Adrenal Insufficiency

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Case 1

- A 32-year-old lady presents with fatigue, abdominal pain and weight loss for 2 years
- Irregular menses (every 2 months)
- Visited many doctors
- Told she has “anemia”, “irritable bowel”, “depression”
- Hb 10.6, glucose, kidney & liver function tests normal
- Thyroid function tests: normal
- Weight 52, BMI 20.1, BP 100/60
- **How would you approach?**

When to suspect adrenal insufficiency?

- Symptoms not explained by other tests
- Presence of autoimmune diseases such as:
  - Type 1 DM, hypothyroidism, or vitiligo
- Acutely ill patients with volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain
- The diagnosis of adrenal insufficiency is usually delayed

Manifestations of adrenal insufficiency

- Fatigue
- Dizziness
- Decreased appetite, weight loss
- Nausea, vomiting, abdominal pain, diarrhea
- Salt craving
- Depression, anxiety, psychosis
- Amenorrhea
- Skin hyperpigmentation
- Postural hypotension

Skin hyperpigmentation in adrenal insufficiency

A) Skin hyperpigmentation over the face

B) Skin hyperpigmentation of the hands (normal hand on the right side)

C) Hands of the patient after treatment

Laboratory findings in adrenal insufficiency

- Hyponatremia
- Hyperkalemia
- Metabolic acidosis
- Anemia
- Eosinophilia
- Hypoglycemia
- Hypercalcemia

Causes of adrenal insufficiency

- **Primary:**
  - Disease of the adrenal gland “Addison’s disease“
- **Secondary:**
  - Interference with ACTH
  - Disorders of pituitary gland
- **Tertiary:**
  - Interference with CRH
  - Disorders of the hypothalamus
  - Occurs when taking exogenous steroids

Causes of primary adrenal insufficiency

- Autoimmune
- Infections (such as TB, fungi, HIV)
- Hemorrhage
- Infiltrative diseases
- Malignancy, metastasis
- Medications (ketoconazole, mitotane, metyrapone)

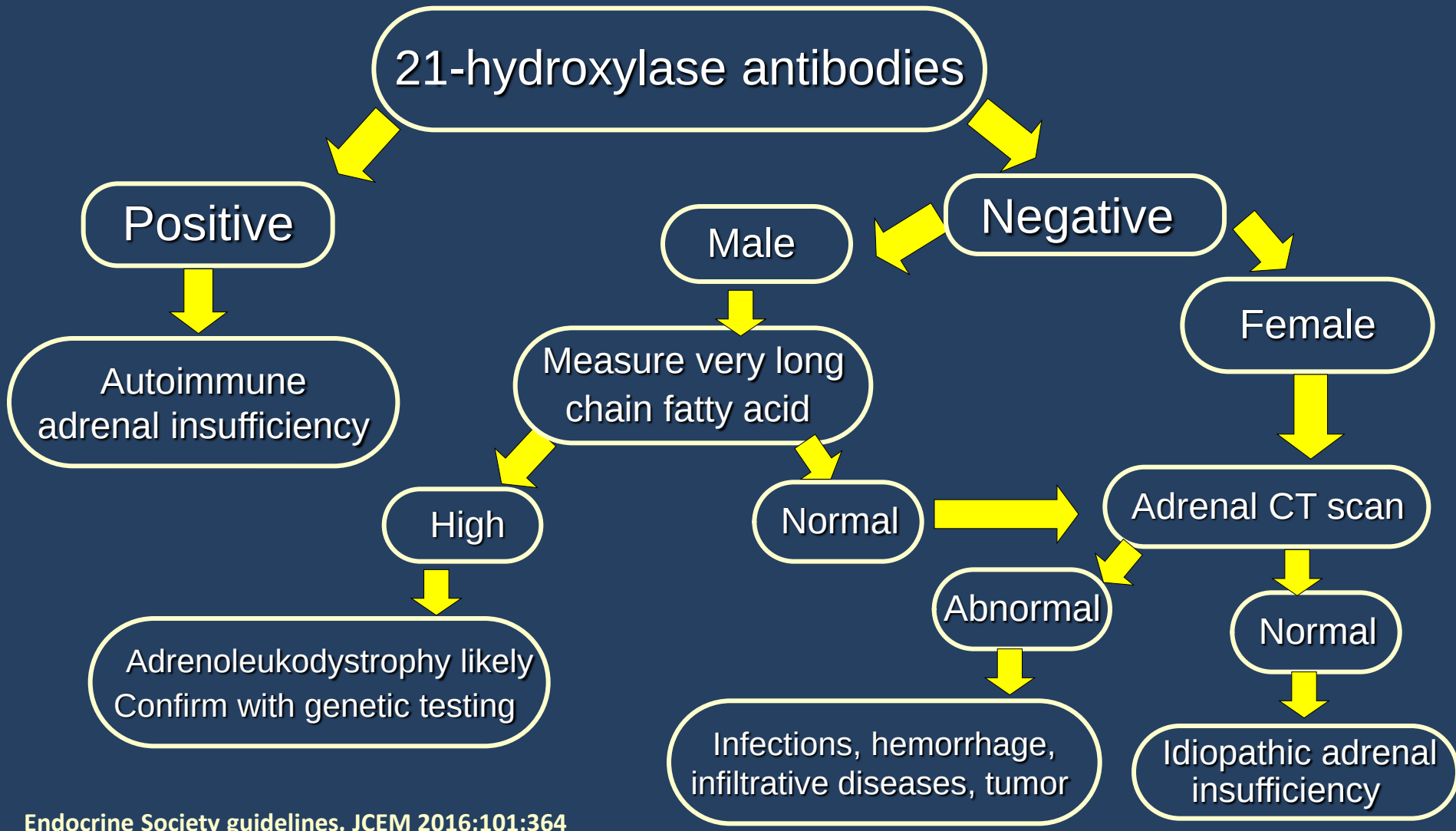
Causes of secondary adrenal insufficiency

