Adrenal Insufficiency (AI)

Michael Leeson, MD
Pediatric Residency Program
Harbor UCLA Medical Center

Illustrative Cases – for instructor use for sim

- 25do, M, ex 37+0 born by CS for placental abruption and with 6d NICU stay for respiratory support, presenting for episode of regurgitation after feeding followed by skin pallor and decreased activity, at -9.3% weight loss from birth
  - Initial labs pH 7.28, Na 112, K 9.3; EKG shows sine wave pattern
  - Received 10cc/kg bolus and empiric ampicillin and cefotaxime
  - On NICU admission, treated with hydrocortisone and fludrocortisone, with hyperK treated with insulin/glucose, sodium bicarb, salbutamol, and rectal ion permuting resin
  - Found to have elevated 17-OH-P (416 nmol/L) in dried blood spot (Patient was born in Portugal, which does not include CAH on NBS)

- 16yo, F, with 1 week of nausea, vomiting, lightheadedness, with initial exam showing dehydration and generalized weakness
  - Initial labs pH 7.25, Na 126, K 7.9, BUN 61, and Cr 1.9
  - Received 2L bolus that improved nausea and vomitting, but continued to have hyponatremia (Na 126) and hyperkalemia (8)
  - Working diagnosis of acute renal failure 2/2 severe dehydration
  - On PICU admission, noted to have tan appearing skin with numerous hyperpigmented patches
  - Found to have low cortisol (<0.8 ug/dL), elevated ACTH (1463 pg/mL), and 21-hydroxylase antibody, indicating autoimmune etiology
  - Started on IV hydrocortisone and PO fludrocortisone

- 17yo, M, with 3 weeks abdominal pain, nausea, and vomiting, and progressive asthenia, weakness, cough, and weight loss for 3 months, with exam showing poor peripheral perfusion, hypotension, tachycardia, and dry mucous membranes,
  - Initial labs Na 112, K 5.9, BUN 100 and pH 7.22
  - Diagnosed initially with sepsis and given a 20cc/kg NS bolus, started on NS for MIVF, inotropic support (DA, NE), and ceftriaxone and imipenem
  - On PICU admission, noted to have continued dehydration and diffusely increased pigmentation, most notably at mucous membranes and palmar creases
  - Found to have low cortisol (4.4 ug/dL), elevated ACTH (948 ng/dL), low aldosterone (1.5 ng/dL), and increased plasma renin (540 uIU/mL)
  - Diagnosed with primary adrenal insufficiency
  - Started on IV hydrocortisone and PO fludrocortisone

Etiology

- Impaired secretion of adrenal glucocorticoid and mineralocorticoid hormone
  - Generally concern for mainly cortisol (glucocorticoid) and aldosterone (mineralocorticoid) clinical effects

- Primary AI: Adrenal gland destruction or dysfunction
  - Congenital adrenal hyperplasia (CAH)
  - Autoimmune polyendocrine syndrome
  - Adrenoleukodystrophy

- Secondary AI: Hypothalamic-pituitary-adrenal axis impairment
  - Exogenous corticosteroid therapy withdrawal
    - Most common cause in older kids
    - HPA axis suppression after approx 14 days
  - Poor compliance with scheduled corticosteroid dosing

CAH Pathophysiology

- CAH = most common cause of AI in infancy
  - Most often 21-hydroxylase deficiency with high 17-hydroxyprogesterone
    - Impaired cortisol secretion -> Increased CRH & ACTH release -> Adrenal hyperplasia

- Classic
  - Increased cortisol precursors -> redirected to sex hormone biosynthesis & hyperandrogenism -> prenatal virilization of girls + rapid somatic growth
  - 75% have an aldosterone deficiency causing a salt losing form -> hyponatremic dehydration and shock
    - Associated with large genetic mutations -> No enzyme activity
    - Presentation: at 1-3wks old, will have nonspecific vomiting, dehydration, and poor feeding
  - 25% without salt wasting form
    - Associated with point mutations -> Low, but detectable enzyme activity
    - Presentation: at 2-4 years old, will have rapid postnatal growth and precocious puberty

