Adrenal Insufficiency

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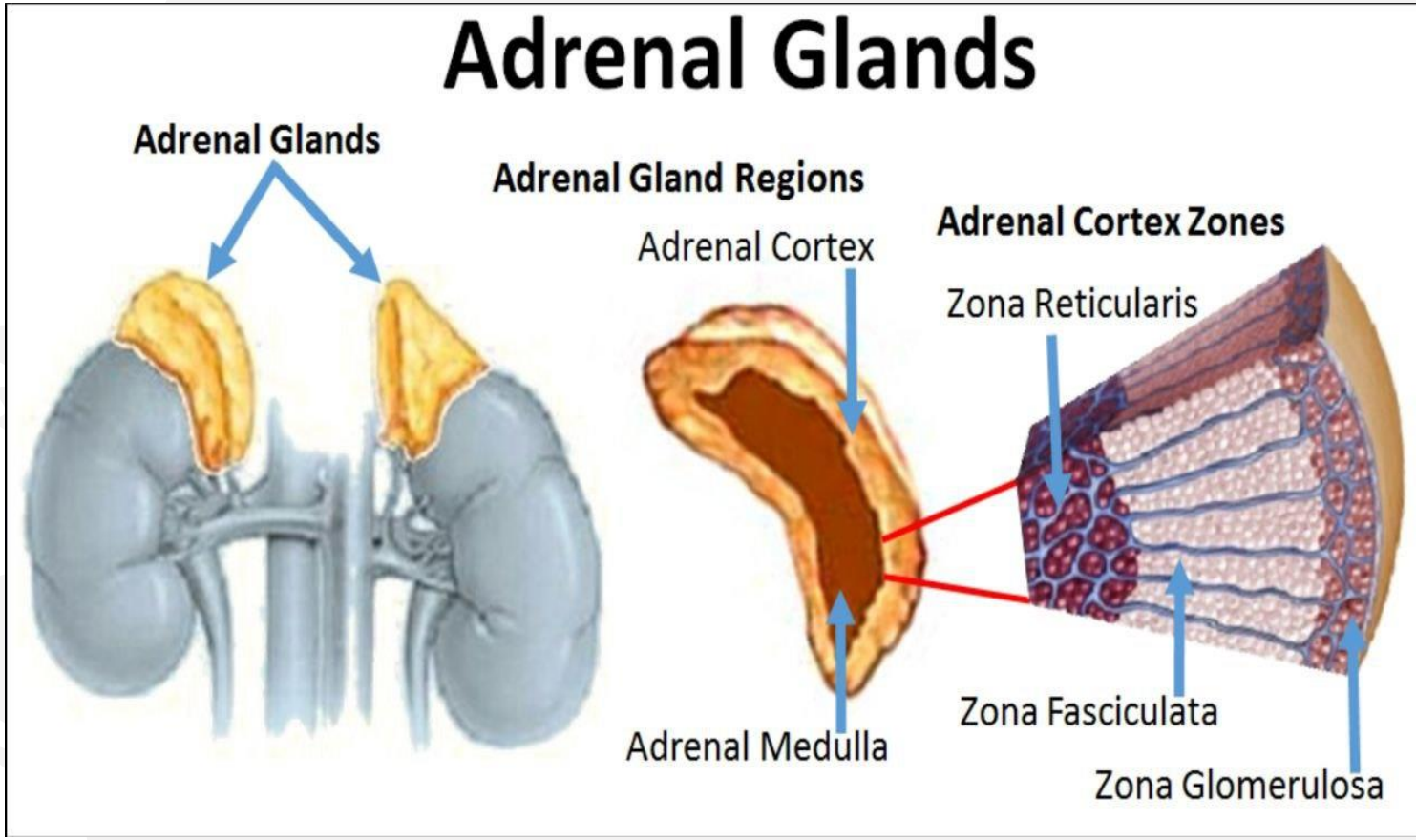

