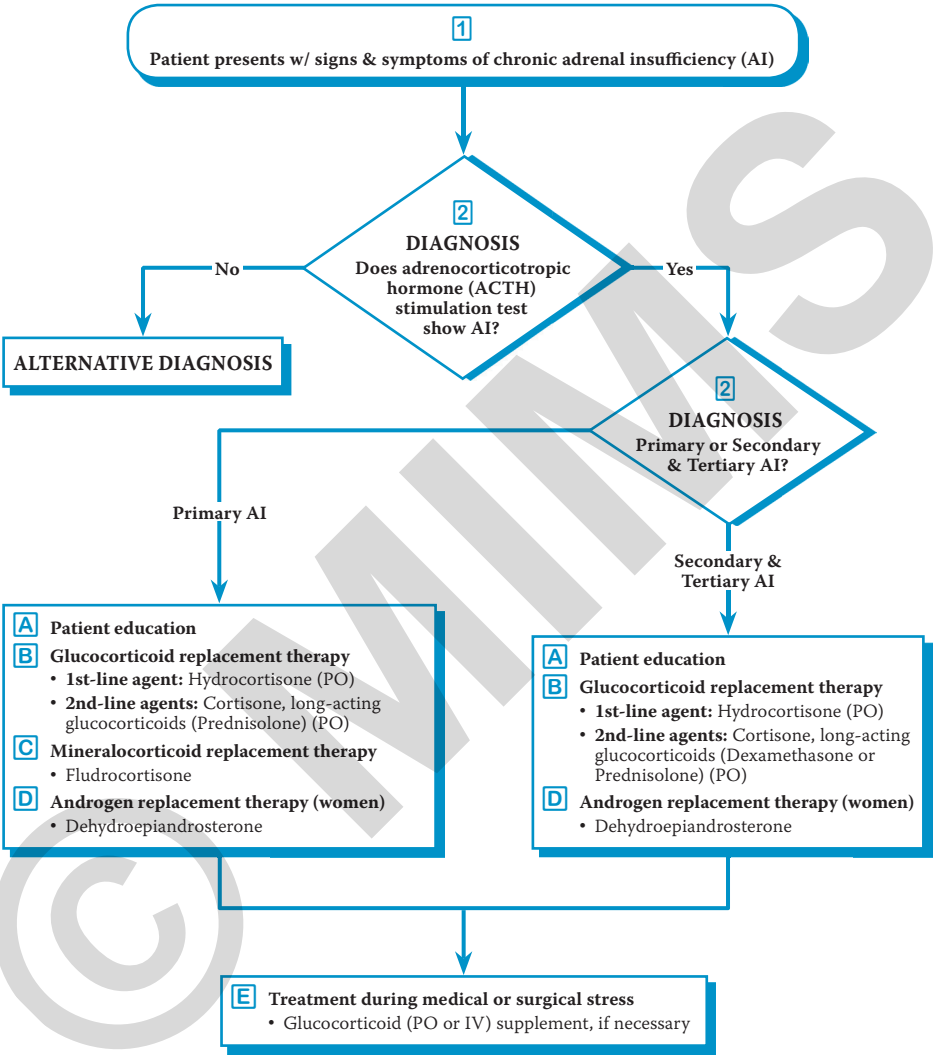
Adrenal Insufficiency (1 of 9)



