meetings. These gatherings have become a vital source of connection, allowing families to share experiences and find comfort in knowing they are not alone.

We've also celebrated the designation of nine Centers of Excellence in the United States, which provide specialized care and resources to those living with CAH. These centers are at the forefront of advancing both care and research. Additionally, our "Ask the Expert" service connects patients and caregivers with CAH specialists, providing expert guidance and peace of mind regarding treatment questions. Our most recent educational initiative, the CAH Pulse podcast, is now in its second season, helping raise awareness and share important information.

Since our last edition, we've had the rare opportunity to host a Patient-Focused Drug Development meeting with the FDA. This groundbreaking event allowed us to directly share the unmet needs and daily challenges faced by the CAH community, strengthening our advocacy efforts for meaningful change.

And in a truly thrilling development, I am beyond excited to announce that our ongoing collaboration with industry partners has resulted in the approval of the first new treatment for CAH by the FDA in more than 70 years.. This monumental breakthrough highlights the tireless dedication of our community—researchers, clinicians, patients, and supporters alike—who are all working together to create real change.

As we celebrate this milestone 25th anniversary, I am filled with immense pride and gratitude for each and every one of you—the families, individuals, clinicians, researchers, and supporters who have made these remarkable achievements possible. You inspire us to do more each day. Together, we've made a lasting impact, and we're only just getting started.

Thank you for being part of this incredible journey!

Warmly,

Dina M. Matos
Executive Director

Article Highlights

- Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is a rare genetic condition characterized by deficiency of cortisol and aldosterone, as well as excess production of adrenal androgens.
- The patient journey with CAH is a lifelong balancing act that requires weighing the need to reduce excess androgens, which typically require glucocorticoids (GCs) at supraphysiologic doses (i.e. higher than required to replace missing cortisol), against the risks of GC- related complications.
- Therapeutic decisions for patients with CAH are multi-factorial and complex and should be individualized to each patient's life stage and treatment goals.
- Emerging non-GC therapies for CAH could provide a way to reduce excess androgens without using supraphysiologic GC doses.
- Over a lifetime, even small reductions in daily GC doses can decrease the risk of GC-related complications and lower the cumulative burden of GC exposure.

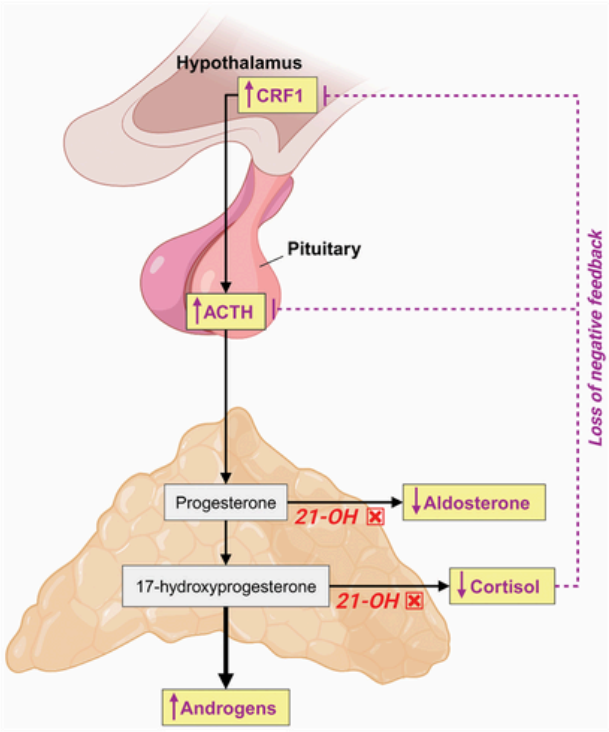

Figure 1. Pathophysiology of CAH. In classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21-OH) deficiency, cortisol deficiency results in a loss of negative feedback to the hypothalamic-pituitary-adrenal axis, resulting in an increased secretion of corticotropin-releasing factor (CRF) from the hypothalamus and adrenocorticotrophic hormone (ACTH) from the pituitary. Elevated ACTH drives the production of excess adrenal androgens. Created in BioRender, O'Connell, M (2025) https://biorender.com/h23×060. Adapted with permission from Mallappa et al, *Nat Rev Endocrinol 2022* [7].

reduced to a more physiologic dose (i.e. sufficient for replacing missing endogenous cortisol).

To navigate this emerging therapeutic landscape, we conducted a narrative review of the literature based on English- language publications in PubMed with no restriction on publication dates. We specifically searched for articles authored by experts in the field that provided evidence for and/or clinical insight into the current challenges of CAH treatment, the difficulty of interpreting androgen levels as biomarkers of disease control, and the need to better understand what might constitute a physiologic GC dose range in this patient population.

2. Clinical considerations in patients with CAH

2.1 Consequences of cortisol and aldosterone deficiency

Cortisol and aldosterone deficiency contribute to a myriad of symptoms, including fatigue, weakness, low blood pressure, dizziness, decreased appetite, digestive issues, unintentional weight loss, depressed mood, and irritability [32]. When cortisol deficiency is severe, as in cases of acute intercurrent illness, life-threatening adrenal crises can occur; the presentation can be even more severe when aldosterone is also deficient. Replacement with GCs and mineralocorticoids are needed to address these symptoms, and both under- and overtreatment can lead to serious consequences. Regular monitoring of blood pressure, electrolytes, and plasma renin levels is used to guide mineralocorticoid replacement [3].

Throughout all stages of life, patients with CAH are at risk of developing potentially life-threatening adrenal crisis [1,33]. Cohort studies have reported that adrenal crisis is the leading cause of death in patients with CAH [34,35]. If not diagnosed and treated within the first 3 weeks of life, approximately 75% of infants with CAH will experience salt-wasting adrenal crisis [1]. A recent prospective observational study in 38 children and 187 adults with CAH reported an incidence of adrenal crisis of 8.4 and 5.1 per 100 patient years, respectively [36]. A longitudinal study of 156 patients conducted by the National Institutes of Health (NIH) found adrenal crises to be occurring at an incidence of 7.55 per 100 patient-years (7.2 for children, 10.2 for adults) [37].

Patients with CAH are also at increased risk of developing hypoglycemia due to cortisol deficiency, particularly during infancy and childhood [4]. Within the first few years of life, 8% of patients experience a hypoglycemic episode [33,38], and episodes may occur at any age during adrenal crisis [4]. Given these risks, selecting a therapeutic regimen that sufficiently replaces missing cortisol is an ongoing challenge throughout each patient's lifetime.

2.2 Consequences of excess androgens

The consequences of excess androgen production must be considered at every stage of each patient's life. In addition to avoiding GC undertreatment (to prevent symptoms of adrenal insufficiency, adrenal crises, and hypoglycemic episodes), clinicians must consider how much additional GC dosing is needed to lower androgen levels. At some points in a patient's life, higher GCs are needed to ensure that androgens are controlled to within normal limits; at other points, lowering GC doses to mitigate GC-related risks might be a higher priority.

Beginning in utero, high androgen levels can cause virilization of external genitalia in female (46, XX) newborns, which can require surgery [3,4,39]. Continued exposure to excess androgens throughout childhood and adulthood can cause further virilization (e.g. clitoromegaly), possibly requiring additional surgical procedures [40]. Male (46, XY) newborns typically have no differences in genital appearance but may have subtle hyperpigmentation or possible penile enlargement [33].

During childhood, patients with CAH often experience precocious puberty along with advanced bone age [1,3,4]. Excess androgen production causes suppression of the hypothalamic- pituitary-gonadal axis and results in pseudo-precocious puberty (e.g. adrenarche, excess growth, and advanced bone age) [41]. Furthermore, long-term exposure to excess androgens leads to central precocious puberty, characterized by early breast and testicular development [42]. Advanced bone age during childhood may also impact the final adult height [43,44]. A retrospective cohort study of 496 children with CAH showed that advanced bone age at 8 years of age was correlated with reduced adult height [43]. Consequently, as estimated in a meta-analysis of 35 studies, final adult height in the CAH patient population is 1.38 standard deviations below the general population [44], corresponding to an approximate mean difference of −10 cm [1].

With the transition from childhood into adolescence and adulthood, female patients may experience hirsutism, acne, and menstrual irregularities as a result of excess androgens [4,45,46], while male patients can develop testicular adrenal rest tumors (TARTs) due to elevated ACTH levels [4,45,47,48]. The estimated prevalence of TARTs is approximately 40%, with reported prevalences ranging from 14% to 86% depending on age, disease control, and frequency and method of detection [49,50]. Although rare and difficult to detect using ultrasonography, female patients with CAH can develop ovarian adrenal rest tumors in the ovaries and uterine ligaments [5,11].

During adulthood, androgen excess affects fertility in both women and men [51–54]. Menstrual irregularities due to androgen excess can impair a woman's ability to get pregnant; anovulation, anatomical barriers, psychosexual factors, and reduced desire to have children are also cited as factors contributing to decreased fertility [4,55]. In men, TARTs can cause seminiferous tubular obstruction and irreversible damage to the surrounding testicular tissue, eventually leading to infertility [53,54], and misdiagnosis of TARTs can result in unnecessary orchidectomy [21]. Secondary gonadal dysfunction due to suppression of the hypothalamic-pituitary-gonadal axis can also

cause infertility, which is generally reversible when treated [12,48]. However, testosterone concentrations are often within the normal range due to conversion of adrenal androgens to testosterone; thus, secondary hypogonadism is not always detected if follicular stimulating hormone and luteinizing hormone levels are not routinely assessed [48], resulting in potential underdiagnosis or delayed diagnosis.

Along with issues related to growth, sexual maturation, and fertility, children and adults with CAH have an increased risk for obesity, insulin resistance, and diabetes [56,57]. Although these conditions are predominantly due to chronic supraphysiologic GC treatment (Section 3.3), excess androgens also contribute to the metabolic symptoms of CAH [58]. Moreover, excess androgens can negatively affect mental health and behavior throughout a patient's lifetime, as demonstrated by the increased prevalence of depressive disorders, anxiety disorders, and attention deficit hyperactivity disorder in patients with CAH [59–61]. A cross-sectional study of 55 girls with CAH found that poor disease control (i.e. excess androstenedione, excess testosterone, and advanced bone age) was independently associated with behavioral problems and peer relationship problems compared to controls [60]. Furthermore, female patients who exhibit genital virilization due to excess androgens may experience psychological challenges that can negatively impact sexual/romantic relationships and self-esteem [60,62,63].

2.3. Challenges in monitoring androgen levels

Effective treatment of CAH requires regular monitoring of key adrenal androgens and androgen precursors. Serum androstenedione, serum 17-hydroxyprogesterone (17-OHP), and testosterone (to a lesser extent) are steroid biomarkers used to assess disease control and adjust GC treatment regimens [3,45,64], with androstenedione having the advantage of less diurnal variation [45]. To avoid overtreatment with GCs, the 2018 Endocrine Society guidelines for classic CAH recommend targeting 17-OHP and androstenedione levels that are in the upper limit of normal (ULN) to mildly elevated range, based on age and sex [3].

Regular monitoring of androgen levels is crucial for CAH management; however, making treatment decisions based on these biomarkers is very challenging. Androgen levels vary due to normal diurnal variation, with androgens peaking in the early morning and reaching a nadir during the night [65,66]. Other variables that affect androgen levels include sex, age, pubertal status, menstrual cycle phase, physical stress (e.g. strenuous exercise or illness), and psychosocial stress (e.g. death of a family member) [7,45,65,67]. For patients with CAH, androgen levels also vary diurnally based on the type of GC medication (e.g. dexamethasone versus prednisolone) and the timing of the laboratory assessment relative to GC dose (e.g. before or after morning GC dose) [11,65,68,69].

