wjpmr, 2025, 11(9), 152-160

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

SJIF Impact Factor: 6.842

Review Article

ISSN (O): 2455-3301

ISSN (P): 3051-2557

ADVANCES IN PRECISION DIAGNOSTIC MEDICINE AND EMERGING THERAPEUTICS FOR CONGENITAL ADRENAL HYPERPLASIA (CAH) DUE TO STEROID 21-HYDROXYLASE DEFICIENCY: A MINI REVIEW

Ashraf T. Soliman[1]*, Vincenzo De Sanctis[2], Fawzia Alyafei[1], Shayma Elsayed[3], Dina Fawzy[3], Ahmed Elawwa[3], Nada Alaaraj[1], Noor Hamed[1], Nada Soliman[4] and Ahmed Khalil[5]

[1]Department of Paediatrics, Hamad General Hospital, Doha, Qatar.
[2]Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy.
[3]Department of Pediatrics, University of Alexandria Children Hospital, Alexandria, Egypt.
[4]Department of Public Health, North Dakota State University, ND, USA.
[5]Department of Pharmacy, Hamad General Hospital, Doha, Qatar.

***Corresponding Author: Dr. Ashraf T. Soliman**

MD, PhD, FRCP, Department of Paediatrics, Hamad General Hospital, Doha, Qatar.

Article Received on 01/07/2025 **Article Revised on 22/07/2025** **Article Accepted on 12//08/2025**

ABSTRACT

Background: Congenital genital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (21-OHD) is a difficult endocrine condition. This results in decreased secretion of cortisol and aldosterone, accompanied by an increase in adrenal androgen secretion as a compensatory mechanism. CAH presents with a wide range of clinical manifestations. Although glucocorticoid (GC) and mineralocorticoid (MC) treatment regimens have been proven to be effective, many patients still struggle to strike a balance between managing their condition and avoiding overtreatment side effects such as slow linear growth and an elevated risk of developing metabolic syndrome. New treatments and increased diagnostic accuracy could revolutionize CAH management strategies. **Objectives:** The objectives of this mini-review are to: (a) assess the diagnostic precision of traditional hormonal biomarkers such as 17-hydroxyprogesterone (17-OHP), androstenedione, testosterone, and DHEAS; (b) provide an overview of recent developments in steroid-sparing medications and gene-targeted therapies and (c) assess their clinical influence on the Prognosis of children with CAH. Methods:. Using PubMed, Scopus, Web of Science, and Clinical Trials. gov databases, a systematic literature review was carried out. The inclusion criteria included research on children and adolescents with genetically and/or clinically confirmed 21-OHD, conducted between 2000 and 2025. Research was considered eligible if it included information on hormone levels**,** treatment results, and emergent treatment trial design. Editorials, case reports and non-human research were among the exclusion criteria. The data are presented as a narrative review. **Results:** To maximize treatment, hormone monitoring with 17-OHP, androstenedione and testosterone is crucial. The most consistent and dependable biomarker for disease management is androstenedione. Age-appropriate norms for testosterone androstenedione (0. 3–1. 5 nmol/L) and 17-OHP (12–36 nmol/L) are all considered adequate treatment ranges. Corticotropin-releasing factor receptor 1 antagonists (CRF-1) such as crinecerfont and tildacerfont have been shown to minimize glucocorticoid exposure and significantly reduce ACTH-driven adrenal androgen production. In pediatric trials, the recently FDA-approved crinecerfont demonstrated a strong ability to lower 17O-HP and androstenedione. Gene-targeted treatments have advanced to preclinical or early clinical stages, including mRNA–LNP platforms, CRISPR/Cas9 editing, and AAV–CYP21A2 vectors. Despite the limited effectiveness of BBP-631 gene therapy, recent research supports the potential for adrenal-directed gene correction. **Conclusion:** Advances in steroid-sparing agents and modified biomarker-guided monitoring are improving the precision of CAH management. More clinical value can be obtained from androstenedione as a monitoring tool. While gene therapy may offer future curative potential, CRF1 antagonists show promise in the near term to lessen the burden of GC. For kids and teenagers with CAH, a shift to customized mechanism-targeted treatment plans is essential to enhancing endocrine stability and growth outcomes.

KEYWORDS: Androstenedione, crinecerfont, congenital adrenal hyperplasia 21-hydroxylase deficiency, gene therapy, and pediatric endocrinology.

1. INTRODUCTION

The most common form of congenital adrenal

hyperplasia (CAH) is 21-hydroxylase deficiency (21-OHD) is the most common inborn error in adrenal function and the most common cause of adrenal insufficiency in the pediatric age group. This enzymatic abnormality causes excessive adrenal androgen synthesis and reduces the production of cortisol and frequently of aldosterone.[1] The clinical spectrum is quite diverse, from salt-wasting crises in infancy to hyperandrogenism, premature puberty/adrenarche, precocious puberty, clitoromegaly rapid growth, and accelerated skeletal maturation (simple virilizing CAH) to late-onset hyperandrogenism, generally manifested either in the peri-pubertal stage or during adulthood (non-classical CAH).[2]

In order to control androgen excess and suppress adrenocorticotropic hormone (ACTH), management depends on lifelong glucocorticoid and if required, mineralocorticoid replacement therapy.[3] Achieving an ideal hormonal balance still presents significant obstacles even with standardized treatment plans. While excessive glucocorticoid treatment carries the risk of reduced or arrested growth velocity, metabolic syndrome, and decreased bone mass, on the other hand, inadequate therapy may result in poor growth outcomes, early puberty, and compromise of final height.[4] Therefore, careful clinical and biochemical monitoring is necessary to customize treatment.