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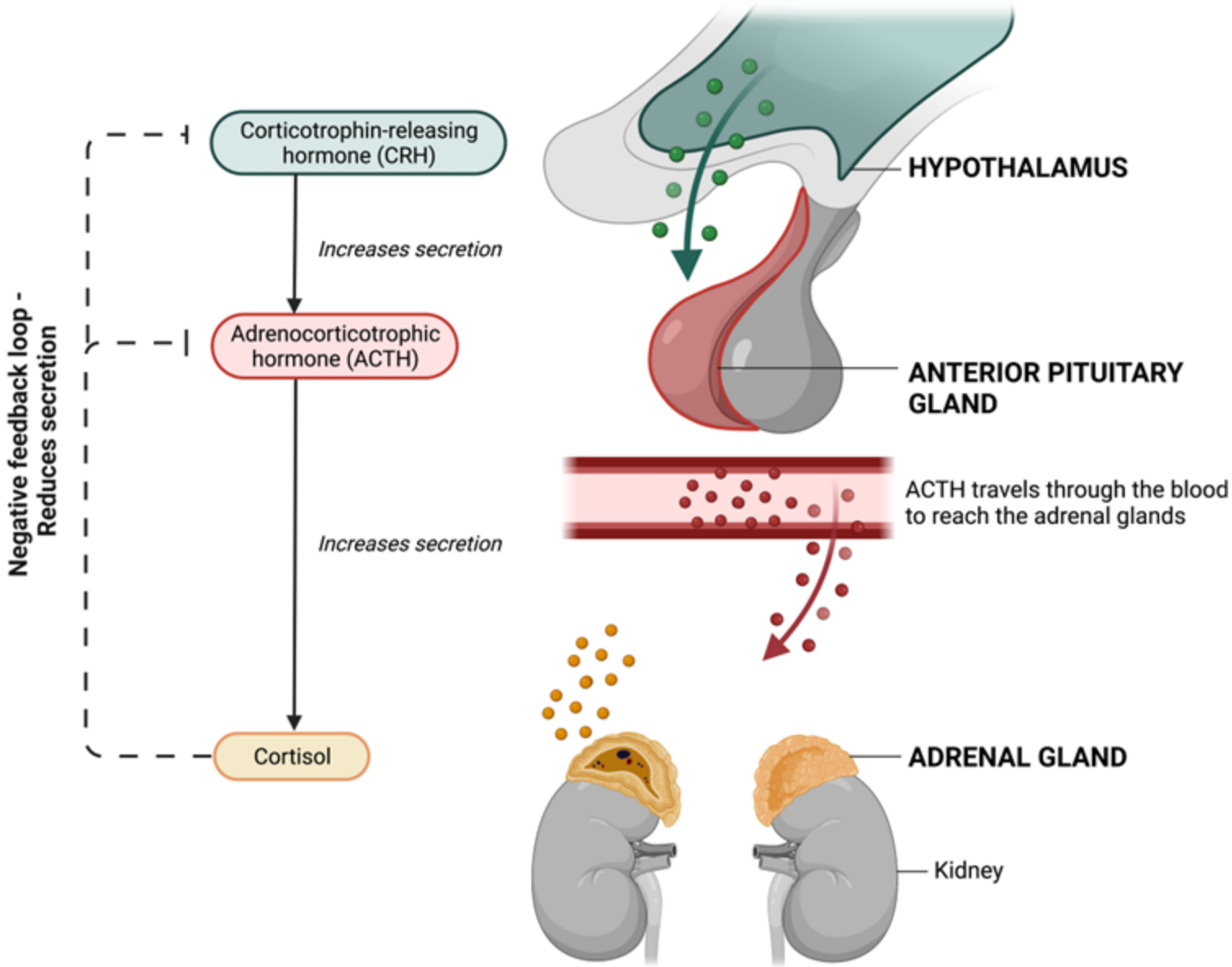
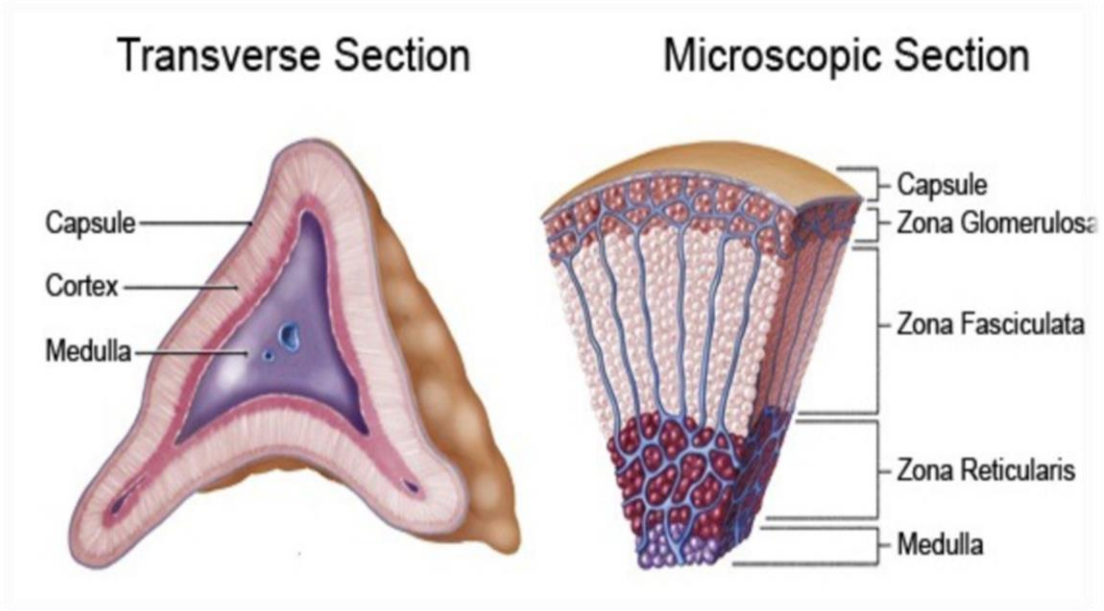

Corticotrophin-releasing hormone (CRH)
Increases secretion
Adrenocorticotrophic hormone (ACTH)
Increases secretion
Cortisol
Negative feedback loop - Reduces secretion
HYPOTHALAMUS
ANTERIOR PITUITARY GLAND
ACTH travels through the blood to reach the adrenal glands
ADRENAL GLAND
Kidney

ZONA GLUMERULOSA → **MINERALOCORTICOID**

ZONA FASICULATA → **CORTISOL**

ZONA RETICULARIS → **ANDROGEN**



Pathophysiology

Corticotrophin- releasing hormone (CRH) is secreted in the hypothalamus in response to circadian rhythm, stress and other stimuli.

