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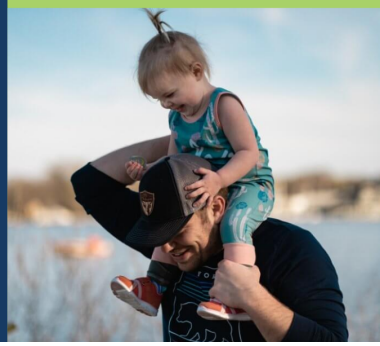

In This Issue

Assisted Reproduction in Congenital Adrenal Hyperplasia

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of seven autosomal recessive diseases. The genes responsible for congenital adrenal hyperplasia encode enzymes involved in cortisol biosynthesis. These enzymes are: 21-hydroxylase (21OH), 11β-hydroxylase (11βOH), 17α-hydroxylase (17OH; also known as 17, 20-lyase), 3β hydroxysteroid dehydrogenase type 2 (3βHSD2), steroidogenic acute regulatory protein (StAR), P450 cholesterol side-chain cleavage (P450scc), and P450 oxidoreductase (POR). Multiple hormonal imbalances occur and CAH manifests with a range of clinical and biochemical phenotypes, with or without alterations in glucocorticoid, mineralocorticoid, and sex steroid production. Congenital adrenal hyperplasia can be distinguished clinically in two forms, "classic" and "non-classic" (non-classic CAH; NCCAH) (1). Mutations in these enzymes result in reduced cortisol production, which leads in its turn to increased secretion of corticotrophin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) causing adrenal cortex hyperplasia (2). As a result, precursor steroids accumulate before the point of enzymatic disruption shifting the biosynthetic pathway toward production of sex steroid hormones, more specifically adrenal androgens, which are found in excess. Approximately 90–95% of cases with CAH are attributed to 21OH deficiency (3). Clinical distinction to "classic" and "non-classic" forms depends on the severity of the clinical expression of this deficiency (3). "Classic" CAH can also be distinguished in two forms, "salt-wasting" and "simple virilizing." Seventy-five percent of cases with "classic" CAH represent the "salt-wasting" form presenting with cortisol and aldosterone deficiency. In "salt-wasting" CAH, the enzyme activity is completely silenced. In "simple virilizing" CAH, there is 1–2% enzyme activity with normal mineralocorticoid concentrations. In NCCAH, enzyme activity is satisfactory (20–50%) and thus, patients remain asymptomatic, or symptoms appear much later (this form is otherwise called "late-onset CAH") (3). Females with NCCAH are not virilized at birth (4). The incidence of "classic" CAH is 1:10000–1:20000 live births and that of NCCAH 1:1000 live births (3, 5). This classification is artificial because CAH has a wide and continuous range of clinical features depending on residual enzyme function (5).

Pregnancy rate is related to the clinical severity of the disease (6, 7). Severe infertility is associated with "salt-wasting" CAH. The low rates of fertility in women with "classic" CAH are also related to the decreased libido of these patients, with less chance of heterosexual relations and less desire to engage in family formation (8, 9). Many women with NCCAH present with mild symptoms and therefore remain undiagnosed. It is difficult to assess accurate infertility rates in NCCAH (8).

FERTILITY IN CAH

Fertility in "Classic" CAH

Fertility rates in women with "classic" CAH and especially those with "salt-wasting" CAH are significantly lower compared to those in the general population (6, 9–12). On the other hand, it is difficult to estimate these rates in women suffering from CAH because they do not usually seek pregnancy while studies include a small number of patients. These rates are improved when studies include only women with CAH who are actively trying to conceive which means women who undergo surgical and/or pharmaceutical therapy (8, 10). Indeed, in a study of 81 women with "salt-wasting" CAH evaluated since birth, only nine sought pregnancy, with eight of them

Continued on pg. 3

A Message from the Executive Director

Dear Friend,

As we approach the end of the year, I reflect on what an incredible year it has been for CARES and the CAH community, how privileged I am to work with such an amazing community group of people. Our patients, families, medical professionals, researchers, and supporters have helped make 2022 another remarkable year.

We returned to in-person events which allow us and members of our community to make those all-important connections. Our 22nd Annual Gala at the legendary, Sony Pictures Studios in Culver City, CA., this always special event, was even more memorable we were able to celebrate our honorees in person, along with family, friends, and colleagues.

Our in-person walks in California and Florida were again in-person. Families and patients enjoyed the exercise, fun and games, injection training, and learning about new clinical trials.

Patients and families were excited to attend our patient education conference held by Cook Children's Medical Center in Ft. Worth, TX. Participants learned about important topics from CAH experts, as well as their peers. Some sessions were led by teenagers, young adults and parents who provided a first-hand account of life with CAH. It warmed my heart to hear from patients and families for whom the conference was their first opportunity to meet others just like them. No matter how technically advanced we become, nothing can replace the power of face-to-face communication.

We also had the opportunity to host a meeting of our comprehensive care center directors. The group exchanged ideas, research, and educational opportunities, as well as other tools aimed at improving the care provided to CAH patients. I'm always wowed by their commitment to the patients and families they serve. We are so fortunate to work with such a caring and dedicated group!

The CAHtalog patient registry and PACE (Preventing Adrenal Crisis Events) app were also welcome additions in 2022.

Thanks to the support of our entire community – patients, families, medical professionals, members of industry, and donors, we continue reaching higher to make life with CAH better.

Please consider CARES in your year-end-giving and together, we will reach even higher in 2023!

Continued from pg 1

conceiving in the end (8, 13). Independently of these women's infertility, pregnancies are usually normal and uneventful (11).

Fertility in NCCAH

"Non-classic" CAH is a frequent cause of infertility, often undiagnosed (14). Pregnancy rates in women with NCCAH who visit infertility clinics due to infertility or hyperandrogenemia, vary according to studies and range between 65 and 95% (8, 15–18). There is a significant phenotypic overlap between PCOS and NCCAH, often leading to misdiagnosis of patients who seek advice in fertility clinic. Patients with PCOS manifest hirsutism, hyperandrogenemia, variable degrees of insulin resistance, and anovulation (19). Because of the similarity of clinical features between the two conditions, it has been postulated that about 33% of patients diagnosed with PCOS actually suffer from NCCAH (20). Due to the different treatment of these two conditions and the possible incidence of NCCAH in the fetus during pregnancy, the correct differential diagnosis of patients with infertility is critical (20).

Etiology of Infertility in CAH

The etiology of infertility in patients with CAH is multifactorial, including ambiguous genitalia and their complications, excessive androgen secretion, adrenal progesterone hypersecretion, co-existence of PCOS, and various psychosocial factors (5–7, 11,14, 20–22).

Female fetuses with "classic" CAH and adrenal androgen hypersecretion during endometrial life present with malformations of external genital organs such as presence of a urogenital sinus, labial fusion, and variable degrees of clitoral hypertrophy. These malformations render sexual intercourse unpleasant and sometimes prohibitive, reducing the chance of pregnancy. The possibility of sexual intercourse is related to introital width, vaginal length, and clitoral integrity. Internal genitalia remain intact (8). Exposure to increased androgens in endometrial life also affects psychosocial development of these patients. Women with "classic" CAH, experience gender-related disorders such as participation in games of masculine orientation as children and pursuit for men's occupations in adult life. An increased rate of homosexual and bisexual relationships among patients with CAH is reported. In addition, reduced libido and decreased desire for family formation are observed (8, 9, 20).

Chronic exposure to adrenal androgens causes disorders of the hypothalamic-pituitary-ovarian axis leading to hypersecretion of LH. In addition to increased androgen concentrations in peripheral blood, CAH is also associated with increased concentrations of progesterone. Progesterone secretion in these patients is continuous resulting to modification of GnRH pulsatility, prevention of normal endometrial development, defective quality of cervical mucus, and decrease of tubal motility, resulting thus, in significant decrease in fertility (7, 8, 14, 20). Thirty to sixty-eight percent of women with "salt-wasting" CAH and 30–75% of women with "simple-virilizing" form manifest menstrual irregularities and anovulation (10).