- Hypopituitarism caused by pituitary tumors, infections (TB, fungi), infiltrative diseases, hemorrhage, lymphocytic hypophysitis
- Autoimmune
- Traumatic brain injury
- Isolated ACTH deficiency

Causes of tertiary adrenal insufficiency

1) Abrupt cessation of high-dose glucocorticoids:
   - They decrease CRH
2) Cure of hypercortisolism (Cushing's syndrome):
   - After removal of a pituitary or non-pituitary ACTH-secreting or a cortisol-secreting adrenal tumor
   - The chronically high serum cortisol before surgery suppresses the hypothalamic-pituitary-adrenal axis
3) Tumors, infiltrative diseases (sarcoidosis), cranial radiation

Investigating the cause of primary adrenal insufficiency



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Evaluation for adrenal insufficiency

- Check am serum cortisol (6-9 am)
- Note cortisol units
- μg/dL, μg/L, nmol/L, ng/mL

  18 μg/dL = 500 nmol/L
- Check on conversion formulas

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SI UNITS (recommended)		CONVENTIONAL UNITS	
nmol/L	nmol/L	µg/dL	µg/dL
		µg/100mL	µg/100mL
		µg%	µg%
		µg/L	µg/L
		ng/mL	ng/mL

CALCULATE CLEAR ALL

* The SI units is the recommended method of reporting clinical laboratory results

Synonym

Hydrocortisone, Compound F

Units of measurement

nmol/L, µg/L, µg/dL, µg/100mL, µg%, ng/mL

The determination of cortisol is used for the recognition and treatment of functional disorders of the adrenal gland.

Cortisol (hydrocortisone) is the most prominent glucocorticosteroid, and it is essential for the maintenance of several body functions. Like other glucocorticosteroids, cortisol is synthesized from the common precursor cholesterol in the zona fasciculata of the cortex of the adrenal gland. For the transport of cortisol in blood, about 90 % of cortisol is bound to corticosteroid binding

SI UNITS (recommended)		CONVENTIONAL UNITS	
nmol/L	82.7586	µg/dL	3
		µg/100mL	3
		µg%	3
		µg/L	30
		ng/mL	30

