Congenital Adrenal Hyperplasia - Full Clinical Guideline – Burton only

Reference no.: WC/NP/17N/Aug 22

This guideline is intended to help any Paediatrician:

a) Considering the diagnosis of congenital adrenal hyperplasia

b) Managing a patient known to have congenital adrenal hyperplasia who is acutely unwell

Definition

A group of autosomal recessively inherited defects in the production of enzymes involved in the adrenal steroid hormone synthesis pathway (Incidence 1:10,000 to 1:20,000 live births). The classical type is 21-Hydroxylase deficiency (CYP21A2 gene mutation).

The pathophysiology is typically characterised by excessive androgens (virilisation of females), deficient glucocorticoids (hypoglycaemia and shock) and deficient mineralocorticoids (hyponatraemia and hyperkalaemia). However, there are rare forms of the condition, which may lead to a varied presentation.

Presentation

The children will typically (21 hydroxylase deficiency) present in one of three ways:

1. At birth

- Ambiguous genitalia in a female with hyperpigmentation- enlarged clitoris, hyperpigmented and fused genitalia
- Hyperpigmented scrotum, enlarged penis in a male

NB: A pigmented scrotum may be a normal finding in some ethnic groups

2. Deficient mineralocorticoids and glucocorticoids – usually first two weeks of life

- Vomiting, poor feeding, faltering growth, acute wt loss or poor wt gain
- Hypoglycaemia
- Hyponatraemia
- Hyperkalaemia
- Shocked (appearing septic)
- Cardiac arrhythmia, cardiac arrest and death

3. Late diagnosis of simple virilizers (non-classical CAH)

History

Postnatal diagnosis

- Poor feeding, Vomiting, poor weight gain, wt loss

Late diagnosis

- excessive growth (tall for age), hirsutism, acne, pubertal signs
- Family history of unexplained neonatal deaths/stillbirths
- Consanguinity

Examination

Genitalia

- Testes – present or not
- Labia fused or not, labial/scrotal pigmentation or not

For information see ambiguous genitalia guideline (Neonates)

- Phallus – small or large
- Vaginal opening – present or not
- Anogenital anomalies

Dehydration

- Sunken eyes, Sunken fontanelle, Reduced skin turgor, Dry mucous membranes,
- wt loss, signs of shock ,Pulse, Hypotension,
- Capillary refill (> 2 Seconds)

Diagnostic work up

The following investigations should be performed to help confirm your provisional diagnosis:

The order set **PAED.CAH on V6** will bring in all the relevant investigations**.** It is mainly used for follow-up patients but can be used in new patients with additional tests as required

1. **Serum 17 hydroxyprogesterone** (17-OHP) - if very **high (>100 nmol/L) then the diagnosis of 21-OH deficiency is confirmed (normal < 15nmols/l)**. If moderately high and taken in the first few days of life it may reflect normal physiology. **So do this after day 3 (ie 72 hrs).**

2. **Serum Androstenedione** and **testosterone** –It is a useful marker in this clinical context for CAH. **If it is very high in the context of ambiguous genitalia, (normal pre pubertal level < 2 nmols/l)** then 21 OH deficiency is the most likely cause.

3. U&Es, Blood gas, Glucose , Cortisol, Renin, ACTH

Check Urea & Electrolytes frequently during the initial stages of diagnosis to alter management and adjust salt replacement, and once stable 3 monthly along with 17 OHP ,Renin, Androstenedione, Dihydroepiandrostenadione (DHEA) .

4. Karyotying (request cytogenetics lab for urgent verbal reporting to determine sex in ambiguous genitalia before parents can name the baby)

5. **Book a pelvic ultrasound scan in <u>any case of sexual ambiguity</u>**

6.Urinary steroid profile or CAH genetics if suggested by the **Endocrinologist**

(urine 11-deoxycortisol levels,is increased in 11- hydroxylase deficiency)

7. 1-2 yearly Bone age may be required from 2 years of age

Note: ensure appropriate sampling bottles and minimum required amount is collected

Management:

Discuss all cases of CAH or Disorders of Sexual Differentiation with the on-call Consultant Endocrinologist at Birmingham Children's Hospital for advice and management and future appointments (follow this with an email to the consultant regarding the patient details). They can provide psychological support and early involvement of the MDT management in the DSD clinic.

Book any new patient into the next Endocrine Joint clinic and inform Dr Vasista (local endocrine lead) and Dr Kershaw (visiting BCH consultant Endocrinologist).

