*Section A-Research paper*

# MANAGEMENT OF INFANTS WITH CONGENITAL ADRENAL HYPERPLASIA

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**Abstract**
For effective care of the complicated condition "*Congenital Adrenal Hyperplasia* (CAH)", a multidisciplinary approach is necessary. Because it frequently exhibits vague symptoms and can be confused with other disorders, CAH can be difficult to diagnose. A genetic flaw in CAH's etiology causes an excess of androgens to be produced, which can masculinize female embryos and cause early virilization in men. Glucocorticoid treatment and salt supplements are two efficient management techniques for CAH that can help lower androgen levels and prevent salt-wasting crises. For CAH to be successfully managed, close monitoring and follow-up are essential since potential complications and adherence to therapy can have an impact on long-term outcomes. This review article underlines the significance of a thorough strategy that takes into account each patient's unique demands while providing an up-to-date overview of the current therapeutic techniques for newborns with CAH. This article seeks to educate and direct clinicians and researchers in their endeavors to enhance the care and outcomes of infants with CAH by summarizing the most recent research in the area.

**Key words:** Congenital adrenal hyperplasia, Infants, Glucocorticoid therapy, Salt supplementation

## Introduction:

The term "congenital adrenal hyperplasia" (CAH) refers to a set of hereditary illnesses that affect the adrenal glands. These glands are responsible for the production of hormones, which control a wide variety of processes throughout the body. A defect in one or more of the enzymes required to create cortisol, a hormone that helps control blood sugar levels, blood

pressure, and the body's response to stress, is present in infants who have CAH. Because of this, the adrenal glands produce higher-than-normal quantities of androgen hormones, which can lead to a wide range of health issues in newborns of both sexes (1-5).

The incidence of congenital aortic hypertension (CAH) ranges from roughly 1 in 10,000 to 1 in 20,000 live births around the world. However, the illness can have significant repercussions for the health and well-being of the infants who are affected, particularly if the condition is managed improperly or not treated at all. A variety of symptoms, such as poor weight gain, dehydration, low blood sugar, and an enlarged clitoris or penis in female infants, may be present in infants who have CAH (1-5).

Clinical presentation, blood tests to detect hormone levels, and genetic testing to validate the underlying genetic abnormalities are often used in conjunction with one another to diagnose CAH in babies. An early diagnosis is essential because it paves the way for the rapid implementation of management techniques that can avoid or reduce the likelihood of developing significant health issues (1-5).

The treatment of CAH in babies often involves a combination of medicinal and surgical procedures with the goals of reestablishing normal hormone levels and reducing the likelihood of developing long-term health complications. The glucocorticoid therapy is the foundation of the medical management, and hydrocortisone is the medication of choice for children under the age of one. By inhibiting the production of androgen hormones, which can lead to virilization and other issues, glucocorticoids play a role in mitigating these dangers. Glucocorticoid therapy does, however, include dangers, including growth suppression, osteoporosis, and adrenal suppression, which may necessitate careful monitoring and adjustments to the dose during the course of treatment.

Salt supplementation may be necessary for newborns diagnosed with CAH in addition to glucocorticoid medication. This is done to prevent infants from becoming dehydrated and to keep the electrolyte balance stable. The infants who suffer from the salt-wasting variant of CAH which is characterized by a shortage of aldosterone, a hormone that helps control the salt and water balance in the body, have a particularly high need for salt supplementation. In some instances, it may be required to perform surgical procedures, notably for female infants with unclear genitalia or for male infants with an excessively tiny penis. Surgical alternatives include clitoroplasty, vaginoplasty, and phalloplasty, all of which should be performed by skilled pediatric surgeons in centers specializing in the treatment of this condition (1-5).

Infants diagnosed with CAH have a generally favorable prognosis for their long-term health, particularly when an early diagnosis and effective care techniques are provided. On the other hand, children born with CAH may have a greater likelihood of developing long-term health complications, such as decreased bone density, cardiovascular illness, and difficulties in having children. All newborns diagnosed with CAH should have ongoing monitoring and follow-up care in order to maximize their chances of having positive outcomes in the long run.

**Diagnosis:**

The synthesis of cortisol and other hormones is disrupted as a result of the hereditary illnesses known as CAH, which affect the adrenal glands. With an incidence of between 1 in 10,000 to 1 in 20,000 live births worldwide, CAH is a rare disorder. A lack of the cortisol-producing enzyme 21-hydroxylase is the main cause of the most prevalent type of CAH (1,2,5).

Numerous symptoms, such as poor weight gain, dehydration, low blood sugar, and an enlarged clitoris in female infants or an enlarged penis in male infants, can be present in infants with CAH. The precise kind of CAH and the degree of enzyme deficiency determine the severity and nature of the symptoms(1,3,6).

