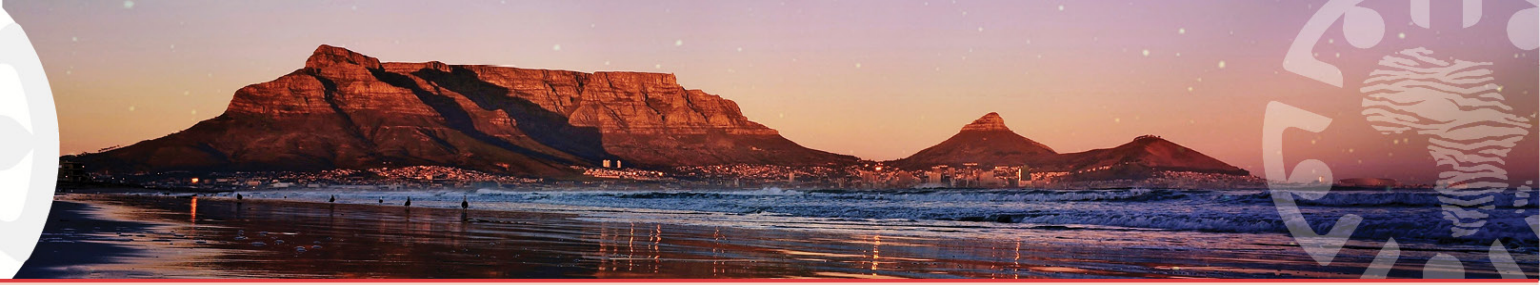
ICE 2018
18th International Congress of Endocrinology
53rd SEMDSA Congress
1 - 4 December 2018 - Cape Town - South Africa



Diagnosis and Management of CAH in the United Kingdom

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London South Bank University

Conflict of interest disclosure

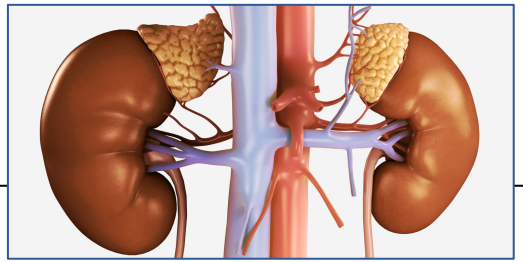
- Invited lectures
  - Merck
  - Sandoz
  - Diurnal
- International paediatric endocrine nurse advisory board
  - Merck

Introduction

- What is CAH
- Diagnosis in the UK
  - Newborn screening
  - International practice
- Treatment
- Management
- Education and Support

CAH – reminder of key points

- An adrenal enzyme defect
- Classical 21-hydroxylase deficiency is the most common
  - 1 in 15,000 births in the UK
- Results in glucocorticoid and mineralocorticoid deficiency
  - ↑ ACTH secretion by the anterior pituitary
  - Accumulation of steroid precursors prior to the enzyme defect
  - ↑ androgens production



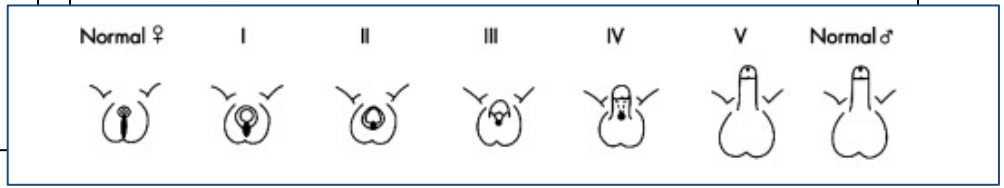
Diagnosis

Boys

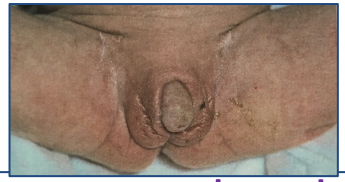
- *Can* have hyperpigmented scrotum and genitalia at birth, but usually look 'normal'
- Presentation
  - Day 5
  - Second week of life
    - Poor feeding, weight loss, failure to thrive
  - If CAH not recognised
    - Salt losing crisis
      - Due to the aldosterone loss

Girls

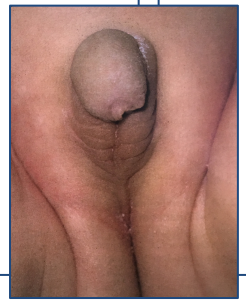
- Genitalia are usually virilized due to excess androgens
  - Allows earlier diagnosis
- Mild clitoromegaly to full masculinisation
  - Prader staging
- DSD service



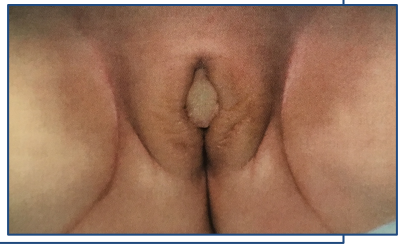
46XX CAH



- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy's:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
  - Need karyotype
  - Will still have normal internal structures
  - Surgery may be needed to correct outer appearance
    - CONTROVERSIAL