CRH travels down the portal system to stimulate adrenocorticotrophin (ACTH) release from the anterior pituitary.

ACTH is derived from the prohormone pro-opiomelanocortin (POMC), which undergoes processing within the pituitary to produce ACTH and a number of peptides like MSH and others. Circulating ACTH stimulates cortisol production in the adrenal.

The secreted cortisol (or any other synthetic corticosteroid administered to the patient) causes negative feedback on the hypothalamus and pituitary to inhibit further CRH/ACTH release.

Unlike cortisol, mineralocorticoids and sex steroids do not cause negative feedback on the CRH/ACTH axis.

Mineralocorticoid secretion is mainly controlled by the renin– angiotensin system

Androgens produced by the adrenals makes the majority of androgens in female but are negligible in males (produced mainly in the testicles)

Following adrenalectomy or other adrenal damage (e.g. Addison's disease), cortisol secretion is absent or reduced; ACTH levels will therefore rise

Introduction

Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids.

Adrenal insufficiency may be caused by disease of the adrenal glands (primary) or Disorders of the pituitary gland (secondary).

Primary disease (eg. Addison disease) results in loss of cortisol, aldosterone, and adrenal androgens; while secondary insufficiency causes only cortisol and adrenal androgen deficiencies (aldosterone synthesis is not acth-dependent ➔ it's controlled by the RAS system).

Causes

⍰ Primary hypoadrenalism

In primary adrenal insufficiency there is destruction of the entire adrenal cortex.

→ Glucocorticoid, mineralocorticoid and sex steroid production are therefore all reduced.

→ This differs from hypothalamic–pituitary disease, in which mineralocorticoid secretion remains largely intact, being predominantly stimulated by angiotensin 2.

Cause:

1. Autoimmune (addison's disease) >> most common causes of primary adrenal insufficiency in developed countries .

Which might be isolated or part of APS

- Autoimmune polyendocrine syndrome type I

(Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism, dental enamel hypoplasia)

- Autoimmune polyendocrine syndrome type II (schmidt's syndrome) :

Addison's disease + primary hypothyroidism, or insulin-dependent diabetes.

2. Infections (tuberculosis, fungal infections, CMV, HIV)

3. Metastatic tumor

4. Infiltrations (amyloid, hemochromatosis)

5. Intra-adrenal hemorrhage (waterhouse-friderichsen syndrome) after meningococcal septicemia

6. Congenital adrenal hypolasia

7. Bilateral adrenalectomy

Secondary hypoadrenalism

1. Exogenous glucocorticoid therapy >> most common cause of secondary adrenal insufficiency .

Look for patients who recently discontinued glucocorticoid
Therapy or did not increase their glucocorticoid dose in times of stress.

2. Hypopituitarism
3. Pituitary apoplexy
4. Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
5. Secondary tumor deposits (breast, bronchus)
6. Postpartum pituitary infarction (sheehan's syndrome)
7. Pituitary irradiation (effect usually delayed for several years)
8. Isolated ACTH deficiency
9. Idiopathic

? Clinical features

The sign and symptoms of AI are rather nonspecific such as :

O weakness, fatigue

O musculoskeletal pain

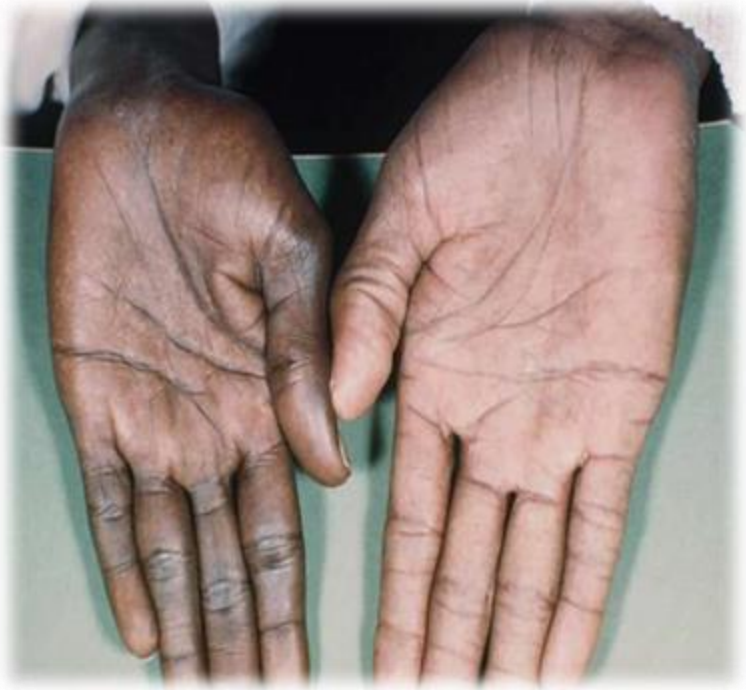
O weight loss, depression, and anxiety.

