Adrenal crises

Definition

-acute adrenal insufficiency
-It is an endocrine emergency condition precipitated by internal or external processes in the setting of known or unknown adrenal insufficiency and corticosteroid deficiency.

Epidemiology

- Acute adrenal crisis may be the first presentation of previously unrecognized adrenal insufficiency.
- Historically, **tuberculosis** was the most common cause (≈70%).
- After the discovery and widespread use of cortisone, TB became less dominant in developed regions.
- **Autoimmune adrenalitis (Addison's disease)** is now the most common cause of primary adrenal insufficiency in developed countries.
- **Tuberculosis** remains the leading cause of adrenal insufficiency in developing countries.
- **Neisseria meningitidis** infection can still lead to adrenal hemorrhage in **Waterhouse–Friderichsen syndrome.**

Risk factors

1. **Previous History**
   - Known history of adrenal insufficiency or prior adrenal crisis.
2. **Type of Adrenal Insufficiency**
   - Primary adrenal insufficiency → higher risk than secondary adrenal insufficiency.
3. **Glucocorticoid Therapy**
   - Ongoing use of glucocorticoids (oral, topical, inhaled).
   - Suppresses HPA axis; sudden withdrawal can trigger crisis.
4. **Anticoagulation Therapy**
   - ↑ Risk of adrenal hemorrhage.
5. **Pregnancy**
   - ↑ Cortisol requirement, especially in the third trimester.
6. **Older Age**
7. **Comorbidities**
   - e.g., Type 1 diabetes mellitus.
8. **Adrenal Metastasis**
9. **Adrenal Hemorrhage**

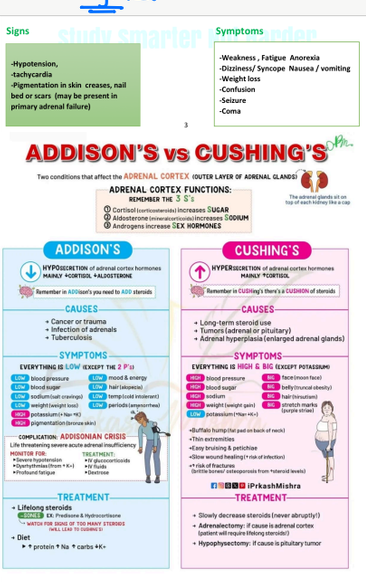
Precipitation factors

1. Stressors
- Trauma.
- Pregnancy.
- Surgery.
- Extreme hot or cold weather.
- Dehydration.
- Significant emotional distress.
- Strenuous physical activity.

2. Medications
- Non-adherence to glucocorticoid replacement therapy.
- Abrupt cessation of chronic glucocorticoid therapy.
- Thyrotoxicosis or initiation of levothyroxine in untreated adrenal insufficiency (↑ cortisol metabolism).
- Antiadrenal medications.
- Anticancer medications.

Pathophysiology

CVS	Adrenergic receptors in the heart and the vessels> Catecholamines are unable to exert a full effect on these receptors in the absence of GCs.
Immune	Infectious or noninfectious stressors > activation of the immune system.
Intravascular volume	GCs suppress the expression and secretion of anti-diuretic hormone (ADH)
Glucose Homeostasis	GCs lead to increased glucose levels by increasing glycogenolysis and gluconeogenesis . GCs also increase insulin resistance.
Appetite regulation	Corticotropin-releasing hormone (CRH) suppresses apetite in response to stress. GCs are a powerful inhibitor of CRH release, leading to increased appetite.
Electrolytes	Mineralocorticoid deficiency is seen in primary adrenal insufficiency due to the direct destruction of the adrenal cortex. The cortex remains preserved in secondary and tertiary adrenal insufficiency. Aldosterone production and secretion are regulated by renin-angiotensin-aldosterone system. An isolated deficiency in ACTH secretion seen in secondary or tertiary adrenal insufficiency does not significantly affect the aldosterone levels. Aldosterone deficiency leads to volume loss, loss of sodium (leading to hyponatremia), and potassium retention (leading to hyperkalemia). > Hypotension &Hyperkalemia



Sign and symptom

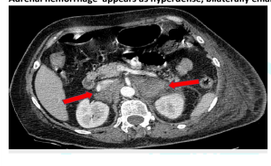
Evaluation

1. Clinical Assessment
   - Absolute hypotension: systolic BP <100 mmHg.
   - Relative hypotension: systolic BP ≥20 mmHg lower than usual.
   - Shock may develop → rapid organ damage; untreated, mortality up to 20%.