- Exposure to prenatal androgens and Prader 3 virilisation at birth
- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment
- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader IV)



Diagnosis

- Confirmed by a raised 17OHP level after day 3 of life
- Salt wasting confirmed by:
  - Low plasma sodium
  - High potassium
  - Increased urinary sodium excretion
  - Virilised girls
    - Chromosome analysis
    - Pelvic ultrasound

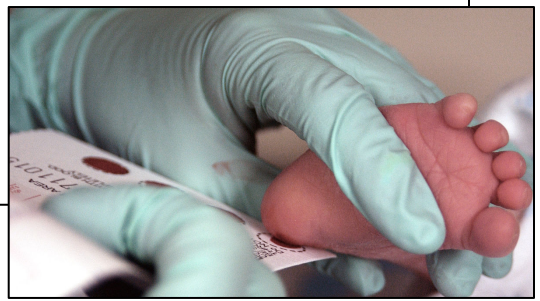
- Short synacthen test – IM or IV
  - 0 – 6 months: 62.5mcg
  - 6 months – 2 years: 125mg
  - Over 2 years: 250mcg

- Urine
  - Steroid analysis to confirm the 21-hydroxylase deficiency defect

Time	Cortisol	17-OHP	11-DOC	A4	ACTH	Renin
0	✓	✓	✓	✓	✓	✓
30	✓	✓	✓	✓		
60	✓	✓	✓	✓		

Newborn Screening

- Most countries incorporate screening for CAH in the neonatal period
- UK National Screening Committee (2016)
  - Accuracy of test poorer in babies born early and low birth weight
    - Affected babies may be missed
  - Screening takes place too late to benefit people with some types of CAH
  - Current 17-OHP immunoassay – incorrectly identifies a large number of babies with CAH
- Germany
  - Increased number of false positives *(Fingerhut, 2018)*
    - Suggested changes in their biochemical analysis



International Practice

- South Africa *(Ganie, 2018)*
  - 3233 patients in endocrine clinic
    - 44 CAH
      - 60% CSW
      - 46 XY median age 3/12
      - 46 XX median age 1/12
    - 2/3 of the females presented with DSD in neonatal period
    - 1/3 presented later with dehydration and shock
  - Seems to be infrequent in black South African children

- Nigeria *(Osifo & Nwashill, 2008)*
  - All children diagnosed with CAH in one centre – 5 year period
    - 27 children
    - 24 female, 3 male
  - Delayed presentation
    - Influenced by cultural beliefs, and lack of awareness
    - Genital abnormality only reason medical consultation in 85%
    - All females mistakenly raised as males

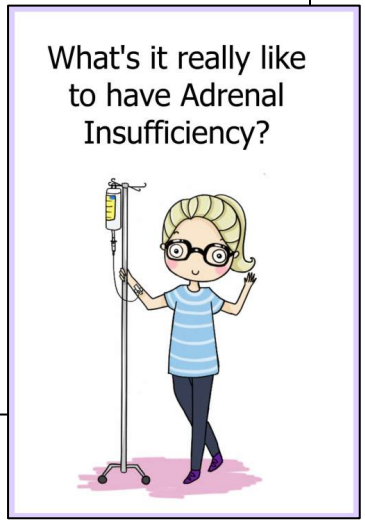
Management

Medical

- Hydrocortisone 10mg tablets
  - 10 – 15 mg/m2/day
  - Total dose spread 3 – 4 times throughout the day
- Fludrocortisone 100 mcg tablets
  - 150 mcg / m2/ day
- Salt supplements
  - Oral salt supplements (until one year of age) in the 5mmol/ml 30% Sodium Chloride solution – 5mmols/kg/day, in 4 divided doses = …….mls per dose four times a day
  - Can stop when fully weaned

Surgical

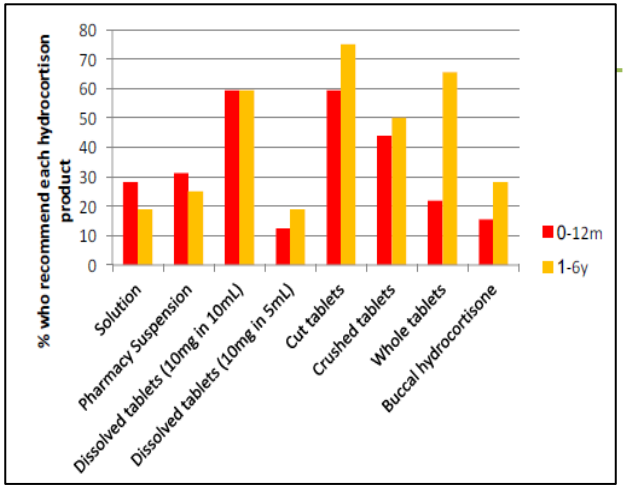
- Should only be performed by experienced surgeons
- Practice
  - 2 – 6 months of age
- Genitoplasty controversial
  - Vaginoplasty
  - Clitoroplasty
  - Labiaplasty



