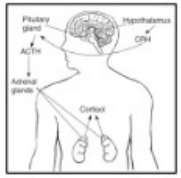
10th MEETING

Insights into MAnaging Growth for Endocrine Nurses



Congenital Adrenal Hyperplasia

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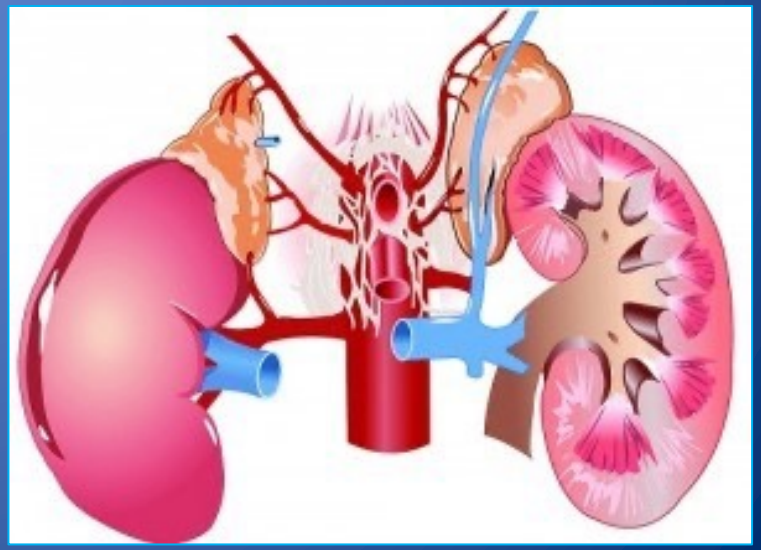
Disclosures

- Honoraria
  - Pfizer Ltd
  - Canadian Pediatric Endocrine Group
  - Springer Nature
  - Healthcare Conferences UK
  - Journal of Prescribing Practice
  - Nursing Children and Young People journal
- Grants / awards
  - Society of Endocrinology
  - British Society of Paediatric Endocrinology & Diabetes
  - Federation of International Nurses in Endocrinology

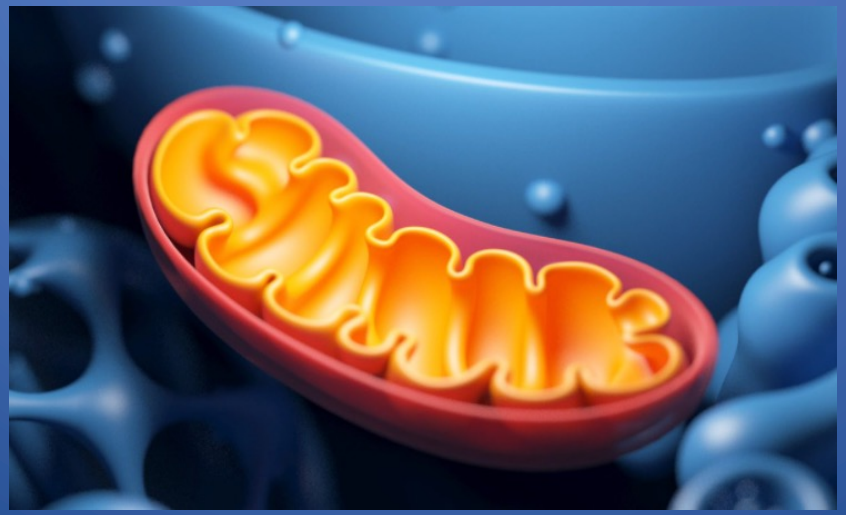
Introduction

- Anatomy and Physiology of the adrenal gland ✓
- Pathophysiology
- Inheritance
- Steroid pathway
- Types of CAH
- Neonatal screening
- Diagnosis
- Management
- Long-term complications



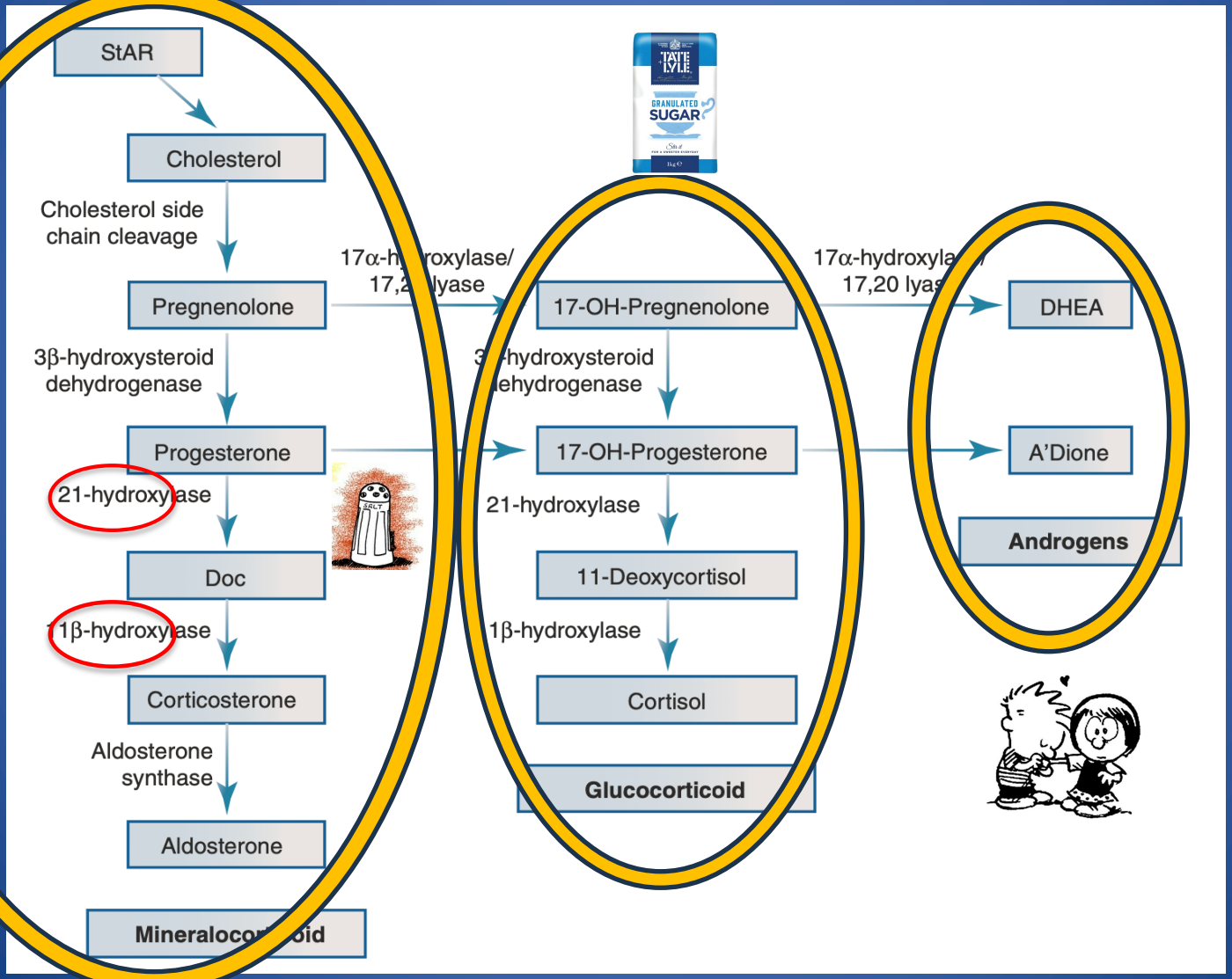
Hormones of the Adrenal Cortex

- All steroids, synthesised from cholesterol
- Most of the reactions of steroid synthesis are catalysed by enzymes of the Cytochrome P450 family, encoded by the CYP gene family
  - Mitochondria in the cell



(Yeoh, 2019)