2. Imaging
   - Chest X-ray: assess for TB, histoplasmosis, malignancy, sarcoidosis, lymphoma.
   - Abdominal CT: evaluate adrenal glands for hemorrhage, atrophy, infiltrative disorders, metastasis.
   - Adrenal hemorrhage: hyperdense, bilaterally enlarged glands.

3. Laboratory Tests
   - Serum chemistry: hyponatremia, hyperkalemia, metabolic acidosis, hypoglycemia.
   - Serum cortisol: <20 mcg/dL in stress or after ACTH stimulation → adrenal insufficiency.
   - ACTH stimulation test:
     - Baseline cortisol → 250 mcg ACTH IV → cortisol at 30 & 60 min.
     - Increase <9 mcg/dL → diagnostic.
   - CBC: mild anemia, lymphocytosis, eosinophilia.
   - Serum thyroid levels: evaluate for autoimmune/infiltrative/multiple endocrine disorders.
   - Cultures: as indicated; infection is a common precipitant.

Adrenal hemorrhage appears as hyperdense, bilaterally enlarged adrenal glands.



Adrenal crises

Management

Severally unwell

Based on Severity: Severe / Moderate / Mild

1. Stabilization (ABC)
- Ensure airway, breathing, circulation.

2. Steroid Replacement

- Severely unwell:
  - **IV hydrocortisone 50–100 mg/m² immediately.**
  - If IV unavailable → IM dose while establishing IV access.
  - Repeat dose if poor response.
  - Then **hydrocortisone 6-hourly IV**.
  - Switch to **oral triple dose (~30–50 mg/m²/day)** once stable, gradually taper to maintenance.
- Mineralocorticoid replacement: **fludrocortisone 0.05–0.1 mg/day** orally once tolerating fluids.

3. Intravenous Fluids

- Shock / moderate-severe dehydration: 0.9% NaCl 10–20 mL/kg first hour; repeat as needed.
- Replace deficit + maintenance over 24h with 0.9% NaCl + 5% glucose.
- Mild/no dehydration: 1–1.5 × maintenance fluid over 24h.

4. Hypoglycemia

- **IV 10% dextrose 2–5 mL/kg.**
- Recheck after 30 min; continue maintenance fluids with up to 10% dextrose as needed.

5. Treat Precipitating Illness/Injury

- Identify & manage infection, trauma, surgery, or other triggers.

Recommended stress hydrocortisone dose

Glucocorticoid "Stress Doses" (if no sick-day plan)

- Mild illness: 20 mg/m²/day.
- Moderate illness / fever >38°C / vomiting/diarrhea: 30 mg/m²/day + ↑ fluids & carbs.
- Severe illness / shock / vomiting, diarrhea, drowsy: IV/IM hydrocortisone 50–100 mg/m², follow as above.

Age	Initial dose of IM/IV hydrocortisone	THEN hydrocortisone every 6 hours*
Neonate – 6 weeks	25 mg	5 – 10 mg
6 weeks – 3 yrs	25 mg	10 mg
3 yrs – 12 yrs	50 mg	12.5 mg ages 3-6 yo 25 mg ages 6-12 yo
≥12 years	100 mg	25 mg

Recommended doses of 'Stress' Hydrocortisone (given IM or IV)by age:

Prevention

Children with known adrenal insufficiency will have an individualised sick day management plan. This should be followed in the first instance. The following guidance is for when there is no sick day plan available

Addesion disease

Addison's Disease (Primary Adrenal Insufficiency)

Clinical Presentation

- Hyperpigmentation
- Salt craving
- Postural hypotension
- Fasting hypoglycemia
- Anorexia, weakness
- Episodes of shock during severe illness.