<u>Drugs</u>: Guided by clinical criteria (growth, weight gain, BP, pigmentation) and biochemical results

Hydrocortisone	**10-15 mg/m^2/day orally in 3-4 divided doses**
Fludrocortisone	**100-200 microgms daily orally (infants)**
	50 -100 microgms daily orally (over 1)
Sodium Chloride	**4-10 mmols/kg/day divided into each feed from infancy up, or sometimes over 2 years of age.**

Doses of fludrocortisone/salt are adjusted according to electrolytes,renin,BP and weight gain.

Hydrocortisone dose is adjusted according to growth, weight gain, androgens, 17-OHP and clinical symptoms.

All dose changes need to be done jointly with the local and tertiary Endocrinologists.

Acute problems

Acute adrenal crises – an emergency, follow ABCD….

- Suspect if child is drowsy, shocked, sweaty, hypoglycaemic or generally unwell.
- Urgent blood glucose and electrolytes and consider infection screening
- Give 20 ml/kg of 0.9% normal saline
- Give 2 ml/kg of 10% dextrose
- Give intravenous Hydrocortisone stat (see dose schedule below), ***followed by 6 hourly doses (2-4 mg/Kg)***
- If the child remains shocked give a further 20 ml/kg of normal saline.
- Start intravenous fluids (0.9% saline with 5% glucose) at maintenance plus calculated deficit and modify fluid according to electrolytes
- Regular blood glucose and electrolyte monitoring
- No need for fludrocortisone administration in initial stages as stress-dose hydrocortisone has sufficient mineralocorticoid action. In that respect guidelines for management of hyponatraemia are to be used with caution as hydrocortisone administration will correct electrolyte abnormalities (risk of correcting hyponatraemia too quickly).

Hydrocortisone bolus

Initial Dose Schedule: **< 1 year 25 mgs IV Qid**

1-5 yrs 50 mgs IV Qid

>5 yrs 100 mgs IV Qid

Followed by ***2-4 mg/Kg 6 hourly IV Hydrocortisone***

Hyperkalaemia –beware of cardiac arrhythmias

- Plasma potassium >5.5 mmol/l (ensure not haemolysed sample)
- Reflects deficient mineralocorticoid replacement
- Will often correct with your management of the adrenal crises – intravenous hydrocortisone & intravenous sodium chloride
- **Urgent therapy will be required, however, if**
  o Plasma potassium >7.5 mmol/l

o Plasma potassium > 6.5 mmol/L with ECG abnormalities (tall T waves, arrhythmias)

Treat Hyperkalaemia as per the Trust Guidelines CH CLIN G44/ Jul 21/v009

If the child is otherwise well & able to tolerate meals

Prescribe the child's usual oral glucocorticoid (usually hydrocortisone) replacement

Prescribe the child's usual oral mineralocorticoid (usually fludrocortisone) replacement

Allow the child to go home

If the child is still clinically unwell

Prescribe oral hydrocortisone **30mg/ m^2 in 4 divided doses (6 hourly).** If child is vomiting soon after taking the dose, repeat the hydrocortisone and for recurrent vomiting give IM Hydrocortisone and admit if persistent.

Prescribe the child's usual oral mineralocorticoid (usually fludrocortisone) replacement

Consider continued observation in hospital

Pyrexial Child

- Defined as a temperature greater than 38^{o}C.
- The child will be under greater metabolic stress as a result of the associated illness and will therefore need increased glucocorticoid replacement.
- Give illness dose of oral hydrocortisone till the child is better
- Give the usual oral fludrocortisone dose.
- Once the child is apyrexial for 24 hours, reduce the hydrocortisone replacement dose back to normal.

Admitted for surgery

- Whilst the child is nil by mouth, intravenous hydrocortisone will be needed.

Intravenous hydrocortisone is cleared faster than oral hydrocortisone. Therefore

intravenous doses of hydrocortisone are greater and given more frequently than

oral hydrocortisone.

- The child will be under greater metabolic stress as a result of surgery and will therefore need increased glucocorticoid replacement.

Minor surgery – i.e. likely to be able to take oral fluids within a few hours of the operation

- Give intravenous hydrocortisone at induction (**see dosage schedule for crisis**)
- Give postoperative oral hydrocortisone as per the illness dose for at least 24 hours or until well enough for discharge, whichever is the later.