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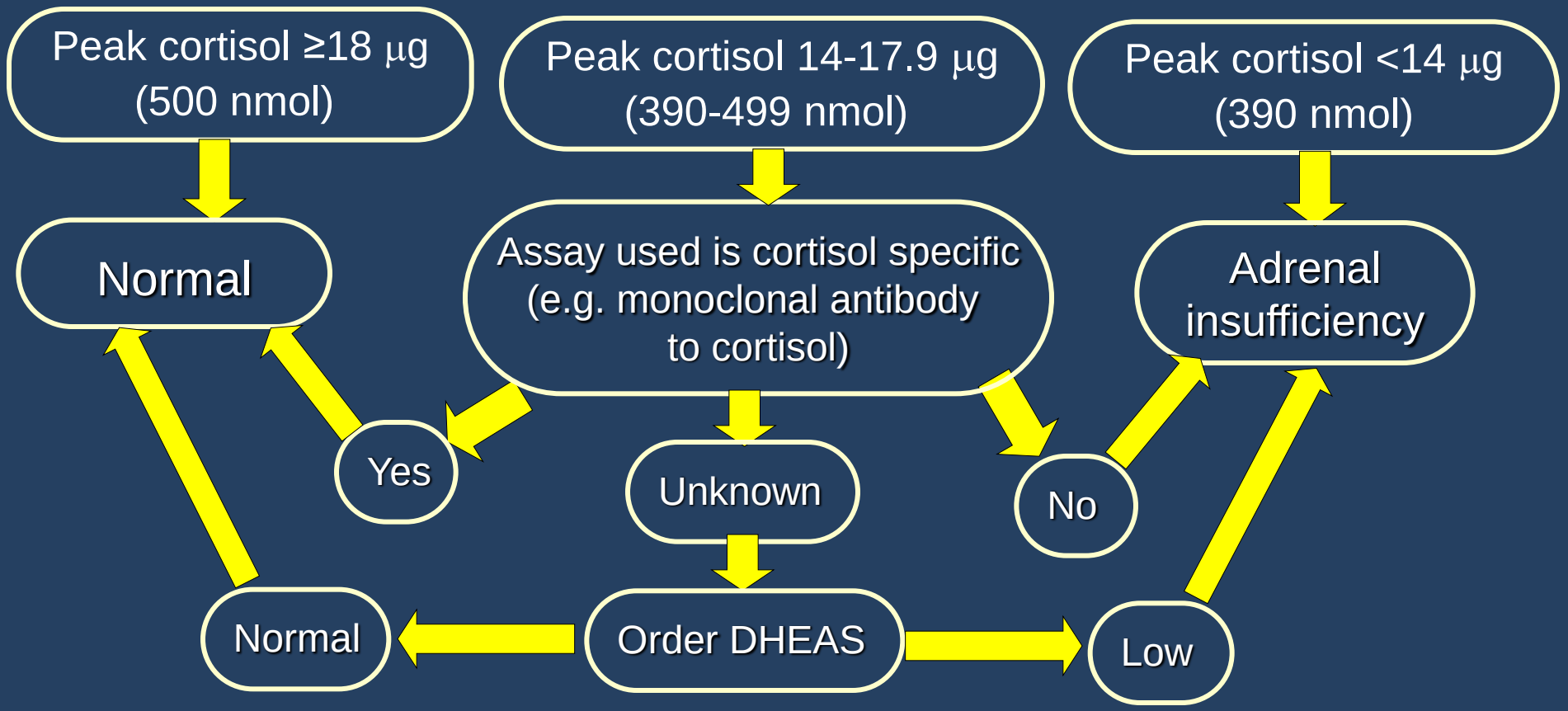
Diagnosis of adrenal insufficiency

- Check serum cortisol (at 6-9 am)
- **Cortisol ≤ 3 μg (83 nmol):**
  - Highly suggests adrenal insufficiency
  - Repeat, if the same = adrenal insufficiency
- **Cortisol ≥18 μg (500 nmol):**
  - Normal
  - No need for ACTH stimulation test
- **Cortisol >3 & <18 μg:**
  - Do ACTH stimulation test