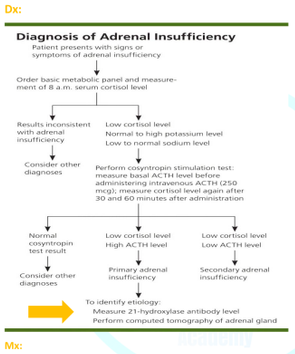
Diagnostic Findings

- Subnormal baseline & ACTH-stimulated cortisol.
- Hyponatremia, hyperkalemia, ↑ plasma renin → mineralocorticoid deficiency.

Associated Conditions

- Autoimmune polyglandular syndromes.
- Rare causes:
  - X-linked adrenal leukodystrophy.
  - Hypothalamic-pituitary disorders (e.g., craniopharyngioma).
  - Iatrogenic (radiation for malignancy).

Dx:



Mx:

- Replacement treatment with 10-15 mg/m* per 24 hours of hydrocortisone is indicated, with supplementation during stress at three times the maintenance dosage or the use of intramuscular hydrocortisone. The dose is titrated to allow a normal growth rate. Mineralocorticoid replacement with flud-rocortisone is monitored by plasma renin activity along with serum sodium and potassium determinations.

	Congenital adrenal hyperplasia (ACH)
Overview of hormone synthesis	**Adrenal Steroid Synthesis: First Steps** • Cholesterol → Pregnenolone via cholesterol desmolase (first step for all adrenal hormones). • Zona glomerulosa (aldosterone production): 1. Pregnenolone → Progesterone (3β-HSD) 2. Progesterone → 11-deoxycorticosterone (21-hydroxylase) 3. 11-deoxycorticosterone → Corticosterone (11β-hydroxylase) 4. Corticosterone → Aldosterone (aldosterone synthase) • Zona fasciculata (cortisol production): 1. Pregnenolone → 17-hydroxypregnenolone (17α-hydroxylase) 2. Progesterone → 17-hydroxyprogesterone (17α-hydroxylase) 3. 17-hydroxyprogesterone → 11-deoxycortisol (21-hydroxylase) 4. 11-deoxycortisol → Cortisol (11β-hydroxylase) • Zona reticularis (androgens): 1. 17-hydroxypregnenolone → DHEA (17,20-lyase) 2. 17-hydroxyprogesterone → Androstenedione (17,20-lyase) 3. DHEA → Androstenedione (3β-HSD) 4. Androstenedione & DHEA → Testosterone

	21-Hydroxylase Deficiency (Most Common CAH, >90%)
Types	1. Classic CAH: early infancy/childhood ◦ Salt-wasting form: cortisol + aldosterone deficiency → adrenal crisis ◦ Simple virilizing form: cortisol deficiency only, no salt loss 2. Non-classic CAH: mild, presents later in childhood/adolescence
Clinical Features:	• Females: clitoromegaly, urogenital sinus, partial/complete labial fusion; internal organs normal • Males: normal external genitalia, subtle hyperpigmentation, enlarged phallus • Salt-wasting: hyponatremia, hyperkalemia, failure to thrive • Simple virilizing: premature pubic/axillary hair in boys
Diagnosis	• Neonatal screening: 17-hydroxyprogesterone >1000 ng/mL • Karyotype: confirm genetic sex in ambiguous genitalia
Management	• Lifelong glucocorticoids (hydrocortisone) → suppress ACTH, prevent adrenal hyperplasia & androgen excess • Mineralocorticoids (fludrocortisone), even in non-salt-wasting form • Surgery for females (clitoroplasty/vaginoplasty)
Monitoring:	• Serum 17-hydroxyprogesterone, androstenedione • Blood pressure, plasma renin activity • Growth velocity & bone age (prevent early epiphyseal closure) ← glucosteroid = premature closure
Non-Classic 21-Hydroxylase Deficiency	• Milder form; females present with primary amenorrhea, hirsutism, acne, polycystic ovaries in adolescence • Males may show precocious puberty • Usually no stress glucocorticoid doses needed unless on chronic therapy

