STEM-S

LAST MINUTE REVISION

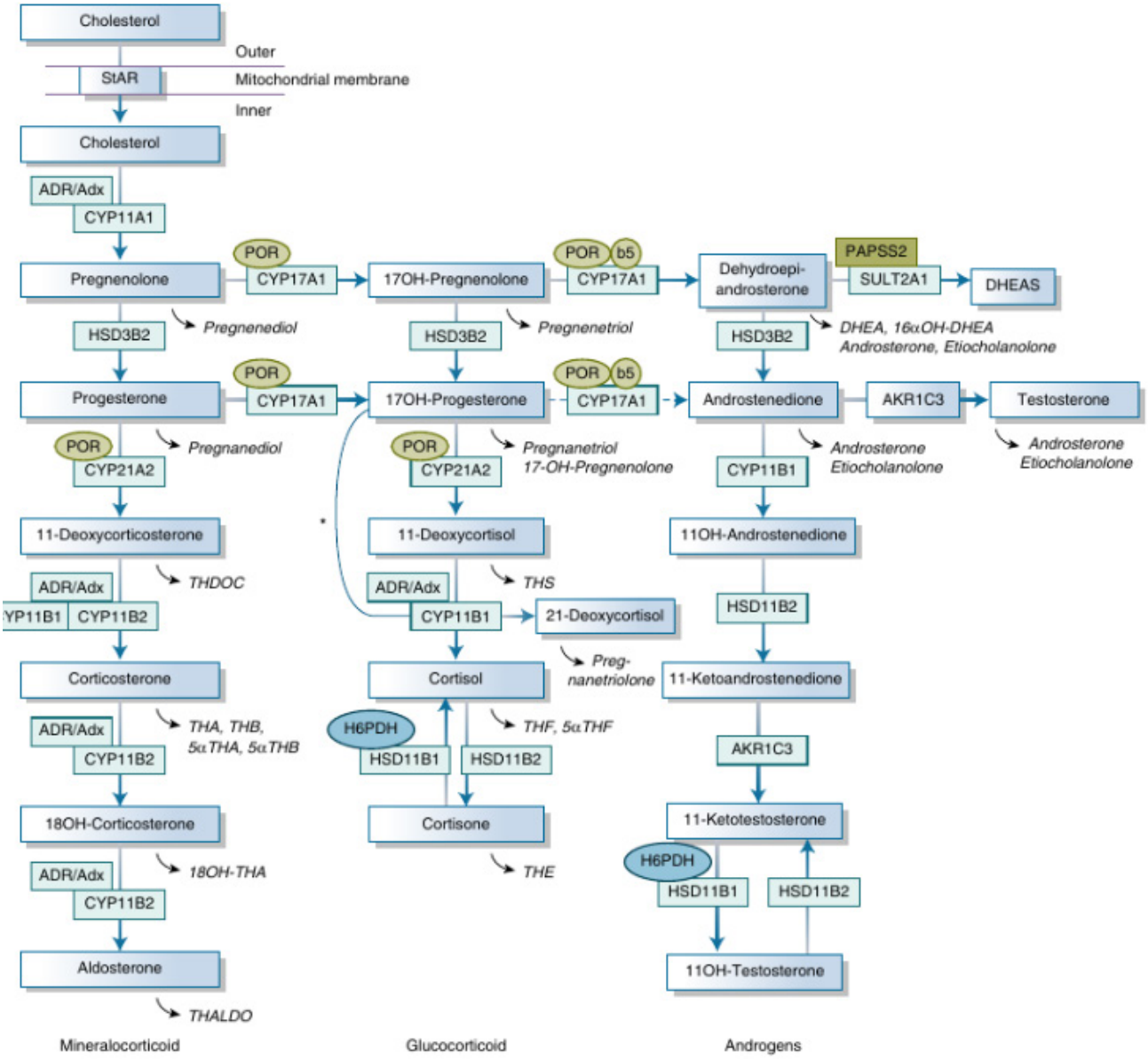
LMR NOTES

INI-SS Sample Notes

PRESENTED BY

Stem-S

- **Steroid pathways**



- **Fetal vs. Adult Adrenal Cortex**

Feature	Fetal Adrenal	Adult Adrenal
Size	Large (comparable to kidney)	Small (fraction of kidney size)
Zonation	Fetal Zone (80-90%)	Definitive Zones (G, F, R)
Primary Product	DHEAS (precursor for estriol)	Cortisol and Aldosterone
CYP17 Activity	Very high in Fetal Zone	Restricted to F and R zones
Post-natal Fate	Rapid involution of Fetal Zone	Persistence and maturation

- **Regulation of aldosterone**

Regulator	Mechanism of Action	Physiological Outcome
Angiotensin II	Binds AT1 receptors; increases calcium signaling and CYP11B2 expression.	Primary regulator of volume and blood pressure.
Potassium (K+)	Direct depolarization of G-zone cell membrane; opens voltage-gated Ca2+ channels.	Most sensitive regulator for plasma K+ homeostasis.
ACTH	Increases early steps of steroidogenesis via cAMP.	Transient rise in aldosterone; "escape" occurs after 48h.
ANP / BNP	Increases cGMP; inhibits CYP11B2 and blocks Ang II-stimulated secretion.	Inhibitory; promotes sodium excretion (natriuresis).
Dopamine	Binds D2 receptors on glomerulosa cells.	Exerts a tonic inhibitory effect under normal conditions.