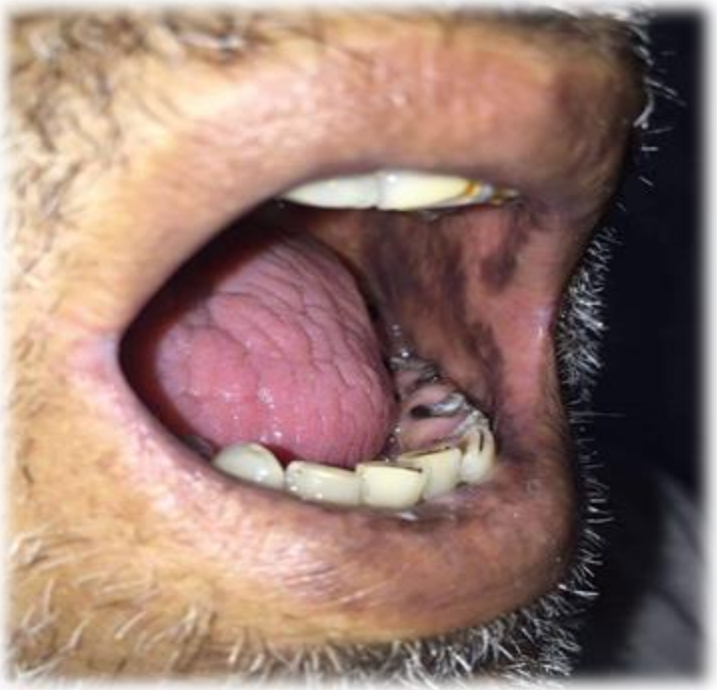
O abdominal pain, nausea , vomiting

As a result, the diagnosis is frequently delayed, resulting in a clinical presentation with an acute life-threatening adrenal crisis .

Or sign and symptoms related to hormonal changes .....

Hormonal changes	Clinical features	Laboratory findings	Primary adrenal insufficiency	Secondary adrenal insufficiency	Tertiary adrenal insufficiency
Hypoaldosteronism	• **Hypotension** • Salt craving	• **Hyponatremia** • **Hyperkalemia** • Normal anion gap **metabolic acidosis**	✓	• **Absent**	• **Absent**
Hypocortisolism	• Weight loss, anorexia • **Fatigue, lethargy**, depression • Muscle aches • Weakness • **Gastrointestinal complaints** (e.g., nausea, vomiting, diarrhea) • Sugar cravings • **(Orthostatic) hypotension**	• **Hypoglycemia** • **Hyponatremia**	✓	✓	✓
Hypoandrogenism	• Loss of **libido** • Loss of axillary and pubic hair	• ↓ DHEA-S	✓	✓	✓
Elevated ACTH	• **Hyperpigmentation** of areas that are not normally exposed to sunlight (e.g., palmar creases, mucous membrane of the oral cavity)	• ↑ MSH	✓	• **Absent**	• **Absent**





Primary adrenal insufficiency **P**igments the skin. **S**econdary adrenal insufficiency **S**pares the skin. **T**ertiary adrenal insufficiency is due to **T**reatment (cortisol).

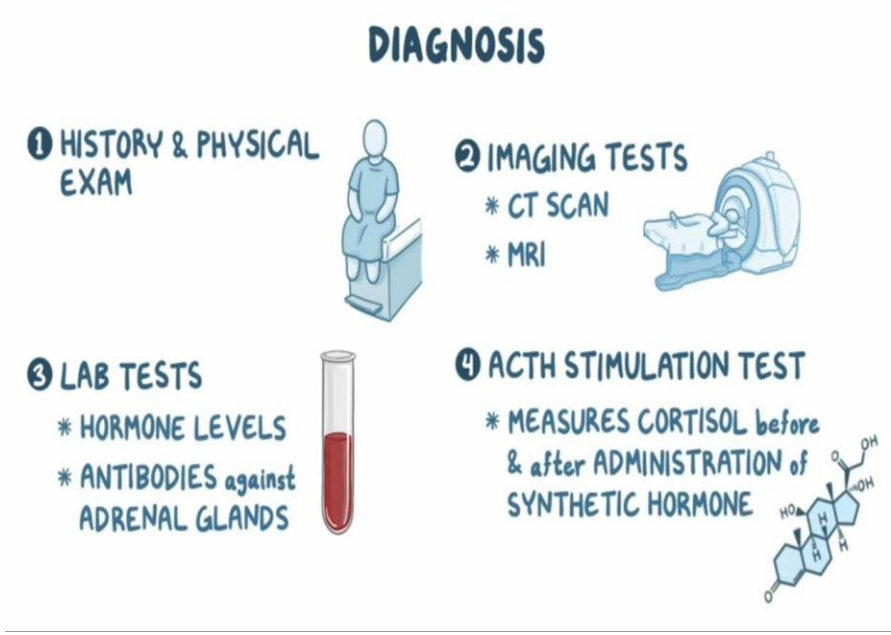
Most cases of adrenal insufficiency are subclinical and only become apparent during periods of stress (e.g., surgery, trauma, infections), when the cortisol requirement is higher!