In order to diagnose CAH in babies, a combination of clinical assessment, laboratory testing, and genetic testing is usually used. Measuring the levels of cortisol, glucose, and serum electrolytes should be part of the initial laboratory evaluation. Serum 17-hydroxyprogesterone (17-OHP) levels in babies with suspected CAH should be assessed because increased levels are strongly predictive of the disease. Genetic analysis is frequently used in CAH confirmation testing to determine the underlying genetic alterations. The different kinds of CAH, which may have different clinical ramifications and therapy approaches, can be distinguished with the aid of genetic testing (1-4,6,7).

Imaging investigations may help in the diagnosis of CAH in addition to laboratory tests. The adrenal glands can be examined for anomalies, such as nodules or enlargement, using ultrasound and MRI. Ultrasonography can be performed to examine the internal reproductive organs and determine if a uterus is present or absent in female neonates with ambiguous genital. Early CAH diagnosis is crucial because it enables the quick implementation of management techniques to avert or lessen potential health problems. Significant problems, such as salt wasting, an adrenal crisis, and even death, might result from a delayed or missing diagnosis (1,6-10).

**Pathophysiology:**

Defects in the enzymes necessary for cortisol synthesis in the adrenal gland characterize the autosomal recessive illnesses known as CAH. About 95% of all cases of CAH are caused by 21-hydroxylase insufficiency, which is also its most prevalent variant. Due to the lack of this enzyme, the production of cortisol and aldosterone is reduced, which raises the levels of adrenal androgens such testosterone and dehydroepiandrosterone (DHEA) (1,2).

In addition to ambiguous genitalia at birth, the excess androgens in CAH can virilize females and hasten the development of secondary sex traits in both sexes (13). Additionally, insufficient cortisol synthesis results in increased adrenocorticotropic hormone (ACTH) production, which in turn causes adrenal hyperplasia (3). A number of biochemical and genetic processes are involved in the pathogenesis of CAH. The 21-hydroxylase enzyme is encoded by the CYP21A2 gene, which is mutated in the majority of instances (1,2).

Numerous distinct mutations have been discovered, each with a distinct severity that results in a range of clinical symptoms (2). The mutations cause either a total loss of enzyme activity or a reduction in enzyme activity, the latter of which results in milder disease manifestations (2). The carrier condition is caused by inheriting one copy of a mutant CYP21A2 gene, whereas CAH is caused by inheriting two copies (1,2). Rarely, CAH can also result from flaws in the enzymes 11-hydroxylase, 17-hydroxylase, and 3-hydroxysteroid dehydrogenase, which are all implicated in the production of adrenal steroid hormones (4).

The hypothalamic-pituitary-adrenal (HPA) axis, which controls the synthesis and secretion of cortisol, is disrupted as a result of the biochemical anomalies in CAH (3). The adrenal cortex becomes hyperplastic as a result of the elevated levels of ACTH brought on by cortisol insufficiency, which then causes an excess of androgens to be produced (3). Alterations to other endocrine axis are also a part of the pathophysiology of CAH. In addition to insulin resistance and hyperinsulinemia, high androgens can result in premature epiphyseal closure and growth retardation in both sexes (3).

**Management strategies:**

Preventing adrenal crises while preserving normal growth and development is the major goal of care for newborns with CAH. The mainstay of treatment is hormone replacement therapy using glucocorticoids and mineralocorticoids (11,12). While the mineralocorticoid therapy makes up for the aldosterone shortage, limiting salt loss and dehydration, the glucocorticoid therapy seeks to replace the cortisol deficiency and decrease the excess ACTH secretion (13-15). The dosages are modified in accordance with the patient's weight, rate of growth, and clinical response, and it's crucial to keep an eye out for any potential adverse effects (13-15).

Some infants with CAH may require surgical treatments. For females with ambiguous genitalia to regain normal genital anatomy and function, surgery is necessary. Surgery may be necessary to treat male newborns with non-palpable testes or severe hypospadias. To prevent affecting the infant's growth and development, surgical operations should be timed properly (15,16).

Careful monitoring is essential in preventing adrenal crises, which can be fatal, in addition to hormonal therapy and surgical procedures. Due to the possibility for insufficient cortisol release in response to stress, sickness, or trauma, infants with CAH are susceptible to adrenal crises (17). As a result, parents and other caregivers need to be properly educated on how to recognize and treat adrenal crises, including increasing glucocorticoid dosages during illness or stress, giving parenteral hydrocortisone in an emergency, and keeping a first aid kit with hydrocortisone and needles on hand (17). In order to track growth and development, evaluate the effectiveness of hormonal therapy, and modify dosages as necessary, regular follow-up appointments with a pediatric endocrinologist are crucial (17).