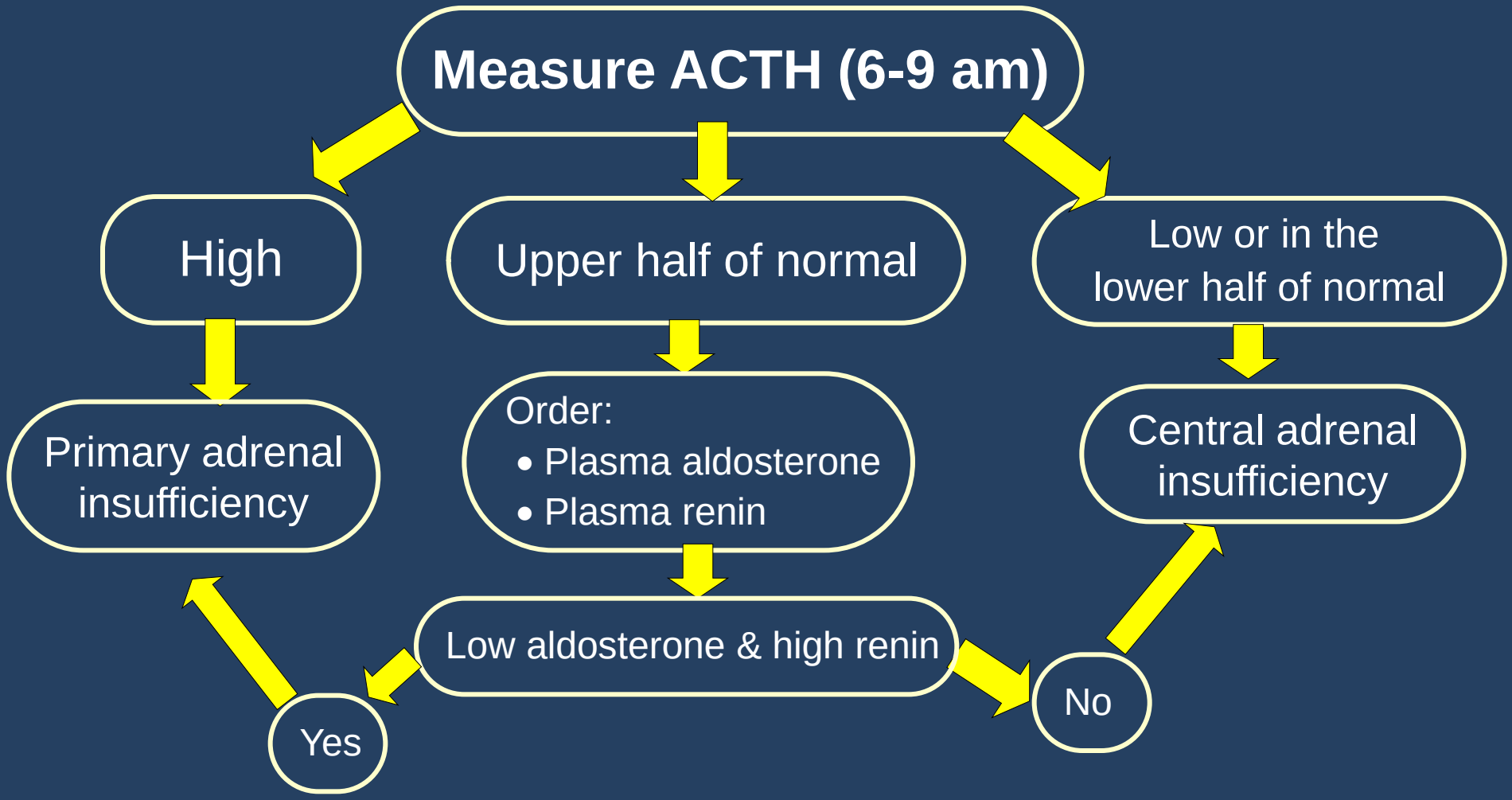
Diagnosis of adrenal insufficiency

- **ACTH (Cosyntropin, Synacthen) stimulation test:**
  - Baseline serum cortisol (no need if done before)
  - Can be done at any time of the day
  - Give ACTH 250 micrograms IV or IM
  - Then check cortisol 30 & 60 minutes after injection
  - If doing ACTH, do the test in early morning
  - Look at peak (higher) cortisol level

Interpretation of ACTH stimulation test



Adrenal insufficiency: primary or secondary?



Diagnosis of adrenal insufficiency

- **Plasma aldosterone & renin:**

  - Low aldosterone and high renin in primary disease

  - Normal levels in secondary disease

- **DHEAS:**

  - Low in primary & secondary disease; confirms the diagnosis

  - Use if ACTH stimulation test result is indeterminate

Treatment of adrenal insufficiency

- All patients (1^{ry} & 2^{ry}) require **glucocorticoids**:

  - **Hydrocortisone** (15-25 mg/d) divided in 2-3 doses/day

    or **Cortisone** 20-35 mg/day (depends on patient's weight)

- Hydrocortisone: 10 am, 5 pm or 15 am, 5 pm
- Some will feel fatigue at night or morning: give 3 doses

  - 10 am, 5 afternoon, 5 evening

  - or 15/5/5

Alternative treatment of adrenal insufficiency

- **Prednisone or Prednisolone:**

- Dose: 3 to 5 mg/day: 1-2 times/day

- Use if patient is not compliant with multiple daily doses of hydrocortisone

- Or in those with late-evening or early morning symptoms that are not relieved by three-times daily hydrocortisone