MANAGEMENT OF INFERTILITY IN WOMEN WITH CAH

Treatment of CAH

Women with "classic" CAH have ambiguous external genitalia. Female embryos are exposed to adrenal androgens from the 7th week of pregnancy resulting in clitoral enlargement, fusion, and scrotalization of the labial folds, and rostral position of the urethral/vaginal perineal orifice, placing the phallus in male position while the internal female reproductive organs are developing normally. These changes are classified according to the five Prader stages (14). In case of patients with "classic" CAH and ambiguous genitalia, the possibility of surgical rehabilitation should be considered (23). It includes clitoroplasty, vaginoplasty, and labiaplasty and aims at removing redundant erectile tissue, preserving the sexually sensitive gland clitoris, and providing a normal vaginal orifice that functions adequately for menstruation, intromission, and birthing. In addition these interventions protect from recurrent urinary tract infections which result from pooling of urine in the vagina or urogenital sinus (10, 14, 23, 24). The main complications of surgical interventions include urinary incontinence, clitoral pain, painful intercourse and inadequate introitus, vaginal stenosis, and anorgasmia. These complications lead to decreased intercourse frequency. Secondarily, they have been observed strictures, fibrosis and scarring, fistulas, and recurrent urinary infections (10, 14, 24). Glucocorticoid therapy is the pharmaceutical treatment of choice, both for patients with "classic" CAH and for those with NCCAH, with addition of mineralocorticoid to patients with "salt-wasting" CAH (9α-fludrohydrocortisone acetate) (1–3, 9, 23). Glucocorticoids substitute the deficient endogenous cortisol synthesis and thus, CRH and ACTH hypersecretion is reduced, leading to decreased adrenal androgens secretion (25). Subsequently, progesterone levels are reduced and normal ovulation, endometrial proliferation and implantation ensue (5, 12). In "classic" CAH, to control overnight HPA-driven increase of adrenal androgens, a variety of glucocorticoid treatment regimens have been used. Treatment with hydrocortisone administration in three equal doses (starting at 8.00 am) seems to be the most appropriate. Many specialists used to administer prednisolone in adult patients because of the more convenient dosage regimen. However, this treatment is gradually abandoned because it is accompanied by side effects, such as obesity, insulin resistance, bone loss, hypertension, and dermal atrophy (25). Combination therapies employing glucocorticoids for adrenal replacement and androgen suppression (even 2 different glucocorticoids) as well as anti-androgens and androgen biosynthesis inhibitors for treatment of hyperandrogenism might be useful for treatment optimization and minimization of side effects. Treatment regimens and goals should be individualized, while these targets might be modified throughout patient's life. Laboratory data for adults with 21OH deficiency are useful as markers, but they are eventually less important than clinical evaluation. They can be improved by incorporating steroid profiling by mass spectrometry (26). When necessary, low doses of glucocorticoids may be used in patients with NCCAH (1). In these patients, when signs of hyperandrogenemia manifest, treatment is sometimes successful only with oral contraceptives alone or with spironolactone (1, 23).

Although most patients will become ovulatory with the routine dose of hydrocortisone, some will require greater doses for suppression of progesterone of adrenal origin. In patients who do not achieve pregnancy, progesterone plasma concentrations should be measured in the follicular phase of the menstrual cycle. In most cases adequate suppression of 17-hydroxyprogesterone results in adequate peripheral concentrations of adrenal-derived progesterone (although in this case one might not avoid exogenous hypercortisolism) (9, 20). Of note, greater doses of glucocorticoids are required when the therapeutic aim is the reduction of androgen concentrations, as compared to replacement doses required only for substitution of hormonal deficiency. For women who attempt to conceive when in glucocorticoid treatment, hydrocortisone, which is inactivated by the placenta, is employed. This treatment continues during pregnancy (1). Unilateral or bilateral adrenalectomy has been used as last resort for patients who do not respond to other treatments, especially those with "salt-wasting" CAH and large adrenal myelolipomas (most commonly developing in poorly controlled "classic" CAH) as well as in persistent hyperandrogenemia (3, 6), but it is not recommended because of its life-time invalidating risks (6, 8, 20, 27).

Ovulation Induction in CAH

For those patients who cannot achieve ovulation despite adequate treatment and reduction of progesterone and androgen concentrations, gonadotropins or clomiphene may be useful to induce ovulation (20). In vitro fertilization (IVF) can be another treatment option for those, who fail to achieve pregnancy with these therapeutic means (8). By the time ovarian stimulation is achieved, the possibility to freeze all embryos and transfer them to a subsequent cycle should be considered in an effort to avoid the IVF protocol-induced increased progesterone concentrations. In cases where both parents are carriers of a CAH mutation or one parent is affected by CAH and the other is a carrier, there is an increased risk that the fetus will be affected from CAH. In this case it is essential to perform pre-implantation genetic diagnosis (PGD) (6, 8).

PREGNANCY IN CAH CARRIERS AND IN CAH PATIENTS

Prenatal diagnosis of CAH in the embryo or fetus can be done by performing chorionic villus sampling (9–11th week of pregnancy) or amniocentesis (15–20th week of pregnancy) followed by genetic testing (28). Specific probes for 21-hydroxylase mutations allow direct and rapid identification of known mutations through the use of polymerase chain reaction (i.e., allele specific). Panels of oligonucleotide probes, currently available for use in prenatal diagnosis, are expected to identify well more than 95% of current 21-hydroxylase mutations (4). In embryos belonging to a high-risk group for CAH, prenatal therapy to prevent virilization of external genitalia of a female embryo affected with CAH should be regarded as experimental. Recent studies address four areas of concern when dexamethasone is used as treatment: potential teratogenicity (cleft lip with/without cleft palate), reduced birth weight, potentially brain/behavior problems such as verbal working memory, reduced self-perception of scholastic competence and increased self-rated social anxiety, and potential long-term effects (insulin resistance) (27). There are no recommended specific treatment protocols and prenatal treatment should be obtained only through approved clinical protocols or trials (27). In embryos with increased probability of CAH (because of family risk), treatment with glucocorticoids should be introduced before the 9th week of pregnancy which effectively lowers excessive adrenal androgens amounts and thus, prevents masculinization of female external genitalia. The results from the villocentesis or amniocentesis will determine further patient's management. Treatment is discontinued when the fetus is male or unaffected female. Otherwise, it is continued until term in three divided doses based on maternal pre-pregnancy bodyweight (28). Concerns arise regarding the unnecessary corticoid treatment of pregnant women in case of male and unaffected female fetuses. Therefore, it is important to identify female affected fetuses before 9 weeks of pregnancy (4). Non-invasive techniques introduced in 2011 are based on extraction of fetal cell-free DNA (cfDNA) from maternal blood (28). This may become the new standard diagnostic approach in the future (4). The advantage of this test is that it can be done at the 6th week of pregnancy, allowing early diagnosis before the onset of genital organogenesis (9th week of pregnancy) and by that unnecessary treatments would be avoided (23, 28).

Spontaneous abortion rates appear to be greater, as compared to healthy pregnant women, in patients with CAH, as well as in patients with NCCAH who were not treated with glucocorticoids. These rates are normalized after glucocorticoid treatment (5, 8, 9). Pregnancies of women already diagnosed with CAH seem to be normal and uneventful (9). Genetic counseling is essential (5).

Monitoring of pregnancy should be performed by a specialized team, which should include obstetrician, pediatrician and endocrinologist (5, 12). Symptoms of fatigue, nausea, and vomiting are common in pregnancy and overlap those of adrenal insufficiency. Overtreatment with hydrocortisone can lead to fluid retention, excessive weight gain and hypertension. Mothers should be evaluated for signs of adrenal insufficiency in pregnancy (i.e., postural hypotension) and stress dose steroids should be administered during labor. In the second and third trimester of pregnancy, the dose of hydrocortisone may need to be increased by 25–40%, although there is no consensus on this (5, 6, 8, 27). No dose adjustment of hydrocortisone is required in the early stages of pregnancy (9). Dose control of treatment with hydrocortisone during pregnancy should not be performed with plasma renin activity levels as they increase normally during pregnancy, but with testosterone and androstenedione concentrations (5, 6). Pregnant women with CAH appear to be at greater risk for developing gestational diabetes mellitus. The incidence of pre-eclampsia and premature delivery does not seem to change (5, 7, 9). Finally, cesarean section is preferable, especially for women who have prior genital reconstructive surgery, although vaginal deliveries have also been reported (5, 8, 9).

Babies from mothers with CAH and NCCAH have an increased risk to be small for gestational age (SGA) babies, especially when parents suffer from NCCAH. The long-term follow-up of the offspring has shown normal physical and intellectual development although these children might show deranged renal (particularly evident in females below the age of 5) and liver biochemistry (9, 29).

CASE REPORTS

In the literature there are a few cases of severe CAH which needed to undergo IVF. Albarel et al. reported a patient with StAR deficiency, homozygous for 1 bp delection in the StAR gene (719del). The patient, after missing ovarian response to clomiphene, underwent IVF with a long agonist protocol with 300 units menotropin per day. The procedure resulted in pregnancy with delivery of a normal female child (weight: 3.150 kg) at 40 weeks of gestation (30).

Bianchi et al. reported a 26 years old patient with CAH, associated with 17OH deficiency, a rare defect of steroid biosynthesis characterized by inability to synthesize cortisol, androgens or estrogens, complete absence of follicular maturation, hypergonadotropic hypogonadism, primary amenorrhea, and hypertension. The defect was due to a compound heterozygous mutation (p.W406R/P428L) in the CYP17A1 gene. The patient underwent IVF with a long agonist protocol receiving 112.5 I.U. recombinant FSH per day. Four mature oocytes were retrieved and 3 blastocysts were obtained. Two of them were transferred and pregnancy was achieved. Pregnancy was complicated by pre-eclampsia, gestational diabetes (requiring insulin administration), cholestasis gravidarum (requiring ursacol administration), and cellulitis of the lower right extremity. At 30 weeks and 4 days, an emergency cesarean section was performed due to acute fetal distress. A true umbilical knot was identified, and a live normal male newborn was delivered (weight: 1,945 g; length: 43.5 cm) (31).