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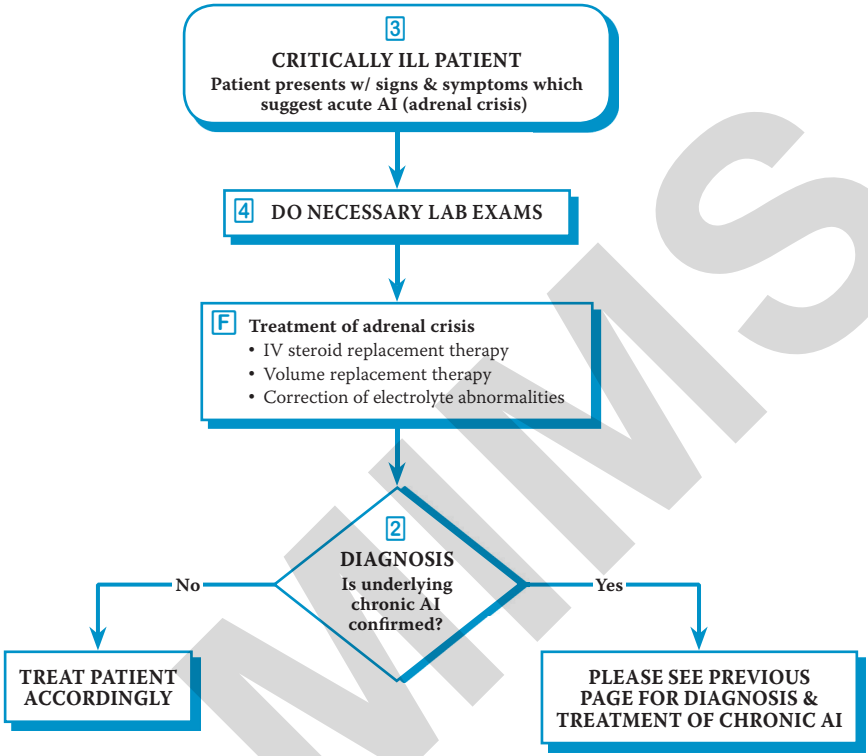

1 ADRENAL INSUFFICIENCY (AI)

- Adrenal insufficiency is the inability of the adrenal gland to produce sufficient adrenocortical steroid hormones
- Primary AI or Addison's disease is due to the inability of the adrenal gland to produce steroid hormones even when the stimulus by the pituitary gland via corticotropin is adequate or increased
  - 80-90% of patients w/ primary AI have autoimmune adrenalitis
  - Autoimmune Addison's disease is the most common idiopathic adrenal insufficiency in developed countries that involves adrenal cortex autoimmune destruction
- Secondary AI is due to disorders of the pituitary gland that causes production of low levels of adrenocorticotropic hormone that will result to reduced cortisol levels
  - Occurs in patients receiving chronic exogenous glucocorticoid treatment (≥5 mg Prednisolone or equivalent for ≥4 weeks) or chronic glucocorticoid cream or inhaler application or long-lasting glucocorticoid injections into joints
- Tertiary AI is the inability of the hypothalamus to produce sufficient amount of corticotropin-releasing hormone
- Adrenal crisis referred to as acute adrenal insufficiency, is a life-threatening emergency

Signs & Symptoms

- Usually nonspecific w/ insidious onset

Primary, Secondary & Tertiary AI:

- Fatigue
- Weakness
- Salt craving
- Orthostatic hypotension, dizziness, hypovolemic shock
- Nausea & vomiting (N/V); abdominal pain, tenderness & guarding
- Fever
- Diarrhea
- Anorexia, weight loss
- Confusion, somnolence
- In severe cases, delirium or coma

Primary AI

- Hyperpigmentation - most characteristic
- Hyperkalemia, hyponatremia
- Autoimmune thyroid disease
- Vitiligo

Secondary & Tertiary AI

- Manifestations usually begin in the first 48 hours after steroid medication has been discontinued
- Similar to primary AI except that hyperpigmentation & dehydration are absent; gastrointestinal symptoms & hypotension are less prominent
- Hyponatremia & volume expansion may be present
- Hypoglycemia is more commonly seen than in primary AI
- Pale skin without significant anemia
- Prepubertal growth deficiency, delayed puberty
- May present w/ clinical manifestations of pituitary or hypothalamic tumor, eg diabetes insipidus (DI)
- Secondary hypothyroidism
- Decreased libido & potency, amenorrhea
- Visual symptoms, headache