Suspension v tablets

- Increased need for higher hydrocortisone doses in children on liquid hydrocortisone
  - Inadequate control of androgens
  - Signs and symptoms of Cushing's syndrome
    - (Endocrine Society Clinical Practice Guideline, 2010)
  - Hydrocortisone suspension not bioequivalent to tablets
    - (Merke, 2001)
  - Instructions to be given on cutting / crushing tablets

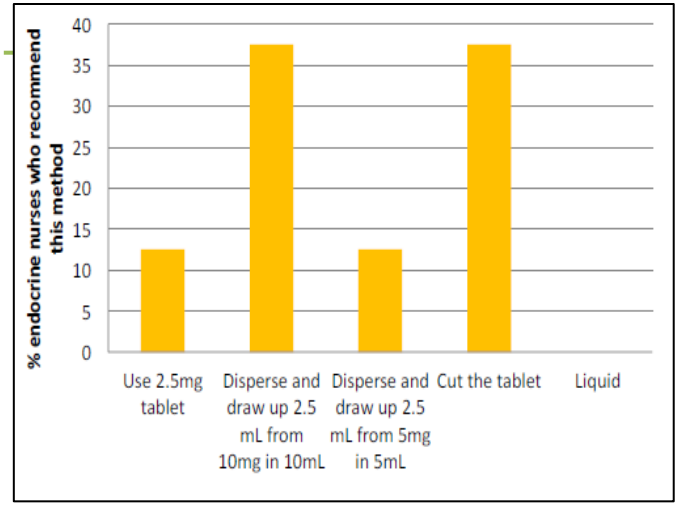
Range of choices and methods to give hydrocortisone



Various methods to administer hydrocortisone dose – survey of 32 paed endocrinologists, 20 specialist nurses, 159 caregivers (Watson et al, 2017)

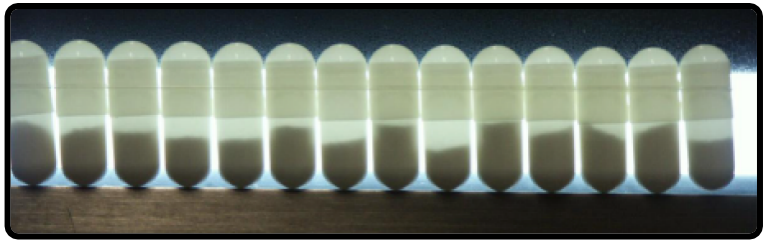
Various methods to administered an oral hydrocortisone dose of 2.5 mg

(Watson et al, 2017)



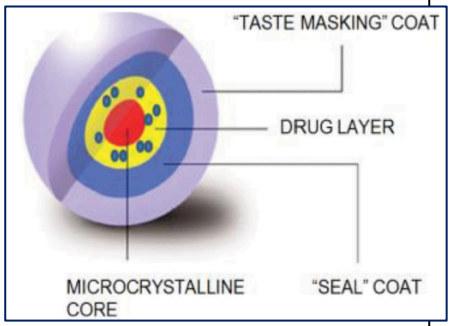
Manipulation of tablets

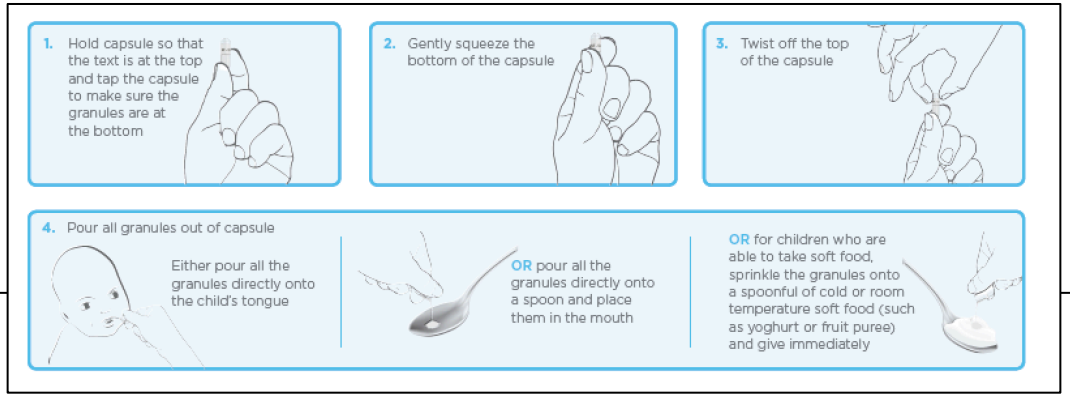
- Quartering 10 mg hydrocortisone tablets
  - *Unacceptable dose variations (Madathilethu et al, 2018)*
    - *Glucocorticoid excess*
    - *Cortisol insufficiency*
- Splitting tablets
  - *Unequal parts / crumbling = unequal doses*
- Common practice in the UK
  - *Renders the medication unlicensed*
  - *No guidelines or evidence (Richey et al, 2017)*
- Compounded hydrocortisone capsules
  - *Variability in capsule content = variation in dose (Neumann et al, 2017)*