The assessment of disease control relies on key biomarkers such as testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone (17-OHP).[5] It is still challenging to establish generally recognized reference ranges for these markers in pediatric populations because of assay heterogeneity, age-dependent variability, and irregular sample collection timing.[6]

The significance of pre-dose measurements in the morning and the dependence on stable markers like androstenedione in addition to 17-OHP are highlighted in recent studies that support standardized monitoring procedures.[7]

Meanwhile, treatments other than glucocorticoid monotherapy have gained popularity, by directly suppressing ACTH, new pharmacologic options like corticotropin-releasing factor type- 1 (CRF-1) receptor antagonists like crinecerfont and tildacerfont seek to reduce the need for high glucocorticoid doses.[8]

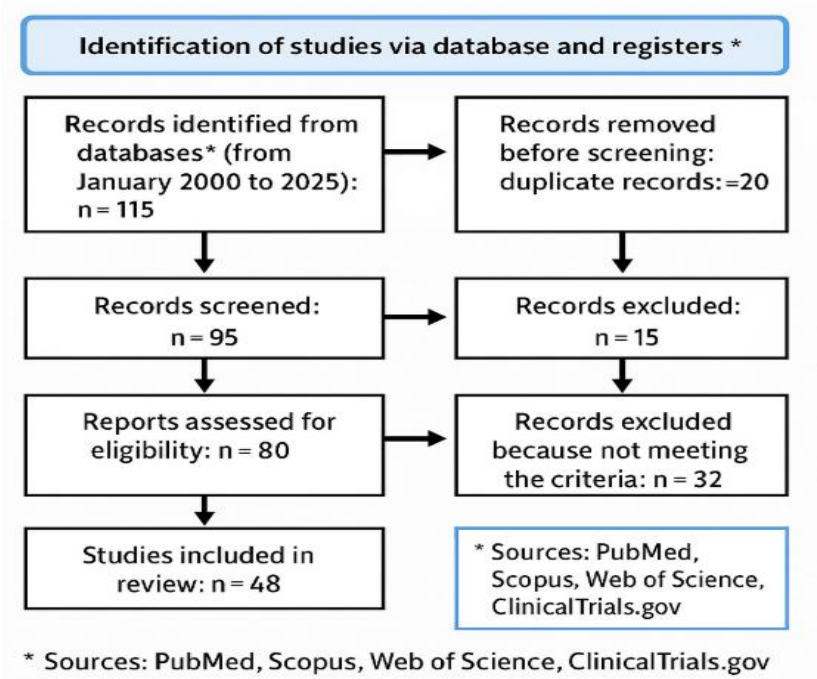
A possible future shift toward curative strategies is also provided by preclinical developments in gene and mRNA-based therapies.[9] When combined these advancements highlight the necessity of reevaluating CAH treatment options as well as diagnostic approaches.

The purposes of this mini review are to summarize basic information on: (a) personalized precision diagnostic medicine and suitable hormonal thresholds for tracking pediatric CAH; (b) the latest developments in treatment strategies, and (c) clinical implications of these developments on disease management and long-term results.[10]

2. MATERIALS AND PROCEDURES

a. Research design

As a structured and narrative synthesis of published literature, this mini-review was carried out in accordance with PRISMA scoping review guidelines **(Table 1).**



Figur 1: "PRISMA Flow Diagram for Study Selection (2000–2025): Systematic Review of Eligible Publications from PubMed, Scopus, Web of Science, and ClinicalTrials.gov.

It documents the number of duplicates removed, the total records screened, and those excluded based on title/abstract. It then details the number of full-text articles assessed for eligibility and those excluded for reasons such as not meeting inclusion criteria or being in a non-English language. Finally, it highlights the number of studies included in the qualitative or quantitative synthesis, offering a transparent overview of the selection and filtering process.

b. Inclusion criteria

(i) Research on children or teenagers (less than 21 years old) who have had a diagnosis of 21-hydroxylase deficiency (classic or non-classic CAH) that clinically or genetically verified and samples including at least 20 patients (ii) acceptable or target ranges for at least one biomarker, such as DHEAS, testosterone, androstenedione or 17-OHP; (iii) clinical trials or cohort studies assessing novel treatments like gene-based interventions, crinecerfont or tildacerfont; (iv) peer-reviewed indexed journal, and (v) articles published only in English language.

c. *Exclusion criteria*

(i) Animal research except preclinical therapeutic models for CRF-1 antagonists or gene therapy; (ii) research with no actionable information on hormonal cutoffs or treatment results; (iii) editorials case studies, letters to editors, and commentary that lack hormonal data; (iv) datasets published twice, with the most recent version being kept.