Adrenal steroid pathway



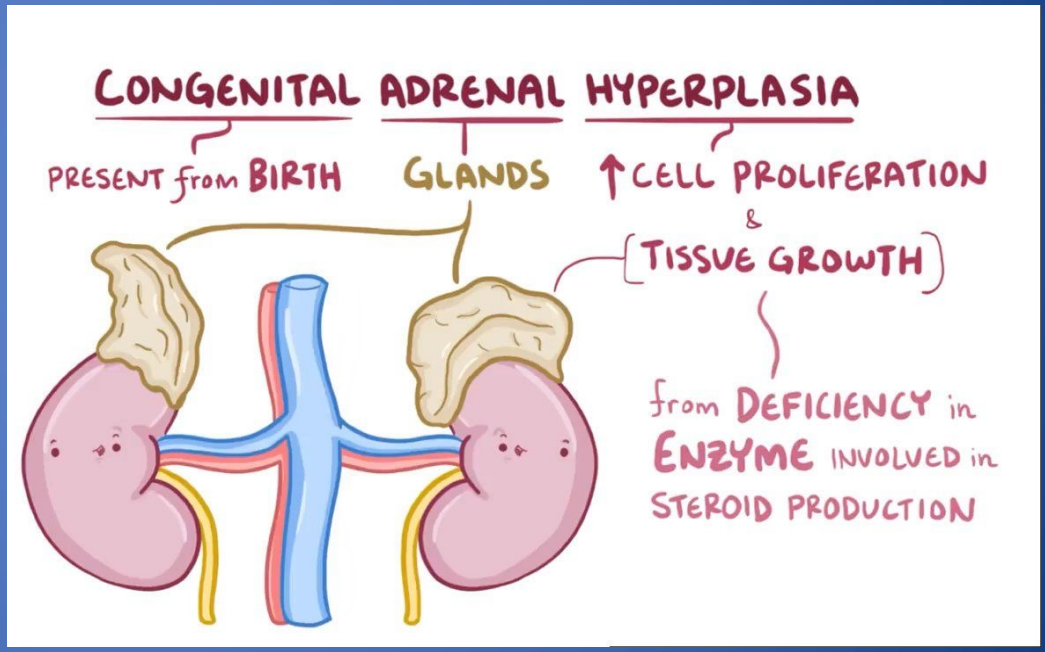
Congenital Adrenal Hyperplasia

Inherited disorder of the adrenal glands

Enzyme defect of steroid synthesis

Results in:

- Cortisol deficiency
- Excess pituitary ACTH secretion
- Adrenal gland hyperplasia



How many types are there?

- A – 2
- B – About 6?
- C – More than this?
- D – It keeps changing with new diagnostic methods

How many types are there?

- A – 2
- B – About 6?
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CAH

CURRENT OPINION

The uncommon forms of congenital adrenal hyperplasia

Richard J. Auchus

INVITED REVIEW

Adrenal

Rare forms of congenital adrenal hyperplasia

Busra Gurpinar Tosun | **Tulay Guran**

0163-769X/00/$03.00/0
Endocrine Reviews 21(3): 245–291

Printed in U.S.A.

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency*

PERRIN C. WHITE AND PHYLLIS W. SPEISER

CAH

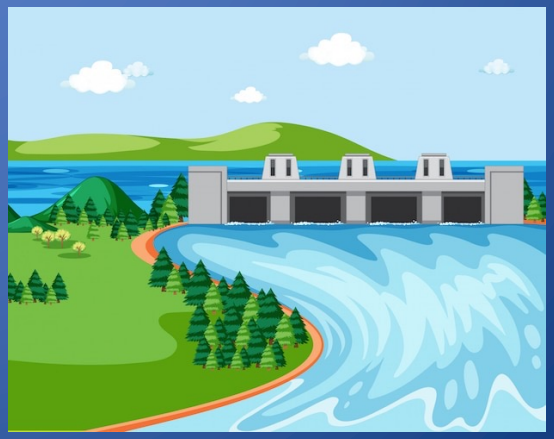
- 11β-hydroxylase deficiency
- 3β- hydroxysteroid dehydrogenase type 2 deficiency
- 17α-hydroxylase/17,20-lyase deficiency
- Cytochrome P450 oxidoreductase deficiency
- Steroidogenic acute regulatory protein deficiency
- Cholesterol side-chain cleavage enzyme deficiency
- **21-hydroxylase deficiency**

CAH

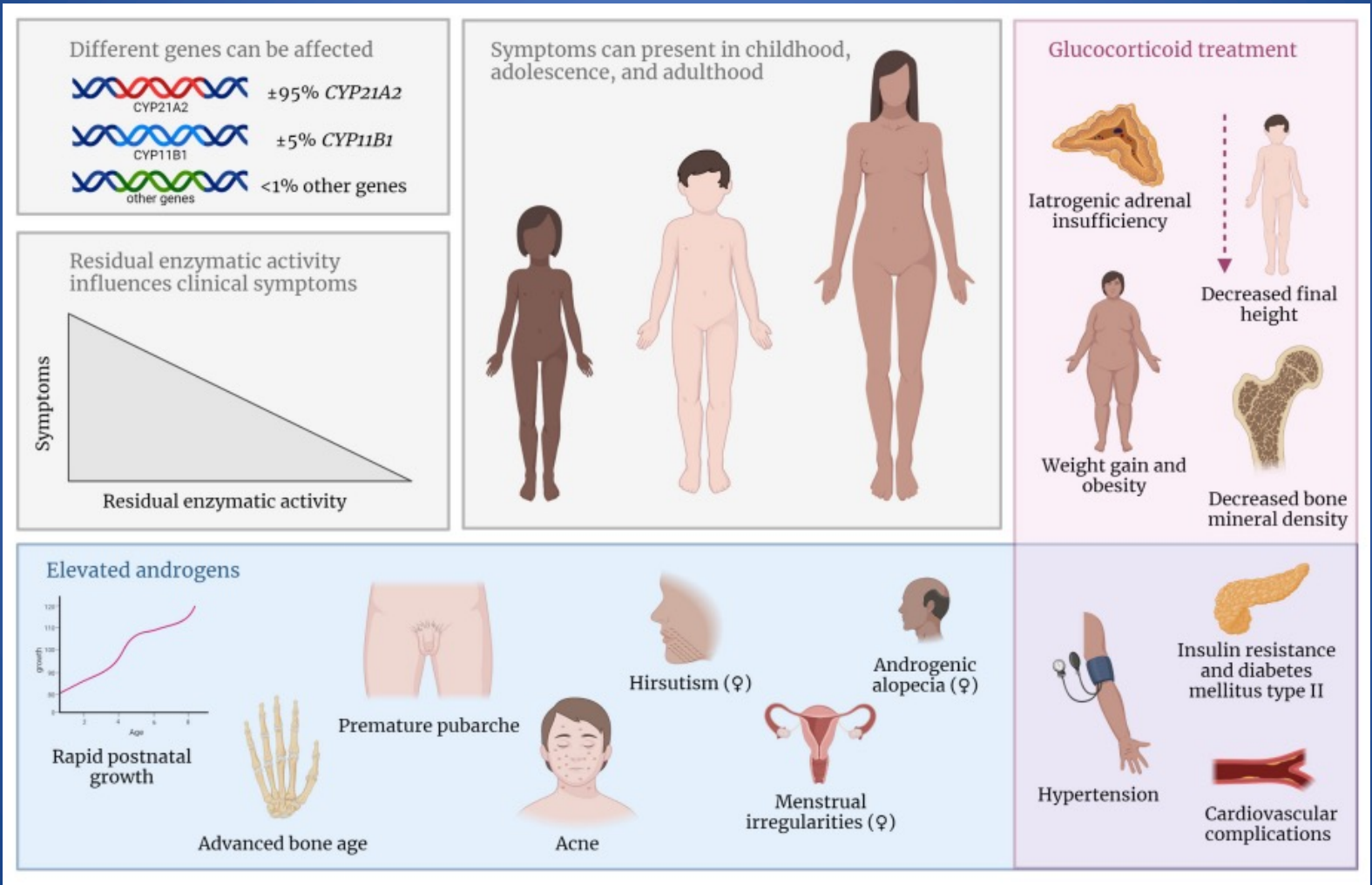
Auchus (2022)

Classic v Non-Classic

- Classic
  - Severe, complete, or near complete loss of function mutations
- Non-Classic
  - Lack clinical manifestations of cortisol deficiency