- **Relative Potency of Synthetic Glucocorticoids**

Agent	Glucocorticoid Potency	Mineralocorticoid Potency	Equivalent Dose (mg)
Hydrocortisone	1	1	20
Prednisone	4	0.8	5
Methylprednisolone	5	0.5	4
Dexamethasone	25 to 30	0	0.75
Fludrocortisone	15	150 to 200	0.1 (standard dose)

- **Enzyme Deficiencies in Congenital Adrenal Hyperplasia**

Deficiency	Hormone Pattern	Clinical Presentation
21-Hydroxylase	↓ Aldo, ↓ Cortisol, ↑ Androgens	Virilization, salt-wasting (75%), or simple virilizing
11-beta-Hydroxylase	↓ Aldo (↑ 11-DOC), ↓ Cortisol, ↑ Androgens	Virilization, hypertension, hypokalemia
17-alpha-Hydroxylase	↑ Aldo (↑ 11-DOC), ↓ Cortisol, ↓ Androgens	Hypertension, hypokalemia, sexual infantilism
3-beta-HSD	↓ Aldo, ↓ Cortisol, ↑ DHEA (weak)	Ambiguous genitalia (both), salt-wasting

- **Adrenal Cushing Etiologies (ACTH-Independent)**

Etiology	Genetic Marker	Characteristic Features
PPNAD	PRKAR1A	Small, dark-pigmented nodules; part of Carney Complex
BMAH / BMAD	ARMC5	Massive, bilateral macronodules (often >2 cm); age 50-60s
AIMAH	GNAS / Others	Food-dependent Cushing (aberrant GIP receptors)
Adrenal Adenoma	GNAS / CTNNB1	Solitary unilateral mass; suppressed contralateral gland

- **Unusual and Severe Cushing Syndromes**

Feature	Ectopic ACTH Syndrome	Adrenal Cortical Carcinoma (ACC)
Clinical	Weight loss, profound weakness, hyperpigmentation	Rapid onset virilization, abdominal pain, large mass
Biochemical	Severe hypokalemia, very high ACTH, high cortisol	Very high DHEAS, high urinary 17-ketosteroids
Pointer	Often due to Small Cell Lung Cancer or Bronchial Carcinoid	Weiss criteria used for malignancy; size > 4 to 6 cm
Investigation	IPSS (gold standard), CRH test, Octreoscan/^{68}Ga-DOTATATE PET-CT	CT/MRI (heterogeneous, necrosis, calcification)

High Yield LMR One-Liners

- Cushing Screening: 24h Urinary Free Cortisol (UFC), Overnight 1mg Dexamethasone Suppression (ODST), or Late Night Salivary Cortisol (LNSC). Two abnormal results confirm the diagnosis.
- CRH Test: ACTH and Cortisol rise in Cushing Disease; no response in Ectopic ACTH.
- IPSS Gradient: Central-to-peripheral ratio > 2 (basal) or > 3 (post-CRH) confirms Cushing Disease.
- Mitotane Pearl: It is a potent inducer of CYP3A4; always increase the dose of concomitant steroid replacement (hydrocortisone).

- **Aldosterone Escape Phenomenon**

Feature	Details
Timeline	Occurs within 2 to 3 days of chronic aldosterone excess
Mechanism	Volume expansion triggers ANP/BNP release and pressure natriuresis
Consequence	Sodium excretion eventually matches intake; ECF stabilizes
Clinical Implication	Patients with Conn's syndrome have HTN but rarely have overt edema