	Other Rare CAH Enzyme Deficiencies (<10%)
17-alpha-hydroxylase deficiency	• ↓ Cortisol & androgens → ↑ 11-deoxycorticosterone & corticosterone → hypertension, hypernatremia, hypokalemia • Females: primary amenorrhea, sparse body hair • Males: undervirilization • Diagnosis: high 11-deoxycorticosterone/corticosterone, low cortisol/androgens • Management: glucocorticoids; females: estrogen + progestin; males: testosterone
11 beta hydroxylase deficiency.	• ↓ Cortisol, mild ↓ aldosterone, ↑ 11-deoxycorticosterone → hypertension • Excess DHEA → virilization in females • Neonatal females: ambiguous genitalia; males: enlarged phallus • Diagnosis: ↑11-deoxycortisol, 11-deoxycorticosterone, testosterone; hypokalemia • Management: hydrocortisone; adult females: add spironolactone; adult males: amiloride/triamterene
3-beta-hydroxysteroid-dehydrogenase deficiency.	• Rare; ↓ all adrenal hormones → ACTH ↑ → ↑ Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, DHEA) • Both sexes: ambiguous genitalia at birth • Diagnosis: high Δ5/Δ4 steroid ratio • Management: replace adrenal & gonadal steroids; puberty: estrogen/progestin in females, testosterone in males

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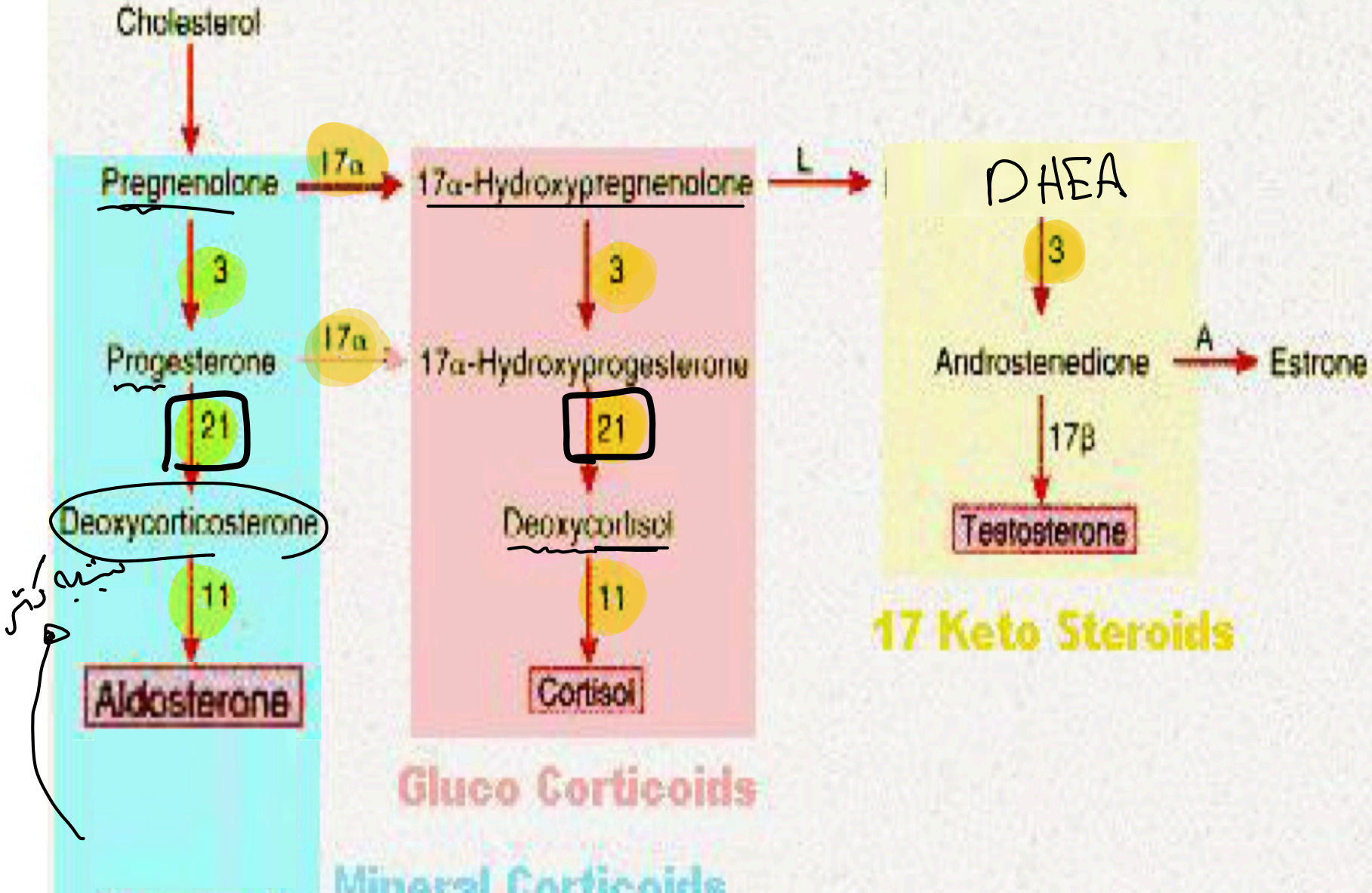
Major Pathway for Adrenal Steroid Synthesis