Neuwinger et al. also treated a 28 year female with 17OH deficiency. Because the ovaries of these patients contained numerous primordial follicles, the authors hypothesized that the absence of spontaneous follicular maturation could be due to a lack of aromatizable substrate. To provide this substrate, testosterone was administered either by intra-ovarian injection or by vaginal administration. Ovarian stimulation was performed with human urinary gonadotropins. Follicular maturation and ovulation were induced with this treatment, as confirmed by ultrasonography, measurement of LH, estradiol and progesterone serum concentrations and finally, aspiration of oocytes from the mature follicles. Fertilization of these oocytes in vitro, however, did not succeed (32).

Ben-Nun et al. reported the first viable pregnancy in a woman with 17OH deficiency in which embryos produced with donated oocytes were transferred to the uterus. At the fifth embryo transfer attempt, the treatment resulted in a twin pregnancy which was further complicated with severe pre-eclampsia, hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, and premature delivery. One newborn died minutes after delivery, whereas the other was kept for several weeks at the neonatal intensive care unit and discharged without apparent disabilities (33).

DISCUSSION

As previously described, the clinical presentation of "classic" CAH and NCCAH is in direct correlation with the genomic and biochemical background of the disease. Therefore, it is important to emphasize that treatment should be individualized. Moreover, it should be a matter of collaboration between health-providers of many disciplines.

Managing patients with "classic" CAH is challenging. These patients, in addition to treatment with glucocorticoids and mineralocorticoids depending on the form of the disease, might need surgical treatment of ambiguous genitalia. The right moment to operate these patients is a field of controversy. In the past, the decision on surgery was taken on the basis of appearance of external genitalia and the possibility of conception. However, in the past two decades it is preferred that surgery is postponed so that the patients gives his/her informed consent (1). Because of this controversy over gender behavior,gender identity, surgical outcome, and long-term sexual function, it is imperative to consider all therapeutic options on an individual basis (23).

In an infertility clinic, health professionals are much more frequently confronted with patients with NCCAH compared to patients with "classic" CAH because the former represent a larger undiagnosed population while the latter are identified early in infancy (20). Many patients with NCCAH are undiagnosed due to the mild symtoms

that lead them to seek medical advice only in case of infertility (8). Moreover, there is a phenotypic overlap between NCCAH and PCOS (20). The distinction is made as women with NCCAH manifest greater concentrations of 17-hydroxyprogesterone and progesterone than women with PCOS, who present insulin resistance, obesity, polycystic ovary morphology, and increased LH/FSH ratios (28).

The main problems in NCCAH women are the increased progesterone concentrations which alter endometrial receptivity and tubal motility and lead to ovulation disorders. Appropriate therapy usually leads to regular menses and spontaneous pregnancies. Sometimes ovulation induction regimens (i.e., clomiphene) can be used as well as IVF techniques in case of insufficient ovarian function and pregnancy is not achieved.

CONCLUSION

The treatment of infertility in CAH patients is a major challenge. Hydrocortisone is at the time being the gold standard treatment which restores ovarian function, ovulation, and endometrial receptivity. Performing PGD should be taken into consideration in cases where both parents are affected. Pregnancy should be followed by an expert team in a tertiary hospital in case of suspected affected fetus with CAH. Finally, patients with CAH should be followed by a multidisciplinary team including gynecologist, endocrinologist, and pediatrician.

AUTHOR CONTRIBUTIONS

AC AND ES: LITERATURE REVIEW. RV AND MP: MANUSCRIPT. GM: REVISION.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GV declared a past co-authorship with one of the authors GM to the handling editor.

REFERENCES

1. El-maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet. (2017) 390:2194–210. doi: 10.1016/S0140-6736(17)31431-9
2. Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. (2015) 44:275–96. doi: 10.1016/j.ecl.2015.02.002
3. Sharma R, Seth A. Congenital adrenal hyperplasia: issues in diagnosis and treatment in children. Indian J Pediatr. (2014) 81:178–85. doi: 10.1007/s12098-013-1280-8
4. Yau M, Khattab A, New MI. Prenatal diagnosis of congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. (2016) 45:267–81. doi: 10.1016/j.ecl.2016.01.001
5. Witchel SF. Congenital adrenal hyperplasia. J Pediatr Adolesc Gynecol. (2017) 30:520–34. doi: 10.1016/j.jpag.2017.04.001
6. Han TS, Walker BR, Arlt W, Ross RJ. Treatment and health outcomes in adults with congenital adrenal hyperplasia. Nat Rev Endocrinol. (2014) 10:115–24. doi: 10.1038/nrendo.2013.239
7. Weiss RV, Clapauch R. Female infertility of endocrine origin. Arq Bras Endocrinol Metabol. (2014) 58:144–52. doi: 10.1590/0004-2730000003021
8. Lekarev O, Lin-Su K, Vogiatzi M. Infertility and reproductive function in patients with congenital adrenal hyperplasia: pathophysiology, advances in management, and recent outcomes. Endocrinol Metab Clin North Am. (2015) 44:705–22. doi: 10.1016/j.ecl.2015.07.009
9. Falhammar H, Nordenstro A. Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome. Endocrine. (2015) 50:32–50. doi: 10.1007/s12020-015-0656-0
10. Bachelot A, Grouthier V, Courtillot C, Dulon J, Touraine P. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: update in management of adult patients and prenatal treatment. Eur J Endocrinol. (2017) 4:167–81. doi: 10.1530/EJE-16-0888
11. Kamoun M, Feki MM, Sfar MH, Abid M. Congenital adrenal hyperplasia: treatment and outcomes. Indian J Endocrinol Metab. (2013) 17:14–7. doi: 10.4103/2230-8210.119491
12. Speiser PW. Congenital adrenal hyperplasia [version 1; peer review: 2 approved]. F1000Res. (2015) 4:21–4. doi: 10.12688/f1000research.6543.1
13. Casteras A, Silva De P, Rumsby G, Conway GS. Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): normal pregnancy rate but reduced fertility rate. Clin Endocrinol. (2009) 70:833–7. doi: 10.1111/j.1365-2265.2009.03563.x
14. Yau M, Khattab A, Poppas D, Ghizzoni L, New M. Congenital adrenal hyperplasia: unresolved issues. Front Horm Res. (2016) 46:184–95. doi: 10.1159/000443919
15. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. (2010) 95:5110–21. doi: 10.1210/jc.2010-0917
16. Bidet M, Bellanne C, Morel Y, Coussieu C, Boudou P, Mowzowicz I, et al. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase. J Clin Endocrinol Metab. (2010) 95:1182–90. doi: 10.1210/jc.2009-1383
17. Feldman S, Billaud L, Thalabard J-C, Raux-Demay M-C, Mowszowicz I, Kuttenn F, et al. Fertility in women with late-onset adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. (1992) 74:635–9. doi: 10.1210/jcem.74.3.1310999
18. Moran C, Azziz R, Weintrob N, Witchel SF, Rohmer V, Dewailly D, et al. Reproductive outcome of women with 21-hydroxylase- deficient nonclassic adrenal hyperplasia. J Clin Endocrinol Metab. (2006) 91:3451–6. doi: 10.1210/jc.2006-0062
19. Mastorakos G, Lambrinoudaki I, Creatsas G. Polycystic ovary syndrome in adolescents: current and future treatment options. Pediatr Drugs. (2006) 8:311–8. doi: 10.2165/00148581-200608050-00004
20. Reichman DE, White PC, New MI, Rosenwaks Z. Fertility in patients with congenital adrenal hyperplasia. Fertil Steril. (2014) 101:301–9. doi: 10.1016/j.fertnstert.2013.11.002
21. Auchus RJ. Management considerations for the adullt with congenitaladrenal hyperplasia. Mol Cell Endocrinol. (2015) 408:190–7. doi: 10.1016/j.mce.2015.01.039
22. Zainuddin AA, Grover SR, Shamsuddin K, Mahdy AZ. Research on quality of life in female patients with congenital adrenal hyperplasia and issues in developing nations. J Pediatr Adolesc Gynecol. (2013) 26:296–304. doi: 10.1016/j.jpag.2012.08.004
23. Parsa AA, New MI. Steroid 21-hydroxylase deficiency in congenital adrenal hyperplasia. J Steroid Biochem Mol Biol. (2017) 165:2–11. doi: 10.1016/j.jsbmb.2016.06.015
24. Merke DP, Poppas D. Management of adolescents with congenital adrenal hyperplasia. Lancet Diabetes Endocrinol. (2013) 1:341–52. doi: 10.1016/S2213-8587(13)70138-4
25. Turcu AF, Auchus RJ. Novel treatment strategies in congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes. (2016) 23:225–32. doi: 10.1097/MED.0000000000000256
26. Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. (2013) 98:2645–55. doi: 10.1210/jc.2013-1440
27. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society * clinical practice guideline. J Clin Endocrinol Metab. (2018) 103:4043–88. doi: 10.1210/jc.2018-01865
28. Podgórski R, Aebisher D, Stompor M, Podgórska D, Mazur A. Congenital adrenal hyperplasia: clinical symptoms and diagnostic methods. ACTA Biochim Pol. (2018) 65:25–33. doi: 10.18388/abp.2017_2343
29. Sidiropoulou EJ, Paltoglou G, Valsamakis G, Margeli A, Mantzou A, Papassotiriou I, et al. Biochemistry, hormones and adipocytokines in prepubertal children born with IUGR evoke metabolic, hepatic and renal derangements. Sci Rep. (2018) 1:15691. doi: 10.1038/s41598-018-34075-6
30. Albarel F, Perrin J, Jegaden M, Roucher-Boulez F, Reynaud R, Brue T, et al. Successful IVF pregnancy despite inadequate ovarian steroidogenesis due to congenital lipoid adrenal hyperplasia (CLAH): a case report. Hum Reprod. (2016) 31:2609–12. doi: 10.1093/humrep/dew239
31. Bianchi PH, Gouveia GR, Costa EM, Domenice S, Martin RM, de Carvalho LC, et al. Successful live birth in a woman with 17α - hydroxylase deficiency through IVF frozen-thawed embryo transfer. J Clin Endocrinol Metab. (2016) 101:345–8. doi: 10.1210/jc.2015-3201
32. Neuwinger J, Licht P, Munzer B, Sir-Petermann T, Siebzehnrubl E, Wildt L. Substitution with testosterone as aromatizable substrate for induction of follicular maturation, estradiol production and ovulation in a patient with 17a-hydroxylase deficiency. Exp Clin Endocrinol Diabetes. (1996) 104:400–8. doi: 10.1055/s-0029-1211475
C33. Ben-Nun I, Siegal A, Shulman A, Ghetler Y, Kaneti H, Lunenfeld B, et al. Induction of artificial endometrial cycles with oestradiol implants and injectable progesterone: establishment of a viable pregnancy in a woman with 17-α-hydroxylase deficiency. Hum Reprod. (1995) 10:2456–8. doi: 10.1093/oxfordjournals.humrep.a136319