3. Data extraction and statistics

Two separate reviewers manually extracted the data into Excel. Disputes were settled by consensus. The study design included: age, sex, and genotype, intervention specifics, hormone targets, and clinical results. The acceptable hormonal cutoffs (mean, median, and range values) were compiled using descriptive statistics. Heterogeneity was observed in the pooling and, when feasible, cross-country comparison of prevalence data for acute and chronic complications.

4. Ethical considerations

All the information presented came from primary studies that were ethically approved and made available to the public. The review was conducted by the International Committee of Medical Journal Editors (ICMJE) guidelines and ethical standards for secondary research. •To check for possible bias, conflicts of interest, and funding disclosures were examined in every included study.

5. RESULTS

The results of this review encompass a comprehensive synthesis of clinical, biochemical, genetic, and therapeutic findings from studies on congenital adrenal hyperplasia (CAH), with a particular focus on 21-hydroxylase deficiency **(Table 1).** The table outlines target hormone levels for tracking CAH treatment. The most trustworthy indicator for disease management is androstenedione. As long as androstenedione levels are normal, moderate increases in 17-OHP are acceptable. While DHEAS is mostly supportive and has limited utility, testosterone needs to be closely watched to prevent early virilization.

Table 1: Hormonal monitoring cutoffs in pediatric subjects with congenital adrenal hyperplasia (CAH), including normal vs accepted treatment ranges.[3,11-18]

Hormonal assays	Normal range (Age-appropriate)	Accepted ranges during the treatment (nmol/L)	Clinical significance
17- OHP	< 6 nmol/L	12–36 nmol/L (up to 50 was tolerated if androstenedione was considered normal)	Full normalization unnecessary; < 12 nmol/L may reflect overtreatment, > 50 nmol/L suggests under-treatment
Androstenedione	0.3–1.5 nmol/L (age/sex-specific)	0.3–1.5 nmol/L	Most stable indicator of adrenal suppression; elevated levels associated with virilization
Testosterone (Prepubertal)	< 0.17–0.69 nmol/L	< 0.69 nmol/L	Elevated testosterone may indicate early virilization; requires monitoring and dose adjustment
DHEAS	0.54–2.7 µmol/L (age-specific)	Not defined.	Weak correlation with disease activity; not reliable for routine monitoring

The table outlines target hormone levels for tracking CAH treatment. The most trustworthy indicator for disease management is androstenedione. As long as androstenedione levels are normal, moderate increases in 17-OHP are acceptable. While DHEAS is mostly supportive and has limited utility, testosterone needs to be closely watched to prevent early virilization.

Figure 1 This bar chart visually compares the **normal ranges (green)** and **treatment target ranges (blue)** for key adrenal and androgenic hormones—**DHEAS, testosterone (prepubertal), androstenedione, and 17-hydroxyprogesterone (17OHP)**—commonly monitored in patients with **congenital adrenal hyperplasia (CAH)**. While DHEAS, testosterone, and androstenedione have narrow normal and treatment ranges, **17OHP has a substantially broader therapeutic range**, extending up to ~35 nmol/L, indicating a wider acceptable fluctuation during treatment. This reflects the clinical tolerance for elevated 17OHP levels during glucocorticoid therapy compared to other hormones.

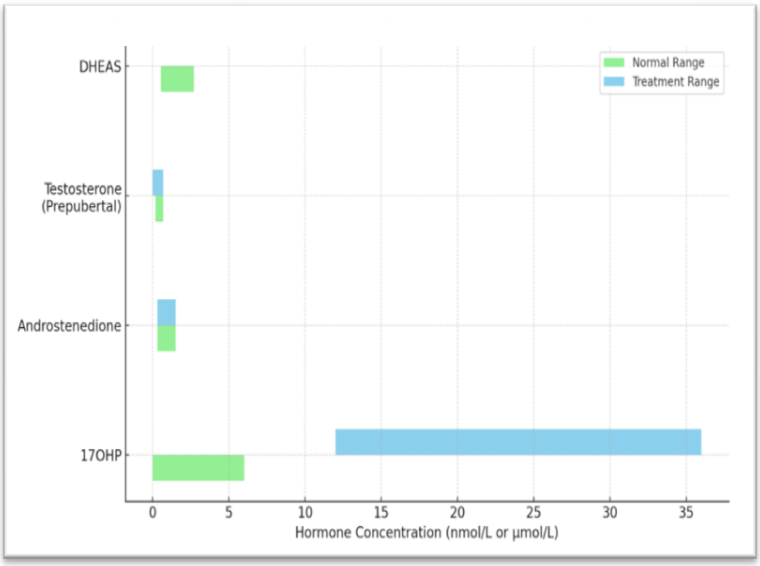


Figure 1: Target hormonal cutoffs over time in pediatric congenital adrenal hyperplasia (CAH).