- salt + water retension ⟵ Adrenal Crisis

21
- classic
  - salt wasting = Ado + Cortesol ⇒ ↓ Na, ↑ K, ↓ FTT
  - simple virilizing = cortesol ⇒ premature pubic / Axillary hiar in boys
- Non classic
  - Normal boy
  - Not girls

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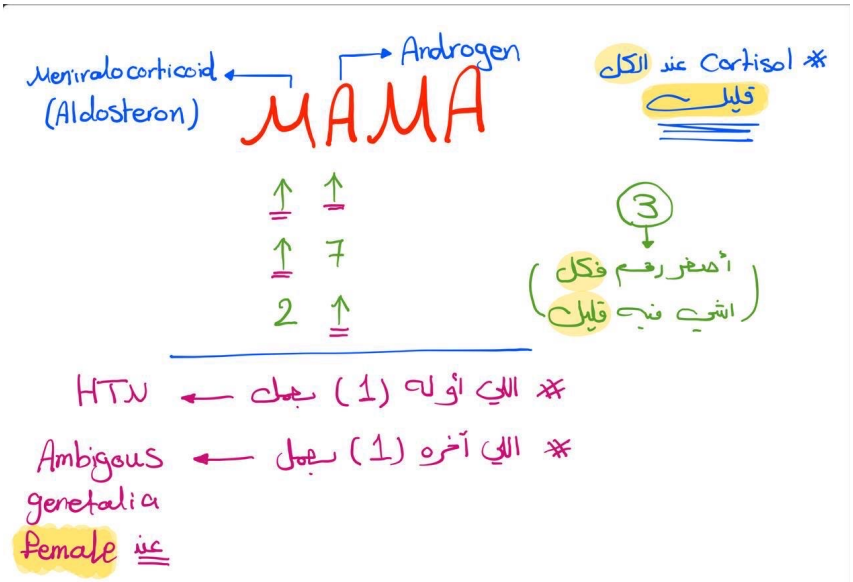
21 هو جين الانكتال
في الخط الصاعدي الواحد

17 هو خط الوصل
بين الاول والثاني



MAMA

11 ↑ ↑
17 ↑ 7
21 2 ↑
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