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RECRUITMENT FOR MULTI-CENTER STUDY

Phase 1 Multi-Center Study to Assess the Efficacy and Safety of Abiraterone Acetate as Adjunctive Therapy in Pre-Pubescent Children with Classic 21-Hydroxylase Deficiency

This study is for girls and boys age 2-9 years old, who will receive abiraterone acetate for 7 days, in addition to the standard of care treatment of hydrocortisone and fludrocortisone. To qualify for the study, children must be taking standard of care fludrocortisone (any dose) and ≤10 mg/m2/day of hydrocortisone for at least 1 month prior to the study consent and have a morning serum androstenedione concentrations >1.5 x upper limit normal (ULN) after 7 days of dosing with doses of hydrocortisone required for physiologic replacement. The study sites are:

- University of Texas Southwestern Medical Center
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- University of Michigan
- Children's Hospital Los Angeles

For more information, go to clinicaltrials.gov and search for study NCT02574910.

RESEARCH PROPOSAL SUBMITTED: Cognition and Development in Congenital Adrenal Hyperplasia

Dr. Mimi Kim, Children's Hospital Los Angeles, Dr. Maria Vogiatzi, Children's Hospital of Philadelphia, & Dr. Selma Witchel, Children's Hospital of Pittsburgh, have submitted a very interesting research proposal to CARES Foundation.

Research would involve evaluation of youth with CAH at their large Children's Hospitals. The study will be for children with CAH between the ages of 3-18 and their families. They will be evaluated with age-appropriate neuropsychological assessments that will improve understanding of neurodevelopment in CAH.

"Our goal is to improve the understanding of neurodevelopment in youth with CAH. . . , by performing neuropsychological assessments in the clinic setting in 300 pediatric patients with CAH, along with comprehensive behavioral questionnaires completed by their parents. . . with an improved understanding of the trajectory of neurodevelopment in children with CAH, we hope that early intervention strategies could then be implemented to improve the quality of life in individuals with CAH."

The impetus for the study came after observations that older children, adolescents, and adults can exhibit neuropsychological impairment, developmental delay, and mental health concerns (e.g., anxiety, depression), but not much is known about when these develop in children.

Stay tuned about how you can get involved in this important study.

Adrenas Therapeutics, a BridgeBio company, is a biotech company exploring the potential of a gene therapy for classic CAH (Congenital Adrenal Hyperplasia). If successful, Adrenas' investigational gene therapy for CAH may restore the body's hormone and steroid balance by enabling people with CAH to naturally make their own cortisol and aldosterone. It could also allow for people with CAH to eliminate or significantly reduce their daily glucocorticoid or mineralocorticoid doses. Exploration of the unique qualities of gene therapy, gene therapy clinical trials, and Adrenas' gene therapy program for CAH, will help to expand and improve understanding of this unique and encouraging treatment approach.

OVERVIEW OF GENE THERAPY AND THE POTENTIAL OF GENE THERAPY FOR CAH	
What is gene therapy?	Gene therapy involves the introduction of a gene in a person's body with the goal of treating or curing a disease. In general, gene therapy involves delivering a functioning copy of a gene into cells that are missing or do not have a fully functioning copy of that gene. Unlike other approaches (e.g., gene editing or CRISPR), gene therapy is not designed to change the cells that pass on genes to our children.
How might Adrenas' investigational gene therapy work in CAH?	People with CAH due to 21-hydroxylase deficiency have changes (mutations) in the *CYP21A2* gene. The *CYP21A2* gene is important for the production of 21-hydroxylase, a critical enzyme necessary for proper function of the adrenal glands. Mutations in *CYP21A2* cause 21-hydroxylase to either not be produced or not be fully functional. Adrenas' investigational gene therapy uses a common virus called adeno-associated virus (AAV) as the delivery vehicle for the *CYP21A2* gene. You can think of AAV as a "delivery truck," with the cargo being a functional gene. AAVs used in gene therapy are not associated with any known diseases in people, which is why they are used in gene therapy as the transport vehicles to deliver functioning genes to the body.
What if a person has antibodies for the AAV?	Based on what is currently understood about anti-AAV antibodies, a positive test would suggest that the potential participant may be less likely to benefit from the investigational gene therapy. However, the situation may change in the future as there is significant research underway exploring the possibility for dosing or redosing of participants with positive antibodies. The results of these studies are being closely monitored as they could provide valuable information as to whether or how AAV antibodies may impact Adrenas' investigational gene therapy trial for CAH.
While all therapeutic approaches carry a risk of causing side effects, are there any additional safety concerns that are specific to gene therapy?	Although AAV gene therapy is new to CAH, it's not a new therapy for genetic conditions. A number of AAV gene therapies have been approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency). Gene therapies have also been studied extensively in clinical trials for adults with hemophilia, one of which was recently approved in the EU (European Union). In total, gene therapies have been used to treat thousands of people around the world, and more patients are being treated with gene therapy every day. There are currently 100+ active AAV gene therapy trials for a variety of diseases. Long-term safety information for both the approved gene therapies and those still in development is being collected continuously. Although immune reactions to gene

	therapy do not always occur, when they do, they often involve the liver. In ongoing clinical trials in adults, AAV gene therapy use in other diseases has been generally well-tolerated and with no reports of long-term liver injury. The FDA currently recommends gene therapy clinical trial recipients participate in 5 years of follow up to monitor safety. The American Society of Gene and Cell Therapy has additional, up-to-date information about gene therapies on its website (www.asgct.org/genetherapy101/).
How is the Adrenas gene therapy clinical trial structured to emphasize safety?	The Adrenas gene therapy clinical trial has two specific features that emphasize safety: sequential enrollment and dose escalation. A clinical trial with sequential enrollment enrolls one participant at a time during the dose-finding phase, versus traditional drug clinical trials that will enroll multiple participants. Another characteristic is dose escalation. In a dose escalation study, a single dose of the gene therapy is given to a specific number of participants (cohort). Then, the dose of the gene therapy incrementally increases in subsequent cohorts to find the safest and most effective dose. Sequential enrollment coupled with dose escalation allows for careful safety monitoring of each participant. Gene therapy trials focus on safety because the dose cannot be adjusted higher or lower once delivered and because redosing is not possible at this time (although extensive research is underway). Gene therapy trials require 5 years of follow-up after the single dose of the potential treatment.
How is safety monitored in gene therapy clinical trials?	Adrenas' gene therapy trial and all gene therapy trials are designed in ways to maximize patient safety. Sequential enrollment and dose escalation are critical components of the trial design that ensures close monitoring of safety. Additionally, an independent, external Data Safety Monitoring Committee (DSMC) closely examines patient data within each group and provides guidance about dosing at the same level as well as increasing the dose level.