Approach of adrenal insuff. patients

Acute adrenal insufficiency: In acute adrenal crisis, where treatment should not be delayed in order to do the tests, a blood sample for a random plasma cortisol level should be drawn prior to starting hydrocortisone replacement.

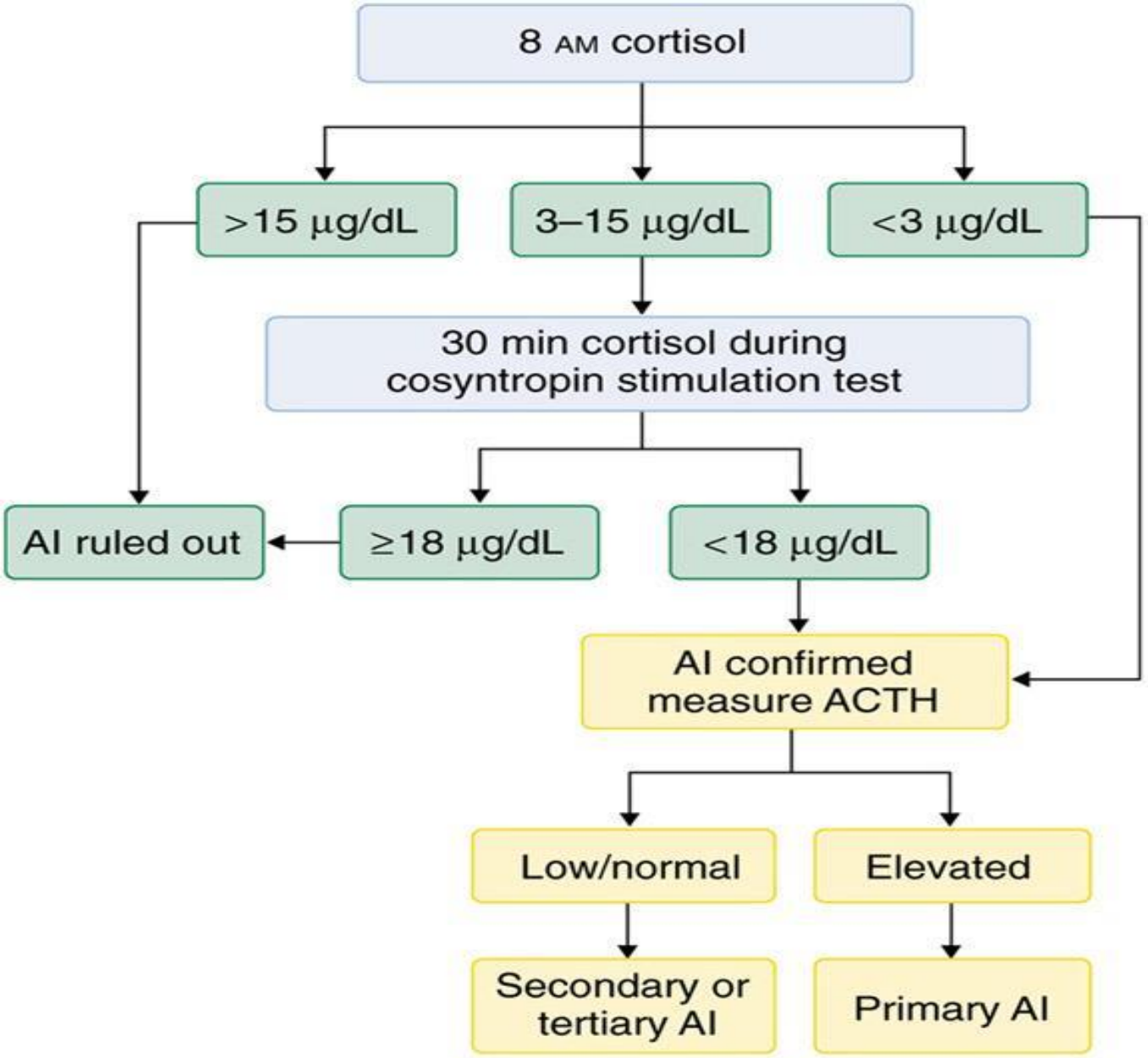
Chronic adrenal insufficiency: Use stepwise endocrine testing in all patients.