Monitoring glucocorticoids treatment for adrenal insufficiency

- Features of **inadequate** dose:
  - Energy level, fatigue, nausea, weight loss, dizziness, impaired sleep, postural hypotension
- Features of **high** dose:
  - Increased weight, increased appetite, puffy face, edema, hypertension
- Hormonal monitoring is **not** recommended

Glucocorticoids potency

- 20 mg Hydrocortisone =
- 5 mg Prednisone/Prednisolone =
- 4 mg Methylprednisolone =
- 0.5 mg Dexamethasone

Mineralocorticoids treatment in primary adrenal insufficiency

- Patients with aldosterone deficiency (↓aldosterone, ↑renin):
  - Should received mineralocorticoid replacement
  - Fludrocortisone (50 to 100 μg once/day)
- Monitoring:
  - Clinical assessment (salt craving, weakness, dizziness, nausea, postural hypotension, edema)
  - Serum electrolytes

When to use DHEAS (dehydroepiandrosterone sulphate) in adrenal insufficiency?

- Can be considered after giving adequate doses of glucocorticoids & mineralocorticoids
- Not needed in males as testes are the main source of androgens
- Consider for females with any of the following:
  - Low energy, depressive symptoms or low sexual desire
- DHEAS: 25-50 mg daily am (can be given every 2-3 days)
- Keep DHEAS level at the middle of normal
- Signs of high dose: hirsutism, acne, oily skin, sweating

Endocrine Society guidelines. J Clin Endocrinol Metab 2016;101:364

Case 2

- A 52-year-old man presents with cough, fever, vomiting
- Family reports weakness & low appetite for 2 years
- Examination: confused, BP 80/45, P 110/min, Temp 38.4
- WBC 13,000, Na 130, K 5.7, Cl 115, HCO_3 16, cr 1.8, glucose 72
- Chest X ray showed evidence of pneumonia
- Antibiotics and IV fluids are started
- **How would you approach?**

Adrenal crisis
(acute adrenal insufficiency)

- **Causes:**
  - Infection or stress in chronic adrenal insufficiency
  - Inadequate doses of steroids in adrenal insufficiency
  - The initial presentation of adrenal insufficiency
  - Decreased absorption of steroids in adrenal insufficiency due to gastrointestinal problem (vomiting, diarrhea)
  - Pituitary infarction (causing central adrenal insufficiency)
  - Sudden withdrawal of high doses of glucocorticoids

Manifestations of adrenal crisis

- Severe weakness
- Acute abdominal pain
- Nausea, vomiting
- Fever
- Syncope
- Confusion
- **Hypotension**
- Coma

Management of suspected adrenal crisis

- Start treatment before testing (can do random cortisol)
- Immediate IV hydrocortisone 100 mg
- Followed by 50 mg hydrocortisone every 6 hours

  Or 200 mg hydrocortisone/24 hours IV infusion
- After 24 hours, hydrocortisone 50 mg IV q12 hours
- IV fluid resuscitation (2-3 liters usually in 12-24 hrs)
- If hydrocortisone is not available, use prednisolone
- Dexamethasone is the least preferred and should only be given if no other glucocorticoid is available

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Adrenal insufficiency: follow up

- Follow up every few months to adjust doses of glucocorticoids and (mineralocorticoids if needed)
- Then follow up to monitor for symptoms of under- or over-replacement at least yearly
- Screen for autoimmune diseases yearly:
  - Thyroid disease
  - DM
  - Primary ovarian insufficiency (premature ovarian failure)
  - Celiac disease
  - Vitamin B_{12} deficiency

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Adrenal insufficiency: patient education

- If acute illness, double the dose of glucocorticoids but no need to increase the dose of mineralocorticoids
- Contact the doctor or go to the hospital if the condition is worse or severe illness
- If severe illness or trauma, use hydrocortisone 100 mg IM or SC (home emergency kit)
- Use medical identification card and medical alert identification (bracelet or necklace)

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Medical identification for adrenal insufficiency

Adrenal insufficiency: before surgery

- **Minor surgery** (hernia, cataract, ENT):
  - Hydrocortisone 25 mg IV on day of surgery
- **Moderate surgery** (orthopedic surgery):
  - Hydrocortisone 50-75 mg IV on day of surgery and postoperative day 1
- **Major surgery** (cardiac, GI):
  - Hydrocortisone 100 IV before surgery
  - Then 150-200 mg/day (3-4 doses) on postoperative days 1 & 2
- Return to usual doses if postoperative course is not complicated