ADvance-CAH is Adrenas Therapeutics' investigational gene therapy program for adults with classic CAH. The ADventure clinical trial, a first-in-human dose escalation study, is currently enrolling to determine the safety, potential efficacy, and optimal dose of the gene therapy. Up-to-date information about the clinical trial, its sites, and high-level eligibility criteria can be found at https://clinicaltrials.gov/ct2/show/NCT04783181, www.cahgenetherapy.com, and www.adrenastx.com.

ADventure Clinical Trial for Adults with Classic CAH	
How are the parts of Adrenas' investigational gene therapy clinical trial program for adults structured?	There are two parts included within Adrenas' investigational gene therapy clinical trial program for adults with classic CAH: the prescreening study and the investigational gene therapy study. 1) The prescreening study provides the opportunity for people to express their interest and determine their eligibility for the ADventure gene therapy clinical trial. The steps involved in the prescreening do not guarantee a slot for participation in the gene therapy clinical trial. 2) The ADventure clinical trial is Adrenas' investigational gene therapy clinical trial for adults living with classic CAH. During this study, a participant will receive Adrenas' investigational gene therapy via a one-time intravenous (IV) infusion.

Continued on pg 13

FUN-RAISING!

FAMILY FUNDRAISERS - (continued on pg 12)

We had several successful Family Fundraisers this year! In May, there was the Captain Jack's Quest for a Cure Golf Tournament. This sold-out, 4th annual event was held on May 9, 2022 at the Pinehills Golf Club in Plymouth, MA.

Captain Jack Porter was there in person to greet the guests and take a few golf swings. He joined his parents, Kaitlin & Zach Porter as hosts of this terrific event. Golfers and guests were treated to lunch and wonderful prizes at the silent auction. Over 120 people gathered in the sunny weather in support of CARES Foundation.
We are grateful to all of the attendees, donors, volunteers & sponsors.

A SPECIAL THANK YOU TO KAITLIN, ZACH & JACKSON PORTER!

MT. HOREB HIGH SCHOOL SENIOR HOSTS "CAH NIGHT" SOFTBALL GAME

Sydnee Swiggum, pictured left, with her sister Madeline, both SWCAH patients, hosted a CAH Awareness Night/Fundraiser at her high school, Mt. Horeb High in Mt. Horeb, WI on May 6, 2022. Sydnee, a senior in high school, hosted this event in conjunction with her school team's softball game. They sold refreshments & had a 50/50 raffle with proceeds going to CARES Foundation. The team sported CARES' "1 in 10,000" emoji t-shirts and helped raise awareness of CAH by displaying posters and CARES' brochures.

THANK YOU SYDNEE & the Mt. Horeb Vikings!

22nd ANNIVERSARY GALA

Our 22nd Anniversary Gala was a huge success! What fun, to be a part of the first live gala in two years! It was a festive event indeed, held on June 4, 2022 at the iconic Sony Pictures Studios in Culver City, CA. Guests traveled from all across the country to help celebrate the CAH community and to honor this year's distinguished honorees:

VISIONARY AWARD
Karen Bogaard

PIONEER AWARD
Dr. Roger DeFilippo

CORPORATE PARTNER AWARD

NEUROCRINE® BIOSCIENCES

CARES also celebrated The CAREing Society. We recognize the outstanding generosity of these top donors. This group of donors has made a significant impact on CARES Foundation and the development of our Comprehensive Care Centers, research, education, and other programs and services. We wish to thank your society members for playing an integral role in the success of CARES.

Guests enjoyed a gourmet-catered meal & hors d'oeuvres by Wolfgang Puck, James Bond-themed specialty cocktails, the antics of a clever magician, both silent & live auctions, and mostly being together! THANK YOU TO EVERYONE WHO HELPED TO MAKE THIS NIGHT ONE TO REMEMBER!

The 7th Annual Clay Shoot for CARES took place on October 14, 2022 at Lehigh Valley Sporting Clays in Coplay, PA. Host, and long-time CARES supporter, Carlos DaSilva did not disappoint and everyone had a great time! Breakfast & lunch were served and trophies were awarded to Top Male Shooter, Top Female Shooter, & Top Foursome.

Thank you to our participants, our sponsors & underwriters, and to our host!

Other Ways to Support CARES

GIVING TUESDAY

"GivingTuesday is a Movement that Unleashes the Power of Radical Generosity Around the World."

It is because of your generosity that CARES Foundation enters its 3rd decade of service to the CAH community. Because of your monetary support, we have been able to help thousands upon thousands of patients, families, and healthcare providers. We hope that you will join this generosity movement and GIVE to CARES on November 29, 2022! (https://caresfoundation.app.neoncrm.com/donation.jsp?campaign=265&)

HOST A FACEBOOK FUNDRAISER!

Have you got a birthday coming up, or a wedding anniversary, retirement, or other special occasion? To honor this special event, try raising money for CARES on Facebook. It's easy to do and Facebook takes you through setting up a fundraiser step-by-step. They even published a guide for your convenience: https://tinyurl.com/pvub644a

Make sure to share your fundraiser and use hashtags to bring attention to the CARES community & others with CAH. (#caresfoundation, #congenitaladrenalhyperplasia, #CAH, etc.)

Please keep us in the know by tagging CARES Foundation in your fundraiser post!

Thank you to everyone who raised money for CARES so far this year!

If you've already hosted a Facebook fundraiser for CARES please let us know that too. We'd like to show our gratitude.

It's also a great way to RAISE AWARENESS!

amazonsmile
You shop. Amazon gives.

Every time you shop at AmazonSmile and select CARES Foundation as your charitable organization, Amazon will donate a portion of your purchase to our mission!

SHOP NOW at AmazonSmile

Congenital Adrenal Hyperplasia AWARENESS WALKS 2022

cares CONGENITAL ADRENAL HYPERPLASIA FOUNDATION

8TH ANNUAL CALIFORNIA

OCTOBER 2, 2022

Arcadia, California

It was a beautiful day in sunny, Southern California as members of the CAH community gathered to raise awareness of this rare disorder at the Santa Anita Racetrack & Park in Arcadia, CA on October 8th. Attendees were treated to official CA Walk t-shirts, refreshments, a silent auction with fabulous prizes, and injection training by the CAH healthcare team at Children's Hospital Los Angeles, as well as an opportunity to mix and mingle with other CAH affected people in the area.

A special thank you goes out to our walk host, Karen Bogaard, volunteers, the CHLA team, and all of our sponsors: Neurocrine Biosciences, Eton Pharmaceuticals, and The Bogaard Family!

5TH ANNUAL FLORIDA

OCTOBER 29, 2022

Sand Point Park, Titusville

What a fun day for members of the CAH community who gathered in Sand Point Park, Titusville, FL for the 5th Annual CAH Awareness Walk. Patients, families, supporters, numbering 50 people walked across the scenic Max Brewer Bridge with their special Walk t-shirts to raise awareness of this rare disorder. Attendees were treated to refreshments, entertainment, games and prizes!

A special thank you goes out to walk host, Lesley Holroyd, all the volunteers, and our sponsors: Neurocrine Biosciences, Eton Pharmaceuticals, and Lesley Holroyd!

Host a walk in your community this Spring! Email Dina@carefoundation.org for more info.

Continued from pg 8

What are the steps to participation?	 1) Science37 is partnering with Adrenas to conduct the prescreening study. The purpose of the prescreening study is to identify potentially eligible individuals for possible participation in the ADventure gene therapy trial but does not guarantee entry. The amount of time in the prescreening study can vary between participants. Participation in the prescreening study is not required for participation in the gene therapy clinical trial. 2) Once consented into the ADventure gene therapy trial, a participant can expect to receive a date for dosing. 3) If deemed eligible, the participant will receive Adrenas' investigational gene therapy. A brief hospitalization is required during dosing. Following dosing, participants will be followed for at least 5 years to assess safety and potential efficacy. After the first year, visit frequency will be reduced for the following 4 years. Participation is voluntary.
What should a person expect when participating in prescreening?	The purpose of the prescreening study is to identify potentially eligible individuals for possible participation in the ADventure gene therapy trial. Science37, a partner of the Advance-CAH team, will contact individuals and begin prescreening on the phone. Home visits and blood tests will confirm potential eligibility. If eligible for the prescreening study, the prescreening participants will be reevaluated periodically by Science37 to determine continued interest and eligibility, until a spot becomes available in the ADventure trial. Potentially eligible participants from the prescreening trial are considered for the investigational gene therapy trial based on the earliest date of a participant's first entry visit. Adrenas or Science37 is unable to provide the length of time in the prescreening study as it varies. Participants in the prescreening study can expect monthly telephone and/or monthly check-in communications from either Adrenas or Science37 team.
How is Adrenas' investigational gene therapy given?	Adrenas' investigational AAV gene therapy will be given in a single intravenous (IV or into a vein) dose. The bloodstream delivers many copies of the modified virus to cells throughout the body, including the adrenal gland. The dose or infusion is expected to take several hours.
Will there be any cost to participate in an Adrenas CAH gene therapy trial?	No, there will not be any cost to participants, or their family related to the investigational gene therapy. Travel, lodging, and other trial related expenses will be entirely paid for by Adrenas.