Figure 2 illustrates the pharmacodynamic profiles of various glucocorticoid (GC) regimens used in the treatment of CAH based on cortisol levels over 24 hours:

- **Conventional GC therapy (green line)** shows a rapid peak shortly after administration, followed by a steep decline, leading to periods of both overexposure and underexposure, which can contribute to adverse effects and poor hormonal control.
- **41-hydroxy hydrocortisone** (purple line) displays a smoother peak and slower decline, indicating more physiological mimicry of cortisol rhythm, though still with suboptimal suppression later in the cycle.
- **Direct GC + Mineralocorticoid (MC) replacement (red line)** offers moderate cortisol elevation but still shows a declining pattern that may inadequately suppress ACTH for a full day.
- **Infusion GC therapy (blue line)** achieves a stable cortisol level with minimal fluctuation, closest to the physiological circadian rhythm, and is potentially most effective for continuous ACTH suppression and adrenal androgen control.
- **Direct GC + Pro-opiomelanocortin (POMC) antagonist (dashed orange line)** demonstrates a flatter cortisol curve, implying ACTH suppression independent of cortisol peaks, highlighting a novel mechanism that may allow lower GC doses.

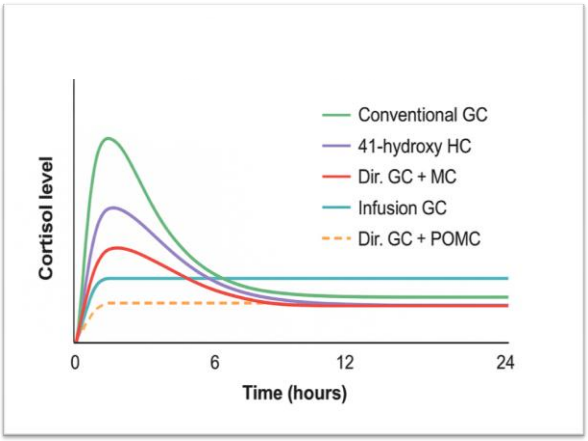


Figure 2: Therapeutic regimens and cortisol profiles in pediatric congenital adrenal hyperplasia (CAH).

The effectiveness of several glucocorticoid (GC) regimens used to treat congenital adrenal hyperplasia (CAH) is contrasted in the bar chart **(Figure 3),** emphasizing how well they can suppress ACTH and replicate physiological cortisol patterns. With a cortisol profile that closely mimics the natural diurnal rhythm and provides superior ACTH suppression, continuous GC infusion exhibits the most stable and sustained profile. Although it still doesn't fully mimic the circadian rhythm, modified-release hydrocortisone (41-hydroxy HC) produces smoother peaks than traditional GC. The efficacy of direct GC combined with mineralocorticoid (MC) and POMC-targeted therapy is moderate, whereas standard GC monotherapy exhibits varying peaks and

troughs, which indicates inadequate hormonal regulation. The addition of more recent POMC-based techniques points to promising pathways for ACTH suppression that may require fewer GC dosages. In managing CAH, this graphic summary emphasizes the therapeutic necessity of striking a balance between physiological hormone replacement and efficacy.

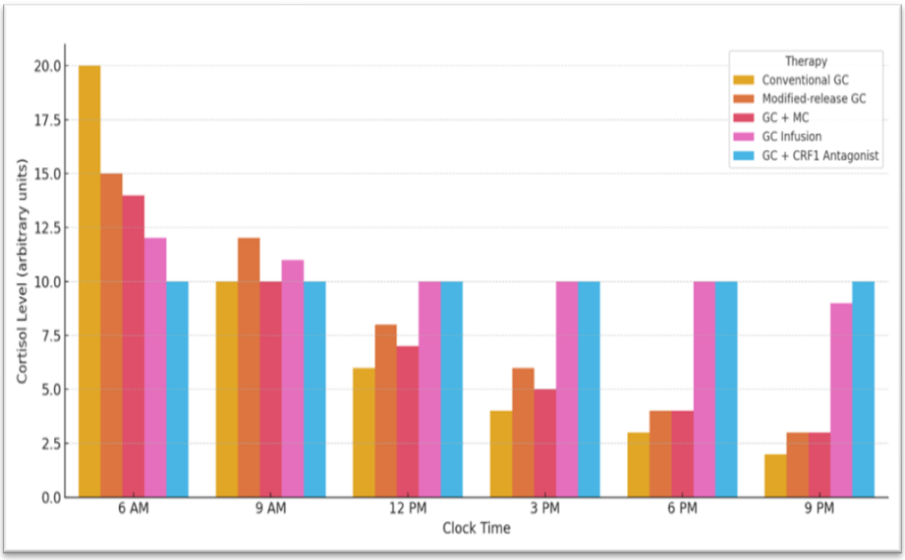


Figure 3: Cortisol profiles over time by therapy type in the management of congenital adrenal hyperplasia (CAH) (adapted from references 30,31). *Abbreviations:* CAH – Congenital Adrenal Hyperplasia; GC – Glucocorticoid; MC – Mineralocorticoid; POMC – Pro-opiomelanocortin; HC – Hydrocortisone; Dir. GC – Direct Glucocorticoid; Dir. GC + MC – Glucocorticoid with Mineralocorticoid; Dir. GC + POMC – Glucocorticoid with POMC-targeted therapy; Infusion GC – Continuous Glucocorticoid Infusion; 41-hydroxy HC – Modified-release Hydrocortisone.