- Non-classic
  - Less severe and later presentation
  - Precocious puberty in later childhood or adult excess androgen
    - Tall stature, acne, hirsutism, temporal hairline recession, amenorrhea, infertility

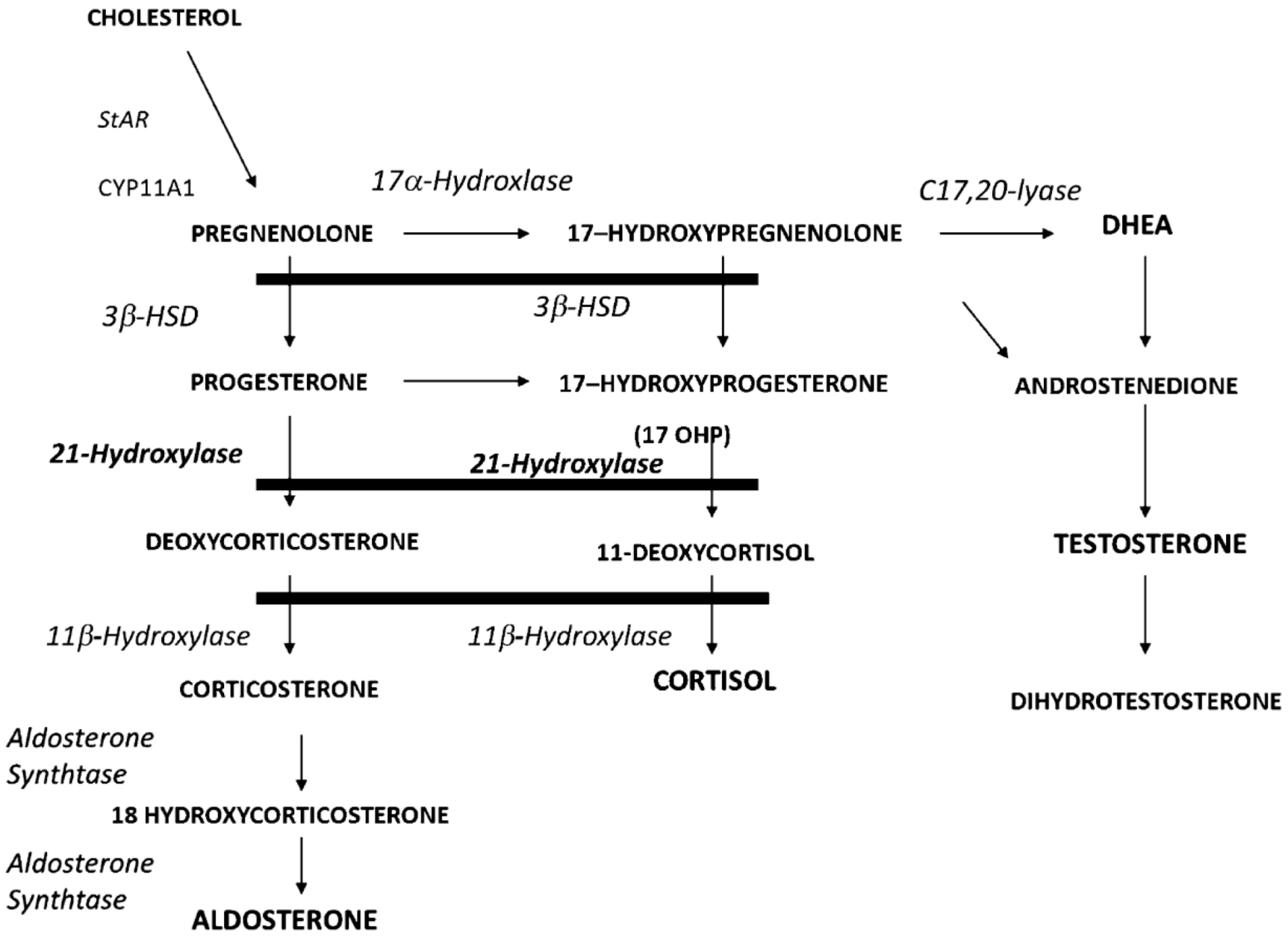


Figure 1. Steroidogenesis pathway.
3β-HSD=3β-hydroxysteroid dehydrogenase; DHEA=dehydroepiandrosterone sulfate; StAR=steroidogenic acute regulatory protein. Adapted from White and Speiser. (9)

CAH Clinical presentation

- Most commonly vague and undefined
- **Classic signs:** hyperpigmentation, fatigue, vomiting/diarrhea —> hypotension, hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis
- Cardiovascular and hemodynamic insufficiency

- Classic CAH
  - 75% present with salt wasting -> hyponatremic dehydration and shock
  - Girls: Prenatal virilization -> ambiguous genitalia
  - Boys: normal male genitalia -> delayed diagnosis to ages 1-3wks with nonspecific vomiting, dehydration, poor feeding
  - Variability in presentation likely due to variation in mutations (point mutations vs. large deletions/insertions)
  - If unrecognized and untreated -> Hyperandrogenism -> Rapid postnatal growth and precocious puberty at 2-4yrs

- Non-classic
  - Late onset
  - Tends to be a less severe phenotype with variable clinical presentation

Newborn Screening For CAH

- Due to the potential fatality of a missed diagnosis of the salt-wasting form of classic CAH, newborn screening programs for CAH have been established in all 50 states

- Measures 17-OH-progesterone from dried blood spots

- Sensitive and specific to detect almost all with classic CAH and some with non-classic CAH
  - Positive screening is confirmed with serum 17-OH-P
  - False positives can be seen in premature infants, and would be followed with serial measurements

Adrenal Destruction & Dysfunction (Addison's Disease)