Adrenas is committed to keeping the CAH community informed as the trial progresses. Stay connected with the CARES Foundation or Adrenas at www.cahgenetherapy.com for current information and additional resources.

US—2200060 20221011

Diurnal

Steroid-sparing – The goal of CAH Therapy

It's been over 70 years since Philip Hench, Edward Kendall and Tadeus Reichstein won the Nobel Prize in medicine and physiology for the discovery of steroids including compound F, better known as cortisol or, when used as a medicine, hydrocortisone. (1,2) To this day it remains the mainstay of steroid treatment in CAH. The most common cause of CAH is 21-hydroxylase deficiency, accounting for 90-95% of cases.(3) The difficulty is that CAH poses two main problems to patients; inadequate cortisol levels and androgen (male hormone) excess. Cortisol is replaced with medicines known as glucocorticoids. These are a subset of steroids that act on the steroid receptor in the same way that cortisol does. Examples include hydrocortisone, prednisolone, prednisone and dexamethasone.

In order to control the excess (high) androgens, higher doses of steroids are frequently used but this can lead to poor health outcomes. The ideal scenario for therapy is to mimic physiological cortisol with replacement at the lowest possible dose. Diurnal have developed a modified-release form of hydrocortisone MR-HC (also known as "Chronocort" during development and called "Efmody" in Europe) that, when given twice daily, has been shown to mimic normal physiology. It is currently undergoing clinical trials in the USA but is already approved as a treatment for CAH in Europe and is the only licensed therapy that is accepted as a physiological replacement.

Steroid therapy is implemented in many patients for a variety of conditions. Therefore, the effects of higher or supraphysiological dosing is well documented - it is associated with significant morbidity.(4) Steroid-sparing is the drive to treat patients with the lowest possible dose, i.e. to use steroids sparingly. In CAH this means giving the least amount possible to ensure a patient is adequately replaced and this is a key target of therapy. Since hydrocortisone is cortisol, it is used to replace the missing hormone. However, it is hard to get the correct levels at the correct times. In CAH it is ideal to mimic the natural over-night rise in cortisol. This suppresses the ACTH hormone from the pituitary gland that drives excess androgens to be produced in the adrenal glands and so allows for a lower overall daily dose of steroid.

Currently, CAH patients are often given high dose long-acting steroids like prednisolone or dexamethasone at night or sometimes they wake in the middle of the night to take their morning dose of hydrocortisone in an attempt to suppress overnight androgen production. However, these actions usually fail to control the androgens and can lead to patients taking higher doses of steroids. A cross-sectional study of 244 CAH patients treated with hydrocortisone, prednisolone and dexamethasone and found only about 30% had a 17-OHP level within the normal range.(5)

Diurnal conducted a 6 month, randomized, phase 3 study comparing its modified-release hydrocortisone (MR-HC) with standard steroid therapy. Patients from this study could then continue to take MR-HC in an extension study. 122 patients were included, from 10 centers in 7 countries and were dose-matched at study start. Patients' doses were then changed (titrated) during the study by doctors who did not know which medicine the patients were on with the purpose of optimizing androgen control. At the end of the study both groups were on a higher dose of steroid (equivalent to hydrocortisone 30mg per day). 91 patients entered the extension study where all patients took MR-HC. Over a year the average daily dose of hydrocortisone was reduced to 20mg whilst also controlling androgen levels.(6) A study with MR-HC is recruiting patients aged over 16 years in the US to help support a license application to the FDA.

The consequences of higher dose steroid therapy are seen both inside and outside the endocrine system, in the brain, skin, muscles, bones and cardiovascular systems.(7) Long-term steroid treatment can suppress growth leading to short stature in adults. Doctors in Minneapolis have shown a relationship between the daily hydrocortisone dose for a young adult and their predicted adult height.(8) Steroid sparing may allow patients to achieve their height potential. Other effects of steroids include changes to bone formation and structure that may lead to an increased fracture risk.(9) A review of 20 studies of steroid-treated CAH patients revealed an increased prevalence of cardiometabolic risk factors like hypertension, obesity and insulin resistance.(10) A recent study from NIH in Washington (2021) demonstrated that patients develop these cardiometabolic risk factors at a young age and they recommend judicious use of steroids.(11) A literature review conducted by Woods (2021) revealed that patients who are over-treated with steroid therapy have significantly worse health-related quality of life outcomes.(12)

In conclusion, although steroids are vital and lifesaving for patients with CAH, they come with side effects and these side effects associated with CAH therapy may be significantly reduced or improved with steroid-sparing treatment.

References

1.Burns CM. The History of Cortisone Discovery and Development. Rheum Dis Clin North Am. 2016 Feb;42(1):1-14, vii. doi: 10.1016/j.rdc.2015.08.001. PMID: 26611547.

2.Cooney, WP. (2013). Compound F: The History of Hydrocortisone and Hand Surgery. The Journal of Hand Surgery. 38(4), pp.774-778. [Online]. Available at: https://doi.org/10.1016/j.jhsa.2012.12.025. [Accessed 7 October 2022].

3.Podgórski R, Aebisher D, Stompor M, Podgórska D, Mazur A. Congenital adrenal hyperplasia: clinical symptoms and diagnostic methods. Acta Biochim Pol. 2018;65(1):25-33. doi: 10.18388/abp.2017_2343. Epub 2018 Mar 15. PMID: 29543924.

4.Kruh J, Foster CS. Corticosteroid-sparing agents: conventional systemic immunosuppressants. Dev Ophthalmol. 2012;51:29-46.doi: 10.1159/000336185. Epub 2012 Apr 17. PMID: 22517202.

5.Finkielstain, G.P et al. (2012). Clinical Characteristics of a Cohort of 244 Patients with Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 97(12), pp.4429-4438. [Online]. Available at: 10.1210/jc.2012-2102 [Accessed 10 October 2022].

6.Deborah P Merke, Ashwini Mallappa, Wiebke Arlt, Aude Brac de la Perriere, Angelica Lindén Hirschberg, Anders Juul, John Newell-Price, Colin G Perry, Alessandro Prete, D Aled Rees, Nicole Reisch, Nike Stikkelbroeck, Philippe Touraine, Kerry Maltby, F Peter Treasure, John Porter, Richard J Ross, Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia, The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 5, May 2021, Pages e2063–e2077, https://doi.org/10.1210/clinem/dgab051

7.Merke, M.D. and Auchus, R.J. (2020). Congenital adrenal hyperplasia due to 21-Hydroxyylase deficiency. The New England Journal of Medicine. 383, pp.1248-61. [Online]. Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMra1909786 [Accessed 10 October 2022].

8. Sarafoglou K et al. Journal of Pediatrics. 2014; 164(5):1141-6.e1

9.Rangaswamaiah, S. et al. (2020). Bone Mineral Density in Adults With Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. Frontiers in Endocrinology. 11, pp.1664-2392. [Online]. Available at: https://www.frontiersin.org/articles/10.3389/fendo.2020.00493/full [Accessed 10 October 2022].

1.Tamhane, S. et al. (2018). Cardiovascular and Metabolic Outcomes in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 103(11), pp.4097-4103. [Online]. Available at: https://academic.oup.com/jcem/article/103/11/4097/5107761?login=true [Accessed 10 October 2022].

2.Torky A, Sinaii N, Jha S, Desai J, El-Maouche D, Mallappa A, Merke DP. Cardiovascular Disease Risk Factors and Metabolic Morbidity in a Longitudinal Study of Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2021 Nov 19;106(12):e5247-e5257. doi: 10.1210/clinem/dgab133. PMID: 33677504; PMCID: PMC8864751.

Matthew Stephen Woods, MSc; BA, Helen Coope, PhD, Kamran Maskin, BSc, MBA, Lotta Elisabet Parviainen, PhD, John Porter, MD, Michael Withe, MSc, Uzmah Sabar, PhD, The Burden of Illness of Congenital Adrenal Hyperplasia (CAH) in Adults: Results: of a Structured Literature Review, Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Pages A96–A97, https://doi.org/10.1210/jendso/bvab048.193

- Insurance Specialists can help you get coverage for ALKINDI SPRINKLE and support you through any insurance changes. In the first half of 2022, 95% of ALKINDI SPRINKLE prescriptions were successfully approved by insurance carriers
- While the prior authorization process is taking place, medication can be provided to the patient's home in as soon as 24 hours through the QuickStart Program

*Restrictions, limitations, and/or eligibility requirements apply

For more information and dosing tips, visit https://www.alkindisprinkle.com/patient/support/

USE INFORMATION

ALKINDI SPRINKLE is a prescription medicine used in children from birth to less than 17 years old as replacement therapy when the adrenal gland is not making enough cortisol.