The Endocrine Society guidelines do not specify when to measure androgen levels, but they do recommend consistency in terms of medication schedule and time of day [3]. Laboratory assessments can be taken before the first morning GC dose to monitor the patient's underlying levels of androgen control without the confounding factor of a recent GC dose [65,70]. However, some clinicians may prefer to assess androgen levels after the first morning GC dose in order to assess the effects of a recent GC dose on the patient's androgen levels.

In practice, consistent timing of biomarker assessments – whether samples are taken before or after the patient's morning GC dose – is not always possible due to physicians' and/or patients' schedules, laboratory hours, or other factors. Moreover, the types of assays used to assess biomarkers may differ between laboratories. The preferred method for assaying steroid biomarkers is liquid chromatography-mass spectrometry due to its specificity and capability to simultaneously determine multiple biomarker levels in a single run [4]. Antibody-based assays are also commonly used; however, antibody cross-reactivity with structurally related substances can result in overestimation of biomarker levels [4].

Given these many potentially confounding factors, the interpretation of biomarker assessments is difficult. Endocrinological expertise is needed to integrate practice guidelines with the clinical picture of each patient (e.g. medical history, current signs of androgen excess, adrenal crisis, and GC toxicity) and patient's personal preferences (e.g. willingness to accept hirsutism rather than increasing GC dose) [3,4,71]. Therefore, a joint decision-making approach, with agreement between the clinician and patient (or patient's guardian[s]), is needed when developing a CAH treatment plan.

3. GC treatment in classic CAH

3.1 Guidelines and recommendations

In infants and growing children, hydrocortisone is the preferred GC therapy due to its short half-life; potent long- acting GCs are generally avoided in younger patients due to the risk of growth suppression or other adverse effects [3,72]. Oral hydrocortisone tablets are recommended over liquid suspensions due to the uneven distribution of doses in the liquid form [3]. For this age group, the Endocrine Society recommends 10–15 mg/m^2/d hydrocortisone divided into 3 daily doses, with exact dosage based on body surface area (BSA) in order to minimize variability in drug exposure in growing patients [3]. It is important to use the lowest effective dose to achieve treatment goals, as adult height of patients with CAH correlates negatively with the GC dose administered in childhood and adolescence [3,72–76]. In addition to regular assessments of androgen levels, growing patients should also be regularly evaluated for clinical signs of hyperandrogenism (e.g. accelerated growth velocity, advanced bone maturation, and signs of virilization) and excessive GC dosing (e.g. reduced growth, accelerated weight gain, high blood pressure), which may indicate the need for treatment adjustment [3,4].

For adults with CAH, the Endocrine Society recommends 15–25 mg/d in hydrocortisone equivalents (HCe) divided into 2–3 daily doses [3]. In addition, once- or twice-daily preparations of equivalent doses of longer-acting GCs, such as prednisone (5–7.5 mg/d), prednisolone/methylprednisolone (4–6 mg/d), and dexamethasone (0.25–0.5 mg/d) can be used in patients who are fully grown [3]. As with children and adolescents, adults with CAH should be regularly monitored for signs of under- and overtreatment to assist in clinical decision-making regarding GC dose [3].

Patients with CAH are unable to produce sufficient cortisol in response to stressors, such as febrile illnesses, gastroenteritis with dehydration, surgery, and trauma; thus, increased GC doses are required to avoid a life-threatening adrenal crisis [1,3]. During these episodes, patients require immediate stress dosing (or 'sick day dosing') with GC doses that are much higher (e.g. hydrocortisone ~40 mg/m^2/d in children [77]) and/or more frequent than their regular daily GC doses, taken as prescribed and instructed by their clinicians [1,3].

For adults with AI not due to CAH, the recommended GC dose range is the same as that recommended for adults with CAH (i.e. 15-25mg/d HCe divided into 2-3 daily doses) [3,9,78]. However, the role of GC treatment differs between these patient populations and recent studies suggest that the higher doses recommended in the current AI guidelines for adults may result in GC overtreatment for some patients with AI [79,80]. For AI not due to CAH, GCs only replace endogenous cortisol but also to reduce excess androgen production. Thus, the recommended hydrocortisone dose range (10-15mg/m(2)/d) for children with CAH is higher than for children with AI not due to CAH, where the recommendation is to start at 8mg/m(2)/d and adjust the dose according to individual need [3,9].

3.2 Real-world evidence of GC dosing in patients with CAH

Although the Endocrine Society guidelines suggest 15–25 mg/d HCe in adults with CAH, real-world observational studies show wide variability in GC regimens, with GC doses that are often higher than the recommended dose range (Table 1) [19,21,73,81–95]. In a large adult study from the United Kingdom, the median daily hydrocortisone dose was at the top of the recommended range (males: 25 mg/d; females: 20 mg/d); moreover, there was wide variation in doses administered, with some male patients receiving up to 60 mg/d and some female patients receiving up to 32.5 mg/d [21]. Mean daily GC doses above the recommended range were also reported in studies from Germany (27 mg/d), France (26 mg/d), Sweden (29 mg/d), and the United States (US) (30 mg/d) [81–84]. Despite higher- than-recommended mean GC doses, approximately 25–60% of patients in these studies had elevated androstenedione or 17-OHP, as described by the study investigators. These data suggest that the guideline-recommended GC dose is often not effective in normalizing androgen excess in adults with CAH.

There is also ample real-world evidence indicating that many children and adolescents are receiving GC doses that are higher than the recommended dose of 10–15 mg/m^2/d (Table 1). For example, data from 461 children with CAH in the International-CAH registry indicated that approximately one-third of patients were receiving doses above the recommended upper limit [90]. In addition, higher than recommended doses were reported in large observational studies in Germany (17.5 mg/m^2/d) [73], the US (18.9 mg/m^2/d) [94], and Poland 17.5mg/m^2/d) [92], as well as several smaller observational studies [87,89,93,95].

3.3 Consequences of treatment with supraphysiologic GC doses

Chronic treatment with GCs, even in the range commonly used to treat CAH, has been associated with a number of potentially serious health complications [11,13–25,72,96,97]. When these GC-related complications are layered onto the disease-related conditions – and sometimes even compounding those conditions – the clinical presentation of CAH becomes very complex (Figure 2).

Prolonged exposure to GCs in patients with CAH, especially at supraphysiologic doses, can exert growth-suppressing effects by

Table 1. Real-world glucocorticoid dosing with androstenedione and/or 17-OHP in observational studies of patients with CAH.

Study	Region(s) or Registry	Glucocorticoid Dose	Androstenedione and/or 17-OHP[a]
In adults (recommended glucocorticoid dose: 15–25 mg/d in HCe unless indicated otherwise)			
Arlt 2010 [21]	United Kingdom ($N = 165$ with classic CAH)	Median hydrocortisone dose (range): • In males: 25 (10–60) mg/d • In females: 20 (10–32.5) mg/d Median prednisolone dose (range): • In males: 7.5 (2.5–10) mg/d • In females: 6 (2.5–10) mg/d Median dexamethasone dose (range): • In males: 0.5 (0.25–0.75) mg/d • In females: 0.375 (0.25–0.75) mg/d	Androstenedione • Elevated: 35% of males; 27% of females • Suppressed: 29% of males; 38% of females 17-OHP • Elevated: 52% of males; 43% of females • Suppressed: 37% of males; 45% of females • 17-OHP was 'much more variable than the androgens'
Auer 2020 [81]	Germany ($N = 97$)	Mean: 27 mg/d[b,c]	Androstenedione • Elevated: 26% of males; 16% of females • Suppressed: 19% of males; 35% of females 17-OHP • Elevated: 76% of males; 49% of females • Suppressed: 0% of males; 11% of females
Bouvattier 2015 [82]	France ($N = 219$ males)	Mean: 26.1 mg/d[b]	• Androstenedione: elevated in 62% of patients • 17-OHP: elevated in 82% of patients
Falhammar 2011 [19]	Sweden ($N = 30$ males)	Mean: 30 mg/d[c]	24-hour median 17-OHP was 'very high' (≥96 nmol/L) in 19% of patients
Falhammar 2007 [83]	Sweden ($N = 61$ females)	Mean: 29 mg/d[c]	• Androgens were 'markedly suppressed' because patients were 'treated with supraphysiologic glucocorticoid doses' • Androstenedione was low compared to controls, but 'rarely suppressed to subnormal values'
Finkielstain 2012 [84]	United States ($N = 44$)	Mean: 30 mg/d[c]	Androstenedione[d] • Elevated: ~42% of patients • Suppressed: ~16% of patients 17-OHP[d] • Elevated: ~53% of patients • Suppressed: ~20% of patients
Gao 2021 [85]	China ($N = 46$)	Mean: 31.6 mg/d[b]	Mean 17-OHP was higher than reference range • 51.0 ng/mL in males (reference: 0.31–2.2 ng/mL) • 27.8 ng/mL in females (reference: 0.10–0.80 ng/mL)
Reisch 2013 [86]	Germany ($N = 50$ males)	Mean: 27 mg/d[b,c]	Median AUC (Q1-Q3) for 17-OHP was 774 (466–1569) ng/mL•year
In children/adolescents (recommended glucocorticoid dose: 10–15 mg/m^2/d in HCe)			
Abdel Meguid 2022 [87]	Egypt, Qatar, Italy ($N = 30$)	Mean (±SD): 22.5 ± 7 mg/m^2/d • 27.1 ± 6.4 mg/m^2/d in 'less controlled' subgroup ($n = 11$)	• 17-OHP: 36.7% categorized as 'less controlled' (>6 nmol/L) • 17-OHP mean (±SD): 8.2 ± 0.7 ng/mL (less controlled subgroup)

(*Continued*)

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Finkielstain 2012 [84]	United States ($N = 44$)	Mean: 30 mg/d[c]	Androstenedione[d] • Elevated: ~42% of patients • Suppressed: ~16% of patients 17-OHP[d] • Elevated: ~53% of patients • Suppressed: ~20% of patients
Gao 2021 [85]	China ($N = 46$)	Mean: 31.6 mg/d[b]	Mean 17-OHP was higher than reference range • 51.0 ng/mL in males (reference: 0.31–2.2 ng/mL) • 27.8 ng/mL in females (reference: 0.10–0.80 ng/mL)
Reisch 2013 [86]	Germany ($N = 50$ males)	Mean: 27 mg/d[b,c]	Median AUC (Q1-Q3) for 17-OHP was 774 (466–1569) ng/mL•year
In children/adolescents (recommended glucocorticoid dose: 10–15 mg/m^2/d in HCe)			
Abdel Meguid 2022 [87]	Egypt, Qatar, Italy ($N = 30$)	Mean (±SD): 22.5 ± 7 mg/m^2/d • 27.1 ± 6.4 mg/m^2/d in 'less controlled' subgroup ($n = 11$)	• 17-OHP: 36.7% categorized as 'less controlled' (>6 nmol/L) • 17-OHP mean (±SD): 8.2 ± 0.7 ng/mL (less controlled subgroup)

(*Continued*)