2 DIAGNOSIS

Corticotropin Stimulation Test

- Also known as cosyntropin test, ACTH test, or Synacthen test
- Performed to rule out AI
  - Assess adrenal reserve & responsiveness
- Baseline cortisol values <5 mcg/dL & ACTH concentration >100 pg/mL are usually diagnostic of primary AI
- Measure cortisol level before & 30 or 60 minutes after administration of 250 mcg of corticotropin IM/IV as bolus injection
  - Gold standard diagnostic test for primary adrenal insufficiency
  - Peak cortisol levels <500 mg nmol/L (18 mcg/dL) indicates adrenal insufficiency
  - A serum cortisol w/ or without ACTH stimulation that exceeds 550 nmol/L (>20 mcg/dL) excludes AI
  - A normal response to ACTH stimulation is doubling of cortisol levels
  - AI is indicated by a serum cortisol level that fails to rise after ACTH administration
  - Mild secondary AI may result in close to normal cortisol levels & further confirmatory work-up may be necessary

Low-Dose Short Corticotropin Test

- Suitable for detecting mild secondary AI or if corticotropin is at low supply
- Measure cortisol response at 20-60 minutes after administration of 1 mcg of Cosyntropin IV
  - Adrenal function is normal if serum cortisol level is ≥500 nmol/L (18 mcg/dL)

Further Testing to Distinguish Between Primary & Secondary/Tertiary AI

- Primary AI
  - Plasma ACTH & associated peptides (β-LPT) are raised
  - Aldosterone increment level will be subnormal (from the same blood sample as stated above)
- Secondary/Tertiary AI
  - Aldosterone increment level, from the same blood sample as stated above, will be normal ≥150 pmol/L (5 ng/dL)
  - Plasma ACTH values are low-normal
  - Insulin-induced hypoglycemia test may be performed to distinguish normal subjects & patients w/ secondary AI
    - Done by administration of 0.15 unit/kg of regular insulin IV bolus followed by every 15-minute interval blood glucose & cortisol measurement throughout the subsequent 2 hours
    - Blood glucose must fall <45 mg/mL for adequate stimulation
    - Normal response: >20 µg/dL plasma cortisol at any time during the test

Other Laboratory Exams:

- CBC, electrolytes, BUN, creatinine, thyroid function test, chest X-ray, 24-hour urinary cortisol
- Computed Tomography (CT) scan of the abdomen
  - May show adrenal hemorrhage, or calcification as seen in tuberculosis (TB) of the adrenal, or metastasis
- Head CT scan or magnetic resonance imaging (MRI)
  - May show pituitary destruction or pituitary mass lesion
- ECG
  - May show peaked T waves in hyperkalemia

Etiology

Primary AI

- Progressive destruction of the adrenals which is most commonly caused by idiopathic atrophy (probably autoimmune in nature), TB, fungal infections, adrenal hemorrhage, AIDS, etc
- May also be caused by insufficient hormone production caused by congenital adrenal hyperplasia, enzyme inhibitors (eg Metyrapone), or cytotoxic agents (eg Mitotane), adrenal surgery

Secondary & Tertiary AI

- Pituitary or hypothalamic disorders
- Suppression of the hypothalamic-pituitary axis by exogenous steroid (ie long-term glucocorticoid therapy) or endogenous steroid (ie tumor)
  - Exogenous glucocorticoid doses of 5 mg or higher Prednisolone or equivalent for >4 weeks either inhaled, injected, oral or topical, is the most common cause of drug-induced adrenal insufficiency

3 SIGNS & SYMPTOMS OF ACUTE AI

- Acute AI or adrenal crisis usually occurs w/ concomitant injury or illness & is difficult to diagnose