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.

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.

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.

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

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. 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

Please see full Prescribing Information for more information. 1220-v1

Alkindi Sprinkle (hydrocortisone) oral granules

The CAHtalyst Studies are looking at whether an investigational medication, crinecerfont, is safe and effective in treating individuals with classic CAH. Crinecerfont is thought to prevent corticotropin-releasing factor (CRF) from binding to its receptor, which may reduce the high levels of adrenocorticotropic hormone (ACTH) and adrenal androgens that can cause problems for patients with CAH. This reduction of adrenal androgens could allow lower dosing of glucocorticoids. Chronic treatment with high glucocorticoid doses can cause side effects and complications.

ALL PARTICIPANTS WILL:

- Receive close follow-up by an expert endocrinologist
- Continue their current treatment with adjustment of glucocorticoid dose as appropriate
- Receive trial-related medical exams and laboratory tests at no cost, with reimbursement for trial-related travel

CAHtalyst STUDY

- Adults 18 years of age or older with classic CAH and a stable glucocorticoid dose regimen
- Expect up to 21 visits over about 1.5 years that can be performed at the trial site or at home
- Approximately 23 sites across the US
- Participants will be asked to take crinecerfont or a placebo (contains no active medicine) twice a day for the first 6 months of the trial
- All participants will be eligible to receive crinecerfont for 1 year after the initial 6-month treatment period
- After completion of the 18-month trial, all participants will have the option to continue taking crinecerfont during an open-label extension treatment period

CAHtalyst pediatric study

- Children and adolescents between 2 and 17 of age with classic CAH and a stable glucocorticoid dose regimen
- Expect up to 14 visits over about 1 year that can be performed at the trial site or at home
- Approximately 21 sites across the US
- Participants will be asked to take crinecerfont or a placebo (contains no active medicine) twice a day for the first 6 months of the trial
- All participants will be eligible to receive crinecerfont for 6 months after the initial 7-month treatment period
- After completion of the 52-week trial, participants will have the option to continue taking crinecerfont during an open-label extension treatment period

YOU CAN FIND OUT MORE ABOUT EACH TRIAL AT CAHPROGRAM.COM

sprucebiosciences

EXPLORE THE POSSIBILITY OF CHANGING YOUR CLASSIC CAH JOURNEY

CAHmelia 203·204

There have been no new treatment options for classic Congenital Adrenal Hyperplasia (CAH) since the 1950's.

About the Clinical Trial

A randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of tildacerfont in adults with classic congenital adrenal hyperplasia, followed by an open-label treatment with tildacerfont. The sponsor of this clinical trial is Spruce Biosciences.

Trial Purpose

The primary purpose of the CAHmelia program is to assess if tildacerfont is effective in lowering androgens (testosterone-related hormones) and daily glucocorticoid doses in adults with classic CAH. The CAHmelia studies are dedicated to exploring solutions for people living with classic CAH.

About Tildacerfont

Tildacerfont is a type of oral, once-daily investigational drug that is NOT a steroid. By reducing the amount of androgens (testosterone-related hormones) your body makes, tildacerfont may improve your classic CAH symptoms. This investigational drug will not replace your steroid treatment but may allow you to manage your condition with lower steroid doses.

Population

Adults at least 18 years of age with classic CAH (including salt-wasting and simple virilizing) taking steroids daily (glucocorticoids with or without mineralocorticoids).

To learn more about the CAHmelia program:
- visit us at www.CAHstudy.com
- email CAHmelia@sprucebiosciences.com

Scan to learn more

A survey of 113 CAH participants stated that they do not feel sufficiently informed about their treatment:

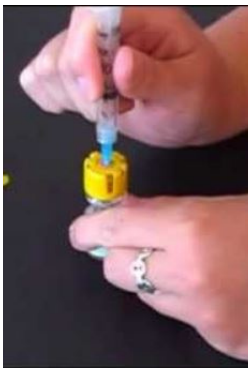
51% of participants felt they did not have enough access to information to make an informed choice about GC treatment

66% of participants are willing to change their current regimen if they could lower their dose of steroid

Data on file Spruce Biosciences participant survey 2022

Email link here: CAHmelia@sprucebiosciences.com

Being Denied Solu-Cortef Coverage?



We have heard complaints about patients being denied coverage for their Solu-Cortef medication. This may be because insurance companies are classifying it as a medical benefit (medical device) and not under pharmacy benefits/prescription coverage.

If you are denied coverage, you need to speak to your insurance company's medical director (not an administrator).

A medical director can appreciate that this medication is for emergency, life-saving purposes, and would be injected by the patient/parent.

It is important that you communicate directly with a medical director who will understand the urgency of your request. Filling out a form will not suffice. Please let us know if you are experiencing difficulty with coverage denial. Email Dina@caresfoundation.org.

NOTEWORTHY

Dr. Richard Rink Awarded the Pediatric Urology Medal

The American Academy of Pediatrics (AAP) Section on Urology (SOU) awarded the 2022 Urology Medal to Dr. Richard Rink, at the Pediatric Urology Fall Congress in Las Vegas, October 20-23, 2022.

Dr. Richard Rink is a pediatric urologist at Riley Hospital for Children at Indiana University Health and a member of the faculty at the Indiana University School of Medicine since 1985. He is also Surgical Director of Riley's Comprehensive Care Center for CAH.

There is only one recipient in the world of this award annually and it is considered the highest award you can receive in Pediatric Urology. It is essentially a lifetime achievement award. First awarded in 1984, Dr. Rink is the 38th recipient in his specialty.

CONGRATULATIONS, DR. RINK!

Dr. Mitchell Geffner, CHLA Wins Prestigious Award

Dr. Mitchell Geffner, a pediatric endocrinologist at Children's Hospital Los Angeles (CHLA) and Co-Medical Director of CHLA's Comprehensive Care Center for CAH, one of CARES-designated Centers of Excellence was awarded the International Outstanding Clinician Award by the European Society for Paediatric Endocinology (ESPE).

This award recognizes an outstanding contribution and lifetime commitment to the practice of clinical paediatric endocrinology in a country outside Europe and the Mediterranean basin. The award aims to strengthen the relationship between ESPE and its sister societies and to acknowledge excellence in paediatric endocrinology around the world.

Dr. Geffner traveled to Rome to accept his award which was conferred during a presentation ceremony at the ESPE annual meeting September 15-17, 2022.

CONGRATULATIONS, DR. GEFFNER!

THE DOCTOR IS IN

Dr. Karen Lin Su

CARES Medical Director

Tips for Fall/Winter 2022

Respiratory Conditions

Covid, the common cold, the flu, and even seasonal allergies may have similar symptoms.

How to tell the difference:

Symptom	Covid-19	Cold	Flu	Allergies
Cough	Common	Common	Common	Sometimes
Muscle aches	Common	Sometimes	Common	Never
Fatigue	Common	Sometimes	Common	Rare
Sneezing	Rare	Common	Common	Common
Sore throat	Common	Common	Common	Rare
Runny/stuffy nose	Common	Common	Common	Common
Fever	Common	Sometimes	Common	Never
Shortness of breath	Common	Never	Sometimes	Never
Diarrhea	Sometimes	Never	Sometimes	Never
Nausea/Vomiting	Sometimes	Never	Sometimes	Never
New loss of taste or smell	Common (without stuffy nose)	Sometimes (stuffy nose)	Sometimes (stuffy nose)	Sometimes (stuffy nose)

Flu and Covid Prevention

- Early fall is the time to start thinking about immunizing your child against the influenza virus, which causes the "flu." Because any severe illness can precipitate an adrenal crisis in individuals with CAH, it is better to be protected ahead of time. Speak to your primary care doctor about the flu vaccine, which is inactivated and cannot cause influenza. It is safe for administration in individuals with CAH.
- Speak to your doctor about Covid vaccination and/or booster dose(s).
- Avoid close contact with anyone who is sick.
- When coughing or sneezing, cover your mouth and nose with a tissue. Wash your hands frequently, and avoid touching your eyes, nose, and mouth, which are susceptible areas for germs to enter the mucous membranes.
- Stay hydrated, get enough sleep, and try to eat a nutritious, well-balanced diet.

Stress-dosing when sick

Stress-dosing is not needed for minor illnesses, such as a common cold, if there is no fever.