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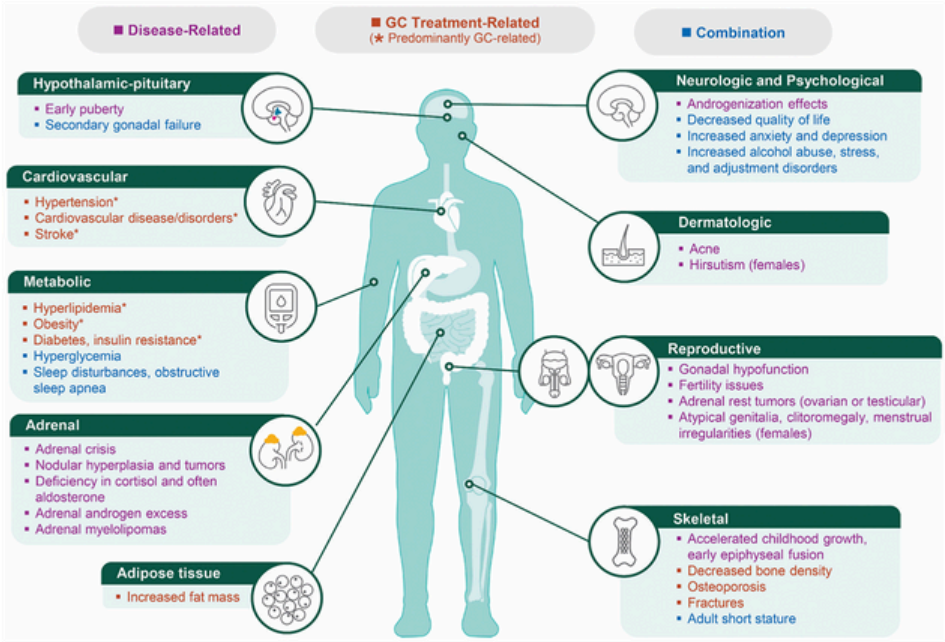


Figure 2. Conditions associated with CAH. The clinical burden of congenital adrenal hyperplasia (CAH) is substantial, due to disease-related consequences associated with little or no endogenous cortisol, the risks for adverse effects associated with lifelong glucocorticoid (GC) treatment, or both. Lack of endogenous cortisol leads to an increased secretion of adrenocorticotrophic hormone (ACTH) from the pituitary along with overproduction of androgens from the adrenal glands, and management of these excess adrenal androgens typically requires supraphysiologic GC doses. A number of cardiovascular diseases and metabolic conditions are predominantly related to GC treatment (*) but are also associated with the disease state. From Merke and Auchus, *N Engl J Med* 2020 [1] (©2020 Massachusetts Medical Society). Adapted with permission from the Massachusetts Medical Society.

interfering with growth hormone secretion and bone metabolism [72,94,97]. In a retrospective study of 92 children, corrected final height (i.e. adjusted for parental height) was reduced in both sexes, and GC doses at the onset of puberty were negatively correlated with final height ($p < 0.01$); doses > 17 mg/m^2/d HCe (-2.7 vs -.1.8 for < 15 mg/m^2/d, $p = 0.038$ [98]. In the NIH Natural History Study, 20% of children wit hCAH had a low predicted adult height (i.e. standard deviation score of -2.0 or lower) and higher GC doses were associated with shorter predicted adult stature ($p = 0.013$) [84]. Longitudinal data from 104 children with CAH demonstrated that for each 1mg/m2/d increase in hydrocortisone dose, final height was significantly decreased by 0.37 cm [94].

Adults with CAH are at risk of low bone mineral density (BMD), osteoporosis, and fractures due to GCs, which can inhibit bone formation and increase bone resorption upon initial treatment but decrease osteoclast activity (resorption) over the long term [15,16,24,99–101]. Approximately 37% of adults with CAH in the NIH study (mean GC dose ~17 mg/m^2/d HCe) had low BMD [84], consistent with previous smaller studies that also showed decreased spine or femoral neck BMD [14,102–104]. One study of 13 women with CAH showed statistically significant correlations between cumulative GC dose and bone mineral content, lumbar spine BMD, and total BMD [103]. In a study of 28 children and young adults, patients with severely reduced BMD Z-scores had a much higher mean GC dose (~29mg/m^2/d HCe) than those with moderately reduced or normal BMD Z-scores (~18 and ~17 mg/m^2/d, respectively); GC doses > 20 mg/m^2/d HCe were significantly associated with lower lumbar BMD Z-scores [104]. Another study found spine BMD to be significantly reduced in 25 adolescents and young adults with CAH as compared with matched controls, with GC dose showing significant negative correlations with BMD and with bone mineral content at the femur and spine [105].

In addition to the negative effects of GCs on growth and bone health in CAH, the increased risks of developing cardiometabolic comorbidities, including hypertension, cardiovascular disease, stroke, hyperlipidemia, obesity, hyperglycemia/insulin resistance or frank diabetes mellitus, and sleep disturbances/ obstructive sleep apnea have been well documented in patients with CAH [11,17–21,23,24,57]. Adverse changes in cardiometabolic risk factors have also been demonstrated in patients with other forms of AI receiving chronic GC treatment. For example, adults with hypopituitarism taking >20 mg/d HCe have increased triglycerides, waist circumference, and waist-to-hip ratio than those taking lower doses [106,107].

The increased risks for mortality with CAH and with exposure to high GC doses have been well documented. In a Swedish national registry of 588 patients with CAH, the mortality hazard ratio was 2.3 for male patients and 3.5 for female patients when compared with matched controls [34]. In a retrospective study of 105 Swiss patients with AI, hazard ratios for all-cause mortality by GC dose (in HCe) were 2.0 for 20–29 mg/d and 4.0 for ≥30 mg/d, as compared to <20 mg/d [108]. Similarly, a Swedish study of 392 adults with AI and non- functioning pituitary adenoma showed increased mortality ratios of 1.42 and 1.56 at GC doses of >20 mg/d and >0.30 mg/kg/d HCe, respectively, compared with the general population [109].

Large cross-sectional studies in inflammatory disease states such as rheumatoid arthritis (RA) and asthma have also shown higher GC doses to be associated with elevated risks of metabolic, cardiovascular, and musculoskeletal complications [110– 116]. In a study of 1,066 patients with RA, prednisone doses >5 mg/d (20 mg/d HCe using a 4× equivalency factor) were associated with weight gain, and doses >7.5 mg/d (30 mg/d HCe) were associated with increased blood pressure and depression [110]. In a study of 12,697 patients with asthma, the odds of developing infections, skin disease, or gastrointestinal, bone/muscle, cardiovascular, metabolic, psychiatric, or ocular complications increased significantly as GC dose increased [111]. Medical records from 87,794 patients with various immune-mediated inflammatory diseases showed that high GC doses were associated with increased cardiovascular risks [112]. Even doses below 5 mg prednisolone (<20 mg HCe) were found to increase the risks for atrial fibrillation, myocardial infarction, peripheral arterial disease, cerebrovascular disease, and abdominal aortic aneurysm [112]. These non-AI studies illustrate the dose-dependent relationship between GC doses and the serious medical risks associated with their use.

Finally, a decreased quality of life has been reported in patients with CAH, along with higher risks for developing psychiatric complications, including depression, alcohol abuse, stress, and adjustment disorders, which have been associated with both adrenal androgen excess as well as GC exposure [24,59,61,117–124].

3.4 Real-world treatment challenges

CAH treatment is a lifelong balancing act with multiple transitions between health states, as defined by the need for supraphysiologic GC doses (to reduce excess androgens) versus the need to decrease GC doses toward more physiologic levels (to mitigate the potentially serious consequences of long-term GC exposure) (Supplementary Figure S1). Many factors can sway the balance, with patients' therapeutic goals changing as they transition from one stage of life to the next.

Exposure to excess androgens causes enlargement of genitalia in the postnatal period, followed by abnormally rapid growth with advancing bone age and signs of precocious puberty during childhood. In this stage of life, the primary therapeutic goal is to manage accelerated growth and prevent precocious puberty. However, finding appropriate GC doses is highly challenging and requires constant reassessment as children grow. Overtreatment with GCs in childhood can lead to overweight/obesity and poor growth outcomes in adulthood (i.e. lower than predicted final adult height), while undertreatment can

accelerate the onset of puberty, leading to early growth plate closure and lower-than-expected final adult height.

GC doses are usually increased during puberty, in part due to increased clearance; however, this is also a period in which minimization of unwanted secondary sex characteristics is an important therapeutic goal. In female adolescents with CAH, GC doses are increased to manage the clinical signs of hyperandrogenism, including irregular or absent menstrual periods, hirsutism, low voice, and acne. In male patients, screening for TARTs should begin during puberty or earlier since tumor size can often (but not always) be reduced by increasing GC doses when detected early. GC stress dosing continues to be an important consideration during puberty, especially in adolescents who participate in demanding physical activities or are experiencing stressful life events. Sleep patterns also change during puberty, which can result in an increase in morning-peak androgen levels and require higher GC doses if the patient is unable to waken early to take their dose. However, as growth remains an important concern during puberty, continued caution is required when increasing GC doses since adult height can be compromised by both androgen excess and GC overtreatment.

The transition from adolescence to adulthood can be challenging, with patients shifting from pediatric to adult endocrinologists and taking greater responsibility for their own disease management. As in the earlier life phases, GC treatment remains highly individualized during adulthood, based on each patient's clinical status and personal goals. Some adult patients might prefer to reduce their GC dose to lose weight, lower their blood pressure, improve their bone health, and/or decrease their risk for the cardiovascular and metabolic consequences of long-term supraphysiologic GC exposure. However, dose reduction might not be possible in some cases – for example, in men with TARTs and in women who are trying to conceive [47]. For these patients, reduction in excess ACTH and androgens remains an important treatment goal.

The balancing act of CAH treatment is illustrated by longitudinal data from a US registry of CAH patients (Supplementary Material, Figures S2 and S3). Reviews of these patients' medical charts over an observation period of 6.5 years showed that approximately 85% cycled through multiple health states characterized by higher GC doses, androstenedione levels above the ULN (based on patients' sex, ages, and pubertal status), or both. This analysis shows the difficulty of lowering GC doses while also managing androstenedione levels to below the ULN [125]. Moreover, even when GC doses are lowered to a physiologic range, while androstenedione levels are managed, this level of ideal control is transient.

4. Recent therapeutic developments in CAH

Novel approaches for adapting GC therapy to achieve a more physiologic pharmacokinetic profile have been developed. GC delivery via continuous subcutaneous hydrocortisone infusion (CSHI) has been explored, with reports of positive impact on androgen precursors [126–128]. Use of CSHI remains unlicensed, but two modified-release formulations of hydrocortisone are authorized in Europe. Modified-release hydrocortisone tablets (Plenadren), licensed for AI but with no CAH trial data, is a once- daily medication with an immediate- and sustained-release profile that is designed to mimic physiologic cortisol levels during the day and low cortisol levels during the night [129]. Modified- release hydrocortisone hard capsules (Efmody, development name Chronocort), licensed in Europe for CAH, is a twice-daily medication with a cortisol-release profile that mimics endogenous diurnal cortisol secretion. Although the phase 3 CAH study missed its primary endpoint [130], single-arm studies have suggested potential benefit in the form of GC dose reduction and improved female fertility [131–133].