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Adrenal insufficiency in pregnancy

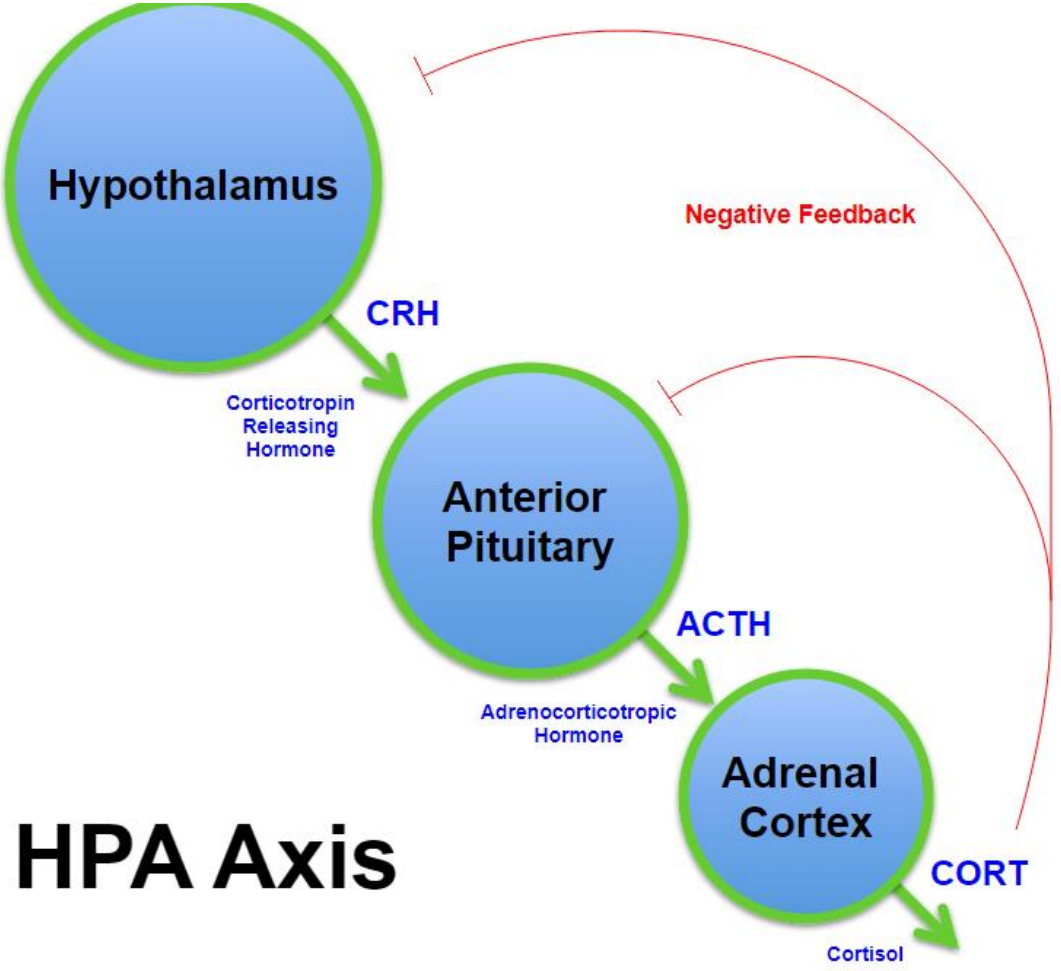
- Monitor for symptoms in each trimester
- Most patients need an increase in steroid doses
- The increase is usually in the 3rd trimester
- Hydrocortisone is recommended over cortisone, prednisolone or prednisone
- Do not use dexamethasone (crosses the placenta as it is not inactivated)
- Use stress doses of steroids during labor

Endocrine Society guidelines. J Clin Endocrinol Metab 2016;101:364

Case 3

- A 22-year-old lady with asthma diagnosed 3 years ago
- Steroids are given frequently for asthma exacerbation
- She is advised to take prednisone for 2 weeks
- She has no complaints
- Examination: normal BP, normal exam
- Medications: budesonide-formoterol inhaler
- **How would you manage prednisone dose?**

Hypothalamic-pituitary-adrenal (HPA) axis



Glucocorticoids for non-endocrine conditions

- Steroids are commonly used
- Such as SLE, rheumatoid arthritis, vasculitis, polymyalgia rheumatica, inflammatory bowel disease
- Exogenous steroids suppress CRH, ↓ACTH, ↓cortisol
- Steroids are usually tapered according to disease activity and to avoid side effects
- Tapering must be done carefully to avoid recurrent activity of the underlying disease and cortisol deficiency from HPA suppression

When can exogenous steroids affect HPA axis?