Signs & symptoms may be non-specific

- Shock or unexplained catecholamine-resistant hypotension is the most predominant manifestation
- Fatigue
- Diarrhea
- Weakness
- Lethargy
- Fever
- Confusion
- Coma
- Anorexia
- Nausea & vomiting
- Metabolic acidosis
- Abdominal pain

Patient w/ underlying chronic AI who presents in crisis may show common symptoms of AI

- Hyperpigmentation
- Vitiligo
- Sparse pubic & axillary hair
- Hyponatremia or hyperkalemia

Etiologies of AI

- Rapid withdrawal of steroids in patients w/ adrenal atrophy due to chronic steroid therapy
  - Most common cause of acute AI
- Rapid intensification of chronic primary adrenal insufficiency caused by sepsis or acute major stress
- May occur in patients receiving glucocorticoids if mineralocorticoid requirements are not met
- Rare in patients w/ secondary or tertiary adrenal insufficiency
- Destruction of both adrenal glands caused by acute hemorrhage
  - In children, may be caused by septicemia
  - In adults, may be caused by anticoagulant therapy or a coagulation disorder
- Patients w/ congenital adrenal hyperplasia who are given drugs that inhibit steroid synthesis or increase steroid metabolism

4 BASIC LAB EXAMS FOR ACUTE AI

- Obtain basal diagnostic bloods to measure cortisol & ACTH levels
- AI is usually ruled out if plasma cortisol level is >700 nmol/L (25 mcg/dL)
- Obtain history of past steroid use
- Diagnosis can be confirmed w/ more detailed tests once patient recovers from acute illness
- When there is prior history &/or strong clinical suspicion of acute AI, treatment is mandatory
- Therapy should not be delayed for diagnostic studies

A PATIENT EDUCATION

Patient should be instructed to carry card & warning bracelet/necklace w/ info about current therapy & emergency treatment recommendations

- Patient should be taught of the nature of hormone deficiency & the rationale of steroid replacement therapy
- Patient should be educated about glucocorticoid adjustments in stressful events & adrenal crisis prevention strategies

Steroid Replacement Therapy

- Glucocorticoid therapy
  - Patient must be taught to double or triple their dose of glucocorticoid replacement temporarily if they have febrile illness or injury
  - If vomiting occurs soon after oral dose, patient should be instructed to take 2nd dose
  - Glucocorticoid injection should be provided for self-injection in cases of major injury, severe vomiting, acute adrenal insufficiency, if the patient becomes unresponsive
- Mineralocorticoid therapy
  - No need for patient to increase mineralocorticoid therapy during illness unless critically ill
  - Patients should be instructed to maintain adequate salt intake (3-4 g/day)
  - May need to increase dose of Fludrocortisone & to add extra salt to diet during hot weather, times of strenuous exercise, sweating, etc

History of Excessive Steroid Use

- Educate patient about risks of excessive steroid use

B GLUCOCORTICOID REPLACEMENT THERAPY

Replacement doses for glucocorticoids are the same for both primary & secondary AI

- Cortisone
  - **Effects:** Potent glucocorticoid w/ some mineralocorticoid activity
  - Requires enzymatic activation in the liver causing the effect to have a slower & less predictable onset
  - Short-acting therefore, 2-3 doses must be given throughout the day
- Hydrocortisone
  - Usually considered 1st-line agent as it is the true replacement of cortisol
  - **Effects:** Potent glucocorticoid w/ some mineralocorticoid activity
  - Short-acting therefore, 2-3 doses must be given throughout the day
- Long-acting glucocorticoids
  - Prednisolone is preferred alternative to Hydrocortisone especially in patients w/ primary adrenal insufficiency who are noncompliant
  - Dexamethasone is least preferred alternative to Hydrocortisone in patients w/ primary adrenal insufficiency due to high risk for Cushingoid side effects because of dose titration difficulties
  - **Effects:** Potent glucocorticoid w/ less mineralocorticoid activity than short-acting glucocorticoids
  - Long-acting which may prevent excessive high peak levels & periods of inadequate replacement that may occur w/ Hydrocortisone & Cortisone