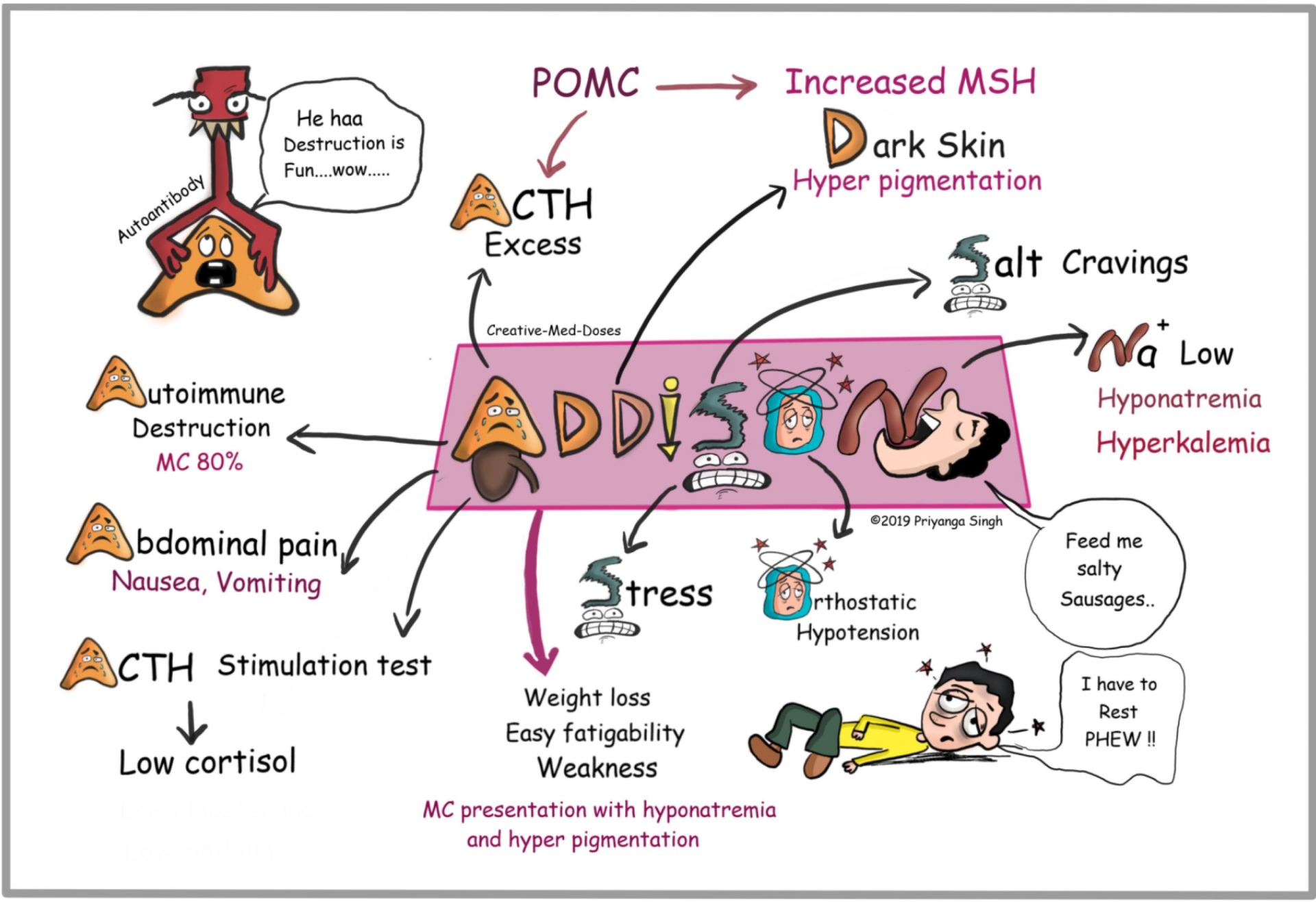
- Rare disorder (90 to 140 per million)
- Variable etiology: neonatal/postnatal adrenal hemorrhage, infection, autoimmunity, tumor invasion, genetic mutation
- Symptoms/Signs:
  - Hyperpigmentation - dark spots on mucous membranes, palmar creases, nailbeds, areola
  - Weakness, fatigue, dizziness, syncope, orthostatic hypotension, weight loss, vomiting/diarrhea, abdominal pain
  - Infants: +poor feeding, decreased alertness, dehydration
- Lab findings
  - HypoNa, hyperK, hypoglycemia, ketonemia, *Eosinophilia*
  - Elevated ACTH and renin, low aldosterone, low AM cortisol
- Diagnosis: ACTH stimulation test

Clinical Manifestations of Adrenal Insufficiency

- **Symptomatic AI:** fatigue, vomiting/diarrhea, diffuse abdominal pain + hyponatremia, hyperkalemia, metabolic acidosis

- **Adrenal Crisis:** +hypotension (or SBP drop >20 from baseline) and/or hypoglycemia
  - Symptoms respond to exogenous hydrocortisone administration
  - Presentation may mimic sepsis

- Triggers: infection, stress, surgery, meds (CYP4 inducers: phenytoin, carbamazepine)



https://creativemeddoses.com/topics-list/addison-disease-primary-adrenal-insufficiency/

Management of Adrenal Crisis

1. Stress dose hydrocortisone
   - TODDLER: 25mg IV (or IM)
   - KIDS (>3yo): 50mg IV (or IM)
   - ADOLESCENT: 100mg IV (or IM)
   - Typically half of 1st dose Q6H (Endocrinologist decides)
     - Hydrocortisone has some mineralocorticoid activity and faster onset than prednisone and dexamethasone
     - Fludrocortisone not needed if hydrocortisone dose => 50mg Q24H

