Application for inclusion of Fludrocortisone tablets in the WHO Model List of Essential Medicines for Children (July 2008)

Submitted by:

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To:

Expert Committee on the Selection and Use of Essential Medicines
Children’s Essential Medicines List
World Health Organization
Geneva

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Introduction

The First List (October 2007) of the WHO Model List of Essential Medicines for Children does not include adrenal hormones nor synthetic substitutes (Section 18.1), however it does state “the Subcommittee noted the need for adrenal hormones and requested that appropriate products be reviewed for possible inclusion”.

This application for fludrocortisone tablets is made with particular reference to the critical role of fludrocortisone in the management of Congenital Adrenal Hyperplasia (CAH) in children (see Section 14.1 for general background reading material on CAH). CAH is a genetically acquired (autosomal-recessive), chronic endocrine condition that is typically diagnosed in infancy or early childhood. Caused by an enzyme deficiency in the adrenal cortex, CAH is characterized by cortisol deficiency, aldosterone deficiency and hyperandrogenism. Oral fludrocortisone is the drug of choice for aldosterone replacement (Section 14.2).

This request for the inclusion of fludrocortisone tablets in the WHO Model List of Essential Medicines for Children acknowledges the previous inclusion of: hydrocortisone powder for injection (Section 3 and 8.3); Prednisolone oral liquid and tablet (Section 3 and 8.3); and Dexamethasone for injection (Section 3 and 8.3). Unfortunately, none of these medications are appropriate routine daily treatments for CAH in children – although hydrocortisone for injection is a vital drug for the management of acute illness and adrenal crises in children with CAH².

The authors of this application are simultaneously submitting an application for hydrocortisone tablets, another essential medication for the management of CAH, necessary for glucocorticoid replacement.

1. Summary statement of the proposal for inclusion

This application is for the inclusion of fludrocortisone into the WHO Model List of Essential Medicines for Children. Fludrocortisone tablets are proposed for inclusion in the WHO Model List of Essential Medicines for Children for the treatment of Congenital Adrenal Hyperplasia (CAH) in childhood.

Fludrocortisone has been the mainstay in treatment for salt wasting variety of congenital adrenal hyperplasia and unfortunately it is the only formulation available to tackle this variant³, as no other synthetic adrenocortical steroid is comparable to its superior mineralocorticoid properties.

This proposal also acknowledges the similarly vital role fludrocortisone plays in the management of Addison’s Disease.

2. Name of the focal point in WHO supporting the application

No focal point.
3. Name of the organisations consulted and supporting the application

**Organisations consulted and writing application:**
- Department of Endocrinology & Diabetes, Royal Children’s Hospital Melbourne, Australia.
- Medical Unit, National Institute of Child Health, Karachi, Pakistan.
- CLAN (Caring & Living As Neighbours) – Australian Non-Government Organisation (NGO)

**Organisations Supporting the application (letters attached in Appendix 3):**
1. CAH Support Network of New Zealand (CAHNZ Trust)
2. Indonesian Pediatric Society (Endocrinology Chapter)
3. CAH Support Group Network of the Philippines (CAHSAPI)
4. CARES Foundation (US based CAH Support Group Network)
5. Royal Children’s Hospital International (RCHI)
6. Australian Addison’s Disease Association Inc.
7. Association Surrénales (French Support Group)
8. The Philippines Society of Pediatric Metabolism & Endocrinology (PSPME)
10. CLAN (Caring & Living As Neighbours)

(Letters attached in Section 14.3).

4. International nonproprietary name of the medicine

Fludrocortisone acetate (tablet).

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested for fludrocortisone acetate (tablets) as an individual medicine.

Fludrocortisone is a synthetic adrenocortical steroid which is given in combination with hydrocortisone (a glucocorticoid) in the management of congenital adrenal hyperplasia². (See Section 14.4 for access to a Glucocorticoid Treatment Clinical Guideline).
6. Information supporting the public health relevance

6.1 Definition of Congenital Adrenal Hyperplasia (CAH)

Congenital Adrenal Hyperplasia (CAH) is a family of inherited disorders of the adrenal cortex that impairs steroidogenic enzyme activity essential for cortisol biosynthesis\(^4\). In over 90% of cases, CAH is due to 21-hydroxylase deficiency (21-OHD)\(^5\). This proposal will deal exclusively with 21-OHD, as it is the most common of all CAH disorders and the other types are very rare. Aldosterone production is interrupted in up to 66% of patients with 21-OHD – these children are identified as having salt-wasting (SW) CAH and require fludrocortisone replacement to survive\(^6\).

The goals of management of CAH are appropriate supra-physiologic replacement of glucocorticoids (as hydrocortisone in childhood, and necessary for all CAH patients), mineralocorticoid replacement (as fludrocortisone, for those with SWCAH), and suppression of the adrenal glands, thereby preventing inappropriate virilisation (caused by androgen excess) and achieving normal growth velocity and pubertal development\(^2\). There is no cure for CAH. Treatment is required every day for life. Long-term inadequate treatment carries serious repercussions for both male and female children (such as progressive virilisation due to androgen excess, short stature, reduced fertility, psychological and social complications, and risk of adrenal crisis and death)\(^8\). Additional glucocorticoid replacement is necessary during acute illness to prevent adrenal crisis (and death)\(^2\).

6.2 Clinical Manifestation and Variability

The spectrum of disease in CAH ranges from the “classical, severe” salt wasting (SW) form to “classic, less severe” simple-virilizing (SV), to “mild, nonclassic” forms\(^4\).\(^5\).

6.3 Epidemiology & Public Health Relevance

The commonest cause of primary adrenal insufficiency in childhood is Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency.

The incidence of CAH has been demonstrated to vary markedly around the world. In western European countries and the USA, where newborn screening for CAH is provided, the incidence is in the range 1: 10,000–17,000 with an average of 1:14,000 births. Statistics from Newborn Screening trials show incidence rates of: 1 in 21270 live births in New Zealand; 1 in 15981 in North America, and 1 in 14970 in Europe. The incidence in Japan is 1 in 19111 live births. Significantly higher incidence rates have been demonstrated in certain populations, such as: rates of 1:5,933 live births in the Philippines; 1 in 5000 in Saudi Arabia; 1:5,000 in the Bahamas; 1:2,575 in India and 1:280 amongst Yupik Eskimos of Western Alaska\(^10\),\(^11\),\(^12\),\(^13\),\(^14\). In many developing countries incidence figures have not been established, by virtue of the fact that no research in the area has been conducted. Anecdotally however, the numbers are significant: at the Endocrine Clinic at the National Hospital of Pediatrics in Hanoi, Vietnam, new patients are diagnosed at the rate of 2-3 per week; a Newborn Screening Trial in Ho Chi Minh City is expected to provide formal incidence figures for Vietnam in the foreseeable future\(^15\).

Prevalence is a separate issue, and not well documented due to insufficient CAH databases. Nonetheless, there are marked population differences in developed versus developing countries. The American CAH Support Group (CARES Foundation) has a national membership of around 2,000 families (population of USA just over 300 million)\(^16\). By comparison there are very low numbers of children known to have CAH in low income countries reflecting high mortality and missed diagnosis.
A survey of Paediatric Endocrinologists from the Asia Pacific region suggested unaffordably available medication plays a major role in determining survival. Examples of low income countries where prevalence figures are known include: no children known to be living with CAH in Timor (population 2 million) or Laos (population 6.5 million); perhaps 2 children known in Papua New Guinea (population 5.5 million), around 100 children in the Philippines (population 80 million); and less than 200 children in Indonesia (population 200 million). Paradoxically there are around 400 children currently receiving treatment for CAH in Vietnam (population 80 million), but “loss to follow-up” figures are high.

Other causes of primary adrenal insufficiency in children include Addison disease, which in developing countries is caused by tuberculous destruction of the adrenals but in the rest of the world, is mainly due to autoimmune disease or rare genetic diseases such as adrenoleukodystrophy, lipoid adrenal hyperplasia and adrenal hypoplasia congenital. Patients with primary adrenal insufficiency require both a glucocorticoid and a mineralocorticoid.

Secondary adrenal insufficiency due to deficiency of pituitary ACTH occurs in congenital hypopituitarism (which is due to a congenital malformation such as holoprosencephaly, septo-optic dysplasia or interrupted pituitary stalk syndrome) or following the removal of a tumour such as a craniopharyngioma. Patients with secondary adrenal insufficiency are treated with a glucocorticoid alone, and do not need mineralocorticoid replacement.

### 7. Treatment details

#### 7.1 Indications

Fludrocortisone Acetate is indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency, as seen in Addison’s disease and the salt wasting (SW) and simple virilizing (SV) variety of classical congenital adrenal hyperplasia.

#### 7.2 Dose

Initial Dose: 0.05-0.3 mg/day *

Maintenance Dose: 0.05-0.2 mg/day *

*Dosage varies according to Sodium intake.

All children with classic CAH require treatment with fludrocortisone at diagnosis in the newborn period. The need for ongoing mineralocorticoid treatment beyond this period should be assessed (based on renin and BP measurements).

Standard fludrocortisone doses of 50-200mcg / day maintain plasma renin activity in the mid-normal range (depending on sodium intake). Requirements are usually higher in infancy, decreasing as the child gets older. Sodium chloride supplements are often needed in infancy, at 1-3gm/day (17-51mEq/day), distributed in several feedings.