Non-GC therapies that target the HPA axis may mitigate the need for supraphysiological GC by decreasing excess ACTH and adrenal androgens. Crinecerfont, a novel CRG type 1 receptor (CRF1) antagonist, is indicated as an adjunctive treatment to GC replacement to control androgens in adults and pediatric (≥4 years old) patients with classic CAH [134]. In two 14-day phase 2 studies, one in adolescents (NCT04045145 [N = 8]) and one in adults (NCT03525886 [N = 18]), crinecerfont was well tolerated with adverse events being generally mild or unrelated to study drug [27,28]. Both studies also showed clinically meaningful reductions in ACTH and key adrenal androgens after 14 days of open-label treatment with crinecerfont.

Two phase 3 trials of crinecerfont, one in pediatric patients (NCT04806451; N = 103 [28 weeks]) and another in adults (NCT04490915; N = 182 [24 weeks]), demonstrated substantial reductions in androstenedione and 17-OHP within 4 weeks of crinecerfont treatment, while GC doses were kept stable [30,31]. By the end of the double-blind periods, participants randomized to crinecerfont had a significantly greater percent reduction in GC dose from baseline (versus an increase with placebo [pediatric] or smaller reduction with placebo [adult]) while also maintaining their androgen levels within 120% of baseline and/or reducing their androgens to within a normal range. Moreover, a significant proportion of crinecerfont- treated participants achieved GC dose reductions to a protocol-defined physiologic range (≤11 mg/m^2/d) while maintaining or improving androstenedione. While 11 mg/m^2/ d HCe falls within the range of physiologic GC replacement doses for patients with CAH, corresponding to the 95th percentile of cortisol production in healthy individuals [135] (see Section 5), it may not represent a physiologic GC replacement dose for all patients with CAH. The threshold was used for the purpose of clinical trials to mitigate the risks of inadequate cortisol replacement during the GC dose reduction periods (after week 4 in both studies).

In the 28-week pediatric study, common adverse events (≥10%) reported more frequently in the crinecerfont group were headache (25% vs. 6% for placebo) and upper respiratory tract infection (12% vs. 0%); those reported more frequently in the placebo group were pyrexia (24% vs. 23% for crinecerfont), vomiting (30% vs. 14%), and nasopharyngitis (18% vs. 10%) [30]. In the 24-week adult study, adverse events occurring more frequently in the crinecerfont group were fatigue (25% vs. 15% for placebo), headache (16% vs. 15%), and coronavirus infection (14% vs. 8%); upper respiratory tract infection was more common with placebo (12% vs. 9% for crinecerfont) [31].

Two phase 2 clinical trials of tildacerfont, another CRF antagonist, have been completed: one in which adult patients received treatment for 6 weeks (Cohort A, N = 10) or 2 weeks (Cohort B, N = 9; Cohort C, N = 7) (NCT03257462); and a subsequent study in which completers from the first study (N = 11) received treatment for 12 weeks (NCT03687242). Both studies showed reduction of androgen biomarkers toward normal levels, with good tolerability and indication of TART shrinkage in two male participants with available ultrasound data [26]. A 4-week, sequential cohort study in pediatric and adult patients (NCT05128942) showed a trend in androstenedione reduction; however, phase 2b studies in adults (NCT04457336, NCT04544410) did not meet their primary end points, and the drug is no longer in development [136].

Drugs in earlier stages of development include atumelnant, an ACTH receptor antagonist, and Lu AG13909, an anti-ACTH antibody. In a phase 1 study of atumelnant in healthy volunteers, ACTH levels were increased 5-fold above baseline, while cortisol and androstenedione levels decreased [137]. The increase in ACTH may have resulted from decreased negative feedback due to lower cortisol levels. In an ongoing phase 2 study of atumelnant in patients with CAH (NCT05907291), preliminary results from the first cohort of participants (N = 4) showed reductions in androstenedione and 17-OHP from 2 to 12 weeks of treatment [29]. Atumelnant was well tolerated in the 4 participants with CAH; safety continues to be assessed in this ongoing study. A phase 1, multiple-dose-ascending trial of Lu AG13909 is underway (EUCT #2023-503711-15-00), with the aim of including 12 participants for each dose level [138].

With these emerging non-GC therapies, patients will still need GC treatment to replace missing cortisol, and care must be taken to not reduce the GC dose below that required for cortisol replacement. The GC-reduction procedures used in the crinecerfont clinical trials were designed to efficiently evaluate a GC efficacy endpoint, and not necessarily as an exact frame work to be used in clinical practice. In the real world, determining appropriate androgen levels and GC dosing regimens must be individualized for each patient, depending on their life stage and clinical goals (e.g. promoting growth in child hood, supporting fertility in adulthood). If GC doses can be safely reduced, the new treatment paradigm could be described as managing excess androgens and/or decreasing GC to more physiologic doses (Figure 3), which over the long term can decrease the clinical consequences of androgen excess and/or lower the cumulative burden of GC exposure and GC-related complications.

5. Defining physiologic GC dosing in CAH

The emergence of non-GC therapies, which might mitigate the need for supraphysiologic GC doses to reduce androgen excess, raises the question about what constitutes a 'physiologic GC replacement dose' for patients with CAH. A comprehensive search of the literature did not yield any studies that directly answer this question. Therefore, several key publications were consulted to map out the relationship between the daily cortisol production rates (DCPR) in healthy individuals and the GC doses required for replacing cortisol in patients with AI (Figure 4(a)).

As reported by Oprea *et al*. [139], 6 DCPR studies have been conducted in healthy volunteers (Supplementary Table S1) [135,140–144]. Of these, the largest and most recent was a study by Purnell et al., which included 24 men and 30 women, with ages ranging from 19 to 70 years [135]. In this study, the mean DCPR was 7.0 mg/m^2/d and ranged from 2.7 to 14.0 mg/m^2/d.

As described in Section 3.1, the Endocrine Society guidelines for both CAH and primary AI (not due to CAH) recommend a GC dose range of 15 to 25 mg/d, which would be equivalent to 8.8 to 14.7 mg/m^2/d (assuming a BSA of 1.7 m^2). Caetano et al. noted that the midpoint of this range (11.8 mg/m^2/d) would be approximately 1.7 times higher

25TH ANNIVERSARY EVERYONE CARES GALA

***DEADLINE TO PURCHASE SEATS AT THIS YEAR'S GALA: APRIL 8, 2025**

SEATS ARE NOW AVAILABLE for the upcoming ***25th Anniversary Everyone CARES Gala***, taking place on Friday, April 25, 2025 at **Current**, at Pier 59, Chelsea Piers in New York, NY.

Ways you can support the Honorees & Event

-Attend the Gala

-Sponsor the Event

-Purchase an E-Journal advertisement

-Donate in recognition of an honoree/honorees

-Underwrite the event

-Purchase a 1-line message for an honoree

Our Honorees

Dr. Alejandro Diaz
Maria I. New Visionary Award

Lesley Holroyd, RN
Pioneer Award

Crinetics Pharmaceuticals
Corporate Partner Award

If you have any questions about this year's event or how you can support CARES or our honorees, please reach out to: contact@caresfoundation.org.

DONATING AUCTION ITEMS

If you have interest in donating items to our auctions, please do not hesitate to reach out to odaly@caresfoundation.org or please call our office at (866) 227-3737, toll-free.

Scan or click here to visit Gala webpage

Events

Make sure to check out these great opportunities to meet and connect with other patients, parents, and individuals living with congenital adrenal hyperplasia (CAH). (https://caresfoundation.org/calendar/)

May 3, 2025

2nd Annual Iowa CAH Awareness 5K

Des Moines Water Works, Des Moines, IA
(Lauridsen Amphitheater)

#VIVISTRONG

LEARN MORE

May 31, 2025

Annual Pennsylvania CAH Awareness Walk

Zelienople Community Park, Zelienople, PA
(Mussig Shelter)

NEW LOCATION

LEARN MORE

SAVE THE DATE!

October 11, 2025

5th Annual Ohio CAH Awareness Walk

Mill Stream Park, Valley City, OH

WWW.CARESFOUNDATION.ORG

If you are interested in hosting an awareness event/family fundraiser in your area, please contact dina@caresfoundation.org.

NEW EVENT

June 7, 2025

1st Annual Washington CAH Awareness Family Fun Day

Woodland Park Zoo, Seattle, WA

co-hosted with Seattle Childrens

LEARN MORE

https://caresfoundation.org/cares-washington-family-fun-day/

SAVE THE DATE

10TH ANNUAL CLAY SHOOT FOR CARES

THURSDAY, OCTOBER 9, 2025
LEHIGH VALLEY SPORTING CLAYS

Make sure to stay up-to-date with CARES social media & website for more information on when registration will become available

June 23, 2025
1st Annual

SWING FOR CAH

Golf Tournament

Johnson City Country Club
Johnson City, Tennessee

Learn more at:
www.caresfoundation.org

A Personal Story...

Being a mom to a 9-month-old with Salt-Wasting CAH has been a beautiful and fulfilling experience. Our daily lives are filled with love, laughter, and the joy of watching our little ones grow. While we stay on top of Nash's medication and attend a few extra doctor appointments, our days feel just as normal as any other family's. Nash is thriving, hitting milestones, and is the happiest baby we could ask for. We're excited for his future and can't wait to see all the amazing things he's destined to achieve.

At the start, the journey with Salt-Wasting CAH was definitely scary, and the unknown made it feel even more overwhelming. But as time has passed, we've adjusted, and our experience as a family has been wonderfully normal. We're now used to the multiple alarms throughout the day and pausing for a few extra seconds to make sure Nash gets his medicine. Beyond that, it's just life—filled with joy, laughter, and the usual chaos of brothers wrestling around. It's always a party at our house, and we couldn't be more grateful for Nash's growth, happiness, and all the great things ahead.

We want to thank Abby, Paden, Archer, and Nash for sharing their story with us!

SAVE THE DATE: September 20 & 21, 2025

2025 ANNUAL PATIENT EDUCATION CONFERENCE

Held at Riley Hospital for Children in Indianapolis, Indiana

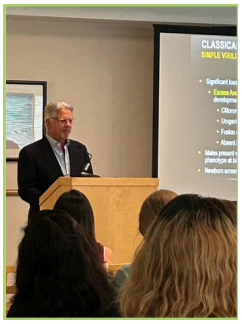
If you are interested in attending this year's conference, and would like to be notified about when registration opens, please fill out the brief questionnaire linked below:

https://caresfoundation.app.neoncrm.com/np/clients/caresfoundation/survey.jsp?surveyId=36&

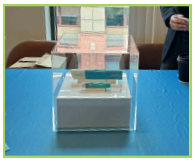
Testimonials from last year's conference in New Jersey:

"Great talks. We loved the new perspective and new context on exercise & diet. This was all very helpful!"

"Amazing! I wish I had those diagrams/videos when we were going through my daughter's surgery. I better understand what her surgery looked like."







"Very relevant information for my current stage in life. Top of mind and looking for this info. Very detailed and easy to follow."

"We heard many great presentations where presenters tried to break down a very confusing topic and had made it easier to understand."

"Incredibly knowledgeable and helpful. Presenters even stuck around to answer my questions. We learned a ton!"

SAVE THE DATE: Monday, September 22, 2025

CARES FOUNDATION'S PATIENT ADVISORY SUMMIT

CARES is seeking patients and caregivers living with Classic CAH to join an advisory session concurrent with the 2025 CAH Patient Education Conference in Indianapolis, IN. The purpose of the advisory board is for representatives from the pharmaceutical industry to listen to patient/caregiver insights on living with and managing CAH.

Participants will be compensated for their time.

If you are interested in participating, please reach out to dina@caresfoundation.org.