2. Fluid resuscitation
   - Likely multiple 20cc/kg NS boluses
   - D5-containing maintenance fluids after immediate resuscitation

3. Correct electrolyte derangement and acidosis

- Initial labs
  - Blood gas + glucose, BMP, Cortisol (can diagnose typically if level < 20 during stress)
  - If highly suspected: +Cortisol, ACTH, plasma renin activity, 17-OH
  - Ideally drawn before hydrocortisone dosing

- PICU admission
  - Hemodynamic monitoring, continuous electrolyte supplementation, glucose monitoring, use of vasporessors

Stress dosing

- Goal: Prevent hypoglycemia, hypotension, and cardiovascular collapse

- Severe stresses necessitating stress dosing
  - Illness with high fever (≥38.5°C), surgery, trauma

- Mild physical stresses that do not require stress doses
  - Immunizations, uncomplicated viral illnesses, low grade fever (<38.5°C), athletic activity, emotional stress

- Dosing
  - Empiric and not determined by evidence-based guidelines
  - Triple oral hydrocortisone maintenance dose for 3 days (“3x3”) is one strategy for milder intercurrent illness
  - Parenteral hydrocortisone is suggested before general anesthesia and surgery

- Generally recommended for 6-12 months after discontinuing chronic steroid use

PIR Questions

1. Fraternal twins, a girl and a boy, were both born with the salt-wasting form of congenital adrenal hyperplasia. Given the same diagnosis, why is the diagnosis of the infant girl more likely to be detected earlier than her brother?
    A. Genital ambiguity.
    B. Higher adrenocorticotropic hormone (ACTH) levels.
    C. Hyperpigmentation.
    D. More severe hypernatremia.
    E. The absence of hyperkalemia.

2. A 6-year-old girl presents with unrelenting, uncharacteristic fatigue. A biochemical workup suggests adrenal insufficiency. An elevation of which of the following would suggest primary adrenal insufficiency?
    A. ACTH.
    B. Blood urea nitrogen.
    C. Glucose.
    D. Sodium.
    E. Cortisol.

3. In a 1-month-old infant with ambiguous genitalia, congenital adrenal hyperplasia is suspected if the following biochemical component is elevated:
    A. Cholesterol.
    B. Serum aldosterone.
    C. Serum cortisol.
    D. 17-Hydroxyprogesterone.
    E. 21-Hydroxylase antibodies.

PIR Questions

4. A 14-year-old boy with chronic asthma had been treated with very high-dose inhaled corticosteroids. His asthma has improved, and use of inhaled corticosteroids was discontinued. His physician has concerns regarding adrenal insufficiency from intercurrent stress due to illness, trauma, or surgery. The duration during which stress doses of glucocorticoids are generally recommended after discontinuation of long-term corticosteroid use is:

    A. 14 days.
    B. 1 month.
    C. 3 months.
    D. 6 to 12 months.
    E. 2 years.

5. A 3-year-old girl is diagnosed as having adrenal insufficiency. Among the following, the preferred cortisol replacement is:

    A. Aldosterone.
    B. Dexamethasone.
    C. Hydrocortisone.
    D. Methylprednisolone.
    E. Prednisone.

Answers

- 1. A
- 2. A
- 3. D
- 4. D
- 5. C

Further Reading

- *Auron, M., Raissouni, N.* (2015). **Adrenal insufficiency.** Pediatrics in review / American Academy of Pediatrics 36(3), 92-102; quiz 103, 129. https://dx.doi.org/10.1542/pir.36-3-92
- *Liz, C., Rocha, A.* (2019). **Congenital Adrenal Hyperplasia-When Clinical Symptoms Are Missing.** Pediatric emergency care https://dx.doi.org/10.1097/pec.0000000000001752
- *Szadkowski, A., Pollock, A., Al-Subu, A.* (2020). **Hyperkalemia and Acute Kidney Injury in an Adolescent Thinking Outside the Box** Pediatr Emer Care 36(), e288-e290.