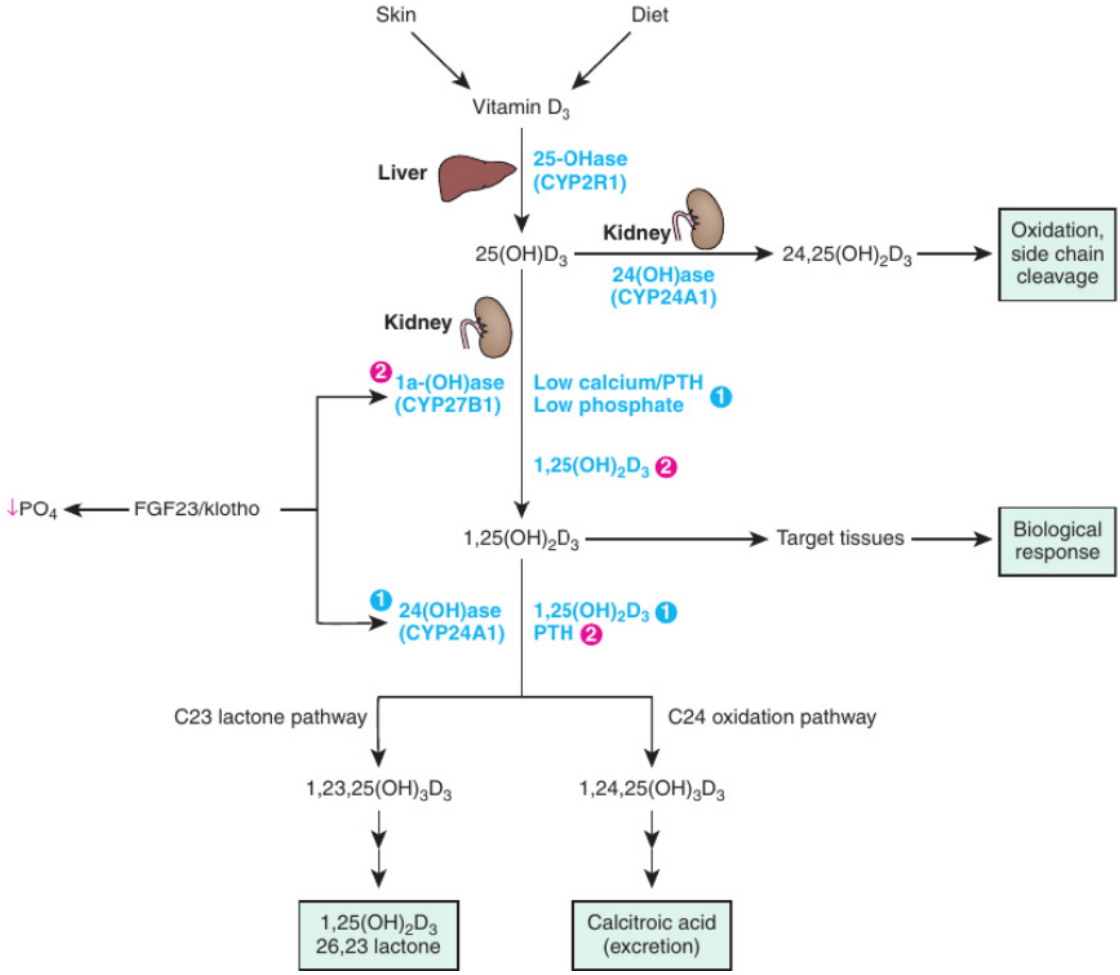
Mineralocorticoid Receptor Antagonists: Spironolactone vs. Eplerenone

Feature	Spironolactone	Eplerenone
Selectivity	Non-selective; binds Mineralocorticoid (MR), Androgen (AR), and Progesterone (PR) receptors.	Highly selective for the Mineralocorticoid receptor (MR).
Potency	High (10 to 20 times more potent at the MR than eplerenone).	Lower relative potency.
Half-life	Long (1.4h for parent; 16.5h for active metabolite Canrenone).	Short (4 to 6 hours).
Dosing Frequency	Usually Once Daily (OD).	Often requires Twice Daily (BID) dosing due to short half-life.
Side Effects (Male)	**Gynecomastia**, decreased libido, erectile dysfunction (due to anti-androgen effect).	Minimal to none; does not block androgen receptors.
Side Effects (Female)	Menstrual irregularities, breast tenderness (mastodynia).	Minimal to none.
Cost / Availability	Inexpensive and widely available.	Generally more expensive.
Clinical Choice	First-line unless sex-steroid side effects occur.	Preferred if gynecomastia or menstrual issues are intolerable.