Monitoring

- Clinical assessment of body weight, postural bood pressure, energy levels & signs of flank glucocorticoid excess are used to monitor glucocorticoid replacement therapy

Dosing Equivalents of Systemic Corticosteroids (IV/Oral)

Glucocorticoid	Equivalent Doses (mg)
Short acting	
Cortisone acetate	25
Hydrocortisone	20
Intermediate acting	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Long acting	
Betamethasone	0.6
Dexamethasone	0.75

C MINERALOCORTICOID REPLACEMENT THERAPY

- Mineralocorticoid replacement is necessary in all primary AI patients
  - Prevents Na loss, intravascular volume depletion & hypercalcemia
- Fludrocortisone is the preferred choice w/ no salt intake restriction
  - **Effects:** Potent mineralocorticoid w/ some glucocorticoid activity
  - Dose reduction is suggested if hypertension developed during Fludrocortisone therapy

Monitoring

- Clinical assessment of salt craving, postural hypertension or edema & blood electrolyte measurements are used to monitor mineralocorticoid replacement therapy

D ANDROGEN REPLACEMENT THERAPY

- Use of Prasterone (Dehydroepiandrosterone, DHEA) may improve well-being & sexuality in women w/ AI
- Recommended in women primary adrenal insufficiency & low libido, depressive symptoms &/or low energy levels despite optimal glucocorticoid & mineralocorticoid replacement therapy
- Initial period of 6 months, if no benefits observed discontinue use

E TREATMENT DURING MEDICAL OR SURGICAL STRESS

- Patients w/ AI may require glucocorticoid (PO or IV) supplement
- Glucocorticoid replacement needs to be individualized
  - Patient w/ secondary AI caused by long-term glucocorticoid therapy may not need replacement
- Mineralocorticoid supplement is usually not needed

F TREATMENT OF ADRENAL CRISIS

- Initial goals of therapy are treatment of hypotension, correction of electrolyte abnormalities & correction of cortisol deficiency
- Immediate IV dose of Hydrocortisone at an appropriate stress dose should be given
  - Prednisolone is the alternative if Hydrocortisone is not available
  - Dexamethasone IV bolus, Hydrocortisone IV bolus or any IV glucocorticoid preparation may be used in patients w/ known diagnosis of adrenal insufficiency
- 2-3 L of saline solution (0.9% or 5% dextrose in 0.9% saline) should be administered as quickly as possible to restore intravascular volume & replace urinary salt losses
  - Monitor for signs of fluid overload
- Mineralocorticoid replacement is not needed acutely because its Na-retaining abilities become apparent only after several days
  - Adequate Na replacement is achieved by IV saline infusion
  - May be started once saline infusion is discontinued
- Monitor blood glucose
  - If blood glucose is <4 mmol/L, give 20% dextrose over 10-15 minutes stat
- Identify & treat underlying problem that triggered the acute crisis
- Most patients who experience adrenal crisis have primary adrenal insufficiency & require lifetime glucocorticoid & mineralocorticoid replacement therapy

Dosage Guidelines

ANDROGEN		
Drug	**Dosage**	**Remarks**
Prasterone (Dehydroepiandrosterone, DHEA)	25-50 mg PO 24 hrly in women	**Adverse Reactions** • Androgenic effects (hirsutism, voice changes)