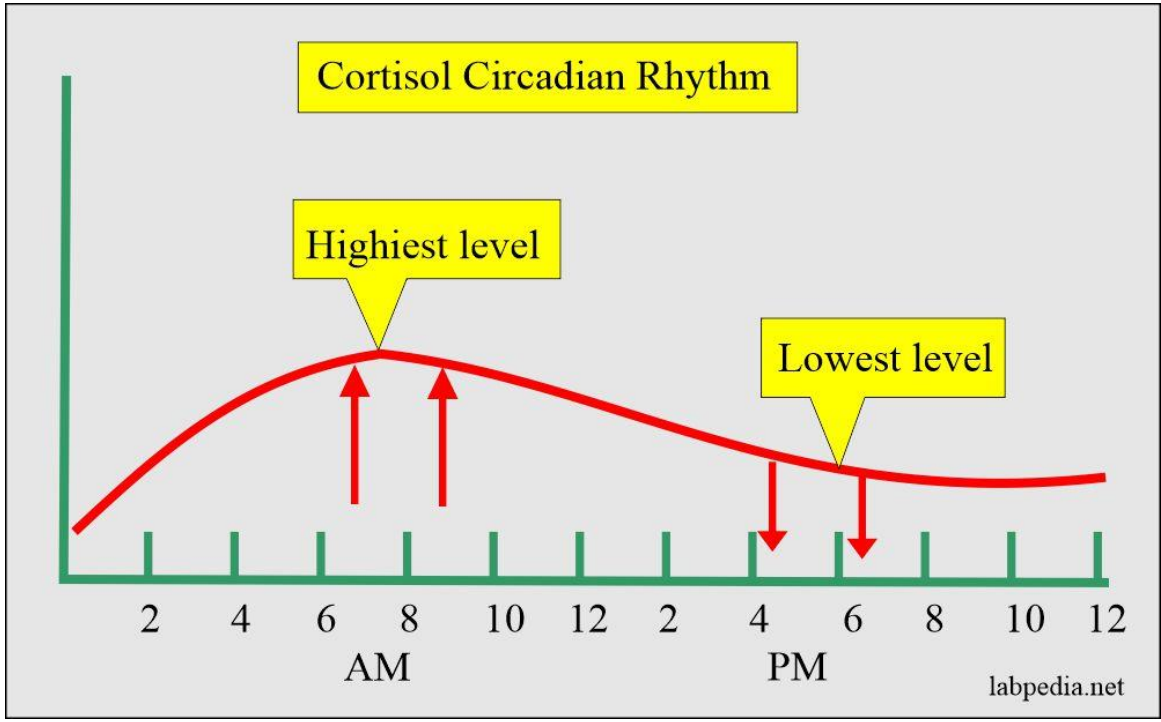
- Morning cortisol
- Morning ACTH
- ACTH stimulation test



Notes:

- Primary adrenal insufficiency: Screen for hypoaldosteronism and hypoandrogenism.
- Secondary and tertiary adrenal insufficiency: Differentiating between the two is often not required, as it does not influence management.
- All patients: Investigate for an underlying cause.


8 AM cortisol
>15 µg/dL
3–15 µg/dL
<3 µg/dL
30 min cortisol during cosyntropin stimulation test
AI ruled out
≥18 µg/dL
<18 µg/dL
AI confirmed measure ACTH
Low/normal
Elevated
Secondary or tertiary AI
Primary AI


Cortisol Circadian Rhythm
Highiest level
Lowest level
2 4 6 8 10 12 2 4 6 8 10 12
AM
PM
labpedia.net

- **Endocrine studies**
- Endocrine testing is typically performed sequentially

1.Morning cortisol level: initial test

1. Levels ≥ 18 mcg/dL have a high negative predictive value for ruling out adrenal insufficiency.
2. Levels < 3 mcg/dL strongly suggest hypocortisolism.

2.Morning ACTH level: obtain if morning cortisol is low

Primary adrenal insufficiency: elevated ACTH levels

Secondary/tertiary adrenal insufficiency: ACTH levels low to normal

ACTH and cortisol secretion is subject to diurnal variation, which is why a morning sample is desirable.

Exogenous glucocorticoids (via any route) can suppress ACTH secretion through negative feedback.

3.Standard-dose ACTH stimulation test (cosyntropin test): gold standard to confirm the diagnosis of primary adrenal insufficiency

Method

Administration of exogenous ACTH to stimulate cortisol secretion

Measurement of cortisol levels before and 30 and/or 60 minutes after injection

Interpretation

In primary adrenal insufficiency: peak cortisol level < 18–20 µg/dL

In secondary/tertiary adrenal insufficiency: usually a rise in cortisol > 18–20 µg/dL