Alkindi Hydrocortisone granules: The future

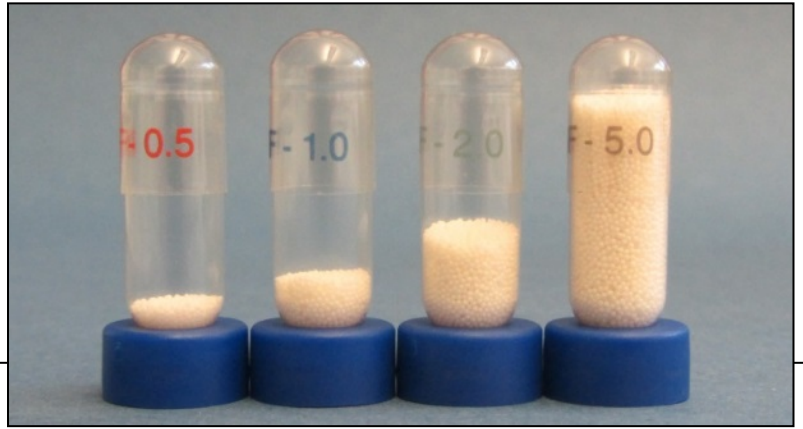
- Granules well tolerated in children less than 6 years of age
  - Cortisol levels measured
  - Smell and taste are neutral *(Neumann et al, 2018)*
  - Tested on healthy adults – report no smell or taste *(Whitaker et al, 2015)*





Alkindi granules – accurate dosing

- The formulation of hydrocortisone with taste masking is based on granule, multi-layered, multi-particulate technology to deliver 0.5mg, 1mg, 2mg and 5mg doses
- Immediate release granules are contained in capsules, which are broken open and the granules administered orally



Instructions for Hospital Doctor

Dear Doctor,
If this patient is brought to hospital as an emergency the following management is advised:

1) Insert an IV cannula
2) Take blood for U&Es, glucose, and perform any other appropriate tests (e.g. urine culture)
3) Check capillary blood glucose level
4) Give 100 mg hydrocortisone intravenously as bolus (unnecessary if patient has already been given IM hydrocortisone)
5) Commence IV infusion of 0.45% sodium chloride and 5% glucose at maintenance rate (extra if patient is dehydrated). Add potassium depending on electrolyte
6) Commence hydrocortisone infusion (50 mg hydrocortisone in 50ml 0.9% sodium chloride via syringe pump)
7) Monitor for at least twelve hours before discharge

IMPORTANT! If blood glucose is < 2.5 mmol/l, give bolus of 2 ml/kg of 10% glucose
If patient is drowsy, hypotensive and peripherally shut down with poor capillary return give 20ml/kg of 0.9% sodium chloride stat.

If in any doubt about this patient's management, please contact the urgent advice numbers

Useful Contact Numbers:

GOSH Switchboard
Tel: 020 7405 9200

For Urgent Advice:
Tel: 020 7405 9200 and ask to be put through to the endocrine registrar on call

University College Hospital Switchboard
Tel: 0845 155 5000

For Urgent Advice:
Tel: 0845 155 5000 and ask to be put through to the endocrine registrar on call.

Great Ormond Street Hospital for Children NHS Trust and University College London Hospitals NHS Foundation Trust

CORTISOL DEFICENCY

THE OWNER OF THIS CARD IS ON CORTISOL REPLACEMENT THERAPY

Name
Address
Tel
Mobile:
Date of Birth ____/____/____
Hospital No.
Consultant
Hospital
Address
Tel Fax
General Practitioner
Address
Tel Fax

Affix photo here

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3. Draw up 2mls of cooled, boiled water into a 2ml syringe
4. Mix the crushed ¼ of a tablet with the 2mls of cooled boiled water
5. Then draw up 1ml of the mixture to give 1.25mg
6. Give by mouth as shown by ward nurses

Great Ormond Street NHS Hospital for Children
NHS Trust

Great Ormond Street
London WC1N 3JH

Tel: 020 7405 9200
Gastroenterology, Endocrinology, Metabolic & Adolescent Medicine (GEMA)
Direct Link: 0207-813-8214

cortisone (oral)
cortisone (oral)
supplements 5mmol/ml 30% solution:
ospital Doctor

nts cortisol deficiency, if this patient is brought to hospital as an emergency,
gement is advised:

wsy and unresponsive give IM hydrocortisone in the following doses
(0-1yr – 25mgs; 1-5 yrs – 50mgs; > 5yrs – 100mgs) if patient has not already
ocortisone administered by ambulance crew or parents.