6. NEW TREATMENT OPTIONS

New treatment options for CA include gene-targeted and pharmacologic approaches. It emphasizes important advantages, including better hormonal regulation, less steroid use, and an improved standard of living. Drug class, mode of administration, and trial results are included to enable a rapid comparative evaluation of the state of each therapy. The FDA approved Crinecerfont after it showed strong efficacy and hormonal stability in Phase 3 trials **(Table 2).** The pediatric study on Tildacerfont (SPR001-205) is still in progress.

Table 2: Emerging and investigational therapies for congenital adrenal hyperplasia (CAH).[19-24]

Author, Journal and Year of publication	Dose and route of administration	Benefits of use	Comments
Merke et al., J Clin Endocrinol Metab, 2021	Modified-release hydrocortisone, oral, daily	Reported improvement in menses, pregnancy rate, reduced dose in extension phase	Phase 3 trial; primary endpoint not met, but long-term benefits observed
Merke et al., J Clin Endocrinol Metab, 2021	Continuous subcutaneous hydrocortisone infusion (CSHI)	Reduced 17-OHP, ACTH, androstenedione, improved QoL and bone markers	Considered for difficult-to-treat adult patients
Auchus RJ et al., J Clin Endocrinol Metab, 2020	Nevanimibe, oral, dose titration	Lowered 17-OHP levels	Trial discontinued due to insufficient efficacy
Reisch N et al., Eur J Endocrinol, 2019	Abiraterone, oral, dose-escalation	Reduced androgen levels in adult females	Phase 1; pediatric phase 1/2 trial ongoing
Sarafoglou K et al., J Clin Endocrinol Metab, 2024	Crinecerfont, oral, daily	Reduced steroid need, lowered androstenedione; FDA approved in 2024	Approved for use in children ≥ 4 years; demonstrated safety and efficacy
Spencer SJ et al., Endocr Rev, 2021	Atumelnant, oral, dose-finding trial	Sustained reduction in morning androstenedione and 17-OHP	Phase 2 trial; early promising findings

Ghayee HK et al., Clin Endocrinol (Oxf), 2023	Lu AG13909, IV monoclonal antibody	Reduced ACTH, androstenedione, 17-OHP in early assessment	First-in-human trial initiated in UK; still under investigation
BridgeBio Pharma, ClinicalTrials.gov, 2024	BBP-631, AAV5 gene therapy, single IV infusion	Targeted restoration of cortisol synthesis	Development halted due to low efficacy in early trials
Spencer SJ, Ghayee HK. Curr Opin Endocrinol Diabetes Obes. 2021	Tildacerfont, CRF1 receptor antagonist.Oral, Phase 2/3	Reduces 17-OHP and androstenedione in adults; pediatric trials ongoing	CRF1 receptor antagonist; well tolerated,with potential steroid-sparing effec

These new treatment options for congenital adrenal hyperplasia (CAH) include gene-targeted and pharmacologic approaches. It emphasizes important advantages including better hormonal regulation, less steroid use, and an improved standard of living. Drug class, mode of administration, and trial results are included to enable a rapid comparative evaluation of the state of each therapy. The FDA approved Crinecerfont after it showed strong efficacy and hormonal stability in Phase 3 trials. The pediatric study on Tildacerfont (SPR001-205) is still in progress.

7. Gene-targeted therapies for CAH

While still experimental, gene-based approaches aim to correct the CYP21A2 defect directly, providing long-term normalization of adrenal hormone synthesis. **Table 3** addresses the emerging gene-targeted therapies for CAH that aim to correct the underlying CYP21A2 deficiency through diverse approaches.

Table 3: Emerging gene-targeted and pharmacologic therapies for congenital adrenal hyperplasia (CAH).[25-29]

Therapy	Type	Mechanism	Key findings	Development status
AAV–CYP21A2	Gene therapy	AAV-mediated delivery of functional CYP21A2 gene	Normalized hormone levels in rodent models for ~40 days after intra-adrenal injection	Preclinical
BBP-631 (BridgeBio)	Gene therapy	AAV5 vector targeting CYP21A2	Phase 1/2 trial showed limited cortisol rise; halted due to insufficient efficacy	Discontinued in 2024
CRISPR/Cas9 Editing	Gene editing	Direct correction of CYP21A2 mutations	High precision editing; delivery and off-target effects remain key challenges	Experimental (Preclinical)
mRNA–LNP Delivery	Gene therapy	Transient expression of CYP21A2 via lipid nanoparticles	Non-viral approach; adrenal-targeted delivery still under investigation	Experimental (Preclinical)

With this: (a) **AAV–CYP21A2** – Preclinical gene therapy using an adeno-associated virus (AAV) vector to deliver a functional *CYP21A2* gene directly into the adrenal glands. In animal models, it achieved short-term hormone normalization (approximately 40 days). It has not yet been tested in humans.

(b) **BBP-631 (BridgeBio)** – An AAV5 vector–based gene therapy aimed at restoring cortisol production in patients with CAH. Phase 1/2 trials showed limited efficacy, and development was discontinued in 2024.