Non-Classic CAH

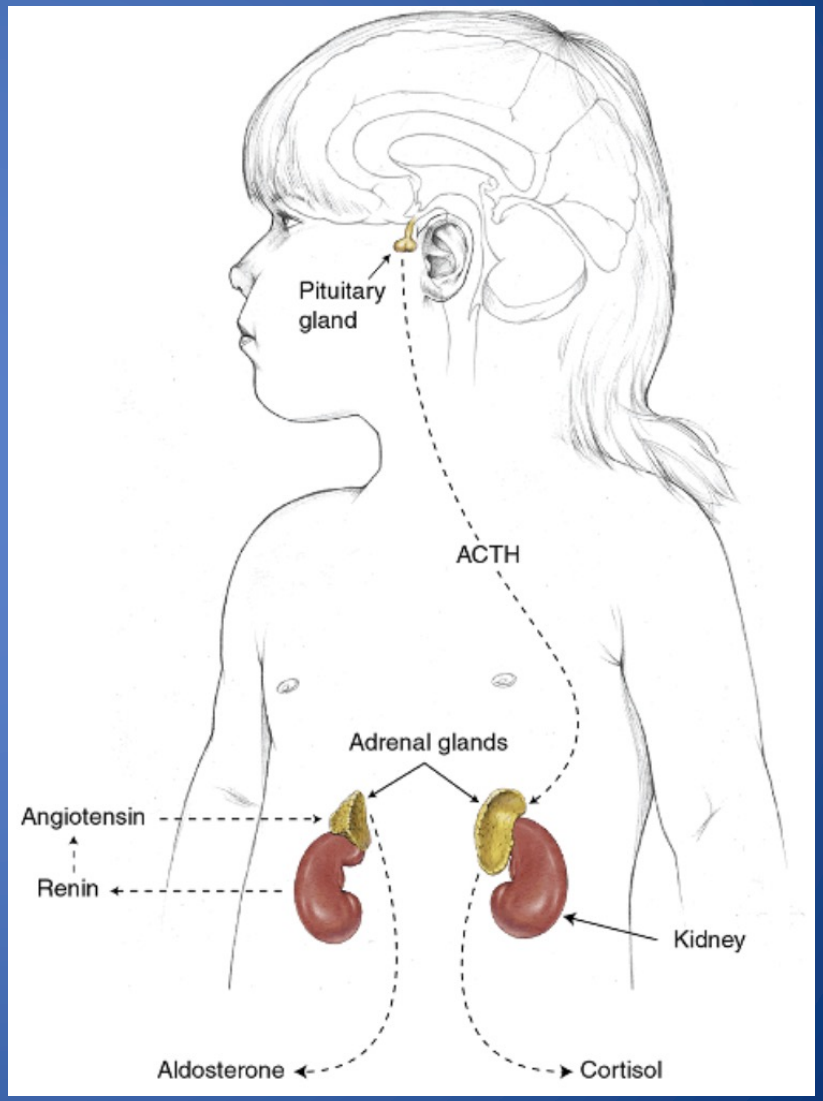


Adriaansen et al (2022)

Classic CAH

- 21-hydroxylase deficiency
- 1 – 16,000 births
- Aldosterone deficiency
- Cortisol deficiency
- SHOCK

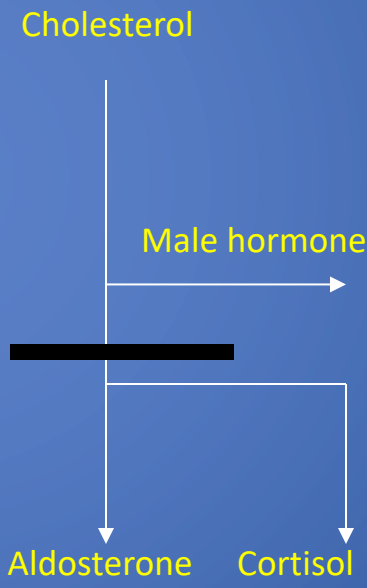
(Speiser & White, NEJM, 2003)



Adrenal Cortex – CAH?

- Steroids made from cholesterol:
  - Cortisol
  - Aldosterone androgens
  - Series of changes brought about by proteins called *enzymes*
- CAH – when one of the enzymes is NOT working properly, so cortisol production is impaired
- Pituitary gland 'senses' not enough cortisol is being made, so makes more ACTH to compensate
- This in turn causes the adrenal gland to thicken – 'hyperplastic'
- Most common type – 21-hydroxylase deficiency:
  - Deficiencies in Aldosterone and Cortisol, but the male hormone continues to be produced
  - Excess of 17-OHP

Steroid Pathway



How is it inherited?

A – Autosomal dominant inheritance

B – Autosomal recessive inheritance

C – X-linked inheritance

D – I’m not sure

How is it inherited?

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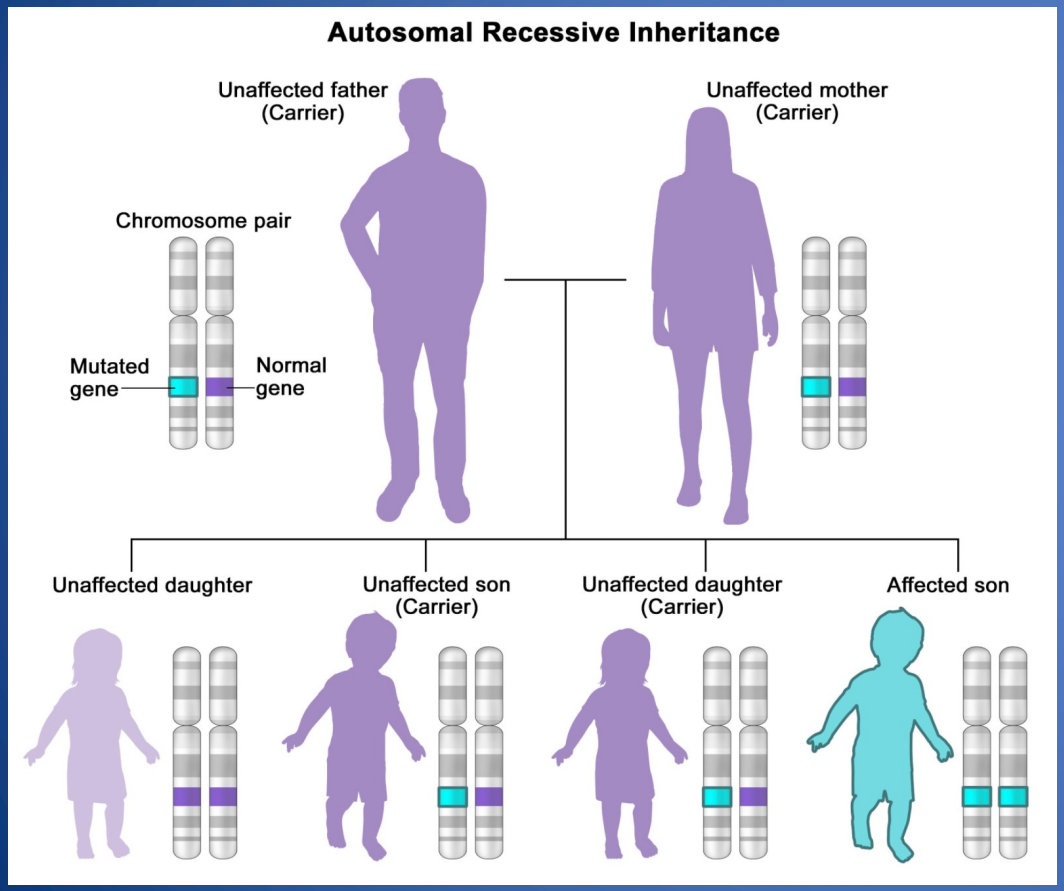
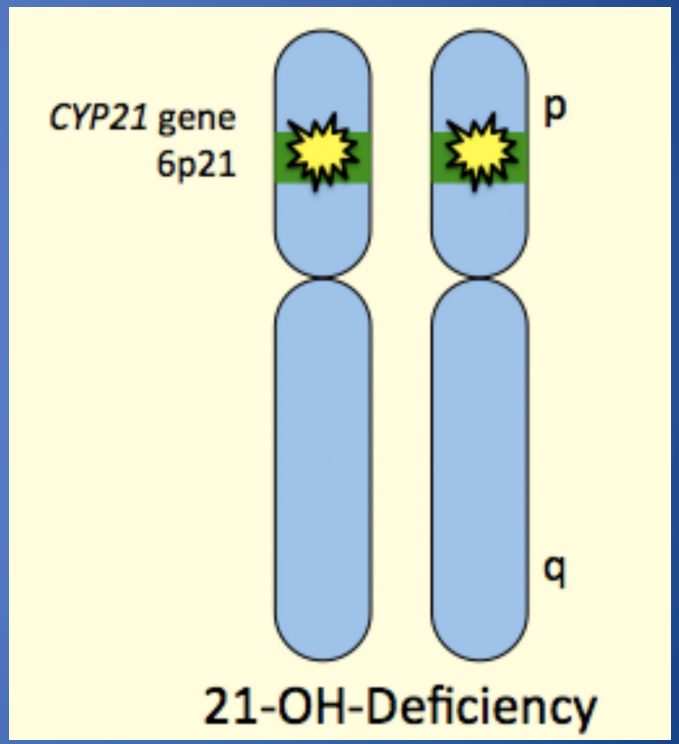