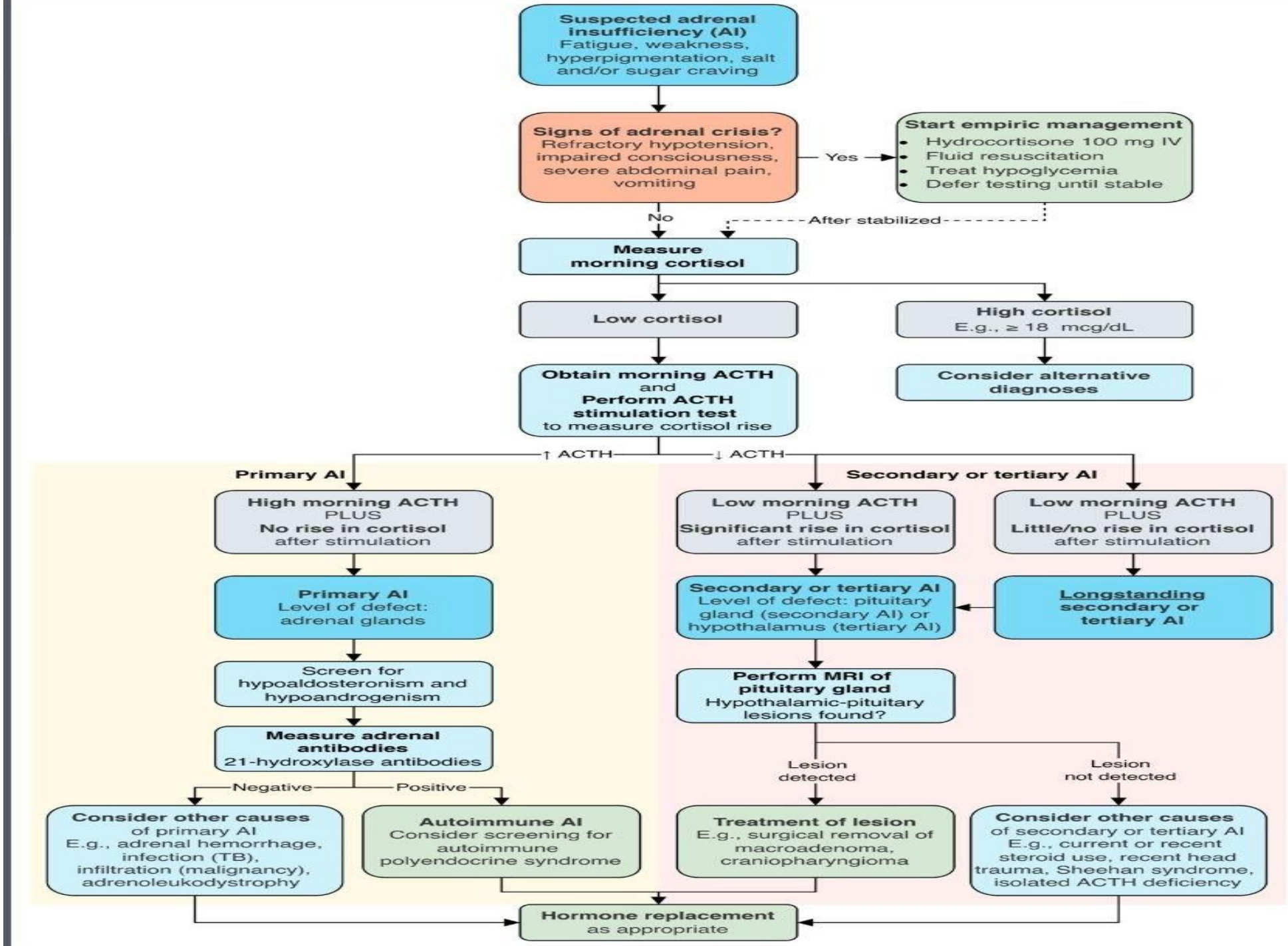
- **Screening for hypoaldosteronism and hypoandrogenism**

Hypoaldosteronism

- ↑ **Plasma renin activity** (PRA) or ↑ **plasma renin concentration (PRC)**
- normal or ↓ **serum aldosterone**

Hypoandrogenism

- ↓ **DHEA-S**


Suspected adrenal insufficiency (AI)
Fatigue, weakness, hyperpigmentation, salt and/or sugar craving
Signs of adrenal crisis?
Refractory hypotension, impaired consciousness, severe abdominal pain, vomiting
Yes
Start empiric management
Hydrocortisone 100 mg IV
Fluid resuscitation
Treat hypoglycemia
Defer testing until stable
No
After stabilized
Measure morning cortisol
Low cortisol
High cortisol
E.g., ≥ 18 mcg/dL
Consider alternative diagnoses
Obtain morning ACTH and Perform ACTH stimulation test to measure cortisol rise
↑ ACTH
↓ ACTH
Primary AI
High morning ACTH
PLUS
No rise in cortisol
after stimulation
Primary AI
Level of defect: adrenal glands
Screen for hypoaldosteronism and hypoandrogenism
Measure adrenal antibodies
21-hydroxylase antibodies
Negative
Positive
Consider other causes
of primary AI
E.g., adrenal hemorrhage, infection (TB), infiltration (malignancy), adrenoleukodystrophy
Autoimmune AI
Consider screening for autoimmune polyendocrine syndrome
Secondary or tertiary AI
Low morning ACTH
PLUS
Significant rise in cortisol
after stimulation
Low morning ACTH
PLUS
Little/no rise in cortisol
after stimulation
Secondary or tertiary AI
Level of defect: pituitary gland (secondary AI) or hypothalamus (tertiary AI)
Longstanding secondary or tertiary AI
Perform MRI of pituitary gland
Hypothalamic-pituitary lesions found?
Lesion detected
Lesion not detected
Treatment of lesion
E.g., surgical removal of macroadenoma, craniopharyngioma
Consider other causes
of secondary or tertiary AI
E.g., current or recent steroid use, recent head trauma, Sheehan syndrome, isolated ACTH deficiency
Hormone replacement
as appropriate

Other investigations

1. **CBC:** eosinophilia, lymphocytosis
2. **Kidney function &electrolytes:** hypoglycemia, hyponatremia and hyperkalemia. High creatinine and urea (prerenal).
3. **Thyroid function abnormalities**

4. Imaging:

- If morning ACTH is elevated (>20pg/ml) → Primary hypoadrenalism → **Adrenal CT**
- If morning ACTH is suppressed or normal → Secondary hypoadrenalism →**Do Pituitary MRI**
- CXR :screen for TB as a cause if sus .