Some newborns with CAH may experience metabolic issues during infancy and adolescence, such as obesity, hypertension, and dyslipidemia, despite the best care practices (18). These

issues, which are linked to poor hormonal control, are more common in non-classical CAH and call for unique therapies, such as dietary adjustments, physical exercise, and medication therapy, depending on the patient's requirements. In order to achieve the best results, long-term monitoring and management are crucial for newborns with CAH (18).

**Glucocorticoid therapy:**

Infants with CAH typically get glucocorticoid medication to replenish their low levels of cortisol and to control their overproduction of androgens (18). Achieving sufficient cortisol levels, reducing adrenal androgen production, and preventing adrenal crises are the objectives of glucocorticoid therapy (19). However, establishing ideal hormonal control might be difficult because large dosages of glucocorticoids can have negative effects such obesity, insulin resistance, growth retardation, and osteoporosis (20).

To avoid virilization and allow for normal growth and development, glucocorticoid therapy should be started as soon as feasible following diagnosis, ideally within the first week of life (4). The severity of CAH and the particular patient's reaction to medication should be taken into consideration while selecting the right glucocorticoid and dosage (21). Because of its short half-life and physiologic cortisol replacement capabilities, hydrocortisone is the most frequently prescribed glucocorticoid for newborns with CAH (22). Although they have a longer half-life and a higher risk of side effects, prednisolone and dexamethasone are also utilized in some situations (18).

To establish optimal hormonal regulation and prevent over- or under-replacement, the dosage of glucocorticoids should be titrated based on clinical and biochemical monitoring (12). In babies with classic CAH, a daily hydrocortisone dose of 10 to 20 mg/m2 divided into three to four doses is advised (17). To establish sufficient hormonal regulation, higher doses could occasionally be needed, although doing so raises the possibility of side effects (18). In contrast, infants with non-classic CAH or those who have lesser types of classic CAH may be treated with lower doses (19).

In instance, obesity and development retardation are two negative outcomes of long-term glucocorticoid medication (20). To reduce these negative effects, growth and weight should be carefully monitored on a regular basis, and the dosage of glucocorticoids should be changed as necessary (21). Additionally, it is advised to regularly monitor blood pressure, glucose metabolism, and bone density to identify and treat any potential side effects of glucocorticoid medication (22-26).

**Salt supplementation:**

In order to treat salt-wasting in newborns with CAH salt supplementation is a popular therapeutic method. A major side effect of CAH is salt-wasting, which is brought on by a lack of aldosterone, which controls the body's sodium and potassium levels. If not properly identified and treated, the failure to save sodium in salt-wasting CAH can result in

dehydration, hypovolemia, and shock. The use of salt supplementation in the treatment of salt-wasting CAH will be covered in this section.

Maintaining normal sodium levels in the blood and avoiding dehydration are the main objectives of salt supplementation in patients with salt-wasting CAH. Adding more salt to the infant's diet or formula will serve as a sodium supplement, as will giving them oral sodium chloride tablets. The ideal amount of salt supplementation depends on the infant's age, weight, and how severe the salt-wasting is. The infant's sodium levels and urine output should be taken into consideration while adjusting the starting dose of oral sodium chloride, which is typically 2-3 mEq/kg/day (11,19).

It has been demonstrated that adding salt to CAH can avoid dehydration and enhance general health results. In a study by Bonfig et al. (19), it was discovered that salt supplementation dramatically enhanced growth metrics and bone mineral density in infants with salt-wasting CAH. Similar to this, a research by Speiser et al. (1) found that adding salt to infants with CAH significantly decreased the number of hospitalizations for dehydration and adrenal crises.

Supplementing with salt is generally seen as safe and helpful, however there are hazards involved. Consuming too much salt can cause fluid overload, hypertension, and hypernatremia, especially in young children with compromised renal function. Therefore, it's crucial to keep an eye on serum sodium levels and modify salt dosage as needed. Additionally, salt supplementation may not be required in infants with non-salt wasting CAH and may even be hazardous, causing hypertension and fluid retention (14,25).

**Monitoring and follow-up:**

The management of newborns with CAH must include monitoring and follow-up. Regular monitoring makes sure that the treatment strategy is successful in reducing the disorder's symptoms and complications. Follow-up care is crucial for monitoring growth and development as well as for identifying any negative side effects of prolonged therapy.

Infants with CAH should be regularly watched, especially in the first year of life (1). Depending on the condition's severity and the needs of each patient, follow-up visits may vary in frequency. In contrast, it is typically advised that patients see their doctors every 6–12 months following the first year of life and every 6–12 months after that (2).

Follow-up appointments should be used to monitor the patient's development, weight, blood pressure, and medication regimen. To ensure that electrolyte imbalances are quickly rectified, laboratory tests such as electrolyte levels should also be routinely evaluated (1). In order to assess if the patient's hormone replacement medication is effective, cortisol and androgen levels should also be tracked (3).