Doses can be split in half and given twice daily. The dose of fludrocortisone does not change during an adrenal crisis – only glucocorticoid doses need to be increased.
7.3 Duration

Treatment for CAH is life-long.

All classic CAH patients should be treated with fludrocortisone at the time of diagnosis in the newborn period and treatment is life-long but the requirement may spontaneously decrease with growing age.²¹

7.4 Monitoring

During child-hood, routine medical review and blood tests are ideally used to ensure the glucocorticoid and mineralocorticoid replacement doses are satisfactory.

Mineralocorticoid replacement is monitored by Blood Pressure (BP) readings, plasma renin activity and electrolytes. During infancy blood tests every 3 months (PRA or direct renin) are indicated, stretching out to 4-12 monthly testing as the child grows older²²²¹.
8. Summary of comparative effectiveness in a variety of clinical settings

Neonates with the salt wasting (SW) form of CAH exhibit adrenal crisis during the first four weeks of life, peaking at approximately 3 weeks of age. This manifests as poor feeding, vomiting, loose stools or diarrhea, weak cry, failure to thrive, dehydration and lethargy. These symptoms may not be evident until serum sodium concentrations are below 125 mEq/L. If untreated, circulatory collapse, shock, and death are inevitable. Permanent brain injury attributable to shock, such as lower cognitive scores and learning disabilities are observed in some with the salt wasting form²⁵.

Below is a comparison of salt retention of different corticosteroids showing Relative Biologic Potencies of Synthetic Steroids in Bioassay Systems²¹.

<table>
<thead>
<tr>
<th>STEROID</th>
<th>SALT RETENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.75</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.5</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>125</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0</td>
</tr>
</tbody>
</table>

In 1977, some researchers demonstrated that patients considered to have SVCAH may also suffer from subtle impairment of aldosterone biosynthesis and recommended mineralocorticoid treatment for these patients²². This view was reinforced in a retrospective study in 2003 which proved that appropriately treated classical congenital adrenal hyperplasia patients showed better outcomes²³. Therefore early diagnosis, the use of more physiological cortisol equivalent dosages during the first years of life, and the extension of mineralocorticoid therapy to all genetically classical patients can improve the auxological outcome of congenital adrenal hyperplasia patients.

Fludrocortisone is the only mineralocorticoid available to tackle the effects of high plasma rennin activity which inevitably leads to salt wasting, life threatening adrenal crisis and sudden death. Therefore, there are no comparative studies on its effectiveness in the management of CAH. Fludrocortisone is recommended in all cases of classical congenital adrenal hyperplasia (salt wasting and simple virilizing) as it considerably helps in lowering the required dosage of glucocorticoids, thus lowering the side effects of treatment²⁴ ²⁵ ²⁶. The mortality rate also drops from a staggering 11.9% (untreated) to 4.3% for treated patients²⁷. The dose recommended by the American Academy of Pediatrics is 0.05mg to 0.3mg daily²⁸, and other reviews have quoted doses between 0.1mg to 0.75 mg daily²⁴ ²⁵ ²⁹.
9. Summary of comparative evidence on safety

As fludrocortisone is the only mineralocorticoid available to manage salt wasting in CAH, there have been no comparative studies on its safety in the management of CAH.

Most of the adverse side effects like hypertension, edema, cardiac enlargement, and congestive heart failure are caused by the drug’s mineralocorticoid activity. These side effects are usually due to over-dosage over long periods of time\(^\text{30}\). When it is used in small recommended doses patients usually don’t experience these side effects\(^\text{15}\).

One study had shown that fludrocortisone, when added to glucocorticoids, improves linear growth\(^\text{19}\), however, another study suggested that it impedes growth velocity when given in high doses\(^\text{31}\).

Clearly the benefits of fludrocortisone outweigh its adverse effects. Until further new treatments are proposed and clinical trials available, there is no alternative to fludrocortisone usage in managing the salt wasting variety of congenital adrenal hyperplasia.

10. Summary of available data in comparative cost within the pharmacological class or therapeutic group

There is no existing literature to describe comparative cost and cost-effectiveness of fludrocortisone in the treatment of CAH.

Range of costs of the proposed medicine
In Australia fludrocortisone acetate (Florinef\(^\text{®}\)) tablets are available at a cost of AUD $5.80 per 100 tablets. This gives an approximate cost of AUD 0.06 per tablet.

No comparative medications available to compare costs.

Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

On average a child with SW CAH will need 1 tablet per day for their whole life. The cost of this treatment would amount to around $21.17 per annum per child. This treatment is life-saving. Without it, the child will die.
11. Summary of regulatory status of medicine

Fludrocortisone acetate is registered as Florinef® in Australia, New Zealand, UK and USA.

Fludrocortisone acetate is not registered in many countries (usually low-income), including Vietnam, the Philippines, Indonesia, Laos, Pakistan, Bangladesh, Cambodia, Burma, Ethiopia, Mexico or Haiti. A generic brand of fludrocortisone is available in India (Manufactured by Samarth Pharma).

12. Availability of pharmacopoeial standard

British Pharmacopoeia

13. Proposed text for the WHO Model Formulary

Fludrocortisone acetate:
Synthetic adrenocortical steroid

Tablet contains: 0.1mg fludrocortisone acetate/tablet
(Available in bottle of 100 tablets/bottle)

Inactive ingredients: lactose, dicalcium phosphate, corn starch, magnesium stearate, talc and sodium benzoate.

Indications\(^3\): Partial replacement in primary and secondary adrenocortical insufficiency in Addison’s disease and in both salt wasting (SW) and simple virilizing (SV) forms of classical congenital adrenal hyperplasia.

Contraindications\(^3\): Hypersensitivity to any of the ingredients. Systemic infections unless specific anti-infective therapy is involved. Should not be used in patients with congestive heart failure.

Precautions\(^3\):
- Because of its marked effect on sodium retention, the use of Fludrocortisone in the treatment of conditions other than those indicated is not advised.
- As fludrocortisone is a potent mineralocorticoid both the dosage and salt intake should be carefully monitored to avoid development of hypertension, edema or weight gain. Periodic checking of serum electrolytes is highly advisable during prolonged therapy.
The glucocorticoid side effects may occur but can be reduced by decreasing the dosage. The lowest effective dose is highly recommended.

Dosage²:

Initial Dose: 0.05-0.3 mg/d

Maintenance Dose: 0.05-0.2 mg/d

*Dosage varies according to Sodium intake in SW CAH.

Adverse Effects³²:

Where adverse reactions occur, they are usually reversible on cessation of therapy. The incidence of predictable side-effects, including hypothalamic-pituitary-adrenal suppression correlate with the relative potency of the drug, dosage, timing of administration and duration of treatment.

Patients should be watched closely for the following adverse reactions which may be associated with any corticosteroid therapy:

- Anti-inflammatory and immunosuppressive effects: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (See Warnings and Precautions).
- Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, cardiac arrhythmias or ECG changes due to potassium deficiency, hypokalaemic alkalosis, increased calcium excretion and hypertension.
- Musculoskeletal: muscle weakness, fatigue, steroid myopathy, loss of muscle mass, osteoporosis, avascular osteonecrosis, vertebral compression fractures, delayed healing of fractures, aseptic necrosis of femoral and humeral heads, pathological fractures of long bones and spontaneous fractures, tendon rupture.
- Gastrointestinal: dyspepsia, peptic ulcer with possible subsequent perforation and haemorrhage, pancreatitis, abdominal distension and ulcerative oesophagitis, candidiasis.
- Hypersensitivity: Anaphylactic reactions, angiodema, rash, pruritus and urticaria, particularly where there is a history of drug allergies.
- Dermatologic: impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, purpura, striae, hirsutism, acneiform eruptions, lupus erythematosus-like lesions and suppressed reactions to skin tests.
- Neurological: euphoria, psychological dependence, depression, insomnia, convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, neuritis or
paraesthesias and aggravation of pre-existing psychiatric conditions and epilepsy.

- **Endocrine/metabolic:** menstrual irregularities and amenorrhoea; development of the Cushingoid state; suppression of growth in childhood and adolescence; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (eg. trauma, surgery or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycaemic agents in diabetes, weight gain. Negative protein and calcium balance. Increased appetite.

- **Ophthalmic:** posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

- **Others:** necrotising angiitis, thrombophlebitis, thromboembolism, leucocytosis, insomnia and syncopal episodes.

- **Withdrawal Symptoms and Signs:** On withdrawal, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss may occur. Too rapid a reduction in dose following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death.