for U&Es, glucose and osmolality

ose is < 2.5 mmol, give bolus of 2mg/kg 10% dextrose

- If patient is drowsy, hypotensive and peripherally shut down, give 20ml/kg of nor
insert an IV cannula and then continue with usual dextrose saline infusion
- Continue with bolus IV hydrocortisone at 2mg/kg every 4 hours until patient is tol
oral fluids and then swap to double usual oral Hydrocortisone doses until patient
recovered and back to normal self (usually 2-3 days on double usual hydrocortis
doses).
- Important: Please admit for a minimum of 12 hours

for Children NHS Foundation Trust: Information for Families

renal hyperplasia (CAH)

reat Ormond Street Hospital
dical condition congenital
what to expect when your
sment and treatment.

Congenital adrenal hyperplasia is

Great Ormond Street NHS Hospital for Children
NHS Trust

Great Ormond Street
London WC1N 3JH

Tel: 020 7405 9200
Gastroenterology, Endocrinology, Metabolic & Adolescent Medicine (GEMA)
Direct Link: 0207-813-8214

Date:
Reference:

Dr
Paediatric Consultant

Dear Dr

RE:

.....is a .....year old ..... under the care of ..... at Great Ormond Street Hospital. He is a boy/girl with ..... he/she was referred with ..... and we have since found he also has cortisol deficiency.

He/She has been commenced on Hydrocortisone at a dose of 2.5mg mane, 2.5mg at lunchtime, and 2.5mg nocte. ..... 's mum has had education in his her management during times of illness and has been trained in giving IM hydrocortisone should the need arise.

I would be extremely grateful if you could arrange for ..... to have first track access at the ..... should he she require emergency IM hydrocortisone. Please let us know on the number below.

Please do not hesitate to contact me should you require more information on 0207 813 8214.

Many thanks,

Yours sincerely

.....
Clinical Nurse Specialist

London Ambulance Service NHS Trust

Patient Specific Protocol
PSP Paediatric Steroid Dependent Crisis

PSP

This protocol has been specifically prepared for STEROID DEPENDENT CRISIS patient: and details the treatment to be given in specified circumstance:

Patient's Name: **Date of Birth:**

NHS Number:

Address:

School:-

Local hospital:

Reason for protocol: Administration of IM hydrocortisone in possible adrenal crisis

Specific Treatment / Instructions: Patient may have an adrenal crisis if IM hydrocortisone not administered in an emergency situation

In the event that this child is involved in an accident or develops diarrhoea or vomiting and presents with any symptoms of a steroid dependent crisis whilst at **Home or at School** they are to be administered IM hydrocortisone as detailed over leaf.

Note:- The IM hydrocortisone (Efcortesol) is kept both by the parents and by the school in an emergency pack.

Please transport this child to the above local hospital if possible, otherwise to the nearest paediatric A&E unit.

All other aspects of clinical care remain unchanged.

For further advice if necessary please contact the Endocrine Registrar on call via switchboard at Great Ormond Street Hospital on 020 7405 9200

1. Efcortesol 1ml ampoule (Hydrocortisone 100mg/ml - as sodium phosphate)

Dose: Age 0-1 years 25 mg IM
Age 1-5 years 50mg IM
Age 5+ years 100mg IM

2. Please also administer Glucogel (Hypotop) 25 gram tube, required dose in an emergency - up to 1/3 tube if not already previously administered by carers.

Following administration of the hydrocortisone remove to hospital with full monitoring and oxygen therapy as required.

All other aspects of clinical care remain unchanged.

If required contact EOC and ask for the Clinical Support Desk

PTO for further general info on Steroid Dependent Crisis

Great Ormond Street Hospital for Childre

Cortisol deficiency steroid replacement the

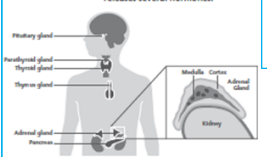
This leaflet explains about cortisol deficiency and how it is treated. It also contains information about how to deal with illnesses, accidents and other stressful events in children on cortisol replacement.

Where are the adrenal glands and what do they do?

The adrenal glands rest on the tops of the kidneys. They are part of the endocrine system, which organises the release of hormones within the body. Hormones are chemical messengers that switch on and off processes within the body.

The adrenal glands consist of two parts:

- the medulla (inner section) which makes the hormone 'adrenaline' which is part of the "fight or flight" response a person has when stressed.
- the cortex (outer section) which releases several hormones.