Please stay up-to-date on CARES Foundation's website & social media for more information on when registration for these events will open. (www.caresfoundation.org)

(continued from page 8)

than the mean DCPR in healthy individuals (7 mg/m^2/d) found by Purnell et al. [79,80]. Therefore, they conducted a retrospective analysis of patients in their practice to test the hypothesis that empirically determined GC replacement doses for patients with AI would be lower than the Endocrine Society guideline doses.

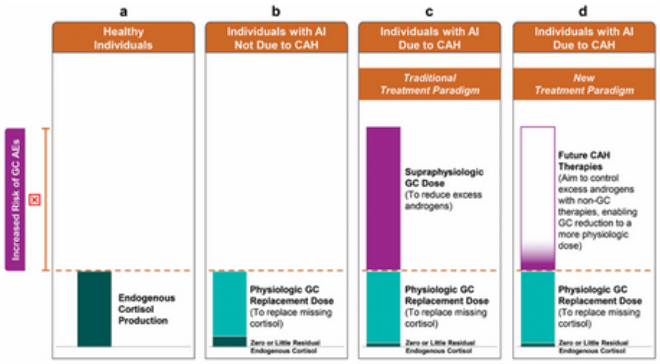


Figure 3. Potential benefits of non-GC therapies. Healthy individuals produce sufficient levels of endogenous cortisol (dark green bar) (a). In contrast, individuals with adrenal insufficiency (AI) – whether due to congenital adrenal hyperplasia (CAH) or not – have zero or little residual endogenous cortisol production and require treatment with glucocorticoids (GCs) (b, c). All patients with AI require a 'physiologic GC replacement dose' (bright green bar) to replace missing cortisol and restore normal functioning. In the traditional CAH treatment paradigm (c), patients typically require a 'supraphysiologic GC dose' (magenta bar) to reduce excess androgens, which increases the risk of GC-related adverse events (AEs). In the new treatment paradigm (d), excess androgens may be controlled with non-GC therapies, thereby enabling GC reduction to more physiologic doses and mitigating the risk of AEs associated with chronic GC treatment at supraphysiologic doses.

The study by Caetano et al. included 25 adults with AI (19 primary, 6 secondary) who were otherwise healthy [79]. Per the authors' standard practice for treating AI, patients' GC treatments were reduced to their lowest tolerated dose or to a pre-specified lower titration limit of 5 mg/d hydrocortisone (or 1 mg/d prednisone); adjustments to GC doses were allowed based on the clinical situation of each patient. Using a BSA of 1.7 m^2, they determined the mean GC replacement dose (±SD) to be 7.6 ± 3.4 mg/m^2/d in HCe, with a range of 1.9 to 14.4 mg/m^2/d; no evidence of adrenal crisis was observed. Additional analyses demonstrated that this range was not biased by residual endogenous cortisol production.

Given the similarity between their findings and the DCPR in healthy adults from Purnell et al. (mean 7 mg/m^2/d, range 2.7 to 14.0 mg/m^2/d), Caetano *et al.* concluded that the replacement GC dose range for AI would be lower and wider than is currently recommended by the Endocrine Society guidelines – and more similar to endogenous cortisol production in healthy individuals. The reason for this discrepancy is unclear, but we speculate that the Endocrine Society AI guidelines recommend a higher GC dose in a narrower range for the following reasons: 1) to provide a dose range in multiples of 5 mg/d, as hydrocortisone is available in 5-, 10-, and 20-mg tablets; 2) to account for inter- and intra-individual variability in terms of the GC pharmacokinetics, GC bioavailability, and GC sensitivity; and 3) to err on the side of safety (e.g. using higher doses to help avoid symptoms of adrenal insufficiency).

By providing evidence for a potential physiologic GC replacement dose for CAH, these studies have important clinical implications. However, a few caveats for real-world management must be mentioned (Figure 4(b)). First, inter-individual variation in cortisol production is very high, as demonstrated by the wide range of DCPR in healthy individuals (2.7 to 14.0 mg/m^2/d) and the physiologic GC replacement dose in patients with AI (1.9 to 14.4 mg/m^2/d). This variation is likely due to many factors, such as age, sex, pubertal status, weight, differences in cortisol metabolism, residual endogenous cortisol production, and sensitivity to GC medications [139]. Second, during periods of physical or emotional stress, especially acute intercurrent illness, cortisol needs can increase greatly. Consequently, in such situations, GC replacement dosing needs will increase in patients with AI or CAH (Supplementary Figure S4). This need for increased dosing triggers physician-guided stress-dosing protocols, and the amount of additional GC needed varies depending on the severity of the stress and, to some degree, on individual patient factors. None of the studies described above (i.e. DCPR studies in healthy individuals and physiologic GC repla cement study in patients with AI) address increases in endogenous cortisol production or the amount by which GC doses need to be increased during stress or illness. Finally, it must be acknowledged that true physiologic replacement would match the normal diurnal pattern of cortisol secretion; however, the currently available GC dosage forms and the practicalities of dosing schedules limit the ability to perfectly replicate cortisol secretion from an intact adrenal gland. Thus, even when the total daily GC dose is physiologic, it is likely that there will be periods throughout the day of slight under- and over-replacement.

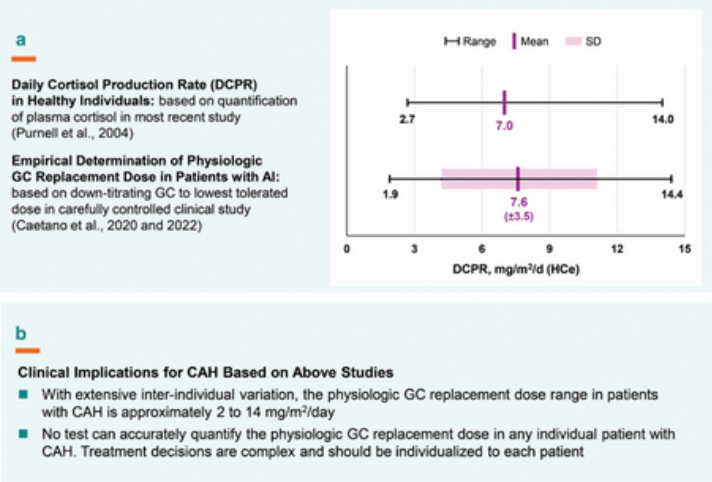


Figure 4. Evidence for determining a physiologic GC dose range in CAH. Two studies provide supportive evidence for determining a potential physiologic glucocorticoid (GC) dose range in patients with classic congenital adrenal hyperplasia (CAH), based on endogenous daily cortisol production rate (DCPR) (a). In the most recent study to include healthy volunteers, Purnell et al. found DCPRs that ranged from 2.7 to 14 mg/m 2 /d, with a mean of 7.0 mg/m 2 /d (no standard deviation [SD] reported). In a study of patients with adrenal insufficiency (AI), Caetano et al. empirically determined DCPRs by down-titrating GC treatments to the lowest possible dose, as tolerated by the patient or to a prespecified limit (1 mg/d prednisone or 5 mg/d hydrocortisone, in divided doses). Similarly to healthy adults, DCPRs in patients with AI ranged from 1.9 to 14.4 mg/m 2 /d, with a mean (±SD) of 7.6 (±3.5) mg/m 2 /d. Clinical implications for CAH based on studies above are presented (b). Most notably, data from both studies indicated extensive inter-individual variation in DCPR and that no laboratory test can quantify the physiologic GC replacement dose for any individual patient. Therefore, all treatment decisions must be made on an individual basis, with shared decision-making between clinicians and patients (or their guardians). Adapted with permission from Caetano et al, J Endocr Soc 2020 [79]

In summary, these studies with healthy individuals and patients with AI indicate that the physiologic GC replacement dose range in a CAH population is roughly 2 to 14 mg/m^2/d [79,135,140–144]. Importantly, it is not possible to define a single cutoff for a physiologic GC dose that applies to an entire CAH population. What may be a physiologic GC dose for one patient could be supraphysiologic for another. Additionally, what might be considered a physiologic GC dose at one point in a patient's life might be too low or too high at a different point in that same patient's life, such as when the patient has increased GC clearance during puberty. Moreover, there are no tests that can accurately quantify an individual patient's physiologic GC dose (i.e. whether an individual's GC dose is sufficient for cortisol replacement). While the benefits of lowering GC doses toward a physiologic range are clear (i.e. lower risk for serious GC- related adverse events), managing a CAH population to a single fixed dose can lead to suboptimal outcomes (e.g. inadequate reduction of adrenal androgens in some patients and GC over-treatment in others) and potential serious safety issues (e.g. symptoms of adrenal insufficiency or side effects of excess GCs). Treatment decisions are multifactorial and complex, and they should be individualized to each patient with shared decision-making between clinician and patient.

6. Conclusions

The traditional treatment paradigm for CAH is a lifelong balancing act. The consequences of excess ACTH and androgens must be constantly weighed against the risk of potentially serious complications arising from the supraphysiologic GC doses typically needed to reduce androgens to a normal range. Treatment decisions shift based on the specific needs of each individual patient at each life stage, from management of growth and bone age during childhood, to hormonal changes during puberty, to preserving fertility and bone health and preventing cardiometabolic comorbidities during adulthood. Even if patients can lower their GC doses while also managing androgen levels within normal ranges, this ideal situation is often transient.

Emerging non-GC therapies that can reduce excess ACTH and/or androgens could also allow lower, more physiologic GC doses. With these therapies, patients with CAH will still need GC treatment to replace missing cortisol. However, these novel non-GC therapies aim to reduce excess androgens without using supraphysiologic GC doses. The emergence of these therapies, which might mitigate the need for supraphysiologic GC doses to reduce androgen excess, raises the

question about what constitutes a 'physiologic GC replacement dose' for patients with CAH. Studies in healthy individuals and patients with AI (not from CAH) suggest that it is not possible to define a single cutoff for a physiologic GC dose that applies to an entire CAH population; rather, the physiologic GC replacement dose ranges from roughly 2 to 14 mg/m^2/d. Moreover, there is no test that can quantify an individual patient's physiologic GC dose, but the benefits of lowering GC dose toward a physiologic range are clear. As non-GC medications for CAH become available, decisions about when and how to decrease GC doses will continue to be made on an individual basis, depending on the patient's life stage, overall clinical picture, and current therapeutic needs.

7. Expert opinion

The patient journey with CAH is long and complicated, and patients' therapeutic needs are continuously in flux. All life stages require different therapeutic approaches, and the tradeoffs of a given GC dose must be constantly reassessed. At every clinical visit, the question arises about which need is currently more pressing – reduce excess androgens or reduce the risk of GC-related adverse events? Once this question is addressed, GC treatment can be modified as needed by adjusting frequency/timing of doses and/or or changing GC medications (e.g. add or switch to prednisone).

With these strategies, adequate androgen control can be achieved – but not in every patient and, for most patients, not consistently over the lifespan. For these patients and these periods of time, new non-GC treatments may be beneficial. For example, crinecerfont has been shown to reduce androstenedione and 17-OHP without increasing GC doses, subsequently allowing GC doses to be lowered toward a more physiologic range. Even with small dose reductions, the cumulative impact of this therapeutic shift could be monumental. Over the many decades of a patient's life, small decreases in the total daily GC dose would add up to a large cumulative dose reduction that could have meaningful impact on reducing the risks associated with long-term supraphysiologic GC exposure. Thus, we believe that any GC dose reduction could be clinically meaningful when considered over a lifetime of GC treatment.