**Drug Interactions**:

- **Amphotericin B injection and potassium-depleting agents:** Patients should be observed for hypokalemia.
- **Anticholinesterases:** Effects of anticholinesterase agents may be antagonised.
- **Anticoagulants, oral:** Corticosteroids may potentiate or decrease anticoagulant action. Patients receiving oral anticoagulants and corticosteroids should therefore be closely monitored.
- **Antidiabetics:** Corticosteroids may increase blood glucose; diabetic control should be monitored, especially when corticosteroids are initiated, discontinued, or changed in dosage.
- **Antihypertensives, including diuretics:** corticosteroids antagonise the effects of antihypertensives and diuretics. The hypokalaemic effect of diuretics, including acetazolamide, is enhanced.
- **Anti-tubercular drugs:** Isoniazid serum concentrations may be decreased.
- **Cyclosporin:** Monitor for evidence of increased toxicity of cyclosporin when the two are used concurrently.
- **Digitalis glycosides:** Co-administration may enhance the possibility of digitalis toxicity.
- **Oestrogens, include oral contraceptives:** Corticosteroid half-life and concentration may be increased and clearance decreased.
- **Hepatic Enzyme Inducers (e.g. aminoglutethimide, barbiturates, carbamazepine, phenytoin, primidone, rifabutin, rifampicin):** There may be increased metabolic clearance of Florinef. Patients should be carefully observed for possible diminished effect of steroid, and the dosage should be adjusted accordingly.
- **Human growth hormone:** The growth-promoting effect may be inhibited.
• Ketoconazole: Corticosteroid clearance may be decreased, resulting in increased effects.
• Nondepolarising muscle relaxants: Corticosteroids may decrease or enhance the neuromuscular blocking action.
• Nonsteroidal anti-inflammatory agents (NSAIDS): Corticosteroids may increase the incidence and/or severity of GI bleeding and ulceration associated with NSAIDS. Also, corticosteroids can reduce serum salicylate levels and therefore decrease their effectiveness. Conversely, discontinuing corticosteroids during high-dose salicylate therapy may result in salicylate toxicity. Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.
• Thyroid drugs: Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in adrenocorticoid dosage.
• Vaccines: Neurological complications and lack of antibody response may occur when patients taking corticosteroids are vaccinated.

Over dosage:

A single large dose should be treated with plenty of water by mouth. Careful monitoring of serum electrolytes is essential, with particular consideration being given to the need for administration of potassium chloride and restriction of dietary sodium intake.
14.1 Appendix 1 – Information on Congenital Adrenal Hyperplasia (CAH)

Useful background information on Congenital Adrenal Hyperplasia (CAH) can be found in the following document (prepared by the National Institutes of Health Clinical Center, Bethesda, MD, USA):
Facts about CAH
Congenital Adrenal Hyperplasia

This information was prepared by your health care team to help you learn about congenital adrenal hyperplasia (CAH). CAH is a genetic disorder of the adrenal glands that affects the body’s general health, growth, and development.

What are the adrenal glands?
The adrenal glands are a pair of walnut-sized organs above the kidneys. They make hormones, which act like chemical messengers to affect other organs in the body.

An organ at the base of the brain, called the pituitary gland, helps regulate the adrenal glands.

Each adrenal gland has two parts: the medulla (the inner part), and the cortex (the outer part). The medulla makes the hormone adrenaline. The cortex makes the hormones cortisol, aldosterone, and androgens.

CAH affects how the adrenal cortex works. In severe cases, the adrenal medulla may also not function normally.

What do adrenal hormones do?
Hormones made by the adrenal glands are important for the body’s normal function. Cortisol affects energy levels, sugar levels, blood pressure, and the
body's response to illness or injury. Aldosterone helps maintain the proper salt level. Androgens are male-like hormones needed for normal growth and development in both boys and girls. Adrenalin affects blood sugar levels, blood pressure, and the body's response to physical stress.

**What is CAH?**
The adrenal glands help keep the body in balance by making the right amounts of cortisol, aldosterone, and androgens. But in CAH, production of cortisol is blocked. Some children with CAH also lack aldosterone. These imbalances cause the adrenal gland to make too much androgen.

**Symptoms**
Too little cortisol may cause tiredness and nausea. During illness or injury, low cortisol levels can lead to low blood pressure and even death.

Lack of aldosterone, which occurs in three out of four patients with classic CAH, upsets salt levels. This imbalance may cause dehydration (too little fluid within the body), and possibly death. Chronic salt imbalance may also cause abnormal growth.

Too much androgen causes abnormal physical development in children. Boys and girls with CAH may grow too fast, develop early pubic hair and acne, and stop growing too soon, causing short stature. Girls exposed to high levels of androgens before birth may have abnormal external genitalia at birth. Although their internal female organs are normal, excess androgens may also affect puberty and cause irregular menstrual periods.

Too much cortisol replacement also causes abnormal development in children. Side effects include obesity and short stature. Also, too much hydrocortisone, the medicine given to replace cortisol in the body, can cause decreased bone density (osteoporosis) and high cholesterol levels.

**Are there different types of CAH?**
There are many types of CAH. The severe form is called classic CAH, while the mild form is called nonclassic CAH.

**Classic CAH**
The most common is 21-hydroxylase deficiency (95 percent of cases). A child with this type of CAH has adrenal glands that cannot make enough cortisol and may or may not make aldosterone. As a result, the glands over-work trying to make these hormones and end up making too much of what they can make: androgens.

The second most common form of CAH is 11-hydroxylase deficiency. A child with this type of CAH has adrenal glands that
make too much androgen and not enough cortisol. Children with this type of CAH may also have high blood pressure. These patients do not have aldosterone deficiency.

Rare other types of CAH include 3-beta-hydroxy-steroid dehydrogenase deficiency, lipid CAH, and 17-hydroxylase deficiency.

**Nonclassic (late-onset) CAH**
This type of CAH is a mild form of CAH and is almost always due to 21-hydroxylase deficiency. Only a handful of people have been described as having nonclassic (mild) CAH due to other causes. People with nonclassic 21-hydroxylase deficiency make enough cortisol and aldosterone, but they make excess androgens. Symptoms come and go, beginning at any time but typically in late childhood or early adulthood. Boys often do not need treatment. Girls usually need treatment to suppress their excess androgens.

Nonclassic CAH is common. One in every 1,000 people has nonclassic 21-hydroxylase deficiency. Incidence is higher in certain ethnic groups including Ashkenazic Jews, Hispanics, Yugoslavs, and Italians.

**How is CAH inherited?**
An inherited disorder is one that can be passed from the parents to their children. CAH is a type of inherited disorder called “autosomal recessive.” For a child to have CAH, each parent must either have CAH or carry a genetic mutation. This means that if two parents are CAH carriers (that is, they have the gene for CAH but not the disorder), their children have a 25 percent chance (1 in 4) of being born with CAH. Each sibling without CAH has two chances in three of being a carrier. Tests can be done to find out if someone is a carrier.

Classic CAH occurs in 1 in 15,000 births.

**How is CAH treated?**
The standard treatment for classic 21-hydroxylase deficiency is hydrocortisone which replaces cortisol, and fludrocortisone (Florinef) which replaces aldosterone. For 11-hydroxylase deficiency, the treatment is only hydrocortisone. Patients can be started on longer-acting forms of hydrocortisone (i.e. prednisone or dexamethasone) when they are done growing.
Because replacement medications cannot mimic the body’s exact needs, patients, on average, are about 4 inches shorter than their peers.

Patients with the nonclassic form of CAH, need only hydrocortisone (or a longer-acting form of hydrocortisone). Some patients with nonclassic CAH are able to come off medication as adults, but patients with classic CAH need lifelong treatment.

What if a child with CAH has an illness, surgery, or a major injury?
During these times, a child with CAH needs closer medical attention and should be under a doctor’s care. More cortisol is needed to meet the body’s increased needs for this hormone. Higher doses of hydrocortisone are given by mouth or sometimes by intramuscular injection. Intravenous medication is needed before surgery.

Medical Alert Identification
In an emergency, it is important to alert medical personnel about the diagnosis of adrenal insufficiency, so wearing a medical alert identification bracelet or necklace is recommended. The information on the medic alert should include, “adrenal insufficiency, requires Cortef.” It is also important for the adult or parent to learn how to administer an intramuscular injection of Cortef in case of emergency.

How long can people live with CAH?
People with CAH have a normal life expectancy.

Can a woman with CAH become pregnant and have a baby?
Increased androgens may cause irregular menstrual periods and make it harder for a woman with CAH to conceive a child. But if she takes her medications as directed, she can become pregnant and have a baby.

Do men with CAH have fertility problems?
Men who take medications as directed usually have normal fertility. Rarely, however, they may develop “adrenal rest tissue” in their testicles. This is when adrenal tissue grows in other parts of the body such as the testicles or scrotum. Having adrenal rest tissue may affect a man’s ability to father a child. The tissue does not turn to cancer, but it can grow enough to cause discomfort or infertility. Large growths are rare, and surgery is usually not needed.

Do children with CAH outgrow it?
CAH cannot be outgrown. Classic CAH requires treatment for life. Some patients with nonclassic CAH may not require treatment as adults. Treatment is tailored for each patient and adjusted during childhood for growth.
Can CAH be diagnosed prenatally?
CAH can be diagnosed before birth. Amniocentesis or chorionic villus sampling during pregnancy can check for the disorder.

Neonatal Screening
Testing for classic CAH is part of the routine newborn screen done in most states.

Can CAH be treated prenatally?
Experimental prenatal treatment is available for fetuses at risk for classic CAH. For this treatment, mothers take dexamethasone, a potent form of hydrocortisone. This drug suppresses androgens in the fetus and allows female genitalia to develop more normally. This treatment lessens or eliminates the need for surgery in girls. It does not, however, treat other aspects of the disorder. Children with CAH still need to take hydrocortisone and Florinef for life. (Florinef is a brand name for fludrocortisone. It is easier to say than fludrocortisone.)