●●●○○ O2-UK 22:02 100%

Great Ormond Street NHS Hospital for Children
NHS Foundation Trust

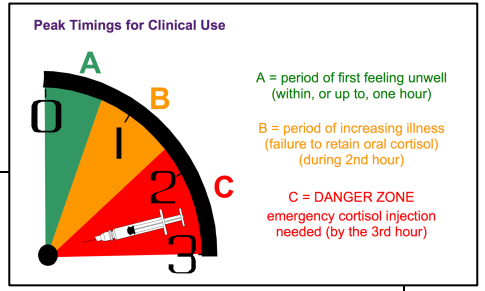
My Cortisol

How to give an emergency injection of Efcortesol®

Information for families

Great Ormond Street Hospital for Children NHS Trust
University College London Hospitals NHS Trust

Sick day rules



- Illness
  - Double the normal Hydrocortisone until well
    - Triple?
    - 4am dose?
  - Guidance for families
    - Fever
    - Antibiotics
    - Vomiting (if within an hour of taking)
    - Diarrhoea
    - 24 hours around administration of childhood immunisations

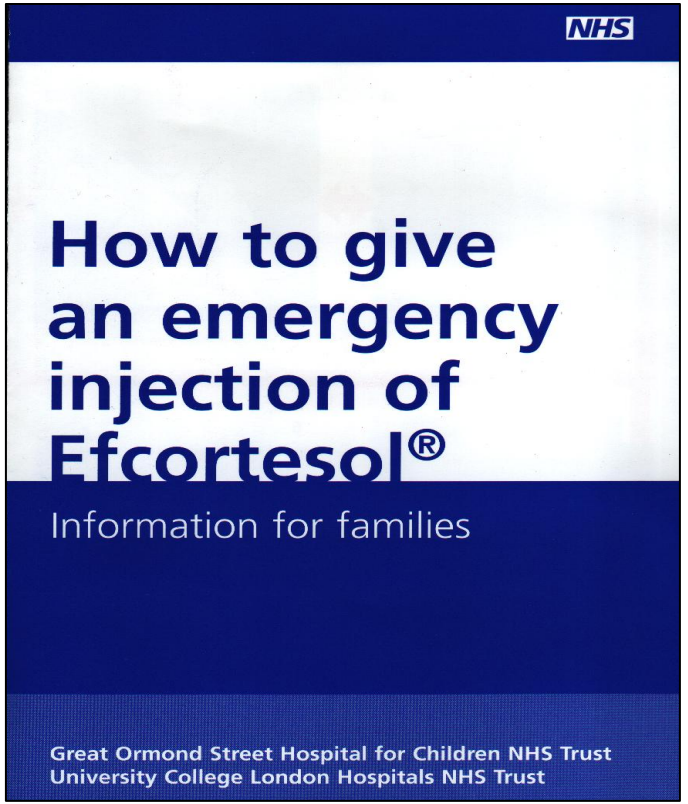
If parents / carers think their child is ill enough to be kept home from school

- Emergency
  - Severe D & V
  - Serious injury
    - Unconscious
    - Severe burns
    - Break a limb
- Administer Emergency injection of Hydrocortisone and / or Glucagel
- Call an ambulance

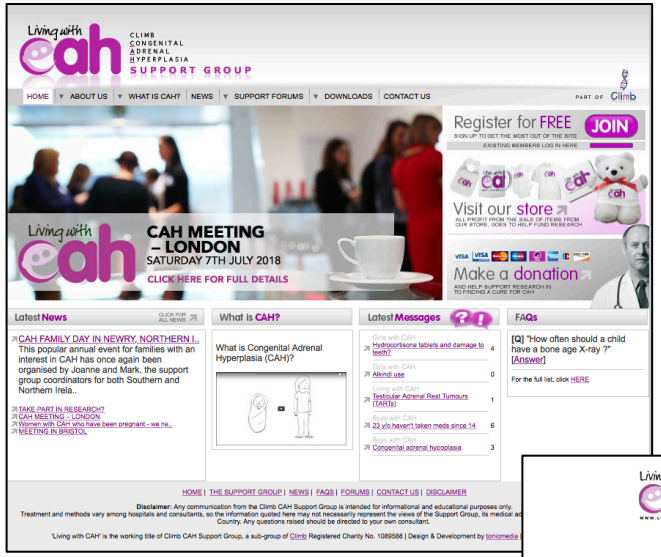
If parents / carers think the child is ill enough to attend an Emergency Department