Febrile illnesses:

- -For fever <102 degrees F, double the usual total daily amount of hydrocortisone and and divide into 3-4 equal doses. Doses should be given every 6-8 hours until the fever is gone. For specific dosing instructions, ask your endocrinologist.
- -For fever ≤102 degrees F, give three times the usual total daily amount of hydrocortisone and divide into 3-4 equal doses. Doses should be given every 6-8 hours until the fever is gone. For specific dosing instructions, ask your endocrinologist.
- Vomiting:
  -For a one-time episode of vomiting, repeat the dose if vomiting occurred within one hour of taking an oral dose of hydrocortisone. Otherwise, monitor for continued vomiting. If vomiting persists and you are unable to hold anything down by mouth, then give injectable hydrocortisone (Solu-Cortef) as instructed by your endocrinologist and go to the emergency room.

Trauma

Trauma can occur at any time, but icy roads and participation in winter sports create more opportunities for accidents to occur. Be prepared for trauma by making sure you or your child is s wearing a Medical Alert bracelet and Solu-Cortef is easily accessible at all times.

Travel

Be sure to keep handy plenty of fluids and snacks, extra medication, Solu-Cortef, and a letter from your doctor explaining your medical condition and what treatment you require. It may be helpful to obtain the name of a local doctor and hospital in case of an emergency. Please see our "Traveling with CAH/AI Packet" (https://tinyurl.com/4axwjjmc).

Stress-dosing for outpatient procedures

Always consult with your endocrinologist regarding the need for stress-dosing for outpatient procedures. However, here are some general guidelines:

- Procedures that are performed under local anesthesia, such as dental work, do not require any additional hydrocortisone.
- Procedures performed under sedation usually warrant stress-dosing prior to the procedure, but generally do not require additional hydrocortisone after the procedure if able to go home.
- Procedures performed under general anesthesia will require IV hydrocortisone prior to the procedure as well as during the procedure if it lasts 2 hours or longer. Additional stress-dosing after the procedure will depend on the patient.

ADVOCACY

We can't stress enough the importance of a visit to your local EMS station. Not only will you be assuring that you as a CAH patient or parent, relative, or caregiver of a child with CAH will get the emergency care you need in a time of crisis, but you will also help pave the way, be an advocate, for other adrenal insufficient/CAH people who may be in need of the same care.

We have observed that the more EMS stations that adopt proper CAH and AI protocols, the more others take note and realize that their stations need the same protocols in place.

It's simple, and CARES provides you with the tools and tips you need for a successful visit. Please take a few moments to visit our EMS Campaign page on our website: https://caresfoundation.org/advocacy-ems-campaign/.

We continue to update our state protocols as they appear. The most recent protocols can be found on the EMS campaign page linked above.

If you need assistance, please contact our Program Coordinator, Odaly Roche: Odaly@caresfoundation.org.

PLEASE MAKE SURE TO ALWAYS WEAR/CARRY MEDICAL IDENTIFICATION. Make sure that emergency personnel know you are adrenal insufficient and have CAH!
For more information including I.D. resources and what exactly your I.D. should say, visit our website: https://caresfoundation.org/be-prepared-in-an-emergency/

cares SUPPORT

Support Group Leaders

Did you know that CARES recruits and trains Support Group Leaders to help the CAH community in times of need? There are currently 54 support group leaders around the country, as well as 16 international leaders and a Spanish-speaking leader here in the U.S. That's a total of 72 CAH community members ready and willing to support you on your CAH journey.

Please visit our support pages on our website to see if there is a leader in your area.
https://caresfoundation.org/support/

Leaders are also organized by topics like "Women", "Teens & Young Adults", "Parents of Newborns", "Parents of Teens & Young Adults", "Men", etc. We hope that you will take advantage of this program. We appreciate our leaders and know that they are there for you when you need extra support!

We appreciate our leaders and know that they are there for you when you need extra support!

We welcome our newest leader, Candice Johannssen in Canada!

Support Group Meetings

Don't forget to check out our monthly, bi-monthly, & regularly scheduled Support Group Meetings. These meetings are hosted on Zoom and there is always a CAH-expert medical professional 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 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/).

Please visit our support pages on our website to see if there is a leader in your area.
https://caresfoundation.org/support/
Support can also be found on Facebook on our group page:

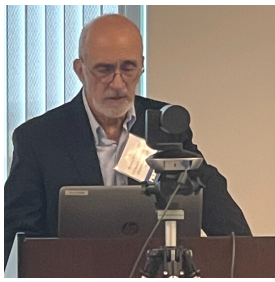
CAH Champions (Congenital Adrenal Hyperplasia Support Network).

Here you will find several secret groups where members share stories and experiences.

We remind you not to give medical advice here. All medical questions should be addressed by a physician or other healthcare professional. We offer a Ask-the-Expert program on our website where you can email your questions/concerns to our Medical Director, Dr. Su, via email. https://caresfoundation.org/ask-the-expert/

EDUCATION

Our first in-person education conference in two years, was held on October 8, 2022 in Fort Worth, TX. Patients, parents, relatives, medical professionals & industry representatives gathered at a Cook Children's medical building to attend a variety of sessions on topics that included: "Adulthood Psychosocial Challenges", "Family Planning and Fertility", "Behavioral Issues in Teens", "Long Term Effects of CAH", and many more.



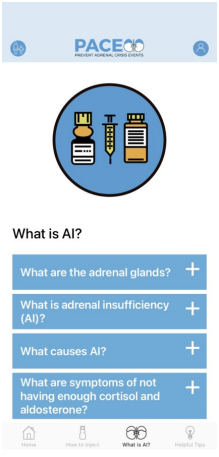
cares CONGENITAL ADRENAL HYPERPLASIA FOUNDATION
PATIENT EDUCATION CONFERENCE 2022
Patient-Centered CAH Care
Cook Children's Health Care System

Attendees were served both breakfast and lunch, had an opportunity to attend injection training, and to make connections with other people in the CAH community.

We'd like to extend our gratitude to Cook Children's for hosting this important event as well as all of our presenters and our sponsors:
Neurocrine Biosciences, Eton Pharmaceuticals, Adrenas Therapeutics (a BridgeBio company), Spruce Biosciences, Diurnal, Crinetics and Halozyne.

PACE App

Preventing Adrenal Crisis Events



The new PACE app is now 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.

To download the app, click here: "PACE by ChaiCore". (Apple) There are both iPad and iPhone options. Also available for Android devices.

You will need a code from CARES to access the app. If you have already joined the CARES community, please email us to request that code. To join our community, click here. (https://caresfoundation.org/join-the-cares-community/) It takes only a few minutes, and it's free!

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 Courtney@caresfoundation.org.

www.CARESFoundation.org

CARES Foundation, Inc.
2414 Morris Ave, Ste 110
Union, NJ 07083

Phone: (908) 364-0272 Toll Free: (866) CARES37
Fax: (908) 686-2019
Email: contact@caresfoundation.org

COMPREHENSIVE CARE CENTERS for CAH

Centers of Excellence

If you are seeking expert CAH medical care, then plan a visit to one of 8 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
1935 Medical District Dr
Dallas, Texas 75235

For appointments, contact Merritt Lamm or Emily Silva, (214) 456-5980
VISIT WEBSITE

Children's Hospital Los Angeles
4650 Sunset Blvd
MS #61
Los Angeles, CA 90027

University of Southern California/Keck Medical Ctr
8700 Beverly Blvd
Los Angeles, CA 90048

For appointments contact: Janet Guerrero, Comprehensive Care Center Coordinator, 323-361-4630
janguerrero@chla.usc.edu

VISIT WEBSITE

Children's Hospital of Philadelphia/ Main Hospital
3401 Civic Center Blvd.
Philadelphia, PA 19104
Penn Med – Philadelphia, PA

For appointments, 215-590-3174
VISIT WEBSITE

Cook Children's Medical Center
801 7th Avenue
Fort Worth, TX 76104

VISIT WEBSITE

New York-Presbyterian/Weill Cornell Medical Center
525 E 68th St,
New York, NY 10065

646) 962-3442, Option 1
Email, Attn: Koree Richardson, Coordinator
kor2005@med.cornell.edu

VISIT WEBSITE

Riley Hospital for Children/ Indiana University Health
705 Riley Hospital Dr
Indianapolis, IN 46202

Comprehensive Care Center Coordinator – Heather Frady, RN - Email Heather Frady
(317) 412-1206
VISIT WEBSITE

Seattle Children's Hospital and University of Washington Medical Center
4800 Sand Point Way NE
Seattle, WA 98105

For appointments: (206)987-0304 or toll free, (866)987-2000
VISIT WEBSITE

Rutgers-Robert Wood Johnson Medical School (RWJMS), Child Health Center of New Jersey (CHINJ)
200 Somerset Street
New Brunswick, NJ 08901

VISIT WEBSITE

VISIT OUR CENTERS OF EXCELLENCE WEBPAGE FOR MORE INFORMATION: https://caresfoundation.org/centers-of-excellence/

We are fast approaching the Giving Season and we hope that you will consider CARES Foundation in your giving plans this year!

With your help, we can reach even higher to improve the lives of the CAH community.

We hope you have a joyous Holiday Season!