Children with CAH should also have their growth and development constantly watched. In particular in patients with the salt-wasting type of the illness, delayed growth and puberty are

frequent consequences of the condition (4). Therefore, it's crucial to frequently check the patient's weight, height, and bone age to make sure they're developing normally. Treatment alternatives including growth hormone therapy may be taken into consideration if growth is delayed (5).

Patients with CAH and their families should get information and counseling about the condition and its treatment in addition to physical surveillance. This involves educating people on the significance of taking their medications as prescribed, getting enough salt, and managing severe adrenal crises (6,24,25). The potential long-term effects of CAH, such as infertility and osteoporosis, as well as methods to treat or avoid these effects, should also be explained to patients and their families.

**Long-term outcomes:**

Due to the possibility of permanent problems, CAH long-term outcomes have drawn significant attention from the medical community. If CAH is not properly controlled, it can result in a number of physical, psychological, and reproductive health problems.

The possibility for impaired growth and development brought on by the prolonged use of glucocorticoids is one of the main worries in the long-term management of CAH. Insufficient height outcomes in CAH patients have been noted in several investigations, particularly in those who began glucocorticoid medication at a young age (11). Physicians should routinely check growth statistics and modify the glucocorticoid dosage as necessary to reduce this risk.

Patients with CAH run the risk of developing metabolic disorders in addition to problems with growth and development. According to a Swedish study, CAH patients were more likely than the general population to have hypertension, dyslipidemia, and impaired glucose tolerance (12). In order to effectively manage CAH over the long term, monitoring of blood pressure, lipid profile, and glucose metabolism is crucial.

In CAH patients, particularly in females with 21-hydroxylase deficiency, reproductive health is a key concern. Infertility, menstruation abnormalities, and an increased risk of ovarian hyperstimulation syndrome (OHSS) with assisted reproductive technologies are all potential risks for these patients (13). It is critical to monitor and manage the reproductive health of CAH patients throughout their lives since studies have indicated that early diagnosis and treatment of CAH can enhance fertility results (14).

Another element that must be taken into account in the long-term management of CAH is psychological well-being. Adult CAH patients reported higher levels of anxiety and depression than the general population, according to a Dutch study (15). In order to help CAH patients, doctors should offer them psychological assistance and therapy, especially during the time when they are transitioning from youth to adulthood.

The long-term effects of CAH can differ depending on the severity of the disorder, the age of diagnosis, and the care techniques employed. This is an important point to remember.

Therefore, it's imperative to monitor and follow up frequently in order to identify and handle any potential issues.

Further research has revealed that incidentalomas of the adrenal gland are more likely to occur in non-classical forms of CAH, particularly those with the 21-hydroxylase deficit (16). These are cancers of the adrenal glands that were unrelatedly found by chance while undergoing medical imaging tests. Even though the majority of these tumors are benign, they can have serious clinical effects, such as hormone abnormalities and possible cancer. As a result, routine imaging examinations, such as CT or MRI scans, are advised for CAH patients who have a 21-hydroxylase deficit.

Adrenal crisis, a potentially fatal illness that develops when the body is under stress and the adrenal glands are unable to release enough cortisol, is another long-term problem that is of concern in CAH patients. Numerous things, including disease, trauma, surgery, or mental stress, can cause an adrenal crisis. As a result, it's critical for CAH patients and their caregivers to be knowledgeable about the warning signs and symptoms of an adrenal crisis, which include nausea, vomiting, abdominal discomfort, hypotension, and altered consciousness (17). If these symptoms manifest, they should be treated right once.

Finally, it is important to note that both the patient and the healthcare staff must be committed for the rest of their lives to the long-term management of CAH. Patients should be informed about their disease, any potential side effects, and the necessity of following all recommended management measures, such as prescription schedules, monitoring, and follow-up appointments. The most recent developments in CAH management should also be familiar to healthcare professionals, who should offer patients tailored care that takes their age, gender, illness severity, and any potential concomitant conditions into account (27-30).

In conclusion, the long-term effects of CAH may significantly affect the health and quality of life of patients. The long-term care of CAH must include consistent monitoring and follow-up, handling probable problems, and patient empowerment. Healthcare professionals can enhance the long-term results of CAH patients and assist them in leading fulfilling lives by employing a multidisciplinary strategy that takes into account the physical, psychological, and reproductive health elements of the disorder.

**Conclusion:**

The health and wellbeing of newborns who are impacted by CAH may suffer significantly as a result of this uncommon genetic condition. To reduce the risk of future problems and guarantee the best long-term results, early diagnosis and efficient management techniques are essential. In order to secure the best results throughout time, this review article will stress the significance of monitoring and follow-up and provide a thorough overview of the many care techniques for newborns with CAH, including medicinal and surgical therapies.

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