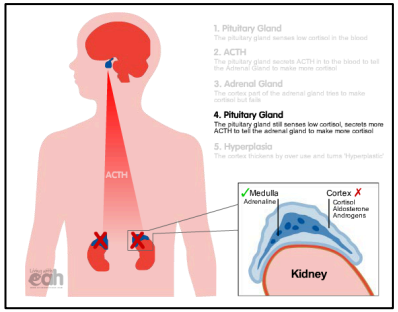
Sick day and emergency management

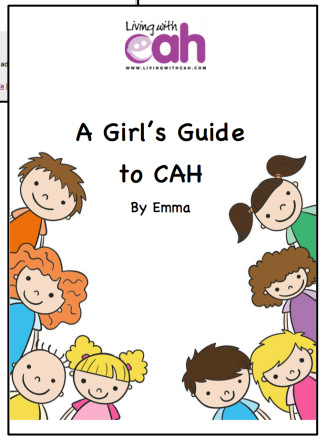
- Emergency injection of hydrocortisone and oral glucogel
- Liaise with nurseries
  - Schools when older
- Medic alert jewellery
- Usually dispense x2 emergency packs
  - Home
  - Bag
    - Another when older for nursery / school



Living with CAH

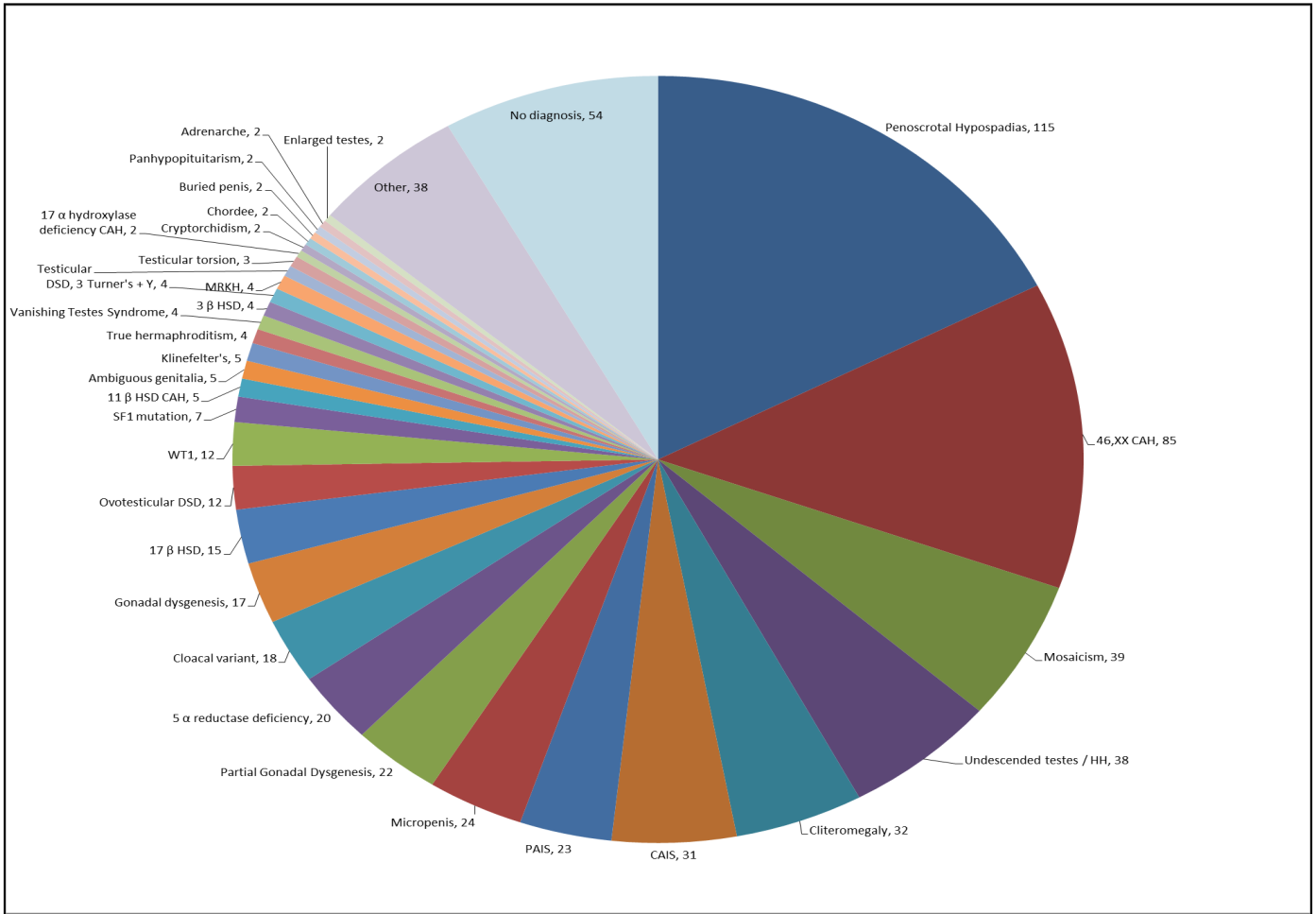




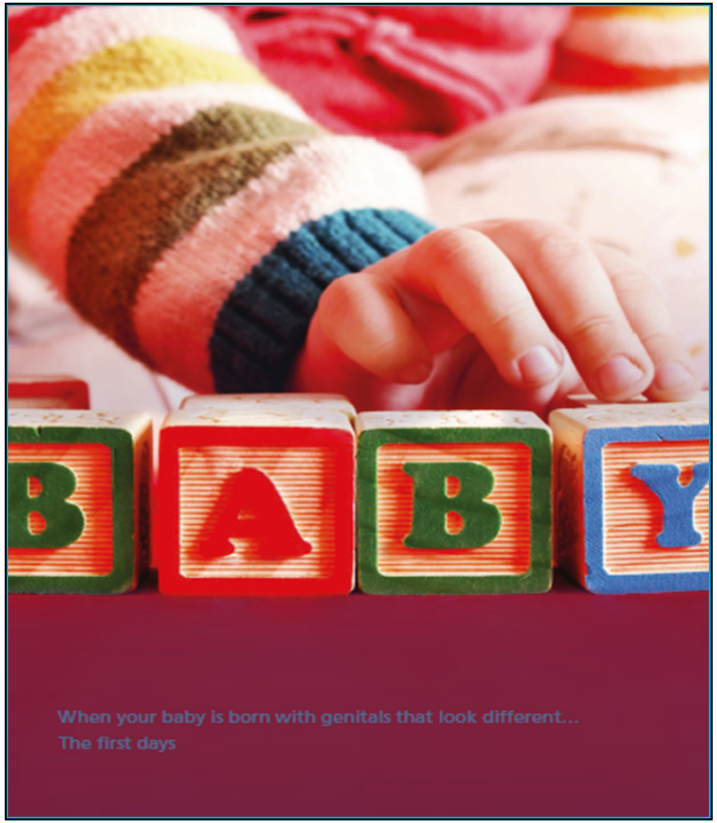


- Give support to families and sufferers
- To increase awareness of the condition to the public and to the medical profession
- To raise funds to support research
  - Regular conferences
  - Family support days
  - Informal meetings

London DSD data over 21 years N= 657



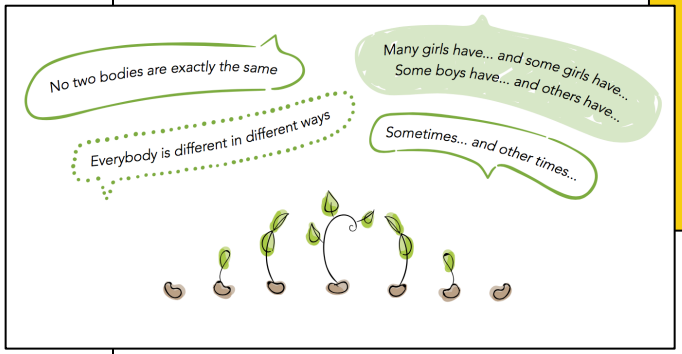
DSD families



- dsdfamilies.org
- UK based support group