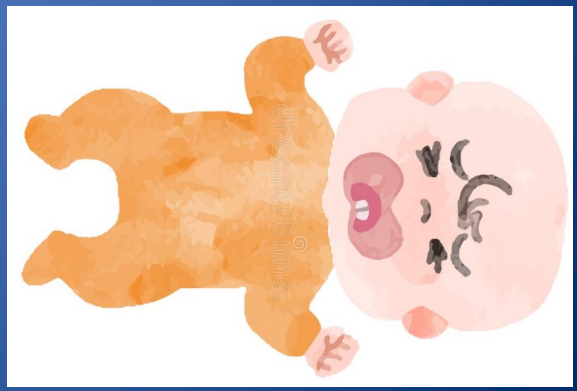


Diagnosis

- Prenatally
- Newborn screening
- Clinical assessment
  - Boys
  - Girls

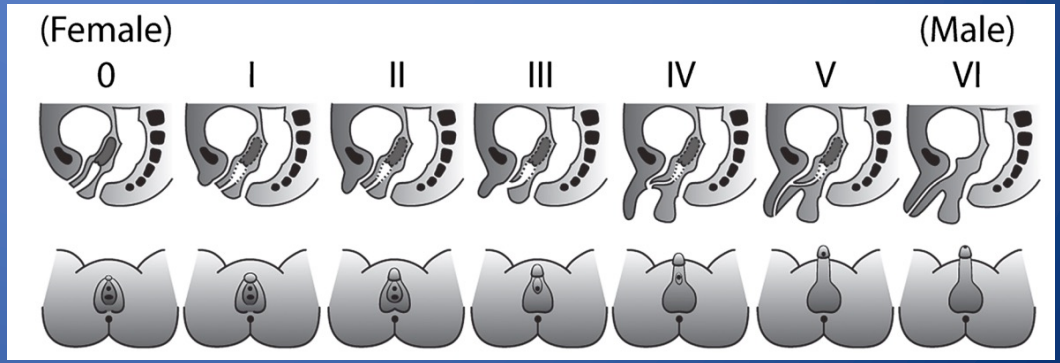
BOYS with Classic CAH

- Baby will look normal at birth
  - Can have hyperpigmented scrotum
- 1st – 2nd week of life
  - Poor feeding, vomiting, weight loss
  - Due to salt and water loss in the urine from aldosterone deficiency, which needs to be treated urgently
- If CAH not recognised
  - Salt losing crisis
    - Due to the aldosterone loss



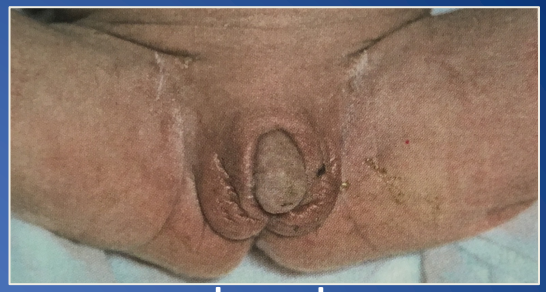
GIRLS with Classic CAH

- Baby will have been exposed to excess male hormone *in utero*
- The genitalia may look like a boy's:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
  - Need to incorporate Prader staging into the physical assessment
- 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

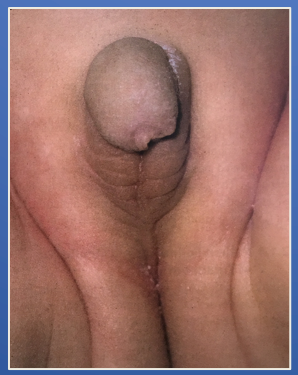


- *Hryhorczuk et al (2022)*

46XX CAH

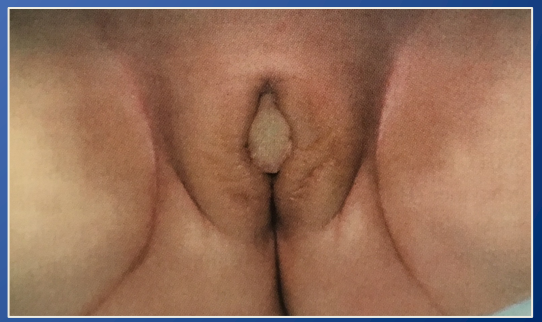


- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy's:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
  - Need karyotype
  - Will still have normal internal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



(Warne & Hewitt, 2012)

- 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

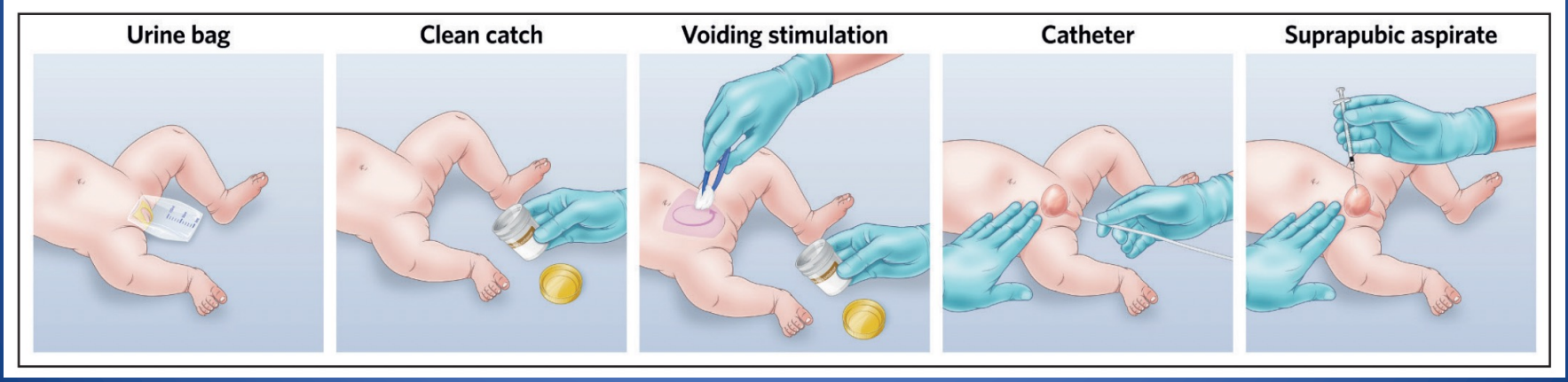
- Confirmed by a raised 17-OHP level after day 3 of life
- Salt wasting confirmed by:
  - Low plasma sodium
  - High potassium
  - Increased urinary sodium excretion
  - Virilised girls
    - Chromosome analysis
    - Pelvic ultrasound
- Short synacthen test – IM or IV
  - 0 – 6 months: 62.5 mcg
  - 6 months – 2 years: 125 mcg
  - Over 2 years: 250 mcg

(Davies & Collin, 2015)

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

Urine analysis

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



Kaufman et al, British Journal of General Practice, 2020

Christakoudi et al, Steroids, 2010

Impact of a new diagnosis

- Underestimate parents' ability to focus on the important issues
  - Affected by emotional state
  - Amount of information provided
  - Understanding of health literacy (Boyse, 2014)
- Want a survival guide
  - Including how to give the medicine
  - Managing an adrenal crisis
  - Clear and concise
  - Easy to do
- What happens if there is overload on patient information
  - What do we include?
- Emphasise that this is a life-threatening condition – discuss adherence