What research is being done?
Researchers are working on many aspects of CAH including discovering new ways to diagnose and treat the disorder and finding the precise genetic defects that cause CAH.

At NIH, scientists are learning more about CAH. They are also searching for better treatments for children and adults with CAH.

For more information:
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Appendix 2 - Consensus Statement on 21OHD Management
CONSENSUS

Consensus Statement on 21-Hydroxylase Deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology

JOINT LWPES/ESPE CAH WORKING GROUP

Writing Committee: Peter E. Clayton, Royal Manchester Children’s Hospital, Manchester, United Kingdom; Walter L. Miller*, University of California, San Francisco, California; Sharon E. Oberfield, Columbia University, New York, New York; E. Martin Ritzén, Karolinska Institute, Stockholm, Sweden; Wolfgang G. Sippell*, University Children’s Hospital, Kiel, Germany; Phyllis W. Speiser, New York University, New York, New York (*co-chairs)

Despite over 50 yr of experience with steroid replacement therapy, the management of congenital adrenal hyperplasia (CAH) remains difficult, and clinical practice varies substantially throughout the world. To consider the evidence for best practice, to formulate management guidelines, and to consider innovative therapies, The Lawson Wilkins Pediatric Endocrine Society (LWPES) and The European Society for Pediatric Endocrinology (ESPE) convened a meeting in Gloucester, MA, March 14–17, 2002. The 40 participating physicians, psychologists, scientists, and surgeons from 12 countries on 4 continents agreed with the following consensus statement; this statement is concerned exclusively with CAH caused by 21-hydroxylase deficiency and does not address the other, rarer forms of CAH.

Neonatal diagnosis and treatment

The newborn female with CAH and ambiguous external genitalia requires urgent expert medical attention. The ambiguity is highly distressing to the family; therefore, immediate comprehensive evaluation is needed by referral to, or a visit by, a pediatric endocrinologist. An important goal is to ensure that the parents develop a positive relationship with their child. A well-organized multidisciplinary team (including specialists in pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics) is essential for the diagnosis and management of the infant with ambiguous genitalia. It is important that the coordinator of the team has experience in the long-term care of the patient with CAH and provides a consistent message to the parents.

Clinical evaluation in term and premature neonates. Every newborn with ambiguous genitalia, a suspected diagnosis of CAH, or an abnormal result in a newborn screen for 17-hydroxyprogesterone (17OHP) should be evaluated by a pediatric endocrinologist. The evaluation of an infant with ambiguous genitalia includes a complete history, a physical examination, a reliable ultrasound investigation of the internal genitalia and adrenals, karyotype or fluorescence in situ hybridization for sex chromosome material, and a rapid, reliable plasma or serum measurement of 17OHP. Premature newborns may need serial measurements of 17OHP to differentiate false positive results from affected infants with CAH.

Newborn screening for CAH. Neonatal mass screening for 21-hydroxylase deficiency identifies both male and female affected infants, prevents incorrect sex assignment, and decreases mortality and morbidity (1–4). Therefore, newborn screening for CAH is beneficial and is recommended. Newborn screening is sufficiently specific and sensitive to detect almost all infants with classical CAH and some infants with nonclassical CAH (NCCAH). Sampling of blood spots should be performed, ideally between 48 and 72 h of age, and sent to the screening laboratory without delay. At present, direct binding assays for blood-spot 17OHP are the only practical method for screening.

Each screening laboratory needs to establish validated cutoff levels related to gestational age and birth-weight, because 17OHP levels decline with increasing gestational age. Only laboratories with excellent internal and external quality control, demonstrated accuracy, and a rapid turn-around time on a large number of samples should be used. The laboratory should report immediately any abnormal result to the physician responsible for the patient.

A reliable CAH screening program requires both clinical evaluation and laboratory investigation for diagnostic confirmation. A positive screening result needs to be confirmed either by a validated 17OHP measurement of a second serum/plasma sample, a urine sample for a steroid profile, or analysis of the CYP21 gene. Newborn screening, using 17OHP, may detect other forms of CAH. In uncertain cases, additional specific tests are required. Measurements of androstenedione, aldosterone, cortisol, and testosterone by direct immunoassays are of limited value for diagnosis in the newborn.
CYP21 analysis. Molecular genetic analysis is not essential for the diagnosis but may be helpful to confirm the basis of the defect, to aid in genetic counseling, and to establish the diagnosis in uncertain cases. Ten mutations account for 90–95% of the affected alleles, but molecular genetic analysis is complicated by multiple copies of the genes and the possibility of multiple mutations on one allele (5, 6). The clinical features may not correlate with the genetic mutation in a small percentage of cases. Parental DNA samples are essential to segregate alleles.

Diagnosis of salt-wasting CAH. Salt wasters may not be apparent in the first days, or even weeks, after birth by electrolyte measurements. Salt wasters may be differentiated from simple virilizers by serial serum/plasma and/or urine electrolytes, plasma renin activity (PRA) or direct renin, and the results of CYP21 molecular analysis.

Prenatal diagnosis and treatment

Prenatal treatment has been advocated for fetuses at risk for classic CAH but is not appropriate for nonclassic CAH. The appropriateness, ethics, and outcomes of the prenatal treatment of CAH with dexamethasone remain controversial (7, 8). However, based on more than 200 fetuses treated to term and more than 1000 partially treated fetuses, it is clear that early institution of treatment ameliorates the genital virilization in all affected females and completely eliminates it in more than 85% (7, 9). Variations in outcome may be attributable to starting treatment late, interruption of treatment, and individual differences in dexamethasone metabolism and androgen sensitivity. No consistent untoward effects have been reported, and birth weight is not reduced. However, few treated fetuses have reached adulthood, and long-term prospective studies have not been done. Thus, all agree that the results to date are very good, but long-term safety has not yet been proven in patients treated to term or in human studies. Long-term follow-up into late adulthood is mandatory for obstetricians, a genetic counselor, and a reliable molecular genetics laboratory. It is not the “standard of care” for obstetricians in the community.

The treatment of 7 out of 8 fetuses who cannot be helped by prenatal treatment creates an ethical dilemma for which there is no clear answer, and parents should be aware of this. We believe that this specialized and demanding therapy should be undertaken by designated teams using nationally or multinational protocols, subject to institutional review boards or ethics committees in recognized centers. Written informed consent must be obtained after the balanced review of the risks and benefits of treatment. Families and clinicians should be obliged to undertake prospective follow-up of prenatally treated children whether they have CAH or not. The data should be entered into a central database audited by an independent safety committee.

Study protocols should consider all psychological/behavioral and somatic effects of excess prenatal glucocorticoids and androgens that have been observed in animal experiments or in human studies. Long-term follow-up into late adolescence is mandatory. Relevant control populations should be identified. These studies should also include the partially treated fetuses. Funding agencies, such as the National Institutes of Health or the European Commission, should be encouraged to support such long-term studies.

Surgical management and psychological issues

Genital surgery. The decision about surgery should be made by the parents, together with the clinical team, after complete preganancy genetic counseling and genotyping of the proband and parents, followed by diagnosis on fetal DNA obtained by chorionic villous biopsy. Fetal sex should be determined by Y chromosome PCR or karyotype. Allele-specific PCR should identify at least 90% of affected alleles. This number can be increased to nearly 100% with microsatellite analysis; Southern blotting; and, occasionally, DNA sequencing (5, 6). Competent core laboratories should study large numbers of samples.

Inclusion criteria for prenatal treatment include: 1) a previously affected sibling or first-degree relative with known mutations causing classic CAH, proven by DNA analysis; 2) reasonable expectation that the father is the same as the proband’s; 3) availability of rapid, high-quality genetic analysis; 4) therapy started less than 9 wk after the last menstrual period; 5) no plans for therapeutic abortion; and 6) reasonable expectation of patient compliance. The optimal dosage and timing is 20 μg/kg maternal body weight-d, in three divided doses, starting as soon as pregnancy is confirmed, and no later than 9 wk after the last menstrual period.

Treatment is continued to term in the affected female fetus and discontinued in all other fetuses. Maternal blood pressure (BP), weight, glycosuria, HbA1C plasma cortisol, dehydroepiandrosterone sulfate, and androstenedione should be measured initially and then every 2 months, adding plasma or urinary estriol after 15–20 wk of gestation.

There is substantial difference of opinion concerning whether prenatal treatment of CAH is a research endeavor. However, all are agreed that this requires a team consisting of a pediatric endocrinologist, an expert in high-risk obstetrics, a genetic counselor, and a reliable molecular genetics laboratory. It is not the “standard of care” for obstetricians in the community.

The treatment of 7 out of 8 fetuses who cannot be helped by prenatal treatment creates an ethical dilemma for which there is no clear answer, and parents should be aware of this. We believe that this specialized and demanding therapy should be undertaken by designated teams using nationally or multinational approved protocols, subject to institutional review boards or ethics committees in recognized centers. Written informed consent must be obtained after the balanced review of the risks and benefits of treatment. Families and clinicians should be obliged to undertake prospective follow-up of prenatally treated children whether they have CAH or not. The data should be entered into a central database audited by an independent safety committee.