As new therapies emerge, questions about appropriate usage and long-term safety must also be addressed. The relatively rapid GC down-titration schedules used in clinical trials (e.g. GC dose reduction every 2 weeks for 2 months in the phase 3 adult study of crinecerfont) were specifically designed for achieving efficient GC dose reduction for the purposes of regulatory approval; therefore, they might not reflect optimal care in real-world settings. In the clinic, less frequent GC dose reductions may be more appropriate to minimize potential side effects with rapid lowering of GC doses.

GC dose reduction to the ~95th percentile of cortisol production (~11mg/m^2/d) would likely provide sufficient cortisol replacement in many patients. However, some patients might require >11 mg/m2/d for cortisol replacement, and determining an actual target dose and optimal dosing schedule for any individual patient could be challenging. GC dose reduction, especially to below the upper limit of the physiologic range, will require careful assessment for symptoms of cortisol insufficiency. Given that reduction of 17-OHP and androstenedione to normal levels has not been a recommended therapeutic goal [3], clinicians have always considered patient symptoms (e.g. fatigue) and other parameters (e.g. growth and body mass index) when treating CAH. This approach will likely continue to be the most sensitive guide for determining the adequacy of GC treatment as non-GC treatments are adopted. Comprehensive clinical assessments and shared decision-making between clinicians and patients will always be need to optimize androgen reduction, GC treatment, or both.

Published clinical trial results indicate that non-GC therapies are well tolerated. Long-term safety data will provide even more information, which needs to be weighed against the potential benefits of reducing excess androgens and/or lowering GC doses. As our knowledge of new therapies increases through clinical research and real-life clinical practice, we will better understand how to tailor treatment regimens during periods of acute stress or illness and in life stages when higher GC doses are warranted (e.g. during adolescence). Adding a non-GC therapy to existing regimens might initially increase pill burden, but these therapies could ultimately reduce GC doses and dosing frequency, including the need for dosing at non-physiologic times (e.g. late at night). Eventually, medication adherence might improve as GC dosing regimens become less burdensome and potential barriers to compliance decrease (e.g. patients being less concerned about the adverse effects of chronic GCs). As physicians and patients become more familiar with new CAH medications and more comfortable with reducing GC to more physiologic doses, the cumulative reduction in GC dose over time should translate into a significant decrease in the risk for GC complications. Thus, these new medications represent potentially important advancements in the treatment of CAH.

Funding

This manuscript was funded by Neurocrine Biosciences, Inc.

Declaration of interest

I. Bancos has been an advisor or consultant (fees to institution) for Camurus Pharma, Crinetics Pharmaceuticals, Xeris Biopharma, Novo Nordisk, AstraZeneca, Adaptyx Biosciences, Corcept Therapeutics, Diurnal Ltd (now Neurocrine UK Ltd), HRA Pharma, Neurocrine Biosciences, Recordati, Sparrow Pharmaceutics, and Spruce Biosciences. I. Bancos has been on the data safety and monitoring board for Adrenas (fees to institution). H. Kim, H. Cheng, M. Rodriguez-Lee, S. Cicero, H. Goldsmith, V.H. Lin, and G.S. Jeha are full-time employees of Neurocrine Biosciences, Inc. and may hold equity in the company. H. Coope is a full-time employee of Neurocrine UK Ltd. and may hold equity in the company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

Acknowledgments

Writing and editorial assistance was provided by Mildred Bahn, Jennifer Kaiser, and Meghan O'Connell from Prescott Medical Communications Group, a Citrus Health Group, Inc. company (Chicago, Illinois) with support from Neurocrine Biosciences, Inc. (San Diego, California).

Ethics statement

Not applicable

Data availability statement

Not applicable

Author contribution statement

All authors contributed to one or more of the following: article conception, critical review of content, interpretation of relevant literature, clinical perspective based on expertise with the disease state. All authors reviewed previous drafts and approved the final manuscript for submission. They agree to take shared responsibility for the contents of the published article.

References

Please visit:

https://caresfoundation.org/wp-content/uploads/2025/04/Scientific-Article-Spring-2025.pdf or scan the QR code for access to the Full PDF of this Article, as well as any accompanying references.

Patient & Caregiver Perspectives on the First and Only FDA-Approved Treatment for Classic Congenital Adrenal Hyperplasia (CAH)

The first new treatment in 70 years is now available.

In December 2024, Neurocrine Biosciences Inc. announced a significant breakthrough: the Food and Drug Administration (FDA) approved CRENESSITY™ (crinecerfont) as a prescription medicine used together with steroids to control androgen levels in individuals 4 years of age and older with classic CAH. **CRENESSITY is the only treatment that allows people with classic CAH to lower adrenocorticotropic hormone (ACTH) and androgen levels and reduce their daily dose of steroids.**

We invite you to explore the personal stories of people and families living with CAH and their experiences with CRENESSITY. These unique perspectives offer insights into the impact of this groundbreaking treatment for classic CAH. Individual results may vary.

The journey to FDA approval was made possible by the dedication of 285 individuals from the CAH community who participated in the CAHtalyst™ Pediatric and Adult Phase 3 global registrational studies. The clinical results from these studies provided robust evidence supporting the efficacy and safety of CRENESSITY.

Please see full Prescribing Information.

The most common side effects were headache, stomach pain, tiredness, nasal congestion, and nosebleeds in children taking CRENESSITY. Tiredness, headache, dizziness, joint pain, back pain, decreased appetite, and muscle pain were the most common side effects in adults taking CRENESSITY.

Kristy, Mom to Grant, who has CAH: Grant has been taking CRENESSITY since 2022.

“In the beginning, when we found out about Grant’s CAH diagnosis, our minds were just racing, wondering what the future was going to bring, wondering if he was going to be just so sick we would have to keep him home all the time. Grant’s blood work showed his bone age was significantly higher than his age and his numbers were showing he was prepubescent at seven years old. The doctor said it was because his androgens were always high.

Grant takes CRENESSITY in the morning with breakfast and he takes it again in the evenings with his dinner. Because CRENESSITY lowered Grant’s androgen levels and 17-OHP (17-hydroxyprogesterone) his doctor was able to lower his steroid dose.

We’ve had a great experience, and it's been truly helpful. One hundred percent.”

To hear more about Kristy and Grant’s story, watch their full video here.

Liam, adult with CAH: Has been taking CRENESSITY since 2023.

“I started taking control of my CAH towards the end of high school. With CAH, you might feel fine, but the blood results don’t show that necessarily. I started to actually care about my results and blood work, and I became more invested as well in wanting to join a trial.

I chose the CAHtalyst trial mainly for the potential to lower my androgens and lower my steroid dosage. After taking CRENESSITY, my 17-OHP went down, along with my A4 (androstenedione) levels.

Because CRENESSITY lowered my androgen levels, my doctor was able to lower my steroid dose. It went down from 25 milligrams to about 17 and a half milligrams of hydrocortisone. Knowing that my steroid dose has gone down because of CRENESSITY, I definitely feel better about the long term.”

To hear more about Liam’s story, watch his full video here.

Susan, adult with CAH: Has been taking CRENESSITY since 2021.

"I learned about the CAHtalyst study from my doctor, and I have been in other studies, and she recommended me for the CAHtalyst study.

Incorporating CRENESSITY into my life wasn't a very big change. I take CRENESSITY twice a day with food as directed. When I first started taking CRENESSITY, I was on three different steroids – prednisolone, fludrocortisone and hydrocortisone. Now with CRENESSITY, I am only taking fludrocortisone and hydrocortisone.

Yeah, the bar has changed absolutely now that CRENESSITY is out, they were able to reduce [my] androgen levels and A4 and reduce the steroids."

To hear more about Susan's story, watch her full video here.

To hear more about patient experiences with CRENESSITY, learn more about CRENESSITY, and access valuable resources, visit CRENESSITY.com.

Approved Uses:

CRENESSITY (crinecerfont) is a prescription medicine used together with glucocorticoids (steroids) to control androgen (testosterone-like hormone) levels in adults and children 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

IMPORTANT SAFETY INFORMATION

Do not take CRENESSITY if you:

Are allergic to crinecerfont, or any of the ingredients in CRENESSITY.

CRENESSITY may cause serious side effects, including:

Allergic reactions. Symptoms of an allergic reaction include tightness of the throat, trouble breathing or swallowing, swelling of the lips, tongue, or face, and rash. If you have an allergic reaction to CRENESSITY, get emergency medical help right away and stop taking CRENESSITY.

Risk of Sudden Adrenal Insufficiency or Adrenal Crisis with Too Little Glucocorticoid (Steroid) Medicine. Sudden adrenal insufficiency or adrenal crisis can happen in people with congenital adrenal hyperplasia who are not taking enough glucocorticoid (steroid) medicine. You should continue taking your glucocorticoid (steroid) medicine during treatment with CRENESSITY. Certain conditions such as infection, severe injury, or shock may increase your risk for sudden adrenal insufficiency or adrenal crisis. Tell your healthcare provider if you get a severe injury, infection, illness, or have planned surgery during treatment. Your healthcare provider may need to change your dose of glucocorticoid (steroid) medicine.

Before taking CRENESSITY, tell your healthcare provider about all of your medical conditions including if you: are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the counter medicines, vitamins and herbal supplements.

The most common side effects of CRENESSITY in adults include tiredness, headache, dizziness, joint pain, back pain, decreased appetite, and muscle pain.

The most common side effects of CRENESSITY in children include headache, stomach pain, tiredness, nasal congestion, and nosebleeds.

These are not all the possible side effects of CRENESSITY. Call your healthcare provider for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Dosage Forms and Strengths: CRENESSITY is available in 50 mg and 100 mg capsules, and as an oral solution of 50 mg/mL.

Please see full Prescribing Information**.**

Crenessity™ (crinecerfont)

Neurocrine Biosciences is deeply grateful to the entire CAH community for their commitment to helping bring this treatment to people living with CAH and their families.

CONNECT
with Crinetics Patient Advocacy

Patients are at the heart of everything we do at Crinetics.

We deeply value our partnerships with advocacy groups and members of the patient community.

Our advocacy team is dedicated to listening, learning, and integrating patient insights to enhance every step of Crinetics' drug discovery and development journey.

SCAN to sign-up with Crinetics Patient Advocacy and stay connected

Crinetics Pharmaceuticals

Crinetics Pharmaceuticals is a clinical stage pharmaceutical company focused on the discovery, development, and commercialization of novel therapeutics for endocrine diseases and endocrine-related tumors.

NP-PAT-0040 3/2025

Alkindi Sprinkle® (hydrocortisone) oral granules

ALKINDI SPRINKLE® (hydrocortisone) oral granules is the first and only hydrocortisone treatment designed to help provide individualized and accurate prescribed dosing for newborns and children with adrenal insufficiency.

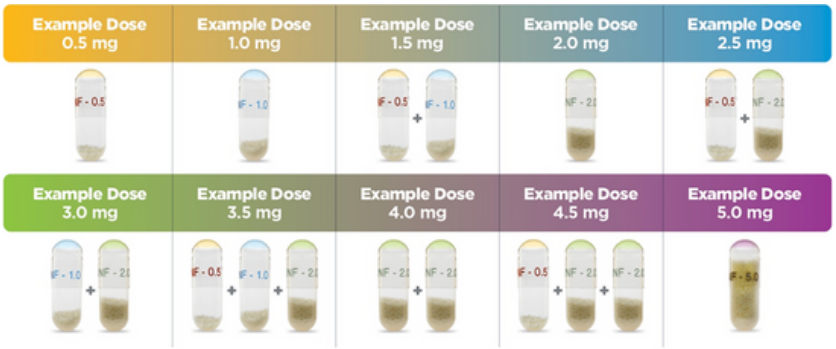
Please see Important Safety Information below.