Major surgery – ie, unlikely to be able to take oral fluids within a few hours of the operation

- Give intravenous hydrocortisone at induction (**see dosage schedule for crisis**)
- Put up a 0.9% saline/5% dextrose infusion at a maintenance rate
- Give intravenous hydrocortisone in a four times a day regimen until well enough

to take oral fluids reliably

- Intravenous hydrocortisone has enough mineralocorticoid activity so parenteral mineralocorticoid replacement is not required immediately.

- When the child is well enough to take oral fluids reliably, prescribe oral hydrocortisone as per the illness dose for at least another 24 hours or until well enough for discharge, whichever is the later.

Patients have open access to the ward; direct their call to the Registrar

CHECK LIST

1. Discussion

2. Fact sheet /

3. Hydrocortisone 100mg ampoule and injection technique

4. Personal care plan (card or the sheet from appendix 2)

5. Necklace or bracelet

6.Referral to Tertiary centre and clinical geneticist

References (including any links to NICE Guidance etc.)

1. 17-Hydroxyprogesterone in children, adolescents and adults

John W Honour April 7, 2014 Review Article https://doi.org/10.1177/0004563214529748

2. Clinical Paediatric Endocrinology, 2005, Brook, Clayton, Brown

3. Congenital adrenal hyperplasia: management during critical illness. E Charmandaria,

E J Lichtarowicz-Krynska, PC Hindmarsh, A Johnston, A Aynsley-Green,

4. New MI. Diagnosis and management of congenital adrenal hyperplasia. *Annu Rev Med* 1998; 49:311-328

5. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline *JCEM* 2010 95: 4133-4160; doi:10.1210/jc.2009-2631 *Phyllis W. Speiser*

Documentation Controls (these go at the end of the document but before any appendices)

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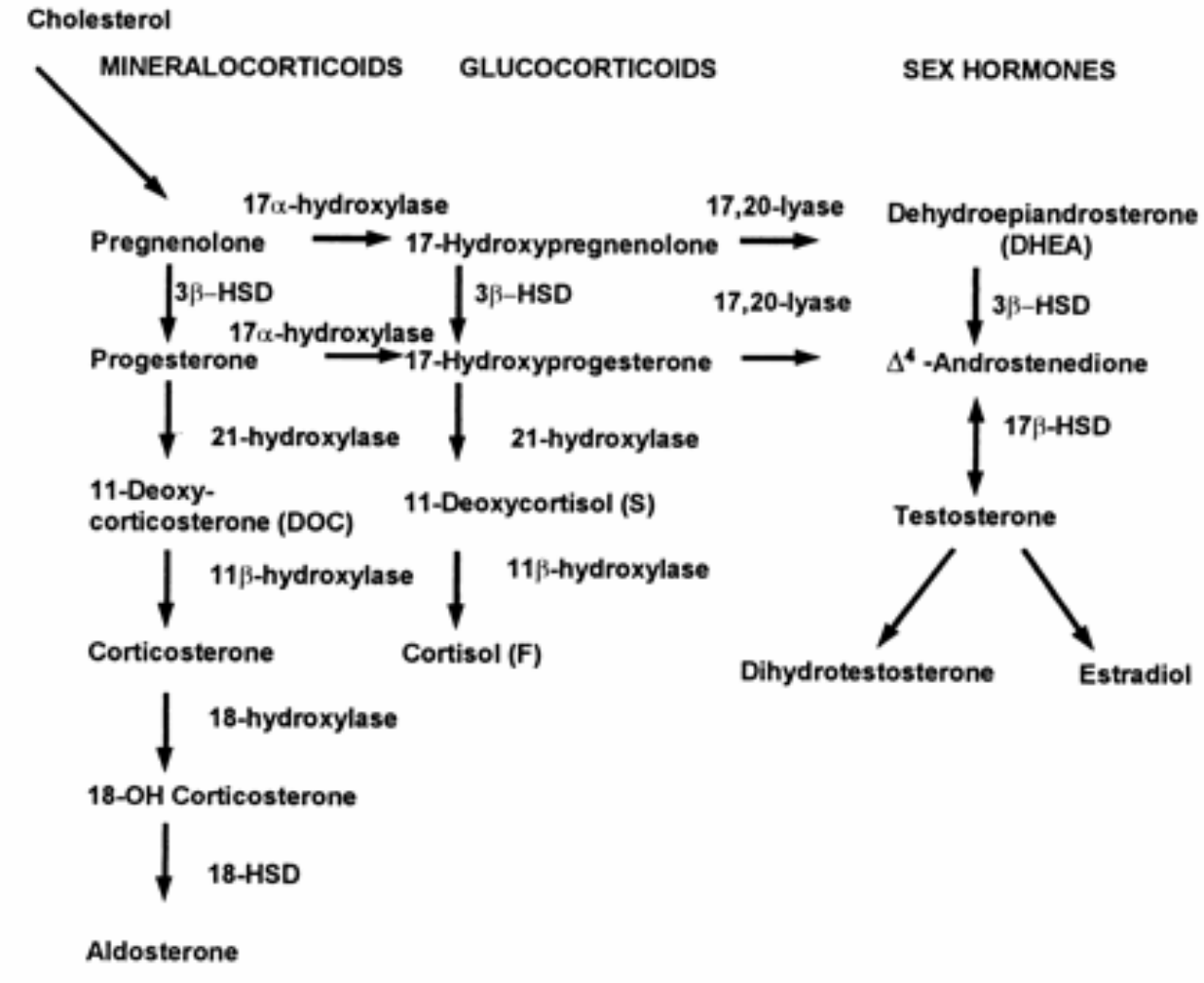
Appendices – below