Study protocols should consider all psychological/behavioral and somatic effects of excess prenatal glucocorticoids and androgens that have been observed in animal experiments or in human studies. Long-term follow-up into late adolescence is mandatory. Relevant control populations should be identified. These studies should also include the partially treated fetuses. Funding agencies, such as the National Institutes of Health or the European Commission, should be encouraged to support such long-term studies.
Disclosure of all relevant clinical information and all available options have been discussed and after informed consent has been obtained. The goals of surgery are: 1) genital appearance compatible with gender; 2) unobstructed urinary emptying without incontinence or infections; and 3) good adult sexual and reproductive function.

Once a decision has been made to raise a newborn as female, surgery for those with virilized genitalia caused by CAH is recommended when the patient has a high proximal junction between the vagina and urethra (12, 13). Surgery on infants with ambiguous genitalia requires a high degree of expertise and should only be performed in centers with significant experience. Based on recent clinical experience, the recommended time for surgery is at age 2–6 months; although, at present, this is not universal practice. It is important to note that surgery at this stage is technically easier than at later stages.

When the degree of virilization is less (minimal clitoromegaly and the junction between the vagina and urethra near the perineum), surgery may not be necessary. In such cases, the decision to operate should be based on appropriate contrast studies of the urinary tract and examination under anesthesia, with cystoscopy. Surgery to reduce clitoral size requires careful consideration. Total removal of the clitoris should never be performed. If clitoral reduction is elected, it is crucial to preserve the neurovascular bundle, the glans, and the preputial skin related to the glans (14, 15). The early operation should be a one-stage complete repair using the newest techniques of vaginoplasty, clitoral, and labial surgery (12–14, 16) and should be carried out at a center with experience of at least 3–4 cases/yr. Revision vaginoplasty is often required at adolescence, and the timing should be decided with the patient and family. Patients who wish to consider further procedures should be treated by a surgeon experienced in the current techniques.

Surgery between the age of 12 months and adolescence is not recommended in the absence of complications causing medical problems. Vaginal dilatations are contraindicated at this stage, although this procedure is often useful in adolescence and in adulthood. Repeated genital examinations should be minimized. Genital photography should be discouraged and only be done with parental consent and, except in infancy, performed only under anesthesia.

At each designated center, one surgical team should be responsible for all surgery involving ambiguous genitalia. There should be close cooperation between centers to broaden experience, to audit results, and to allow adequate evaluation of outcomes. We acknowledge that there are concerns about early surgery. However, surgical techniques have improved. We urge caution in judging outcome from outdated procedures. Systematic studies are needed to evaluate ultimate function for all girls undergoing surgery.

It is recognized that 46,XX children with significant virilization may present at a later age. Consideration for sex reassignment must be undertaken only after thorough psychological evaluation of patient and family. Surgery appropriate to gender assignment should be undertaken after a period of endocrine treatment.

Psychological issues. Females with CAH show behavioral masculinization, most pronounced in gender role behavior, less so in sexual orientation, and rarely in gender identity (17–19). Even in females with psychosexual problems, general psychological adjustment seems to be similar to that of females without CAH. Currently, there is insufficient evidence to support rearing a 46,XX infant at Prader stage 5 as male. Whereas studies of women whose surgery was performed 20–30 yr ago indicate a range of psychosexual difficulties, there is reason for optimism that outcome will be better with current surgical and medical treatment. We recognize a need for greater availability of professional psychological services and support groups for patients and families. Decisions concerning sex assignment and associated genital surgery must consider the culture in which a child and her/his family are embedded. As the pace of societal change, including the flexibility of gender role, increases, more frequent review of management policies and long-term outcomes is important.

Treatment considerations in patients with CAH

Optimal glucocorticoid dosing. Recognizing that treatment does not mimic physiologic secretion, the goal is to replace deficient steroids while minimizing adrenal sex hormone and glucocorticoid excess, preventing virilization, optimizing growth, and protecting potential fertility. Outcome is not always ideal. Consensus is based on clinical experience. During infancy, initial reduction of markedly elevated adrenal sex hormones may require up to 25 mg hydrocortisone (HC)/m²-d, but typical dosing is 10–15 mg/m²-d divided three times daily. HC oral suspension is not recommended (20); divided or crushed tablets of HC should be used in growing children. Cortisone acetate requires conversion to cortisol for bioactivity (21); HC is considered the drug of first choice. Excessive doses, especially during infancy, may cause persistent growth suppression, obesity, and other Cushingooid features. Therefore, complete adrenal suppression should be avoided. Insufficient data exist to recommend higher morning or evening dosages.

Whereas HC is preferred during infancy and childhood, long-acting glucocorticoids may be an option at or near the completion of linear growth. Prednisone and prednisolone need to be given twice daily. Prednisolone may be preferable, because this is the active drug. The dose (2–4 mg/m²-d) should be approximately one fifth the dose of HC. The dosage of dexamethasone is 0.25–0.375 mg/m²-d, given once daily. Monitoring of these more potent glucocorticoids should include BP, in addition to weight, and other clinical and laboratory variables. These steroids have minimal mineralocorticoid effect, compared with HC. In children with advanced bone age, such as in boys with nonsalt-losing CAH, initiation of therapy may precipitate central precocious puberty, requiring treatment with a GnRH agonist.

Mineralocorticoid use. All classic CAH patients should be treated with fludrocortisone at diagnosis in the newborn period. Dosage requirements in early infancy range from 0.05–0.30 mg/d, whereas typical maintenance doses are 0.05–0.2 mg/d, depending on the sodium intake. Such therapy will reduce vasopressin and ACTH levels and lower the
dosage of glucocorticoid required. The need for continuing mineralocorticoids should be assessed based on PRA and BP (22). Sodium chloride supplements are often needed in infancy, at 1–3 g/m²d (17–51 mEq/d), distributed in several feedings (23).

Criteria for the diagnosis and treatment of NCCAH. The standard method of diagnosis involves a 60-min stimulation test with (1–24)ACTH. However, a single early-morning (before 0800 h) level of 17OHP may also serve as a fairly reliable screening tool. Treatment is only recommended for symptomatic patients [e.g., those with an advanced bone age coupled with a poor height prediction (compared with the family target height), hirsutism, severe acne, menstrual irregularities, testicular masses, and (in the young adult) infertility].

Monitoring treatment for classic CAH. Monitoring may be accomplished based on physical and hormonal findings suggestive of excessive or inadequate steroid therapy. Laboratory measurements may include serum/plasma electrolytes, serum 17OHP, androstenedione, and/or testosterone, and PRA or direct renin, every 3 months during infancy and every 4–12 months thereafter. The time from the last glucocorticoid dose should be noted; the diurnal rhythm of the adrenal axis should be taken into account. Patients receiving adequate replacement therapy may have hormone levels above the normal range. Alternative measurements include urinary metabolites (pregnanetriol) or filter paper blood and salivary hormones. Ideally, laboratory data will indicate a need for dose adjustments before physical changes, growth, and skeletal maturation indicate inadequate or excessive dosing.

Stress dosing. Patients with CAH should carry medical identification and information concerning therapy for stress. Caregivers should have an emergency supply of im HC or glucocorticoid suppositories. Because circulating levels of cortisol normally increase during stress, patients should be given increased doses of glucocorticoids during febrile illness (>38.5°C/101°F), when vomiting or when unable to take oral feedings, after trauma, and before surgery. Participation in endurance sports may also require extra steroid dosing. Mental and emotional stress, such as school examinations, does not require increased dosing.

Stress dosing should be 2–3 times the maintenance glucocorticoid dose for patients able to take oral medications. Surgical and trauma patients and those unable to take oral steroids require rectal or parenteral HC. Glucose concentrations should be monitored, and iv sodium and glucose replacement may be required. Surgical or trauma patients may receive rectal, im, or iv HC. When practical, an iv bolus may be followed by continuous iv infusion of HC. Guidelines for iv bolus and subsequent dosage are as follows: for children younger than 3 yr of age, 25 mg followed by 25–30 mg/d; for children 3–12 yr of age, 50 mg followed by 50–60 mg/d; and for adolescents and adults, 100 mg followed by 100 mg/d (24).

Resources for patients and families with CAH. Official CAH websites, videos, and pamphlets should be developed by LWPEs and ESPE and made available to other pediatric endocrine societies. Examples of websites potentially useful as family resources include: <www.hopkinsmedicine.org/pediatricendocrinology/patient.html> and <www.rch.unimelb.edu.au/publication/cah_book/index.html>.

Management of classical CAH and NCCAH in adolescence

Physical and genital examinations over the life span. The prior practice of frequent genital examinations in females should be abandoned. Therefore, unless there is clinical or laboratory evidence of poor control or one seeks to assess the pubertal progress and size of the clitoris, genital examinations should not be performed. In adolescent females or if questions arise regarding the progress of puberty, the use of tampons, or initiation of sexual intercourse, genital examination with attention to the adequacy of the vaginal introitus may need to be performed. Most importantly, the patient and/or her family should be appraised of the reasons for the examinations (25).

Safeguarding psychological well-being. Psychological assessment and support of the patient (with both classic and NCCAH) and his/her family should be a routine component of the comprehensive care and management of these patients. Parents and/or patients should be offered the option of age- and sex-appropriate psychologic counseling at the time of the initial diagnosis. Counseling regarding sexual function, future surgeries, gender role, and issues related to living with a chronic disorder should be addressed.