- Other tests : **Autoantibody testing** - Thyroid autoantibodies, specifically antithyroglobulin (anti-Tg) and antimicrosomal or antithyroid peroxidase (anti-TPO) antibodies, and/or adrenal autoantibodies may be present 21 hydroxylase antibodies

Treatment :

Primary adrenal insufficiency: replacement for hypocortisolism, hypoaldosteronism, and hypoandrogenism.

- **Glucocorticoids**

Agent :Hydrocortisone

S.E: hypercortisolism (Cushing dx)

- **Mineralocorticoids**

Agent: fludrocortisone (a synthetic mineralocorticoid with mostly mineralocorticoid and limited glucocorticoid effects)

S.E are analogous to glucocorticoids (e.g., hyperpigmentation).

Additional side effects include: Worsening of preexisting heart failure or cardiac dx if present.

Edema

- **Androgens**

Consider treatment in female patients with low libido, depressive symptoms, and low energy levels.

Agent: DHEA

- **Secondary/tertiary adrenal insufficiency:** replacement for hypocortisolism and hypoandrogenism

Glucocorticoids

Androgens (as needed)

- **Prevention of adrenal crisis: "Stress-dose steroids"**

Steroid doses should be increased to prevent adrenal crisis in at-risk patients, e.g., in acute illness, surgery, or trauma.

Inpatient steroid doses are adjusted according to the level of stress.

If the dose of glucocorticoids is not increased during periods of stress, the patient may develop an adrenal crisis!

Adrenal crisis

Acute primary (Adrenal crisis)

- Precipitating factors for adrenal crisis :

Stress in patients with underlying adrenal insufficiency :

1. Gastrointestinal illness (most common)
2. Other infections
3. Perioperative period
4. Physical stress or pain
5. Psychological stress

- Sudden discontinuation of glucocorticoids after prolonged glucocorticoid therapy
- Bilateral adrenal hemorrhage or infarction (e.g., Waterhouse-Friderichsen syndrome)
- Pituitary apoplexy

Signs and symptoms of crisis:

➢**Similar symptoms and signs of adrenal insufficiency but are more severe, including :**

1. **1. Severe hypotension,shock (<90/50)**
2. **2. Fever & decreased level of consciousness.**
3. **3. Hyperkalemia & hyponatremia & metabolic acidosis**
4. **Vomiting, diarrhea**
5. **Severe abdominal pain**

Consider adrenal crisis in patients with severe hypotension refractory to fluid resuscitation and/or vasopressors.

Adrenal crisis can be life-threatening, so treatment with high doses of hydrocortisone should be started immediately, without waiting for diagnostic confirmation of hypocortisolism!

- In patients in acute adrenal crisis, intravenous (IV) access should be established urgently, and an infusion of isotonic sodium chloride solution should be begun to restore volume deficit and correct hypotension.

- Some patients may require glucose supplementation.
- no mineralocorticoid replacement is necessary. The mineralocorticoid activity of hydrocortisone in this dosage is sufficient.

Box 21.18 Management of acute hypoadrenalism

Clinical context

Hypotension, hyponatraemia, hyperkalaemia, hypoglycaemia, dehydration, pigmentation often with precipitating infection, infarction, trauma or operation. The major deficiencies are of salt, steroid and glucose.

Requirements

Assuming normal cardiovascular function, the following are required:

- 1 L of 0.9% saline should be given over 30–60 min with 100 mg of i.v. bolus hydrocortisone
- Subsequent requirements are several litres of saline within 24 h (assessing with central venous pressure line if necessary) plus hydrocortisone, 100 mg i.m., 6-hourly, until the patient is clinically stable
- Glucose should be infused if there is hypoglycaemia
- Oral replacement medication is then started, unless the patient is unable to take oral medication: initially, hydrocortisone 20 mg, 8-hourly, reducing to 20–30 mg in divided doses over a few days (see **Box 21.19**)
- Fludrocortisone is unnecessary acutely, as the high cortisol doses provide sufficient mineralocorticoid activity – it should be introduced before discharge

Long term replacement therapy

1. Glucocorticoid Replacement

- Hydrocortisone 10 mg on awakening and 5 to 10 mg in early afternoon.
- Monitor clinical symptoms and morning plasma ACTH.

2. Mineralocorticoid Replacement

- Fludrocortisone 0.1 (0.05 to 0.2) mg orally.
- Liberal salt intake.
- Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.

Patient advice

- All patients requiring replacement steroids should:

1. Know how to increase steroid replacement by doubling the dose for intercurrent illness

2. Carry a ‘steroid card’

3. Wear a MedicAlert bracelet (or similar), which gives details of their condition so that emergency replacement therapy can be given if found unconscious

4. Keep an ampoule of hydrocortisone at home in case oral therapy is impossible, for administration by self, family, ambulance or doctor.