- **Duration of glucocorticoid therapy:**
  - 4 weeks to 3 months (moderate risk)
  - > 3 months (high risk)
- **Dose of glucocorticoids:**
  - **More than:**
    - Hydrocortisone 15-25 mg/day
    - 4-6 mg prednisone
    - 3-5 mg methylprednisone
    - 0.25-0.5 mg dexamethasone

European Society of Endocrinology/Endocrine Society guidelines. Eur J Endocrinol 2024;190:G25

When to taper steroids?

- When the therapeutic benefit has been obtained
- When inadequate therapeutic benefit has been obtained after an adequate trial
- When side effects, such as osteoporosis or hypertension become serious or uncontrollable with medications
- Significant rapid reduction rather than tapering:
  - Steroid-induced acute psychosis unresponsive to antipsychotic medications
  - Herpes-induced corneal ulceration

How to taper steroids?

- If steroids for < 4 weeks:
  - No need to taper (any dose)
- If steroids for > 4 weeks:
  - Tapering is recommended
- If on long-acting steroid (dexamethasone or betamethasone), switch to prednisone or hydrocortisone

European Society of Endocrinology/Endocrine Society guidelines. Eur J Endocrinol 2024;190:G25

How to taper steroids?

- Taper steroids till dose of prednisone is 4-6 mg/day or hydrocortisone 15-25 mg/day
- Then there are 2 options:

  1) Continue to taper till stopping (see table next slides)

  or 2) Test with am cortisol:

  - Cortisol >10 μg (300 nmol): normal: stop steroids
  - Cortisol 5-10 μg (150-300 nmol): continue steroids. Test after few weeks or months
  - Cortisol <5 μg (150 nmol): continue steroids. Test after few months
- If symptoms develop, go back to last steroid dose

European Society of Endocrinology/Endocrine Society guidelines. Eur J Endocrinol 2024;190:G25

Case 4

- A 42-year-old lady with SLE diagnosed 4 months ago
- Prednisone 40 mg/day was started 2 months ago
- She is referred to stop prednisone and start steroid-sparing agents
- She reports joint pains and headaches
- BP 144/72, mouth ulcers
- **How would you manage prednisone dose?**

How to taper steroids?

Current prednisone dose	Dose decrease	Time interval
>40 mg	5-10 mg	Every week
20-40 mg	5 mg	Every week
10-20 mg	2.5 mg	Every 1-4 weeks
5-10 mg	1 mg	Every 1-4 weeks
5 mg	1 mg	Every 4 weeks

European Society of Endocrinology/Endocrine Society guidelines. Eur J Endocrinol 2024;190:G25

Case 5

- A 19-year-old lady presents with fatigue & dizziness
- She reports ↓ appetite & underweight for 1 year
- She was given dexamethasone 4 mg daily for her symptoms “to increase weight” for last 2 months
- She stopped dexamethasone 3 days ago
- Labs: anemia, normal electrolytes, normal TSH
- No prior serum cortisol
- **How would you manage?**

Glucocorticoids dose

- Patient is on dexamethasone 4 mg daily

  This 4 mg is (4 ÷ 0.5) = 8 [8 times 0.5 mg)
- = Hydrocortisone: 8 × 20 = 160 mg
- = Prednisone: 8 × 5 = 40 mg
- = Methylprednisolone: 8 × 4 = 32 mg

- 20 mg Hydrocortisone =
- 5 mg Prednisone/Prednisolone =
- 4 mg Methylprednisolone =
- 0.5 mg Dexamethasone

Case approach

- Adrenal insufficiency was not diagnosed before
- Patient on dexamethasone for 2 months
- She is at risk of suppression of the HPA axis
- Dose (>0.5 mg/day) & duration > 4 weeks
- **PLAN?**
  - Switch to prednisone 40 mg daily (or hydrocortisone)
  - Taper dose
  - When steroids are stopped, can do evaluation for adrenal insufficiency

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