Management issues during transition of care of the young adult patient. Traditionally, the pediatric endocrinologist directly or indirectly cares for infants, children, and adolescents with CAH. In late adolescence or even early adulthood, care is usually transferred to an internal medicine (adult) endocrinologist in the same institution or clinical setting. We recommend that a transition team should also include, as needed, a gynecologist, a urologist, and a psychologist with specific expertise and interest in the treatment of such patients.

Adult males should be counseled that compliance with treatment is important to enhance normal fertility and reduce the risk of a palpable testicular mass (26). Although frequently found by sonography, testicular masses may not be of clinical importance. Nonetheless, we recommend periodic physical examinations and, as indicated, hormonal measurements, sonography, and magnetic resonance imaging of both testes to assist in delineating the extent of such lesions. Surgical removal of a glucocorticoid unresponsive nodule may be effective in preserving or improving fertility (27).

The effectiveness of the genital repair in adolescent and adult women needs to be assessed, and vaginal stenosis should be repaired. Counseling about anxiety, depression, dyspareunia, and other sexual matters, as well as contraception, is useful (28).

Women with NCCAH should be counseled regarding an increased risk of infertility. However, the actual numerical risk is not available and may vary depending on the ethnic background and degree of overlap with polycystic ovarian
syndrome. The risk of women with CAH or NCCAH having an affected fetus is low.

Management of a CAH woman in pregnancy. Pregnant women with CAH should be monitored and delivered in a tertiary center equipped and experienced to handle such pregnancies. Glucocorticoids that do not cross the placenta, such as HC and prednisolone, should be used. Dexamethasone should be avoided (except when used in prenatal therapy). Glucocorticoid doses should be adjusted to maintain maternal serum testosterone concentrations near the upper range of normal for pregnancy (29). When reconstructive surgery has been performed, we recommend elective cesarean section to avoid damage to the genital tract. When cesarean section is performed, doses of HC have to be increased before and tapered after delivery. A pediatrician should be present during delivery to take care of the newborn and to initiate diagnostic procedures when an affected child is expected according to the results of prenatal testing (30, 31).

Experimental therapies and future developments

The place of adrenalectomy in CAH. Bilateral adrenalectomy by laparoscopy is effective in decreasing adrenal androgens and the likelihood of iatrogenic hypercortisolism (32, 33). It should be considered only in cases where conventional therapy is failing. Vigilance in maintaining regular substitution of HC and fludrocortisone is mandatory, with prompt institution of stress dosages at the onset of illness. The patient must be monitored, throughout life, for activation of ectopic adrenal rest tissue. The procedure should only be carried out where long-term follow-up is secured, and in the form of ethically approved clinical studies.

CRH antagonists for adrenal suppression in CAH. The use of CRH antagonists in CAH is promising on theoretical grounds but awaits future developments of drugs with improved pharmacological properties.

Treatment with antiandrogens and aromatase inhibitors in addition to HC and fludrocortisone. Based on the success of an earlier approach in familial male sexual precocity, it was hypothesized that the deleterious effects of elevated androgens on adult height could be prevented by using an antiandrogen to block androgen action and/or an aromatase inhibitor to block conversion of androgen to estrogen. Limited short-term (2 yr) studies in CAH showed improved control of height velocity and bone maturation at reduced glucocorticoid dosage (34). Long-term safety data are not available, and reproductive effects are not known. Liver function has to be carefully monitored.

Epinephrine deficiency in CAH. Patients with CAH suffer from varying degrees of dysplasia and dysfunction of the adrenal medulla, expressed primarily as epinephrine deficiency (35). This may play a role in response to stress. Possible therapeutic implications are under study.

Innovative genetic approaches. Preimplantation genetic diagnosis for CAH is possible, but further research is required to determine its utility. Gene therapy is currently not possible in humans with this disorder.

DHEA replacement in CAH. CAH patients on glucocorticoid treatment have low DHEA levels. Studies in adult patients with Addison’s disease have shown beneficial effects of DHEA replacement (36), but the relevance in CAH is unknown.

11β-Hydroxysteroid dehydrogenase (11β-HSD) inhibitors in CAH. 11β-HSD inhibitors have the potential for modulating tissue-specific activity of glucocorticoids (37). At present, there are no specific compounds that are selective inhibitors of 11β-HSD type I or type II, and clinical experience with nonspecific 11β-HSD inhibitors is limited. Therefore, the use of these inhibitors cannot be recommended, at present.

GH treatment with or without administration of GnRH agonists. A meta-analysis of 561 patients with CAH (the majority with 210H deficiency) revealed an overall mean final height SDS score of –1.4 (38). Thus, an acceptable height is achieved by many patients with CAH, and the mean adult height deficit is substantially less than frequently thought. However, some CAH patients fail to reach normal adult height. A small group of short CAH patients have been treated with GH for 2 yr, either alone or in combination with a GnRH agonist. This significantly improved growth rate and predicted final height (39), but adult height data are not yet available.

Conclusions

These guidelines are designed to cover all aspects of the management of this complex disease in children, from diagnosis through adulthood. The multidisciplinary nature of management is emphasized, with the recognition that such expert teams need appropriate reimbursement and governmental support. There remain important deficits in our knowledge about this disorder; and again, these have been highlighted. New therapeutic strategies are emerging but, as yet, require longer evaluation before being introduced into routine practice. In the meantime, we should focus on early diagnosis, optimal medical and surgical treatment, and attention to compliance.

Acknowledgments

The LWPES gratefully acknowledges Aventis Pharmaceuticals for partial support of the consensus meeting in Gloucester. The following participants convened in Gloucester, Massachusetts, March 14–17, 2002, and contributed to this manuscript: Sheri Berenbaum (College Station, PA), George Chrousos (Bethesda, MD), Peter Clayton (Mancheste, UK), Gordon Cutler (Indianapolis, IN), Sabine De Muinck Keizer-Schrama (Rotterdam, The Netherlands), Patricia K. Donahoe (Boston, MA), Patricia A. Donahoue (Iowa City, IA), Malcolm Donaldson (Glasgow, UK), Maguelone Forest (Lyon, France), Kenji Fujieda (Asahikawa, Japan), Lucia Ghionizz (Parma, Italy), Maria Ginalska-Malinowska (Warsaw, Poland), Melvin M. Grumbach (San Francisco, CA), Annette Grüters (Berlin, Germany), Kersten Hagenfeldt (Stockholm, Sweden), Raymond L. Hintz (San Francisco, CA), John W. Honour (London, UK), Ieuun A. Hughes (Cambridge, UK), Ursula Kuhnle-Krahl (München, Germany), Peter A. Lee (Hershey, PA), Heino Meyer-Bahlburg (New York, NY), Claude Migeon (Baltimore, MD), Walter L. Miller (San Francisco, CA), Jorn Müller (Copenhagen, Denmark), Maria I. New (New York, NY), Sharon E. Oberfield (New York, NY), Michael Peter (Kiel, Germany), E. Martin Ritzén (Stockholm, Sweden), Paul A. Saenger (Bronx, NY), Martin O. Savage (London, UK), Justine M. Schober (Erie, PA), Wolfgang G. Sippell (Kiel, Germany), Janos Solyom (Budapest, Hungary), Phyllis W. Spitzer (Manhasset, NY), Bradford L. Therrell (Austin, TX), Judson J. Van Wyk (Chapel Hill, NC), Garry L.
Warne (Melbourne, Australia), Perrin C. White (Dallas, TX), Ludwig Wildt (Erlangen, Germany), and Selma Witchell (Pittsburgh, PA).

The working group also acknowledges the contributions of Peter C. Hindmarsh (London, UK), Lewis B. Holmes (Boston, MA), Lourdes Ibanez (Barcelona, Spain), Jennifer Lee S. Levin (New York, NY), Songya Pang (Chicago, IL), and Anna Wedell (Stockholm, Sweden).

Received April 19, 2002. Accepted May 19, 2002.

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References
14.3 Appendix 3 – Letters from organisations supporting this application

14.3.1 CAH Support Group of New Zealand (CAHNZ Trust)
Expert Committee on the Selection and Use of Essential Medicines
Children’s Essential Medicines List
World Health Organization
Geneva

24th May 2008

To Whom It May Concern,

For over eleven years I have run a national (New Zealand) support group for individuals and families whose children are affected by the endocrine disorder, Congenital Adrenal Hyperplasia. Recently achieving charitable status, our Trust now represents around seventy people with this condition, whose ages range from 0-40 years. Over a hundred thrice-yearly newsletters are sent out by our organization to members and health professionals. This support group enjoys good standing in the medical community and is highly valued by its members as a source of information and support. Our group is also affiliated with a number of sister organizations both nationally and internationally and is listed as the official New Zealand contact on many other websites.

On behalf of the CAHNZ Trust and its members, I am writing to state our wholehearted support for the inclusion of the medications hydrocortisone and fludrocortisone into the WHO Children’s Essential Medicines List. Our reasons are very simple.