(c) **CRISPR/Cas9 Editing** – A gene-editing approach targeting *CYP21A2* mutations for permanent correction. It offers high precision but remains experimental due to challenges with delivery and safety.

(d) **mRNA–LNP Delivery** – Uses lipid nanoparticles to deliver synthetic mRNA encoding *CYP21A2*, enabling temporary enzyme expression. Still in early preclinical development, with key challenges including targeting efficiency and sustained expression.

8. DISCUSSION

Even though treatment protocols for congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (21-OHD) have been in place for many years, treating these children and adolescents can still be challenging. Finding the ideal balance isn't always simple, but providing the appropriate dosage of glucocorticoids (GCs) and mineralocorticoids helps to replace deficient hormones and to treat the excess of androgens. Poor growth, obesity, and metabolic problems can result from overtreatment while early puberty and rapid bone growth can result from undertreatment.[14,32]

Blood tests used in routine practice to help direct treatment mainly include the 17-hydroxyprogesterone (17-OHP), which accumulates in the body as a result of an enzyme deficiency. Nevertheless, its levels fluctuate throughout the day and are contingent upon when the blood sample is taken.[33,34] This makes it less dependable for long-term follow-up. When measured early in the morning before the daily steroid dose, androstenedione can be particularly useful and is often a more stable marker.[35] Additionally, testosterone can be used to detect early puberty, particularly in younger children.[36]

Since DHEAS does not accurately reflect disease control it is less helpful for routine monitoring.[37] The aim of treatment is not to bring 17-OHP back to normal.

The appropriate goal is to maintain hormone levels within a safe range, such as 17-OHP between 12 and 36 nmol/L, while also monitoring testosterone and androstenedione levels to ensure they are within the typical range for the child's age (14, 36-38). Both undertreatment (which can result in virilization and short adult height) and overtreatment (which can result in weight gain, slowed growth, and high blood pressure) are prevented with this therapeutical approach.

Newer drugs such as CRF1 receptor blockers (like crinecerfont and tildacerfont) have shown promise in recent years. The way these medications function is by decreasing the body's signal to produce ACTH, which lowers the levels of adrenal androgen. They reduce the need for high dosages of glucocorticoids, which is their main goal.[38–40] The recently FDA-approved Crinecerfont has been demonstrated to lower children's levels of 17-OHP and androstenedione while reducing the need for steroid dosages.[41] Early findings from studies on children using Tildacerfont are promising.[21,22,33,42]

In contrast to conventional hydrocortisone which suppresses ACTH through negative feedback these more recent drugs function differently. Even though some more recent hydrocortisone formulations (such as subcutaneous pumps or modified-release tablets) aim to mimic the body's natural rhythm, they don't always maintain ACTH levels low enough overnight.[43,44]

Gene therapy is a very exciting prospect for the future. Initial studies on animals have demonstrated that using viruses (such as AAV) to insert a functional copy of the CYP21A2 gene can temporarily address the hormone imbalance.[45,46] Nevertheless, the initial human trial (BBP-631) was terminated due to inadequate results.[47] Other technologies are still being tested in the lab such as mRNA-based therapies or CRISPR gene editing. Despite their potential, these have drawbacks including the need to ensure that the medication reaches the adrenal gland, prevent immunological reactions, and demonstrate long-term safety.[45-48] Gene therapy may eventually be able to replace the need for daily medications if it proves effective. Careful observation and additional research are still required.[49,50]

9. CONCLUSION

While there has been progress in treating CAH in children careful planning is still necessary. The key to successful results is still regular hormone monitoring, particularly with stable markers like androstenedione and testosterone. It has been demonstrated that androstenedione in particular is a trustworthy indicator for modifying treatment. Some patients who suffer from side effects from high steroid dosages can find safer alternatives with new drugs like CRF1 blockers. Although it is still in the research stage, gene therapy may one day provide a cure. Combining more recent treatments with traditional hormone therapy will yield better outcomes in the future. The future of managing CAHs appears to be individualized treatment plans founded on precise hormone monitoring and patient-specific requirements.

10. RECOMMENDATIONS

1. Employ trusted hormone monitoring equipment. Before administering the child's steroid dosage, measure 17-OHP and androstenedione early in the morning. Always take the child's clinical status into account when comparing results to age-specific normal ranges.

2. In certain situations, try steroid-sparing medications. Think about more recent options like crinecerfont or tildacerfont if a child requires high doses of steroids to stay healthy or has side effects like stunted growth, especially in older kids or teens.

3. Keep an eye on gene therapy research. Promote involvement in carefully planned gene-based treatment clinical trials, but make sure to always maintain close monitoring to watch for any unforeseen side effects.