Appendix 1


Cholesterol
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX HORMONES
17α-hydroxylase
17,20-lyase
Pregnenolone
17-Hydroxypregnenolone
Dehydroepiandrosterone (DHEA)
3β–HSD
3β–HSD
17,20-lyase
3β–HSD
17α-hydroxylase
Progesterone
17-Hydroxyprogesterone
Δ4 -Androstenedione
21-hydroxylase
21-hydroxylase
17β-HSD
11-Deoxy-corticosterone (DOC)
11-Deoxycortisol (S)
Testosterone
11β-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol (F)
Dihydrotestosterone
Estradiol
18-hydroxylase
18-OH Corticosterone
18-HSD
Aldosterone

Appendix 2

PARENTS INFO SHEET (Please print a copy)

STEROID REPLACEMENT IN CONGENITAL ADRENAL HYPERPLASIA and other ADRENAL INSUFFICIENCY conditions

Steroids are hormones (chemical products of endocrine glands which are secreted into the blood and carry messages to other organs) formed in the body by the outer layer (cortex) of the adrenal glands, two small structures lying just above the kidneys.

The two most important steroid hormones are hydrocortisone and aldosterone. Hydrocortisone is essential for

(1) controlling the blood sugar level,

(2) helping the body combat stress and

(3) reducing inflammation,

Aldosterone regulates the body content of salt by controlling the rate of salt loss in the urine.

Adrenalin, the hormone involved in the response to fright, is not a steroid and is secreted by the inner part of the adrenal glands, this system seldom fails and replacement is not necessary.

Steroid replacement is needed when the natural secretion of the adrenals is inadequate. This arises in three different situations

(1) when the drive to the adrenals from the pituitary (an important endocrine gland located in the head just below the brain) is lost, in addition to steroids there is then usually need for replacement of some or all of the other hormones secreted or driven by the pituitary, these are thyroxine, growth hormone, sex hormones and antidiuretic hormone

(2) in congenital adrenal hyperplasia, a genetic condition in which there is a block in the production of steroid hormones and

(3) when the adrenal cortex itself fails.

For replacement only small doses of steroids are needed to mimic the natural secretion of the missing hormones.

Hydrocortisone is available in tablet form as dividable 20 milligram (mg), 10mg or 2.5mg tablets and, if replacement of aldosterone is also needed, fludrocortisone

dividable 100 microgram (mcg) tablets, an artificial steroid which has the same action as aldosterone but is more effective by mouth, is given. It is usually satisfactory to give hydrocortisone thrice daily and fludrocortisone once daily doses except in stress as detailed below. The adequacy of the doses can be checked by mainly blood tests or from saliva.

Side effects:

Because only small doses, aiming to replace the natural secretion of steroids, are needed for replacement the notorious side effects of high dose steroid treatment, as sometimes needed to control inflammatory disorders such as arthritis, and including moon face, obesity, muscle wasting and thinning of the bones, are not seen. In children too large a dose of hydrocortisone will cause slowing of growth possibly with some weight gain and too small a dose a lack of energy and sometimes a tendency to low blood sugar (hypoglycaemia). Too much fludrocortisone will increase the blood pressure and too little will lower it and cause salt craving.