Designed to deliver the right dose at the right time

ALKINDI SPRINKLE is more than just medication––it's a story of precision.

The need for accurate dosing

Accurate dosing in patients with adrenal insufficiency is essential.[2] If a newborn or child gets too much hydrocortisone (overdosing) or too little hydrocortisone (underdosing), they may experience poor health outcomes that can last for years, even into adulthood.[3-6]



Capsules shown are not actual size.

Designed for treatment accuracy

ALKINDI SPRINKLE comes in 4 low-dose strengths to help give growing children the right amount of medicine. Each capsule has the exact number of granules needed for accurate treatment. Caregivers should make sure the child swallows all the granules to get the full dose.

Remember to always give ALKINDI SPRINKLE exactly as prescribed by your doctor.

IMPORTANT SAFETY INFORMATION

Always give ALKINDI SPRINKLE exactly as your doctor has directed.

Do not take ALKINDI SPRINKLE if you are allergic to hydrocortisone or any of its other ingredients.

Please see additional Important Safety Information below.

Eton Cares: Comprehensive and personalized support that puts patients first

$0 copay*

Prescriptions for ALKINDI SPRINKLE must be submitted to Anovo® Specialty Pharmacy.
97% of ALKINDI SPRINKLE prescriptions are successfully onboarded and approved†
QuickStart Program provides medication in as quickly as 24 hours during prior authorization‡

Click here **for more information.**

*Commercially eligible patients can pay as little as $0 per month. Restrictions, limitations, and/or eligibility requirements apply.
†Anovo will work with the doctor to obtain insurance coverage. If insurance is denied, the patient may apply to the Patient Assistance Program.
‡For newborns awaiting hospital discharge, medication may be delivered in as soon as 24 hours. Typical delivery is 3 to 7 days.

IMPORTANT SAFETY INFORMATION (continued)

Adrenal Crisis: giving too low a dose or stopping medication can cause low levels of cortisol, which can result in serious illness or death. Treatment with intravenous hydrocortisone should be started immediately. When switching from another type of hydrocortisone to ALKINDI SPRINKLE, watch your child closely for any changes. If your child doesn't get the entire dose of ALKINDI SPRINKLE because of vomiting or spitting some granules out, contact your doctor to see if another dose is needed.

Immunosuppression and Increased Risk of Infection with Use of a Dosage Greater Than Replacement: Use of a greater than replacement dosage can suppress the immune system and increase the risks of new infections or exacerbation of latent infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. Monitor patients for signs and symptoms of infections.

Infections: all infections should be treated seriously, and stress dosing of hydrocortisone should be started early. Taking ALKINDI SPRINKLE should not stop your child from being vaccinated but let your healthcare provider know prior to vaccination.

Growth Retardation: the long-term use of corticosteroids in high doses may cause growth retardation in children.

(continued from page 18)

IMPORTANT SAFETY INFORMATION

Decrease in Bone Density: corticosteroids can affect your child's bone growth and strength.

Cushing's Syndrome Due to High Doses of Corticosteroids: treatment with high doses of corticosteroids can cause Cushing's Syndrome. Treatment should be limited to the smallest dose required, and your child's growth and development monitored appropriately.

Changes in Vision: tell your doctor if your child has blurred vision or other vision problems during treatment with ALKINDI SPRINKLE.

Psychiatric Changes: corticosteroids can change your child's behavior or mood. Tell your doctor if your child has periods of extreme happiness, extreme sadness, hallucinations, or depression.

Gastrointestinal Reactions: tell the doctor if your child has stomach pain, upset stomach, black, tarry stools, or vomiting of blood. These could be signs of ulcers or tears in the stomach or intestines. Taking anti-inflammatory nonsteroidal drugs, like ibuprofen, naproxen, or aspirin, can increase the risk of ulcers or tears.

The most common side effects of ALKINDI SPRINKLE include retaining fluids, changes in glucose tolerance, high blood pressure, behavioral and mood changes, greater appetite, and weight gain.

Vaccination: Administration of live vaccines may be acceptable in ALKINDI SPRINKLE-treated pediatric patients with adrenocortical insufficiency who receive replacement corticosteroids.

Please visit ALKINDISPRINKLE.com/patient for more information

You are encouraged to report negative side effects of prescription drugs by contacting Eton Pharmaceuticals, Inc. at 1-855-224-0233 or the U.S. Food and Drug Administration (FDA) at www.fda.gov/safety/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information for more information.

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1998-v1

Eton Pharmaceuticals - News

ET-400

In 2020, Eton Pharmaceuticals introduced Alkindi Sprinkle®, a proprietary formulation of hydrocortisone granules that is FDA-approved as a replacement therapy for pediatric patients under 17 years of age with adrenal insufficiency. Alkindi Sprinkle® is the only hydrocortisone treatment specifically designed to provide accurate dosing for newborns and children, addressing a significant unmet need in the management of this condition.

Before Alkindi, the lowest available dose of hydrocortisone was a 5mg tablet. However, young children often require much smaller doses, as low as 1mg or less. Caregivers and patients had to split or crush tablets or use compounded suspensions, all of which could lead to inaccurate dosing.

Alkindi has been a breakthrough for many patients and their caregivers. Despite its success, there remains strong demand for an FDA-approved liquid formulation of hydrocortisone.

ET-400 has been assigned a Prescription Drug User Fee Act (PDUFA) target action date of May 28, 2025. We are optimistic that approval will bring this highly anticipated liquid formulation to children in need. ET-400 will complement the Alkindi Sprinkle® program and provide pediatric patients with congenital adrenal hyperplasia (CAH) additional treatment options.

Hydrocortisone Injection (Auto-Injector)

Patients and caregivers have expressed the need for better rescue medication options for adrenal crises. The current standard of care, Solu-Cortef®, is a lyophilized (freeze-dried) powder that must be reconstituted and mixed before use, then extracted and measured with a traditional syringe. This process can be particularly challenging for patients or caregivers during a potentially life-threatening adrenal crisis.

The Zeneo® (hydrocortisone autoinjector) is a convenient, two-step, needle-free autoinjector device that provides an alternative to the current standard of care. Zeneo® is currently under development, with product filings expected in 2027.

The Voices Study | Learn more

The Voices Study is developing a new self-advocacy tool (with input from young people with CAH and other variations) to help them communicate their needs and healthcare preferences. **We invite young people with CAH to help finalize the questions in the new self-advocacy tool and/or provide feedback about it.**

Young people must be between the ages of 11-21 and must be able to understand basic sentences and questions in English to participate. Young people and families who qualify for the study and who participate will get paid for their time, earning up to $230 depending on which parts of the project they are asked to participate in.

Interested families should reach out to the research coordinator, Alejandro Todd, at datodd@childrensnational.org or 301-765-5573 to see if they qualify. Alternatively, young people or their parents/guardians can fill out an interest form here: https://redcap.link/VOICES

The team is very neurodiversity affirming and supportive, and we welcome families from across the United States (*all appointments are conducted through Zoom*). We also thank the young people who have participated in previous phases of the study for such helpful feedback, and we look forward to working with them again.

PINPOINT
PATIENT RECRUITING

Share Your Experiences With CAH and Help Others

Pinpoint Patient Recruiting, a market research recruitment company, is searching for people who are interested in participating in virtual market research opportunities that help researchers better understand the experiences and opinions of people living with CAH and caregivers of children living with CAH.

The format of opportunities will include online surveys and online interviews. People who participate in the opportunities will receive $50 or more as a thank you for their time and participation.

Who is eligible to participate?

- adults (ages 18+) who have been diagnosed with congenital adrenal hyperplasia (CAH)
- caregivers of children (ages 3-17) who have been diagnosed with congenital adrenal hyperplasia (CAH)

All information and responses will remain confidential. The research opportunities are sponsored by pharmaceutical companies. No medication will be given or tested.

Interested?

To be notified about these market research opportunities or to learn more, please visit www.pinpointpatientrecruiting.com/cah-survey-cares or contact Jenny Fowle at jenny@pinpointpatientrecruiting.com.

(Apple App Store)

(Android App Store)

Preventing Adrenal Crisis Events

PACE App

Have you downloaded it yet?

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The Preventing Adrenal Crisis Events (PACE) app is available to patients, parents/caregivers, and medical professionals and is designed to provide readily accessible information and instructions for effectively managing AI (Adrenal Insufficiency). The app will include stress dosing and intramuscular injection techniques as well as other helpful tools.

Scan the QR codes or search 'PACE by Chaicore' in either the Apple or Android App Store.

Now available in Spanish

Education

ASK THE EXPERT

Do you need expert medical advice before your next appointment?
Do you have unanswered questions about your treatment?
Then, DON'T FORGET about our program!
Click here: https://caresfoundation.org/ask-the-expert/

PREGUNTA EL EXPERTO

Necesita asesoramiento médico experto antes de su próxima cita?
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THE DOCTOR IS IN

DR. KAREN LIN SU
CARES MEDICAL DIRECTOR

FAMILY PLANNING FOR YOUNG ADULTS WITH CAH - FAQS

1 . I have classical CAH. What steps should I take with my endocrinologist before trying to get pregnant?

It is important to have your CAH in good control before trying to achieve pregnancy. Start talking with your endocrinologist at least 6 months before trying to conceive and start looking for a high-risk OB (maternal specialist) if you have classical CAH. If you are taking a birth control pill, it can take 6 months for your cycles to resume. You will need to start taking a prenatal vitamin before conception to ensure that you have all the essential nutrients (e.g. folic acid) to support the fetus during pregnancy.

2. Should my partner get genetic testing for CAH?

Yes, your partner should have genetic testing for CAH carrier status prior to trying to conceive. Many OBs provide preconception genetic counseling and will send a panel from both parents to test for many genes, including the 21-hydroxylase gene (CYP21A2). Just verify that the panel they are ordering includes the CYP21A2 gene if that is the type of CAH you have. If you have 11-beta-hydroxylase deficiency CAH, then make sure the CYP11B1 gene is included. Other options are to meet with a genetic counselor or have your partner's primary care physician order the "CAH Common Mutations" test, which is commercially available at Quest.

3. What should I be aware of if my partner is a carrier for CAH and how does it affect the pregnancy?

If your partner is a carrier for CAH, your offspring will have a 50% chance of having CAH. Depending on the severity of your variants and the severity of the variant that your partner carries, the risk could be for classical or non-classical CAH. You should discuss early fetal sex determination using maternal blood with your OB if you are considering prenatal treatment with dexamethasone (considered experimental). You may also consider doing chorionic villus sampling or amniocentesis during pregnancy to determine whether the fetus is affected.

4. How much does genetic testing for CAH typically cost, and is it usually covered by insurance?

The cost of genetic testing depends on the lab and how many genes are tested at the same time. There are preconception genetic panels that include many genes and may make more sense economically. For example, the "Sema4 Expanded Carrier Screening" tests for 283 genes, including CAH. If insurance does not cover it, the cost is $249/person or $349/couple.

Insurance will usually cover at least part of the cost, but it depends on your insurance. Your provider may need to obtain prior authorization for the test.