REFERENCES

1. Speiser PW, White PC. Congenital adrenal hyperplasia. N Engl J Med., 2003; 349(8): 776–788. doi:10.1056/NEJMra021561
2. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev., 2000; 21(3): 245–291. doi:10.1210/edrv.21.3.0398
3. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet, 2005; 365(9477): 2125–2136. doi:10.1016/S0140-6736(05)66736-0
4. Charmandari E, Chrousos GP. Adrenal insufficiency and glucocorticoid therapy: risk factors for obesity and metabolic syndrome. Horm Res., 2009; 72(1): 26–36. doi:10.1159/000229765
5. Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am., 2015; 44(2): 275–296. doi:10.1016/j.ecl.2015.02.002
6. Witchel SF, Azziz R. Congenital adrenal hyperplasia. J Pediatr Adolesc Gynecol, 2011; 24(3): 116–126. doi:10.1016/j.jpag.2011.01.062
7. Van der Kamp HJ, Otten BJ, Buitenweg N, et al. Longitudinal analysis of growth and puberty in children with 21-hydroxylase deficiency. J Clin Endocrinol Metab, 2002; 87(12): 5464–5470. doi:10.1210/jc.2002-020645
8. Spencer SJ, Ghayee HK. Emerging therapies for congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes, 2021; 28(3): 238–244. doi:10.1097/MED.0000000000000625
9. Auchus RJ. Management considerations for the patient with congenital adrenal hyperplasia: a review

of current and emerging therapies. J Clin Endocrinol Metab., 2022; 107(2): 371–379. doi:10.1210/clinem/dgab682
10. Claahsen-van der Grinten HL, Stikkelbroeck NMML, Otten BJ, et al. New therapeutic strategies in congenital adrenal hyperplasia. Horm Res Paediatr, 2021; 94(3–4): 190–200. doi:10.1159/ 000518470
11. Merke DP, Mallappa A, Arlt W, et al. Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab., 2021; 106(5): e2063–e2077. doi:10.1210/ clinem/ dgab051
12. Besci Ö, Erbaş İM, Küme T, et al. A 4-hour Profile of 17-hydroxyprogesterone in Salt-wasting Congenital Adrenal Hyperplasia: Is the Serial Monitoring Strategy Worth the Effort? J Clin Res Pediatr Endocrinol, 2022; 14(2): 145–152. doi:10.4274/jcrpe.galenos.2021.2021-9-17
13. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. Nat Rev Endocrinol, 2022; 18: 337–352. doi:10.1038/s41574-022-00655-w
14. Yau M, Gujral J, New MI. Congenital Adrenal Hyperplasia: Diagnosis and Emergency Treatment. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. Updated 2019 Apr 16
15. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab., 2018; 103(11): 4043–4088. doi:10.1210/jc.2018-01865
16. Auchus RJ. The classic and nonclassic congenital adrenal hyperplasias. Endocr Pract., 2015; 21: 383–389. doi:10.4156/EP14474.RA
17. Maggio M, Lauretani F, De Vita F, et al. Multiple hormonal dysregulation as determinant of low physical performance and mobility in older persons. Curr Pharm Des., 2014; 20(19): 3119–3148. doi:10.2174/13816128113196660062
18. El-Maouche D, Merke DP, Vogiatzi MG, et al. A Phase 2, Multicenter Study of Nevanimibe for the Treatment of Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab., 2020; 105(8): 2771–2778. doi:10.1210/clinem/dgaa381
19. Auchus RJ, Buschur EO, Chang AY, et al. Abiraterone acetate to lower androgens in women with classic 21-hydroxylase deficiency. J Clin Endocrinol Metab., 2014; 99(8): 2763–2770. doi:10.1210/jc.2014-1258
20. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia. N Engl J Med., 2024; 391(6): 504–514. doi:10.1056/NEJMoa2404656
21. Sarafoglou K, Kim MS, Lodish M, et al. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. N Engl J Med., 2024; 391(6): 493–503.doi: doi:10.1056/ NEJMoa2404655
22. Newfield RS, Sarafoglou K, Fechner PY, et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab., 2023; 108(11): 2871–2878. doi:10.1210/clinem/dgad270
23. Sarafoglou K, Auchus RJ. Future Directions in the Management of Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. J Clin Endocrinol Metab., 2025; 110(1): S74–S87. doi:10.1210/clinem/dgae759
24. Chen X, Liu Y, Ding Y, et al. AAV-mediated gene therapy restores adrenal function in a mouse model of congenital adrenal hyperplasia. Mol Ther Methods Clin Dev., 2020; 18: 345–355. doi:10.1016/j.omtm.2020.07.004
25. BridgeBio Pharma. BridgeBio announces interim data from phase 1/2 clinical trial of BBP-631 in congenital adrenal hyperplasia. BusinessWire. 2024 Mar. Available from: https://www.bridgebio. com
26. Dhir V, Midgley P, Taylor NF, et al. Prospects for gene editing in congenital adrenal hyperplasia. Front Endocrinol (Lausanne), 2020; 11: 495. doi:10.3389/fendo.2020.00495
27. Damiani D, Pugliese-Pires PN, Brito VN, et al. Emerging therapies for congenital adrenal hyperplasia. Clin Sci (Lond)., 2022; 136(17): 1277–1296. doi:10.1042/CS20210943
28. Turcu AF, Auchus RJ. Clinical variants of congenital adrenal hyperplasia. Ann N Y Acad Sci., 2021; 1484(1): 5–14. doi:10.1111/nyas.14520
29. Mallappa A, Sinaii N, Kumar P, et al. A Phase 2 Trial of Chronocort®, a Modified-Release Hydrocortisone, in the Treatment of Classic Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab, 2015; 100(3): 1137–1145. doi:10.1210/jc.2014-3888
30. Kendirci HNP, Ünal E, Dündar İ, et al. Treatment and Follow-up of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency in Childhood and Adolescence. J Clin Res Pediatr Endocrinol, 2025; 17(1): 12–22. doi:10.4274/jcrpe.galenos.2024.2024-6-26-S
31. Sarafoglou K, Merke DP, Reisch N, et al. Interpretation of Steroid Biomarkers in 21-Hydroxylase Deficiency and Their Use in Disease Management. J Clin Endocrinol Metab, 2023; 108(9): 2154–2175. doi:10.1210/clinem/dgad134
32. Güneş SO, Kendirci HNP, Ünal E, et al. Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency. J Clin Res Pediatr Endocrinol, 2025; 17(1): 3–11. doi:10.4274/jcrpe.galenos.2024.2024-6-6-S
33. Bacila IA, Lawrence NR, Badrinath SG, et al. Biomarkers in congenital adrenal hyperplasia. Clin Endocrinol (Oxf), 2024; 101: 300–310. doi:10.1111/cen.14960
34. Nassar GN, Leslie SW. Physiology, Testosterone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Updated 2023 Jan 2. Available from: https://www. ncbi . nlm.nih.