Stress:

In order to combat the stress of illness or injury, the natural secretion of hydrocortisone is increased. Children on treatment with steroids also need an increased dose to cover such illness. Sudden interruption of replacement must be avoided. An important principle is therefore that steroid treatment must be given continuously and must be increased to cover illness. If the dose is repeatedly lost through vomiting it MUST be given by injection. (Do not be too concerned by these warnings, most children on steroids never need an injection).

The rules of treatment are therefore:

*** Devise as reliable as possible a method of giving your child the medication. Even in the most organised households occasional doses are missed and fortunately this seldom matters as long as the child is well. Resume the normal dose as soon as the omission is noted. ***

To cover illness (beyond mild coughs and colds which do not require any change in treatment)

(1) if the child is not eating give regular sweet drinks to avoid a fall in the blood sugar (hypoglycaemia)

(2)Increase the oral hydrocortisone **30mg/m^2** divided equally and give four times daily (dose need to be calculated and entered in the treatment card by the doctor)

It is not necessary to give an increased dose of fludrocortisone.

Continue the increased dose until the child is well.

*** If the child is vomiting increase the dose as above and make sure that the tablets are retained for at least an hour. If the dose is vomited in less than an hour repeat it. If there is any doubt**

that the dose has been retained it must be given as an injection. If such a situation does arise it is certainly appropriate to call the GP or take the child to hospital but all families with a child on steroid replacement need to have available a 100mg ampoule of hydrocortisone and to know how to make it up and give it by intramuscular injection in a crisis. *

Dosage schedule for adrenal crisis

Dosage : **0-1 year 25 mgs Intramuscular**

1-5 yrs 50 mgs Intramuscular

Over 5 yrs 100 mgs Intramuscular

All children on steroids (or their parents) should carry an engraved bracelet or necklace and/or a note of the details of the treatment. Please show this sheet to Ambulance crew, Emergency department reception or Nursing staff on the Ward.

Please refer to https://www.bsped.org.uk/media/1774/congenital-adrenal-hyperplasia-print-version.pdf (bsped.org.uk) for Parent information

BSPED Paediatric STEROID TREATMENT CARD is available on https://www.bsped.org.uk/media/1966/ bsped-adrenal-insufficiency-card-v32.pdf

Please use the following form if the therapy card is not available

CONGENITAL ADRENAL HYPERPLASIA (CAH) and other ADRENAL INSUFFICIENCY conditions

Name **DOB**

UNIT no:/NHS number **Consultant**

Hospital: Queen's Hospital, Burton –on-Trent **Phone: 01283 566333 Ext 4368**

Contact Ward 1 for advise if not sure what to do on Ext No 4608 or 4631

Treatment Plan:

.....'s current steroid treatment is

Hydrocortisone .....mg (.....mls) at 06.00 morning..;

.....mg (.....mls) at 12.00 midday...; and

…….mg (……..mls) at 18.00 evening

Instructions to prepare dose: dissolve one 10 mg tablet in 10 mls of water to give 1mg per ml

Fludrocortisone ..... micrograms (.....tablets) at 06.00 morning.

.....micg (.....tablets) at .....

If small dose is required : dissolve one 100 microgram tablet in 10 mls of water to give 10 mcg per ml)

To cover illness (beyond mild coughs and colds which do not require any change in treatment)

Hydrocortisone (**30mg/*m*^{2}** divided equally). Give .....mg

(.....mls) every 6 hours

If an injection is necessary give Intramuscular hydrocortisone .....mg stat and admit in the hospital.

Appendix 3

RIA REFERENCE RANGES (Heart of England FT)

ALDOSTERONE:

Adult

LYING = 28 – 445 pmol/L

ERECT = 110 – 860 pmol/L

Paediatric

Cord blood upto 2268 pmol/L

6 Days upto 1248 pmol/L

12 months 165 – 2930 pmol/L

1 – 4 years 70 – 950 pmol/L

RENIN:

(Plasma renin mass)

University Hospital Birmingham reports as mIU/L

Adult (Heartlands)

LYING (Adult) = 9.8 – 23.8 mU/L

ERECT (Adult) = 12.9– 33.7 mU/L

Paediatric

(Use these ranges with caution)

6th day 30.4-685.5 mU/L

1 year 61.3-236.8 mU/L

1- 4 years 19.2-195.5 mU/L

5 – 9 years 21.8-68.2 mU/L

10 – 15 years 12.3-73.3 mU/L