CORTICOSTEROID HORMONES		
Drug	**Dosage**[1]	**Remarks**
Short-Acting Glucocorticoids		
Cortisone	**Replacement therapy:** 20-35 mg/day PO divided 8-12 hrly	**Adverse Reactions** • Adverse reactions except for gastritis are rare when given in the proper doses **Special Instructions** • Take w/ food, preferably a meal • Short-acting steroids: Morning dose should be taken upon arising & last dose should be not later than 18:00 hr • Adjust dose based on patient's wt, age & other medications (eg Phenytoin, Rifampicin, etc) which may increase the metabolism of glucocorticoid • Use lowest dose to relieve patient's symptoms, normalize BP, HR & ACTH levels • Monitor ACTH levels • If glucocorticoid-induced effects (hypertension, hyperglycemia, muscle & skin changes, etc) appear, dose is probably too high
Hydrocortisone	**Replacement therapy:** 20-30 mg/day PO divided 8-12 hrly **Some common dosing regimens:** 10 mg PO in the morning upon arising, 5 mg PO w/ midday meal & 5 mg PO in the evening, not later than 18:00 hr ***or*** Give ⅔ total daily dose PO in the morning upon arising & ⅓ of total daily dose PO in the late afternoon **Medical or surgical stress supplement:** **Minor surgery/illness:** 25 mg PO/IV on day of procedure only **Moderate surgery/illness:** 50-75 mg PO/IV on day of procedure & taper to usual dose over 1-2 days **Major surgery/illness:** 100-150 mg PO/IV on day of procedure & taper to usual dose over next 1-2 days **Critically ill:** 50-100 mg IV 6-8 hrly ***or*** Continuous infusion: 0.18 mg/kg/hr IV until shock is resolved which may take >1 wk Taper gradually while monitoring vital signs & serum Na	
Methylprednisolone	**Medical or surgical stress supplement:** **Minor surgery/illness:** 5 mg IV as a single dose on the day of procedure **Moderate surgery/illness:** 10-15 mg IV on day of procedure & taper to usual dose over 1-2 days **Major surgery/illness:** 20-30 mg IV on day of procedure & taper to usual dose over next 1-2 days	

[1]All patients should receive their normal daily glucocorticoid dose along w/ supplement if they encounter medical or surgical stress. Patients w/ AI secondary to chronic steroid replacement: If normal daily dose is <5 mg/day of Prednisone no supplement is necessary, >5 mg/day of Prednisone supplement as above.

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
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Dosage Guidelines

CORTICOSTEROID HORMONES (CONT'D)		
Drug	**Dosage**	**Remarks**
Long-Acting Glucocorticoids		
Dexamethasone	0.5 mg PO 24 hrly or 0.5 mg PO in the morning & 0.25 mg PO in the evening May give total dose at bedtime to prevent early morning adrenal insufficiency If patient suffers from insomnia, may give dose in the morning upon arising **Acute AI:** 4 mg IV May repeat 6 hrly as required, then taper off gradually Injection should be diluted in 50-100 mL NS or D_5W	**Adverse Reactions** • Adverse reactions except for gastritis are rare when given in the proper dose **Special Instructions** • Take w/ food, preferably a meal • Adjust dose based on patient's wt, age & other medications (eg Phenytoin, Rifampicin, etc) which will increase the metabolism of glucocorticoid • Use lowest dose to relieve patient's symptoms, normalize BP, HR & ACTH levels • Monitor ACTH levels • If glucocorticoid-induced effects (hypertension, hyperglycemia, muscle & skin changes, etc) appear, dose is probably too high
Prednisone	5 mg PO 24 hrly or 5 mg PO in the morning & 2.5 mg PO in the evening May give total dose at bedtime to prevent early morning adrenal insufficiency If patient suffers from insomnia, may give dose in the morning upon arising	
Mineralocorticoid		
Fludrocortisone	50-100 mcg PO 24 hrly	**Adverse Reactions** • Adverse reactions except for gastritis are rare when given in the proper dose **Special Instructions** • Take w/ food, preferably a meal • Starting dose is based on patient's glucocorticoid replacement therapy (Hydrocortisone & Cortisone acetate will require lower dose of Fludrocortisone) • Dose may be adjusted based on BP, serum electrolytes & plasma renin activity - BP should be normal without orthostatic hypotension - Serum K, Na, renin, creatinine & BUN should be normal

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