Low Renin and Low Aldosterone Hypertension

Condition	Pathogenesis	Presentation / Key Findings
Liddle Syndrome	Gain-of-function mutation in **ENaC** (sodium channel); causes constitutive Na+ reabsorption.	Autosomal Dominant; early-onset HTN, hypokalemia, metabolic alkalosis. **Amiloride** is the DOC.
AME (Apparent Mineralocorticoid Excess)	**11b-HSD2** deficiency (genetic or liquorice); Cortisol saturates the MR receptor.	Hypokalemia, severe HTN. Low ratio of urinary THF+5aTHF to THE.
GRA (FH Type 1)	**CYP11B1 / CYP11B2** chimera; aldosterone produced in Fasiculata under ACTH control.	HTN and early stroke. Aldo levels are "high" but suppressible with **Dexamethasone**.
DOC-Secreting Tumor	Benign or malignant adrenal tumor secreting **11-Deoxycorticosterone** (potent MC).	Large adrenal mass; very high DOC levels; virilization if malignant.
CAH (11b-Hydroxylase)	CYP11B1 deficiency; accumulation of DOC and Androgens.	HTN, hypokalemia, and **virilization** in females.
CAH (17a-Hydroxylase)	CYP17 deficiency; accumulation of DOC and Progesterone; no sex steroids.	HTN, hypokalemia, and **sexual infantilism** (delayed puberty/primary amenorrhea).
Gordon Syndrome	Mutations in WNK kinases; increased NCC (sodium-chloride) transporter activity.	**Hyperkalemia** (unique), hyperchloremic acidosis, and HTN. Also called Pseudohypoaldosteronism Type II.

Vitamin D Synthesis



PTH vs. PTHrP

Feature	PTH	PTHrP
Gene	Chromosome 11	Chromosome 12
Regulation	Serum Calcium (CaSR)	Paracrine/Local growth factors
Main Role	Systemic Ca homeostasis	Development, lactation, tooth eruption
Receptor	PTH1R (equal affinity)	PTH1R (equal affinity)
1,25 Vit D	Strong stimulator	Weak/No stimulation

Anabolic Therapy

Feature	Teriparatide (PTH 1-34)	Abaloparatide (PTHrP analog)
Mechanism	Intermittent PTH stimulation (Anabolic window)	Selective for RG-state of PTH1R
Bone Effect	↑ Formation > ↑ Resorption	More "pure" formation; less resorption
Side Effects	Hypercalcemia, hypercalciuria	Lower risk of hypercalcemia than Teriparatide
Duration	Limited to 2 years lifetime	Limited to 2 years lifetime

Romosozumab (Evenity):

- **Mechanism:** Monoclonal antibody against **Sclerostin**.
- **Dual Action:** Simultaneously **increases bone formation** and **decreases bone resorption**.
- **Black Box:** Increased risk of cardiovascular events (MI/Stroke) in the past year.

Therapy Principles & GIOP

- **Sequential Therapy:** Always follow an anabolic (Teriparatide/Romosozumab) with an anti-resorptive (Alendronate/Denosumab) to maximize benefits.
- **Glucocorticoid-Induced (GIOP):** Start treatment if taking **≥ 2.5 mg Prednisone for > 3 months** in patients at medium/high risk. Bisphosphonates are first-line.

Monitoring Therapy

Monitoring Parameter	Recommendation
Follow-up DXA	Every 1–2 years after starting therapy; once stable, every 3–5 years.
BTMs (P1NP/CTX)	Check at baseline and 3–6 months to assess early compliance/efficacy.
Drug Holiday	Consider after 5 years (oral) or 3 years (IV) of bisphosphonates if risk is no longer "high."
Denosumab Holiday	**Never.** Stopping leads to rapid bone loss and multiple vertebral fractures, always follow with another anti-resorptive to prevent

Approach to Osteoporosis & Fragility Fractures

- **Treatment Selection:** Use **Anabolics** first in "Very High Risk" (T-score < -3.0 or multiple fractures). Use **Bisphosphonates** for "High Risk."

Indications for Rx: Treat if the patient is symptomatic (pain), or if the disease involves high-risk sites (skull, spine, weight-bearing joints) even if asymptomatic.

- **The "Normal ALP" Caveat:** ALP may be normal in very localized disease (monostotic) or in the late sclerotic/burnt-out phase.
- **Osteosarcoma Clue:** A sudden, dramatic rise in ALP in a patient with known Paget's disease is highly suspicious for malignant transformation.

CKD MBD Pathophysiology: The Sequence of Events

Event	Primary Change	Consequence
1	↑ FGF23 (from osteocytes)	Earliest marker; induces phosphaturia.
2	↓ 1,25-(OH)2 Vit D	FGF23 inhibits 1-alpha-hydroxylase.
3	↓ Serum Calcium	Due to low Vit D and high Phosphorus.
4	↑ PTH (Secondary HPT)	Response to low Ca, low Vit D, and high Pi.
5	↑ Serum Phosphorus	Occurs only when GFR drops below 30 mL/min.

Renal Osteodystrophy: Bone Types

Type	Turnover Rate	Mechanism	Histology
Osteitis Fibrosa Cystica	High	Severe Secondary HPT	Peritrabecular fibrosis; marrow replacement.
Adynamic Bone Disease	**Low**	Excessive PTH suppression (DM, Age, Al, or over-treatment)	Reduced cell numbers; thin osteoid seams.
Osteomalacia	Low	Vit D deficiency or Aluminum toxicity	Wide, unmineralized osteoid seams.
Mixed	Variable	Combination of high and low features	Marrow fibrosis plus mineralization defect.