Medical management

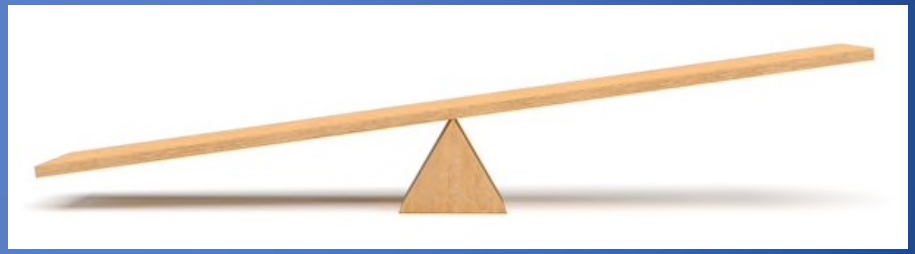
- Hydrocortisone 10 mg tablets
  - 10 – 15 mg/m^2 per day
  - Total dose spread 3 – 4 times throughout the day
- Fludrocortisone 100 mcg tablets
  - 150 mcg/m^2 per day
- Salt supplements
  - Oral salt supplements (until 1 year of age) in the 5 mmol/mL 30% sodium chloride solution – 5 mmols/kg per day, in 4 divided doses = …….mLs per dose four times a day
  - Can stop when fully weaned

Different steroid regimes producing better outcomes?

Maybe so in CAH

Need to strike a balance

- We want a well child
- Not experience side effects



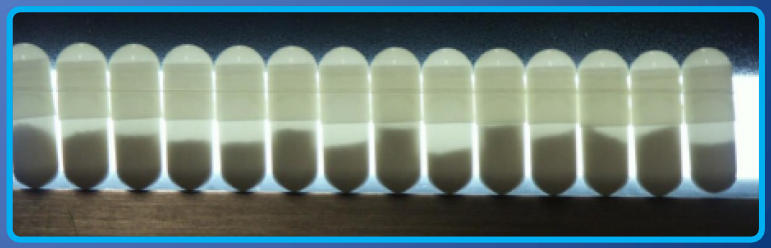
HOW?

- Focus on precision dosing

- Logical way to do this is with specific paediatric dosing

Manipulation of tablets

- Quartering 10 mg hydrocortisone tablets
  - Unacceptable dose variations
    - Glucorticoid excess
    - Cortisol insufficiency
- Splitting tablets
  - Unequal parts / crumbling = unequal doses
- Common practice
  - Renders the medication unlicensed
  - No guidelines or evidence *(Richey, 2013)*
- Compounded Hydrocortisone capsules
  - Variability in capsule content = variation in dose *(Neumann, 2017)*



What about liquid?

Hydrocortisone suspension not bioequivalent to hydrocortisone tablets (Merke, 2001)

↑ 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 (2018)

Unlicensed 'specials' – affect bioavailability

Taste

Taste of medication often cited as a reason for non-compliance *(Mennella, 2015)*

Liquids preferred by caregivers

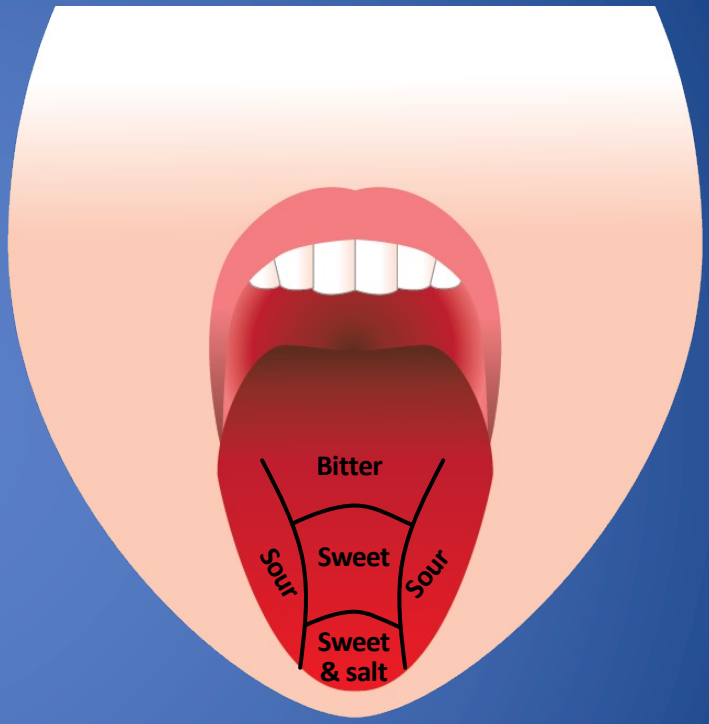
Children scared of pills and choking

Use of tasteless medication

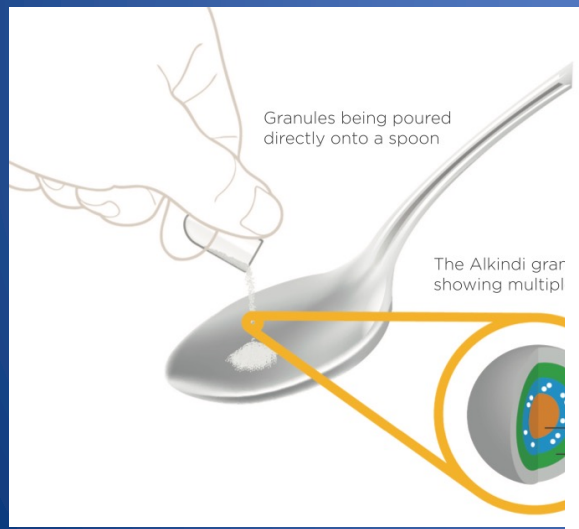
- Minimise the loss of medication from spillage / spitting

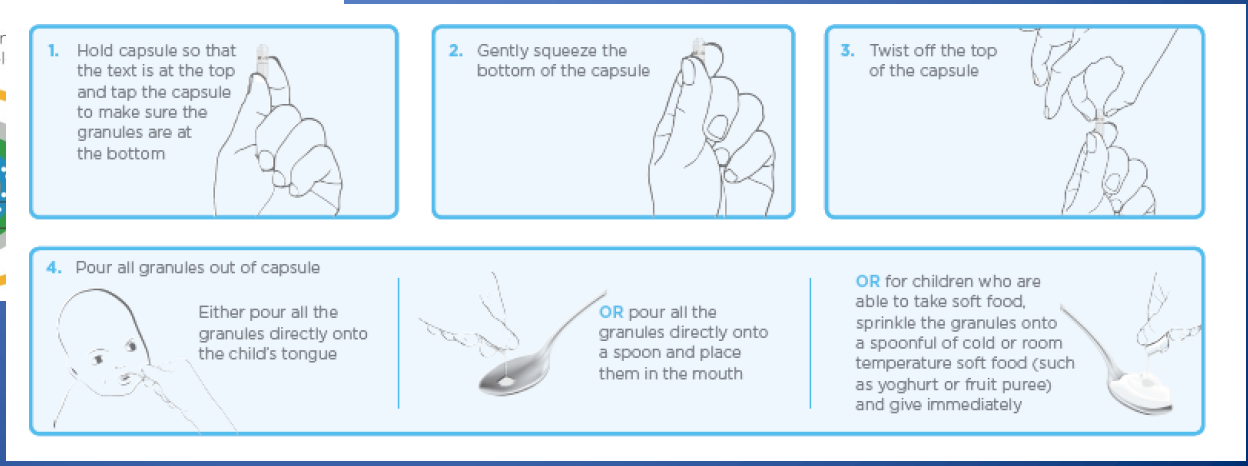
Multiparticulate dosage *(Ivansovska, 2014)*

- HIV / Tuberculosis / Cystic Fibrosis
- Accepted over liquids from 3 months *(Mistry & Batchelor, 2016)*