  - Information and support resource for families with children, teens and young adults with a DSD
  - Links to other support groups throughout the UK
    - CAH, TS, Hypospadias, Klinefelter, AIS
  - Links to international DSD support groups

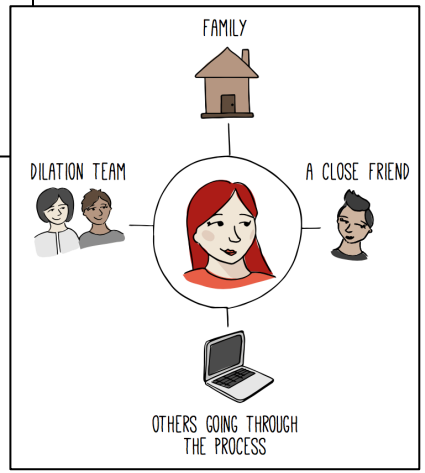
dsdfamilies.org

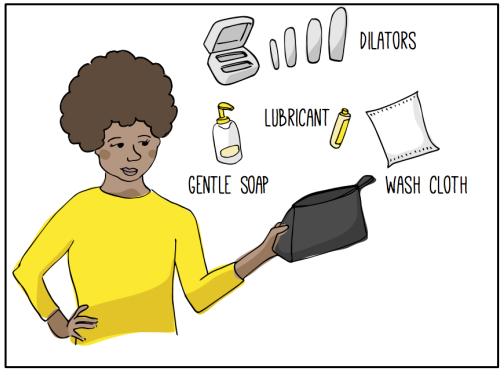
- Advice
  - How to talk to others
  - How to talk with teenagers
  - Dilatation



Top Tips for Talking

about differences of sex development





Conclusion

- Awareness of different practices internationally
  - Newborn screening – change in practice
  - Availability of biochemical and molecular analysis
  - Cultural practices
    - Diagnostic data different due to diagnostic procedures
  - Multidisciplinary teams
- UK practice follows Endocrine Society (2018) and ESPE (2006, 2002) Guidelines