5. What should I expect in terms of physical changes after adjusting my medication when stopping birth control?

Once stopping a birth control pill, it may take up to 6 months for cycles to return. If you had irregular periods or polycystic ovarian syndrome (PCOS) prior to taking the birth control pill, they may not return to a regular monthly cycle after stopping. If the birth control pill was mitigating some of the symptoms of PCOS, such as acne or facial hair, then those may return.

6. How long should I try to conceive before seeking help from a reproductive endocrinologist?

After 6-12 months of trying to conceive without success, consider seeing a reproductive endocrinologist. If your age is 35 or higher, then seek assistance earlier.

7. When should I see a gynecologist versus an OB-GYN?

If your current gynecologist does not do OB, then you should consider switching to an OB/GYN as soon as you are ready to start trying to conceive. For women with classical CAH, you will need to see a high-risk (maternal fetal medicine) OB in addition to another OB for the delivery. Women with classical CAH generally require a C-section for delivery due to a narrow pelvis.

8. What should I do once I'm pregnant and how often do I need to see my endocrinologist?

Once you are pregnant, you should continue your usual CAH treatment. Your maternal fetal medicine doctor will monitor your pregnancy and hormone levels, but your CAH treatment is not adjusted based on labs. If you are taking dexamethasone (which crosses the placenta) prior to pregnancy for your CAH treatment, it is recommended to switch to hydrocortisone during pregnancy unless you are trying to treat the fetus (experimental prenatal treatment with dexamethasone, see #3).

DO YOU WANT TO BE A GUEST ON CAH PULSE?

Take advantage of this incredible opportunity to make a difference in our community

Please reach out to dina@caresfoundation.org if you are interested in sharing your CAH story on our podcast. We truly appreciate all those who have joined us so far!

Season 2 | Episode 6: Dr. Su | *Words of Wisdom: Clearing up the Confusion of Stress Dosing*

Have you listened to our most recent episode yet (https://cahpulse.podbean.com/)? Join Stephanie & Dina as they speak with CARES Medical Director, Dr. Karen Su in Season 2: Episode 6, to try and clear up some of the confusion surrounding "stress dosing" as an adult or child living with CAH. Take full advantage of all of the insightful and thought-provoking free professional insight from one of the top CAH endocrinologists in the country. **Thank you Dr. Su!**

Want to catch up on other episodes? Visit the link in this post's caption or scan the QR Code!

Season 2 | Episode 5: Raelie: CAH Does Not Define THIS Ten Year Old!

Season 2 | Episode 4: Abby: CAH Mom? Or NASCAR Driver!

Season 2 | Episode 3: Ryan: The Son of a Rainbow Maker

Season 2 | Episode 2: Lydia: "I had no idea getting married and having children was a thing"

Support Group Meetings via Zoom

Our support groups are available in a wide variety of demographics. Groups meet via Zoom for beneficial discussions that ultimately have the goal of providing necessary support in the areas that you may need! A CAH expert/medical professional will be there to answer your questions in between doctor appointments or in times of worry or concern.

Use our Event Calendar (https://caresfoundation.org/calendar/) regularly for upcoming dates for these meetings. Registration in advance is required and all you have to do to register is send an email to support@caresfoundation.org with the date of the meeting you'd like to attend. To attend, you must first Join the CARES Community. (https://caresfoundation.org/join-the-cares-community/).

Upcoming Meetings (Please contact support@caresfoundation.org to confirm your attendance at any of the listed meetings!)

May 8, 2025 | 9:00PM(ET) via Zoom
CAH Children (Newborn-Age 5)

May 13, 2025 | 8:30PM(ET) via Zoom
CAH Women

May 21, 2025 | 8:30PM(ET) via Zoom
Parents of CAH Children (School-aged/Teens/Young Adults)

June 12, 2025 | 9:00PM(ET) via Zoom
CAH Children (Newborn-Age 5)

July 10, 2025 | 9:00PM(ET) via Zoom
CAH Children (Newborn-Age 5)

September 11, 2025 | 9:00PM(ET) via Zoom
CAH Children (Newborn-Age 5)

Support Group Leaders

Support Group Leaders are organized by state/topic. We appreciate our leaders and know that they are there for you when you need extra support! Please visit our website to see if there is a leader in your area. https://caresfoundation.org/support/

Support can also be found on our Facebook page by visiting Congenital Adrenal Hyperplasia Support Network.

Interested in joining any of our secret Facebook groups? Visit: Congenital Adrenal Hyperplasia Support Network on Facebook. When on our Profile, select '***More***' and then '***Groups***' to view all joinable groups. (If you are on a mobile device, select '**About**' then '*Groups*'). Click on the group(s) you would like to join, and then request access. We will then review your request, and follow-up as soon as possible.

YOU MUST BE A MEMBER OF THE CARES COMMUNITY TO JOIN ANY PRIVATE FACEBOOK GROUPS

Join the CARES Community here: https://caresfoundation.org/join-the-cares-community/

NEWLY DESIGNATED CENTER OF EXCELLENCE!

We are pleased to announce that **Nicklaus Children's Hospital/University of Miami Health System** has been designated as a comprehensive care center for CAH!

Nicklaus Children's Hospital

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM

COMPREHENSIVE CARE CENTERS FOR CONGENITAL ADRENAL HYPERPLASIA (CAH)

If you are seeking expert CAH medical care, then plan a **visit to one of 9 CARES-designated Comprehensive Care Centers for CAH**. These are highly specialized care centers that offer care throughout a patient's life cycle.

Children's Health/ UT Southwestern Medical Center

Children's Hospital Los Angeles

Children's Hospital of Philadelphia

Cook Children's Medical Center

New York-Presbyterian/ Weill Cornell Medical Center

Nicklaus Children's Hospital/ University of Miami Health Systems

Riley Hospital for Children/ Indiana University Health

Rutgers-Robert Wood Johnson Medical School (RWJMS), Child Health Institute of New Jersey (CHINJ)

Seattle Children's Hospital and University of Washington Medical Center

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Visit our Centers of Excellence webpage for more information on our Comprehensive Care Centers: https://caresfoundation.org/centers-of-excellence/

Medically-Safe Summer Camps

To learn more information about some of the medically-safe summer camps for CAH Patients offered on our website, please visit: https://caresfoundation.org/cah-medically-safe-summer-camps/.

FUNDRAISING | Make a difference today!

Warrior Bracelets | Little Words Project

CARES Foundation is teaming up with the **Little Words Project** to create "Warrior" bracelets for members of our community. CARES Foundation will receive a portion of the proceeds from the sale of each bracelet.

A "warrior" in CARES Foundation's community is someone that continues to battle to help improve their own life/the lives of those living with congenital adrenal hyperplasia (CAH).

The impact of your support resonates not only within our organization, but also in the broader community dedicated to enriching the lives of patients.

Warrior Bracelets will **ONLY** be on sale from April 1-June 30, 2025. Purchase yours by visiting:

https://www.littlewordsproject.com/products/giveback-warrior-4

PURCHASE A DOZEN KRISPY KREME DONUTS TO SUPPORT:
CARES Foundation

Now through May 22, 2025, 50% of your order will be donated back to **CARES Foundation** when you purchase via our fundraising sales page!

You can make your purchase to support CARES Foundation by **SCANNING THE QR CODE or BY CLICKING THE BUTTON BELOW!**

SCAN

GET MY DONUTS TODAY!

$25 in 2025
CARES Foundation's 25th Anniversary

To continue making a lasting difference in our community, we encourage anyone who is able, to commit **$25.00 each month in 2025** towards our mission. Help support & improve the lives of those living with congenital adrenal hyperplasia (CAH).

To make your donation, please visit:
https://caresfoundation.app.neoncrm.com/forms/cares-25th-anniversary?campaignId=307

CARES Foundation Endowment Fund | *Securing a Future of Care and Hope*

A Gift That Keeps on Giving

CARES Foundation's Endowment is designed to provide a stable, permanent source of funding. Your contribution will be carefully invested, with the annual returns supporting our mission in perpetuity. This means your single act of generosity will touch lives year after year, creating a ripple effect of positive change.

Every Gift Matters

Whether large or small, your contribution to the endowment fund is an investment in hope. It's a promise to future generations that they will have the resources, support, and opportunities they need to thrive despite CAH.

How an Endowment Grows...

- An establishing gift is made and forms the principal
- The prinicipal is protected, invested, and continues to grow
- A portion of the fund's value is distributed annually, forever

Ways to Give

Bequests: Include CARES in your will or living trust.
Retirement Plan Assets: Name CARES as a beneficiary.
Life Insurance: Designate CARES as a beneficiary.
Securities: Donate stocks, bonds, or mutual funds.
Real Estate: Gift property to make a significant impact.
Cash

If you would like to name us in your Will/IRA, please add the following as a beneficiary:
Community Foundation of New Jersey
c/o CARES Foundation Congenital Adrenal Hyperplasia Fund EIN 22-2281783

If you have any questions, please do not hesitate to contact us via email or by phone:
Email: contact@caresfoundation.org **Phone:** (908) 364-0272 **Toll Free:** (866) 227-3737

Other ways that you can support CARES Foundation...

Hosting a Family Fundraiser

Anybody can fundraise...You can do this! We are always eager to add new events to our calendar, and appreciate every opportunity to spread awareness in new parts of the country. Events such as CAH Awareness Walks, our annual Clay Shoot for CARES, and other family fundraisers are a key part in our mission. CARES Foundation is more than happy to help you along the way, and will help to provide resources necessary to assist when it comes to planning your event.

If you have any ideas for a future family fundraiser, do not hesitate to contact dina@caresfoundation.org.

Facebook Fundraisers

Fundraising through Facebook is one of the easiest and best ways to fundraise on your own! You can set up a fundraising post for a birthday, holiday, special event, or even to help with our year-end donation campaign.

Simply follow the instructions linked here (https://www.facebook.com/help/990087377765844) to create your fundraiser!

PLEASE UPDATE YOUR ACCOUNT!

Without the proper fields completed, **you may be susceptible to missing out on important information and events**! Please visit: https://caresfoundation.app.neoncrm.com/login to view your account with CARES and edit any incomplete fields in your profile.

CARES SHOP

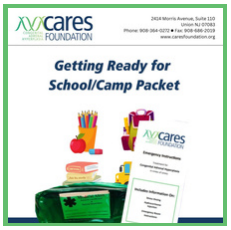
NEW ITEMS - COMING SOON!

Be on the lookout for new items coming to our shop in the coming weeks! View our full catalog by visiting: https://caresfoundation.org/the-cares-shop/.

ADRENAL INSUFFICIENCY CAR SEAT STRAP

$12.00

Velcro pullover strap to go over seatbelts to identify adrenal insufficiency in an emergency



GETTING READY FOR SCHOOL/CAMP PACKET

$4.00

Crucial tips and resources for back to school! (Includes 1 Emergency Response Kit)

EMERGENCY SYRINGE BAG

$5.50

Durable semi-translucent carry-case for syringe or other emergency items

EMERGENCY RESPONSE KIT (SET OF 3)

$5.00

Includes 3 semi-translucent kits, and emergency instructions brochure & checklist

MEDICAL I.D. LUGGAGE TAGS

$6.50

Medical Alert I.D. for luggage, backpacks, and other items when traveling

Please remember that CARES Foundation newsletters have "gone green" and are available digitally. Please make sure we have your current email address to ensure that you continue receiving newsletters and other important information from CARES. Send any updates to john@caresfoundation.org.

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