The daily taking of corticosteroids is a non-negotiable issue for CAH-affected children and adults. Without access to a regular supply of this medication these people would die. Those with affected family members are reminded of this daily. Having access to reliable, quality medicine continues to be a source of ongoing anxiety to many New Zealanders, despite the fact that we live in a part of the world where free, quality health care is available. When there is a worldwide shortage of medication, or when medication is reformulated in some way (alterations to colour, shape, or storage conditions), these changes add stress to lives which already carry extra health burdens. A small domestic incident such as dropping a container of...
hydrocortisone syrup (specially formulated by designated pharmacists), medication being in lost luggage whilst travelling, or being on holiday in a remote area when getting sick, highlight some of the issues that members have to contend with in managing their daily medication regime.

On behalf of our Trust and members I raise these issues for your consideration and sincerely request your support in designating these medications in the children’s essential medicines list. We fully back adoption of this proposal.

Thank you for your consideration of this letter.

Yours sincerely,

Helen Mann

CAHNZ Founder & Director
14.3.2  Indonesian Pediatric Society Endocrinology Chapter
To:  
Expert Committee on the Selection and Use of Essential Medicines  
Children’s Essential Medicines List  
World Health Organization  
Geneva

To Whom it May Concern,

My name is Aman B Pulungan, and I am presently the Chairman of Endocrinology Chapter, Central Board of Indonesian Pediatric Society. On behalf of the organization, I would like to request your consideration to include the hydrocortisone and fludrocortisone in the WHO Children’s essential medicines list and to provide recommendation to our Government to make the above medicines available for CAH children in Indonesia.

Based on the current statistic, there are approximately 15,000 CAH children detected, and the number continues to escalate. The increase is approximately ranges from 327 to 409 cases each year. Most of the children come from lower to middle group of income with annual earning range from USD 500 to USD 40,000. Those children have not received proper medication and some received irregular medication due to unavailability of the drugs in the country. Those who come from upper income group normally purchased the medicine overseas while the remaining mostly expect and receive donation from the organization such as CLAN. These issues may create potential discontinuity of the supply, which will have great impact on the future survival of CAH children in Indonesia.

Due to the increasing number of CAH children, it is our main concern to ensure these children will receive proper and continued medication for life times. Thus, it is essential to have the recommended drugs available in our country and to include these medicines in the WHO Children’s Essential Medicines List. Any information pertaining CAH children are available, if needed, to support the inclusion of these medicines in the WHO list.

As mentioned earlier, there are registered 245 CAH children spread throughout the archipelago. Their health conditions as well as their economic conditions are deteriorating as there is no sufficient drug supply and due to high price of the medicines. Doctors are also unable provide proper treatment without prescribing these drugs and often face difficulties to find alternate medications. Parents feel they are unable to speak for
themselves and/or make recommendation to the Government without support from our organization. On the hand, we need WHO support to convince our Government that these drugs are needed.

There are a number of CAH children detected who have not received any medication at all. These children live in number of region of Indonesia and ranging from the age of 3 months to 18 years where medicines are out of their reach. As highlighted above, those children CAH we have detected to date are in dire need for the hydrocortisone and fludrocortisone and their survivals are very much dependent on these drugs.

In closing, we would highly appreciate your consideration and support to include the above medicines in WHO Children’s essential medicines list. It is our mission to help maintain and improve the health our future generation including CAH children. CAH children also deserve happy life and bright future like any other healthy children in the world.

We thank you for your kind attention and cooperation.

Yours Sincerely

Aman B.Pulungan MD
Chairman of Endocrinology Chapter
14.3.3 CAH Support Group of the Philippines (CAHSAPI)
Introduction of yourself and organisation. Brief indication of number of children with CAH in your country / care (if relevant)

Greetings! My name is Alain Yap and I write to you in behalf of CAHSAPI - the first Philippine Support Group for families dealing with CAH with temporary office located inside the Philippine General Hospital. My wife and I have a daughter who was diagnosed with Congenital Adrenal Hyperplasia or CAH in 2004. Words can barely express the difficulties facing us then. But the threat of death only hardened our resolve to abandon everything else and dedicate our lives to ensure that she will live. As we were able to gather the help we needed, we also were exposed to the plight of other children with CAH who come from poor families and despite the added responsibility and likewise limited resources, I accepted the prodding of doctors when asked to head this group. To date, our members now number around 80 and expecting more as newborn screening in the country continues to detect those born with CAH.

Our group is primarily composed of indigent families who can barely afford their daily needs and do not have the resources to handle the additional burden brought about by the condition. As the medicines we need for our children are not available locally, we were fortunate to receive help from outside sources in the form of medicines which we distribute to members for a nominal fee - which we also use for emergency purchases of additional supplies. Other group activities concern parenting, continuous education for parents regarding CAH and required forms of treatment.

Indication of your support for the inclusion of hydrocortisone and fludrocortisone in the WHO Children’s Essential Medicines List

Why you feel these drugs should be included:
Quite simply, these 2 drugs help keep my child and children with CAH alive. Placing them on the list would give treatment of CAH the importance and priority it needs and would work towards greater understanding of the condition, most of the populace have not even heard exists.

Please include examples from your country on difficulties families face if relevant
Both drugs are not available locally and puts persons with CAH at unnecessary and uncertain risk everyday. It does not help that government imposes duties and tax on such medicine donations during importation, depleting the funds that would be best used on getting more medicines as working on getting the exemptions is almost a futile and effort intensive exercise. Moreover, the families affected belong to low or no-income brackets. No access to those drugs is almost tantamount to letting the babies suffer a slow death.

Any other points you would like to make!
CAH requires a lifetime of treatment and medications. It is a burden which we wish not upon anyone. Access to the medicines on a daily basis remains our priority and any step that would help bring us these medicines also bring us hope that despite all the difficulties, we will overcome.

Yours Sincerely,

Alain Benedict Yap
President

To Whom It May Concern:

29 May 2008

CAHSAPI - CAH Support and Advocacy, Philippines
Pediatric Endocrinology Clinic, Phil General Hospital, Taft Avenue, Manila
Tel: 528450 loc 2109
14.3.4 CARES Foundation (US based CAH Support Group Network)
June 4, 2008

To Whom It May Concern:

Since 2001, CARES Foundation, Inc. has been committed to improving the lives of families and individuals affected by Congenital Adrenal Hyperplasia (CAH) through proactively advancing research for better understanding of CAH, better treatments and a cure; educating the public and healthcare professionals about all forms of CAH; advocating for universal newborn screening; and providing support services and resources vital to the CAH community worldwide. Our national membership includes over 4900 families. Internationally, we have close to 250 families registered in our membership.

We are writing in strong support of the inclusion of hydrocortisone and fludrocortisone in the WHO Children’s Essential Medicines List. These medications are vital to the survival of people living with CAH. Without these medications children with CAH will, and do, die.

Many families with little or no insurance have difficulty obtaining these medications that keep their children alive. Indeed, even families with the best insurances are sometimes not covered for these medications. It is for these reasons that CARES Foundation is in support of including hydrocortisone and fludrocortisones in the Children’s Essential Medicines List.

Sincerely,

Suzanne Levy
Program Manager
14.3.5 Royal Children’s Hospital International (RCHI)
29 May 2008

Expert Committee on the Selection and Use of Essential Medicines
Children’s Essential Medicines List
World Health Organization
Geneva

To Whom it May Concern,

For the past 30 years, I have been providing specialist care for children with congenital adrenal hyperplasia (CAH) at the Endocrine Clinic at the Royal Children’s Hospital Melbourne. Since 1995, I have made over 35 visits to the National Hospital of Pediatrics in Hanoi. I soon became aware that children with CAH in Hanoi did not have access to hydrocortisone or fludrocortisone. Instead, they were receiving prednisolone alone, and when they experienced adrenal crisis (which they did quite frequently) they had to come to the central hospital for an injection of desoxycorticosterone – DOC – and then go home on prednisolone to wait for the next crisis. Not surprisingly, the death rate was horrendous and life for the survivors was terrible, with stunted growth and Cushingoid appearance. Currently NHP has 350 patients with CAH in the Endocrine Clinic.

I strongly advocate the inclusion of hydrocortisone and fludrocortisone in the Essential Medicines List for Children.

Hydrocortisone is a short acting glucocorticoid that has been shown to have a smaller inhibitory effect on growth than prednisolone. It has some mineralocorticoid action as well, which is beneficial in salt-losing congenital adrenal hyperplasia and Addison’s disease. It is recommended as the drug of choice in international consensus guidelines on the treatment of CAH. Fludrocortisone is essential for the treatment of mineralocorticoid deficiency and there is no substitute.

Since children in Hanoi gained access to donated supplies of hydrocortisone and Florinef, mortality has fallen to zero. This is dramatic testament to the benefit that flows from having these two essential medicines.

Yours faithfully,

Professor Garry L Warne,
Director, RCHI
and Senior Endocrinologist, Royal Children’s Hospital, Melbourne
Professor Garry L Warne MBBS FRACP

Director, Royal Children’s Hospital International

The Royal Children’s Hospital, Melbourne

Flemington Rd, Parkville, Victoria 3052

Australia
14.3.6 Australian Addison’s Disease Association Inc.
To Whom It May Concern,

We are the Australian support group for Addison’s disease patients. We have over 400 members all of whom are dependent on Hydrocortisone and Fludrocortisone for life.