Coope et al (2021) www.diurnal.co.uk

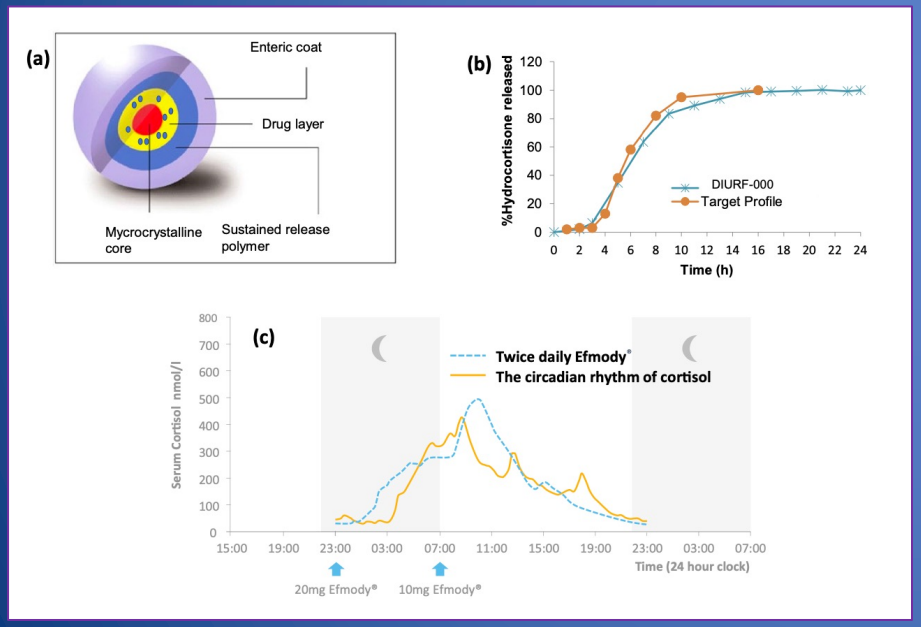




Other medicines

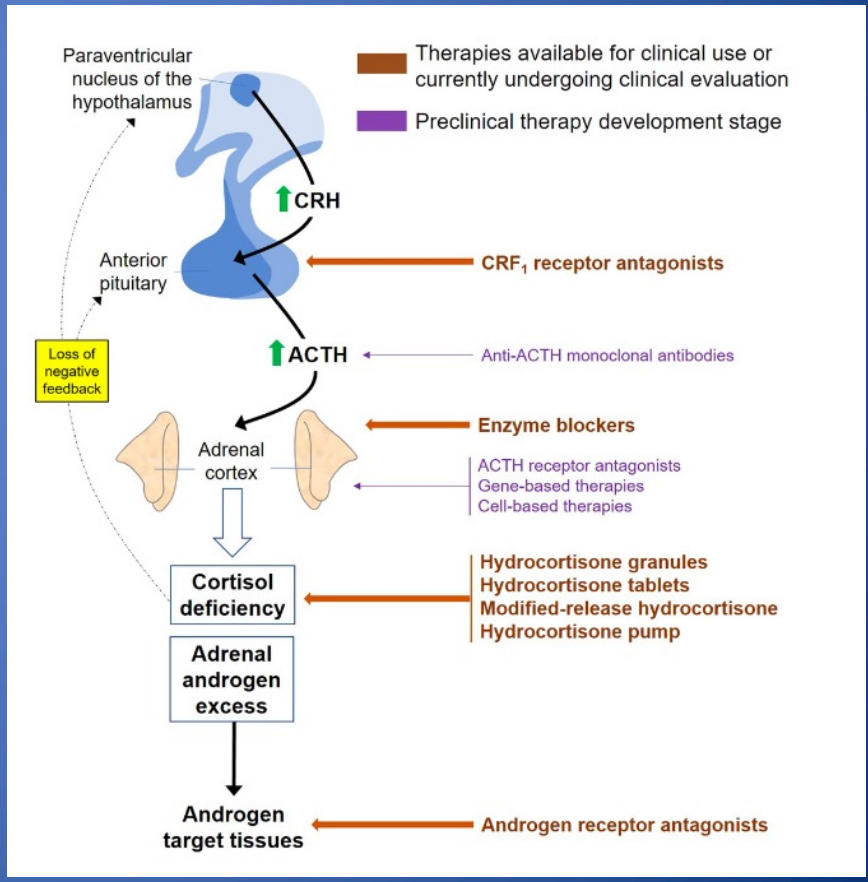
Efmody

Whitaker et al (2022)



Crinecerfont

Prete et al (2021)



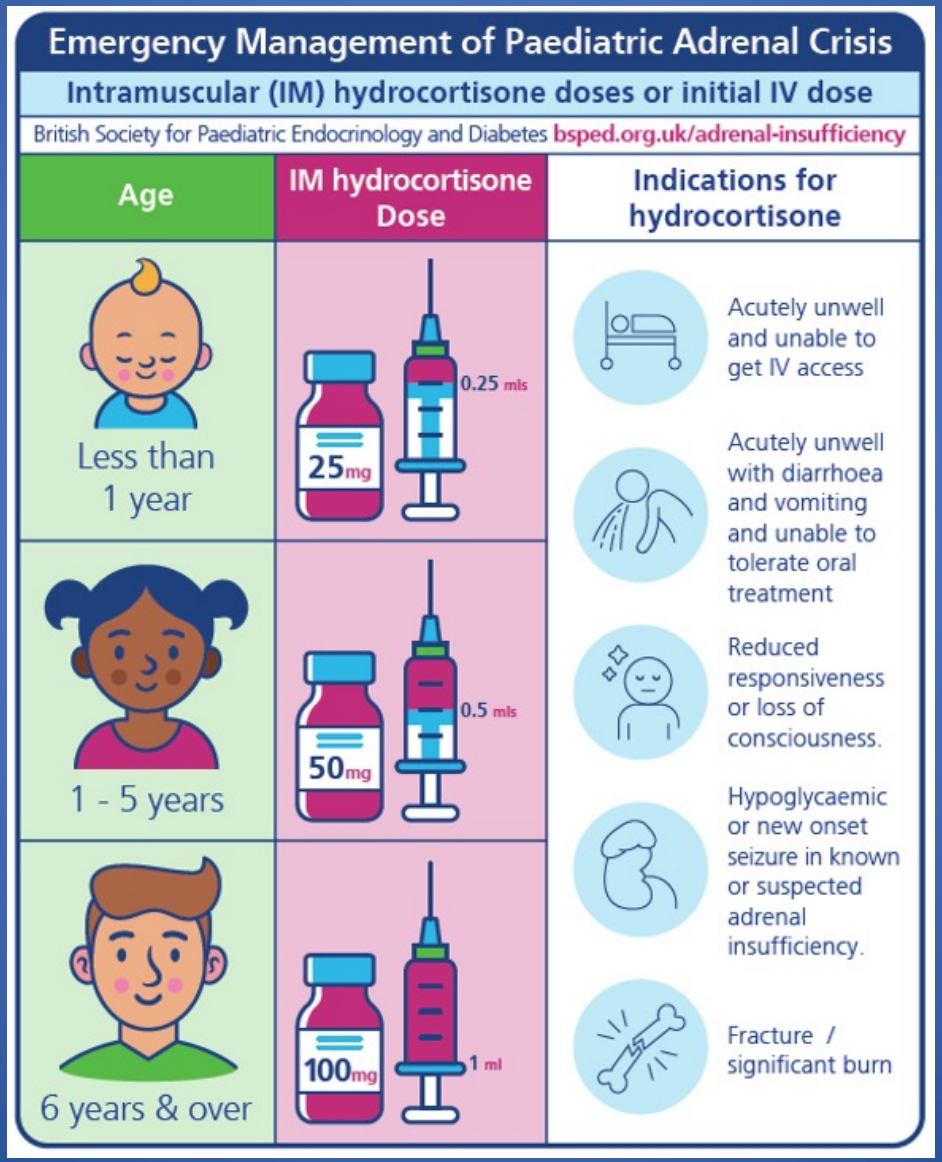
Pumps

THE ADRENAL PUMP

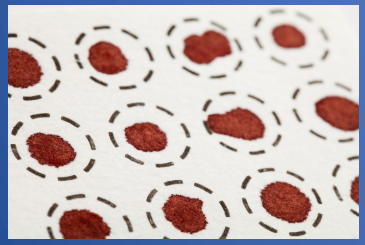
www.theinspirationedit.com . Angela Milnes