gov/books/ NBK526128/
35. Wass JA, Arlt W, Semple R, editors. Modern Management of Congenital Adrenal Hyperplasia and Prospects for the Future. In: Oxford Textbook of Endocrinology and Diabetes. 3rd ed. Oxford: Oxford University Press, 2022.
36. Itonaga T, Hasegawa Y. Monitoring treatment in pediatric patients with 21-hydroxylase. Front Endocrinol (Lausanne), 2023; 14: 1102741. doi:10.3389/fendo.2023.1102741
37. Prete A, Auchus RJ, Ross RJ. Clinical advances in the pharmacotherapy of congenital adrenal hyperplasia. Eur J Endocrinol, 2021; 186(1): R1–R14. doi:10.1530/EJE-21-0794
38. Speiser PW. Emerging medical therapies for congenital adrenal hyperplasia. F1000Res, 2019; 8: 363. doi:10.12688/f1000research.17778.1
39. Sarafoglou K, Barnes CN, Huang M, et al. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. J Clin Endocrinol Metab., 2021; 106(11): e4666–e4679. doi:10.1210/clinem/dgab438
40. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocr Rev., 2020; 41(3): bnaa002. doi:10.1210/endrev/bnaa002
41. Whitaker MJ, Huatan H, Ross RJ. Chronotherapy based on modified-release hydrocortisone to restore the physiological cortisol diurnal rhythm. Drug Deliv Transl Res., 2023; 13(1): 1–8. doi:10.1007/s13346-022-01183-w
42. Graves LE, van Dijk EB, Zhu E, et al. AAV-delivered hepato-adrenal cooperativity in steroidogenesis: Implications for gene therapy for congenital adrenal hyperplasia. Mol Ther Methods Clin Dev., 2024; 32(2): 101232. doi:10.1016/j.omtm.2024.101232
43. Pignatelli D, Carvalho BL, Palmeiro A, et al. The Complexities in Genotyping of Congenital Adrenal Hyperplasia: 21-Hydroxylase Deficiency. Front Endocrinol (Lausanne), 2019; 10: 432. doi:10.3389/fendo.2019.00432
44. BridgeBio Pharma, Inc. BridgeBio Pharma reports topline results from Phase 1/2 trial of investigational gene therapy for congenital adrenal hyperplasia (CAH). 2024 Sep 10. Available from: https://bridgebio.com/news/bridgebio-pharma-reports-topline-results-from-phase-1-2-trial-of-investigational-gene-therapy-for-congenital-adrenal-hyperplasia-cah/
45. Mohammadian Farsani A, Mokhtari N, Nooraei S, et al. Lipid nanoparticles: The game-changer in CRISPR-Cas9 genome editing. Heliyon, 2024; 10(2): e24606. doi:10.1016/j.heliyon. 2024. e24606
46. Schröder MAM, Claahsen-van der Grinten HL. Novel treatments for congenital adrenal hyperplasia. Rev Endocr Metab Disord, 2022; 23(3): 631–645. doi:10.1007/s11154-022-09717-w
47. Bornstein SR, Malyukov M, Heller C, et al. New Horizons: Novel Adrenal Regenerative Therapies. J Clin Endocrinol Metab, 2020; 105(9): 3103–3107. doi:10.1210/clinem/dgaa438
48. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet, 2005; 365(9477): 2125–2136. doi:10.1016/S0140-6736(05)66736-0
49. Auchus RJ, Speiser PW. Congenital adrenal hyperplasia: update on treatment and new therapeutic options. Best Pract Res Clin Endocrinol Metab, 2022; 36(1): 101612. doi:10.1016/ j.beem.2022. 101612
50. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016; 101(2): 364–389. doi:10.1210/jc.2015-1710