We completely support the inclusion of Hydrocortisone and Fludrocortisone in the Who Children’s Essential Medicines List. Being completely dependent on these medications we understand the absolute necessity of these life saving drugs!

The thought of children born with CAH (Congenital Adrenal Hyperplasia) not having access to these life giving medications is utterly abhorrent. These children will sicken and die without these medications. They must be made widely available at a reasonable price.

Please include Hydrocortisone and Fludrocortisone on the WHO’S Children’s Essential Medicines List.

Yours Sincerely,

Noreen Secomb and Sue O’Brien on behalf of AADAI
(President) (Secretary)
14.3.7 Association Surrénales (French Support Group)
Dear Dr Kate Armstrong,

I am Claudine Colin, president of “Surrénales”, French Organisation who helps persons with:

- Congenital Adrenal Hyperplasia
- Addison’s disease
- Cushing’s Syndrome
- Congenital adrenal hypoplasia

Our organization has 400 members and among these members 86 CAH.

We have also members from North Africa

There is about 50/60 children with CAH who born each year in France.

I support your action for the inclusion of hydrocortisone and fludrocortisone in the WHO Children’s Essential Medicines List

- In France, we have hydrocortisone and fludrocortisone, but our members from North Africa have great difficulty to obtain fludrocortisone which is not disponible in their countries.
- Sometimes, they have also difficulties to obtain hydrocortisone

Yours Sincerely,

Claudine Colin

www.surrenales.com
14.3.8 Philippines Society of Pediatric Metabolism and Endocrinology (PSPME)
To Whom it May Concern:

Good day!

Please allow me to introduce myself first. I am currently an Associate professor of the Department of Pediatrics in the University of the Philippines and Philippine General Hospital. I am also the coordinator of the Congenital Adrenal Hyperplasia Project and medical adviser of the CAHSAPI, the patient support group in the Philippines. I was the past President of Philippine Society of Pediatric Metabolism and Endocrinology (PSPME) in 2004 – 2006. My academic and clinical positions have provided me the opportunity of taking care of children with congenital adrenal hyperplasia (CAH) and their families.

The incidence rate of CAH in the Philippines is about 1 in 7,000. (The website of the Newborn Screening Reference Center for the published incidence rate is http://www.newbornscreening.ph/quicklinks/prevalenceupdate06.pdf.) Based on the data of the Newborn Screening Center- National Institute of Health, there are 118 cases of babies confirmed to have CAH as of January 2008. This does not include the patients who’ve missed the newborn screening but have CAH. I believe that there are much more CAH patients and some of them, specifically the salt-losing type, may die prior to the diagnosis of CAH is made because of severe dehydration and absence of proper medication.

We have parenteral form of hydrocortisone in the Philippines. However, it is sad to mention that we have no oral preparations of hydrocortisone and fludrocortisone tablets in the Philippines. Hydrocortisone is a better choice of medicine than the other long-acting glucocorticoid preparation when our patients are babies or children. Clinically, we see good response to hydrocortisone and less complication like Cushing syndrome which may develop due to high dose or potency of steroid preparation. Fludrocortisone is particularly useful in treating patients with salt losing type of CAH. Inclusion of these two drugs, hydrocortisone tablets (4 or 5 mg, 10 mg, 20 mg) and fludrocortisone tablets (0.1 mg) in the WHO Children’s Essential Medicines List will be beneficial to the children with
CAH. Availability of the drugs and maintenance at appropriate dosage can decrease the hospitalization rate due to adrenal crisis in the children with CAH.

In the Philippines, we have to request doctors, friends and relatives abroad to help us to get hydrocortisone and fludrocortisone tablets since they are not available in our country. The medicines are either hand-carried by doctors or patient’s friends or relatives during travel or delivered by commercial couriers. Such acts or methods of delivery are often very time-consuming and can be more costly. Moreover, many poor families do not have friends or relatives abroad to help them. Delay in management with proper medications may push the patients into adrenal crisis and unnecessary deaths.

As physicians, we would always want to promote health and prevent morbidity as well as mortality. We are looking forward to the prompt inclusion of hydrocortisone and fludrocortisone tablets in the WHO Children’s Essential Medicines List.

Yours Sincerely,

Sioksoan Chan-Cua, MD
14.3.9 National Institute of Child Health, Karachi, Pakistan
Expert Committee on the Selection and Use of Essential Medicines
Children’s Essential Medicines List
World Health Organization
Geneva

To Whom It May Concern

My name is Prof. Syed Jamal Raza and I am presently working as Professor in Pediatrics at National Institute of Child Health which is based in Karachi, Pakistan. NICI is a 475 bedded tertiary health care unit which specializes in almost all types of pediatric subspecialties. We cater to the patients from South Punjab, Baluchistan and from all over Sind. We presently have an Endocrine OPD with over 100 registered patients of congenital adrenal hyperplasia.

As Pakistan is a developing country, unfortunately we do not have all endocrinological investigations and drugs available here. For this reason we offer our full support for the inclusion of hydrocortisone and fludrocortisones in the WHO Children’s Essential medicines List. Acceptance of this proposal will make it possible for us to prove to our government that these life saving medicines are urgently required in our country.

There is no replacement for fludrocortisone available internationally that can match its superior mineralocorticoid properties therefore it is a life saving medication for all salt wasting congenital adrenal hyperplasia patients. Its importance is undeniable as it has been a mainstay for treating this disorder for many decades.

As we deal with pediatric patients, hydrocortisone is an essential requirement for all congenital adrenal hyperplasia patients as it ensures that these patients achieve proper height
in addition to maintaining the blood glucose level that is needed for day to day activities. For this reason drugs like dexamethasome are avoided as they accelerate bone age and cause early closure of epiphyses causing stunting of final height outcome.

In Pakistan availability of both medicines is the main issue as they are not freely available. Karachi and Lahore are the only two major cities where the drugs are available and even within the city there are only one or two places where the drugs can be purchased at an extremely high cost, sometimes costing approximately two to three times the international retail price.

Once again I must implore the WHO Expert Committee on the Selection and Use of Essential Medicines to kindly accept this proposal as this will greatly help us and other countries like us to overcome the humongous hurdles we face in providing quality health care to our patients.

Yours Sincerely

Prof. Syed Jamal Raza
Professor of Pediatrics
National Institute of Child Health
Karachi, Pakistan.
14.3.10 Caring & Living As Neighbours (CLAN)
Expert Committee on the Selection and Use of Essential Medicines  
Children’s Essential Medicines List  
World Health Organization  
Geneva  

1st June 2008

To Whom it May Concern,

On behalf of CLAN (Caring & Living As Neighbours), I would like to confirm my very strong support for the inclusion of hydrocortisone and fludrocortisone tablets within the WHO Essential Medicine List for Children.

CLAN is an Australian-based Non-Government Organisation (NGO) that is committed to helping children who are living with chronic medical conditions in resource-poor countries. CLAN was founded in 2004 when articles published in Congenital Adrenal Hyperplasia (CAH) Support Group Newsletters in America and Australia first highlighted the plight of children living with CAH in Vietnam. Because Florinef and hydrocortisone were only available on the black market, families were paying exorbitant prices, and bankrupting themselves trying to care for their children.

Since then, CLAN has facilitated the supply of regular supplies of fludrocortisone and hydrocortisone to children in Vietnam with CAH. We now support over 400 children with CAH in Vietnam and are trying to work with government to ensure the drugs are registered and made available locally, so that families will know the security of long-term availability.

As a result of our work in Vietnam CLAN has since been contacted by health professionals in Indonesia, the Philippines and Pakistan. We are now helping doctors and families in these countries to secure local supplies – and sending humanitarian aid as we are able.

Humanitarian aid from a small NGO such as CLAN is not the answer for the thousands of CAH families living around the world however. CAH is not such a rare condition. The drugs needed for management of CAH are: cheap, safe, effective and also used for the treatment of Addison’s Disease (so could help many others).

On behalf of the many hundreds of anxious, impoverished and heart-broken families CLAN has met and worked with over the years (and this is not an exaggeration on any level), I implore the WHO to include fludrocortisone and hydrocortisone tablets within your Essential Medicine Lists as a matter of urgency.

Yours Sincerely,

Dr Kate Armstrong  
Founder & President

13 Fourth Avenue  Denistone NSW 2114  Australia  
T: +61-(0)2-9874 1276  E: info@cahclan.org  ABN 30 897 322 928
14.4 Appendix 4 – Glucocorticoid Treatment Clinical Guideline

Access is available at:

http://www.ich.ucl.ac.uk/clinical_information/clinical_guidelines/cmg_guideline_00053/
15. References


3 Pediatric Endocrinology 5th Edition Volume II ; Fima Lifshitz pg. 213


15 Authors - personal communication with relevant health professionals (best source of estimates, given no formal data-bases exist in most cases).

16 Personal communication – Suzanne Levy, Acting Executive Director, CARES Foundation (Congenital Adrenal hyperplasia Research, Education and Support). www.caresfoundation.org

18 Food and Drug Administration, United States of America (www.fda.gov/MedWatch/SAFETY/2004/jun_PI/FlorineF_PI.pdf) or Corticosteroid Supplementation for Adrenal Insufficiency; Coursin and Wood; JAMA 2002;287:236-240.