PRO - BETTER MANAGED CORTISOL LEVELS MORE IN LINE WITH THE NATURAL CIRCADIAN RHYTHM	CON- THE COST OF THE PUMP, GIVING SETS AND MEDICATION. (IT IS WORTH IT FOR A BETTER QUALITY OF LIFE)
PRO - DON'T HAVE TO WAKE UP IN NIGHT TO TAKE MEDICATION. ALSO NO WORRYING ABOUT MISSED TABLETS	CON- YOU HAVE TO BE CAREFUL NOT TO GET INFECTIONS AT THE SITE OF YOUR GIVING SET
PRO - LESS ADRENAL CRISIS AND HOSPITAL ADMISSIONS AND CAN EMERGENCY BOLUS WHEN NEEDED	CON- IT CAN BE HARD TO FIND AN ENDO TO SUPPORT YOUR TREATMENT
PRO - LESS PAIN AND FATIGUE. BETTER QUALITY OF LIFE AND ABLE TO DO MORE EACH DAY WITH ADRENAL INSUFFICIENCY	CON- IT DOES NOT HEAL YOU. YOU STILL HAVE THE ADRENAL INSUFFICIENCY AND WILL STILL GET UNWELL

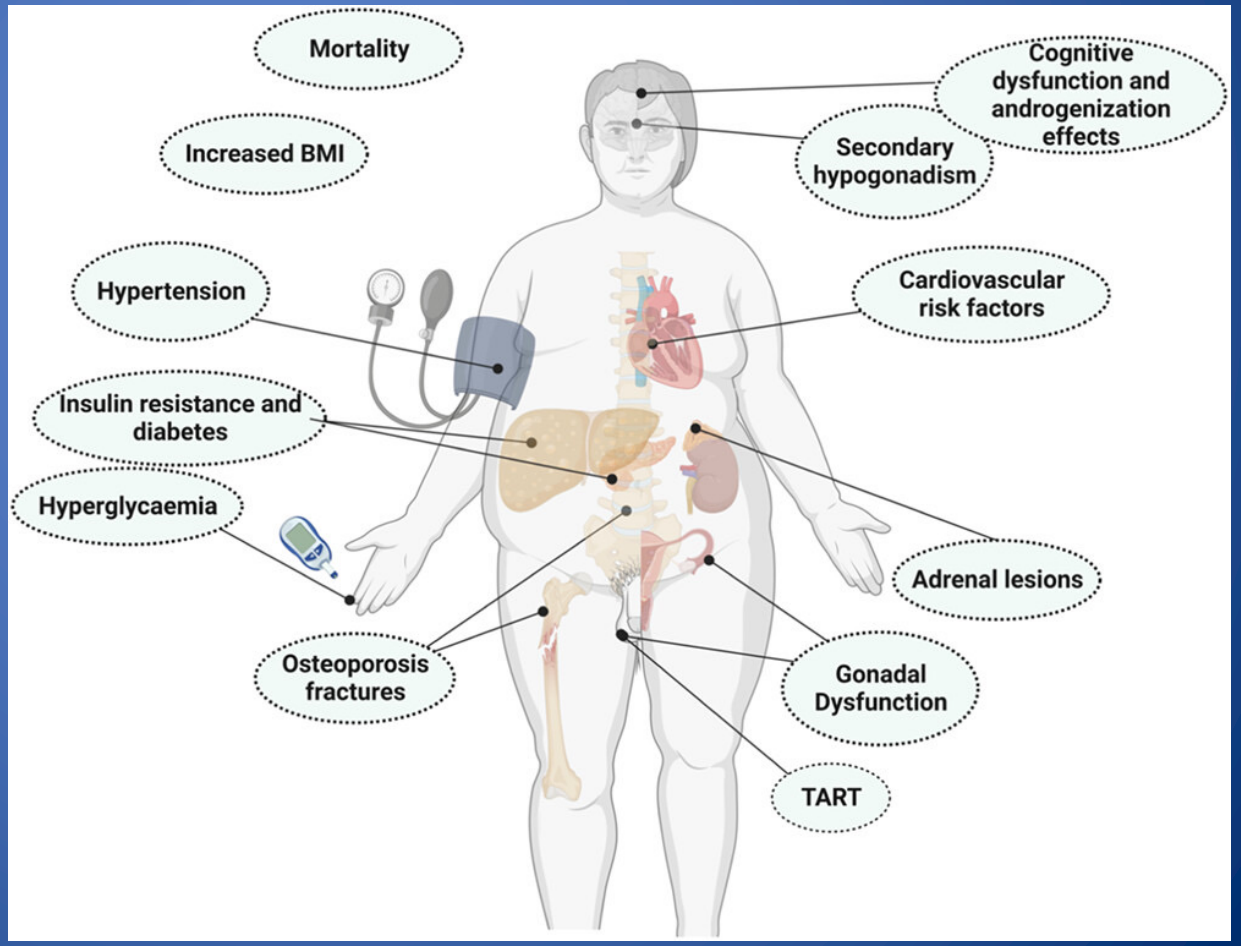
Emergency management

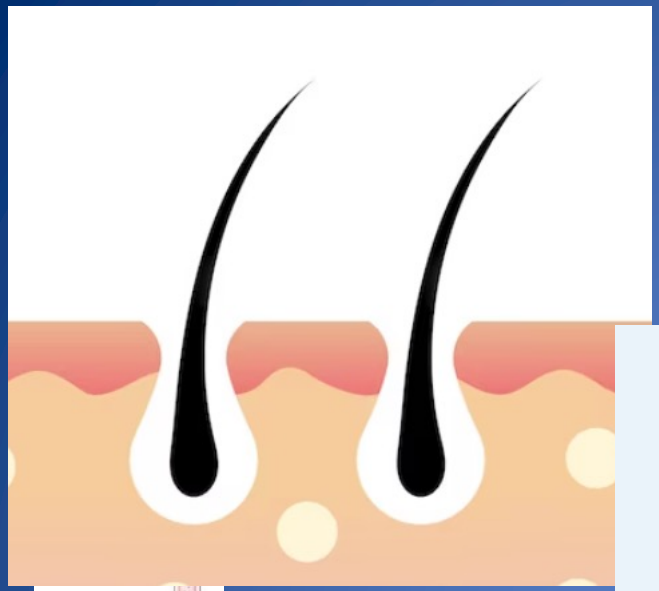


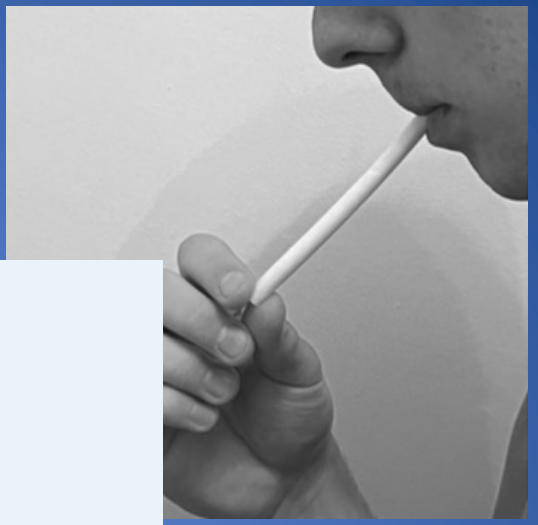
What about monitoring?

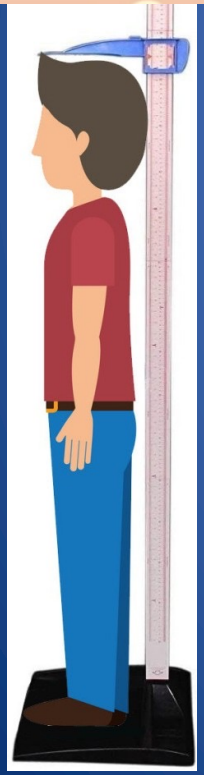


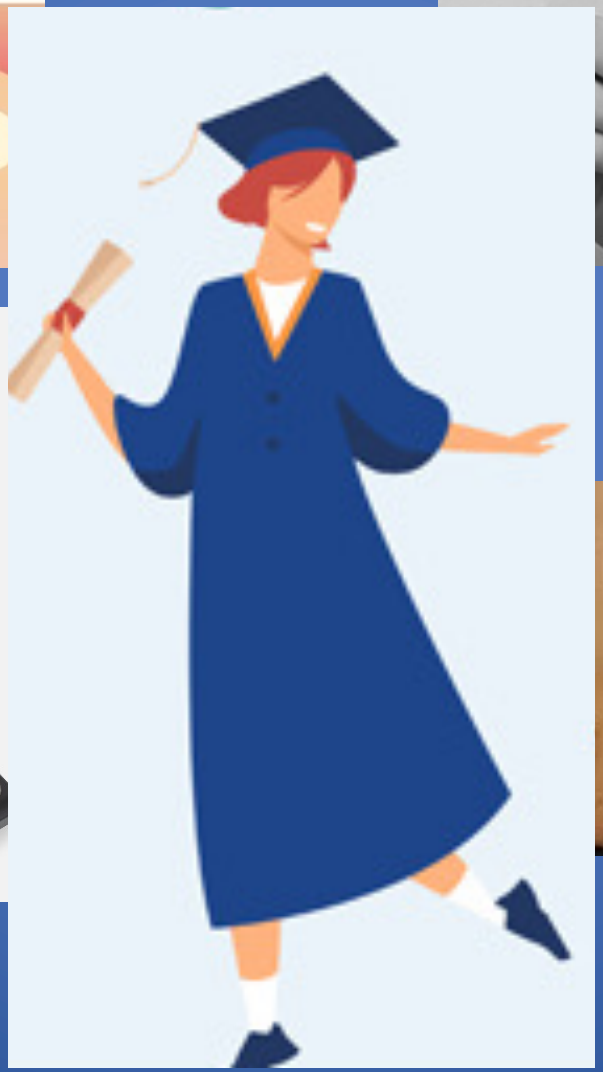
Pofi et al (2023)



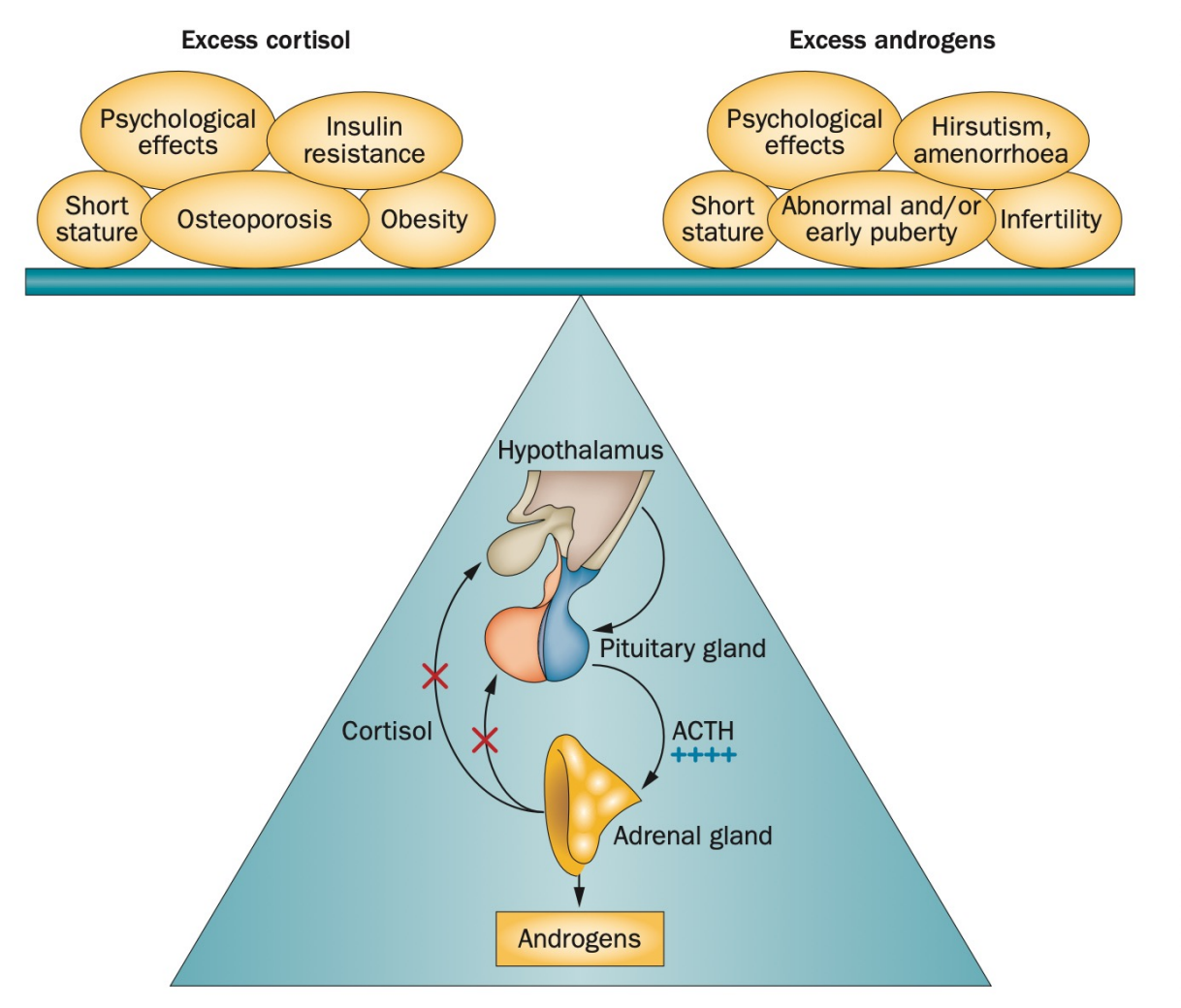








Long-term complications



Han et al (2014)

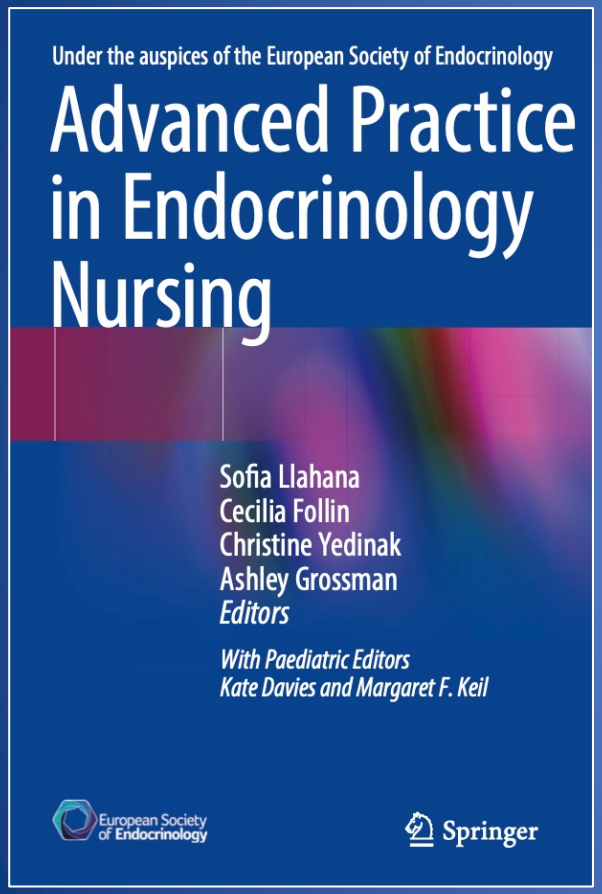
CAH – Conclusion

- An adrenal enzyme defect
- Classic 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
- Different treatments
- Potential for enhanced monitoring
- Long-term complications

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

Phyllis W. Speiser,[1,2] Wiebke Arlt,[3] Richard J. Auchus,[4] Laurence S. Baskin,[5] Gerard S. Conway,[6] Deborah P. Merke,[7,8] Heino F. L. Meyer-Bahlburg,[9] Walter L. Miller,[5] M. Hassan Murad,[10] Sharon E. Oberfield,[11] and Perrin C. White[12]

Further reading



Diagnosis and Management of Congenital Adrenal Hyperplasia in Children and Adults **35**

Alessandro Prete, Chona Feliciano, Irene Mitchelhill, and Wiebke Arlt

An overview of the nursing issues involved in caring for a child with adrenal insufficiency

▸NCYP609 **Moloney S, Murphy N, Collin J** (2015) An overview of the nursing issues involved in caring for a child with adrenal insufficiency. Nursing Children and Young People. 27, 7, 28-36. *Date of submission*: December 23 2014. *Date of acceptance*: May 6 2015.

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Thank you

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