**Adrenal Gland Disorders**

Adrenal glands play essential roles in regulating:

1. water and electrolyte homeostasis,
2. blood pressure,
3. carbohydrate and fat metabolism,
4. physiologic response to stress, and
5. sexual development and differentiation.

**Anatomy and Physiology of the Adrenal Glands**

* Each adrenal gland consists of two functionally distinct endocrine parts: the **cortex** and **medulla**.
* The cortex consists of three concentric zones: The outer glomerulosa secretes the mineralocorticoid **aldosterone**, the intermediate fasciculata secretes **cortisol** (hydrocortisone), and the inner reticularis secretes **androgens** [androstenedione & dehydroepiandrosterone (DHEA)].
* The endocrine cells of the adrenal medulla are the chromaffin cells, which are part of the sympathetic nervous system and produce the catecholamine epinephrine.



* Cortisol secretion follows a **circadian** rhythm, beginning to rise at 4 am & peaking around 6 to 8 am. Thereafter, cortisol levels decrease throughout the day, approach 50% of the peak value by 4 pm, and reach their nadir around midnight.
* The normal rate of cortisol production is about 8 to 15 mg/day. Cortisol is converted in the liver to an **inactive** metabolite known as **cortisone**, while androstenedione and DHEA are converted in the peripheral tissues, largely to testosterone and estrogen.
* Adrenal hormone production is controlled by the **hypothalamus** and **pituitary**. **Corticotropin-releasing hormone** (CRH) is secreted by the hypothalamus and stimulates secretion of **corticotrophin [adrenocorticotrophic hormone (ACTH)**] from the anterior lobe of the pituitary gland. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production.
* The most common conditions associated with adrenal gland dysfunction: glucocorticoid insufficiency (e.g., Addison’s disease) and glucocorticoid excess (Cushing’s syndrome)

**Glucocorticoid insufficiency**

* **Primary** adrenal insufficiency **(Addison’s disease)** occurs when the defect is in the adrenal cortex itself; this disease **affects cortisol mainly**, but affects mineralocosticoid & androgens to a lesser extent. The serum levels of both CRH & ACTH increase in a compensatory manner.
* **Autoimmune dysfunction** is responsible for 80% to 90% of cases in developed countries, whereas **tuberculosis** is the predominant cause in developing countries. Medications that inhibit cortisol synthesis (eg, ketoconazole) or accelerate cortisol metabolism (phenytoin, rifampin, phenobarbital) can also cause **primary** adrenal insufficiency.
* **Secondary** adrenal insufficiency occurs as a result of a **pituitary** gland disorder, whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis. **Tertiary** adrenal insufficiency is a disorder of the **hypothalamus** that results in decreased production and release of CRH.
* ***Aldosterone*** *production is* ***unaffected*** *in the secondary and tertiary forms of the disease*.
* Chronic adrenal insufficiency often has a good prognosis if diagnosed early and treated appropriately.
* Acute adrenal insufficiency (i.e., **adrenal crisis or addisonian crisis**) results from the body’s inability to sufficiently increase endogenous cortisol during periods of excessive physiologic stress. Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions such as surgery, infection, acute illness, invasive medical procedures, or trauma.

**Clinical presentation:**

* The clinical manifestations are observed when destruction of the cortex exceeds 90%. Weight loss, **dehydration**, **hyponatremia**, hyperkalemia, and elevated blood urea nitrogen are common in Addison disease.
* Hyperpigmentation is common in Addison disease and may involve exposed and non-exposed parts of the body. *Hyperpigmentation is usually* ***not seen*** *in secondary adrenal insufficiency because of* ***low amount*** *of melanocyte-stimulating hormone*.

**Diagnosis**

* The short cosyntropin (ACTH) stimulation test can be used to assess patients with suspected hypocortisolism. An increase to a cortisol level of 18 mcg/dL or more rules out adrenal insufficiency.
* Other tests include insulin hypoglycemia test & CRH stimulation test



**Treatment**

Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency

**Pharmacotherapy**

* **Hydrocortisone, prednisone& prednisolone** are the glucocorticoids of choice, administered **twice daily** at the **lowest** effective dose to mimic the normal **diurnal** adrenal rhythm of cortisol production.
* Recommended starting total daily doses are hydrocortisone 15 - 25 mg daily, which is approximately equivalent to prednisone 2.5 - 5 mg.
* **Two thirds** of the dose is given in the **morning**, and **one third** is given 6 to 8 hours later.
* The patient’s symptoms can be monitored every 6 to 8 weeks to assess the response to proper glucocorticoid replacement.
* **Fludrocortisone acetate** 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss.
* During times of severe physical stress (eg, febrile illnesses and after accidents), patients should be instructed to **double** their daily **dose** until recovery to eliminate the risk of adrenal crisis.
* Treatment of secondary adrenal insufficiency is identical to primary disease treatment, with the exception that **mineralocorticoid replacement is usually not necessary**.



**Pharmacotherapy of acute adrenal insufficiency**

* Acute adrenal insufficiency represents a true endocrine **emergency**.
* The most common cause of adrenal crisis is abrupt withdrawal of exogenous glucocorticoids in patients receiving chronic treatment that resulted in hypothalamic pituitary-adrenal-axis suppression.
* Surgery, infection, and trauma are potential stressful **predisposing** events.
* **Hydrocortisone** given **parenterally** is the treatment of **choice** because of its **combined** glucocorticoid and mineralocorticoid activity.
* The starting dose is 100 mg IV by rapid infusion, followed by a continuous infusion (usually 10 mg/h) **or** the recommended dose is administered via IV intermittent boluses of 50 – 100 mg / 6 hours usually for 24-48 hours.
* If the patient is stable, **oral** hydrocortisone started at **50 mg every 6 hours**, followed by tapering to the individual’s chronic replacement needs.
* **Fluid replacement** often is required and can be accomplished with IV glucose-saline (**dextrose 5% in normal saline**) to support blood pressure.
* If hyperkalemia is present after the hydrocortisone maintenance phase, additional **fludrocortisone acetate** 0.1 mg daily.
* Patients with adrenal insufficiency should carry a card or wear necklace that contains information about their condition.
* They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.

**Cushing syndrome**

Cushing syndrome results from effects of **supraphysiologic** glucocorticoid levels originating from either

1. **Exogenous administration** or
2. **Endogenous overproduction**
* The endogenous overproduction results from either elevated levels of ACTH (**ACTH dependent**) or from abnormal adrenocortical tissues (**ACTH-independent**).
* ACTH **dependent** Cushing syndrome (80% of all Cushing syndrome cases) is usually caused by overproduction of ACTH by the pituitary gland, causing adrenal hyperplasia. **Pituitary adenomas** account for ~85% of these cases (**Cushing disease**).
* **Ectopic** ACTH-secreting tumors cause the remaining **20% of ACTH-dependent** cases. Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (eg, small-cell lung cancer).
* ACTH-**independent** Cushing syndrome is usually caused by adrenal adenomas and adrenal carcinomas.

**Clinical presentation:**

* The **most common** findings in Cushing syndrome are central obesity, facial rounding (moon face) & fat accumulation in the dorsocervical area (buffalo hump).
* Other findings may include myopathy, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, and (amenorrhea and hirsutism) in women. Up to 60% of patients develop Cushing-induced **osteoporosis**.

**Diagnosis:**

* **Hypercortisolism** can be established with a 24-hour urinary free cortisol (UFC), and/or low-dose dexamethasone suppression test (DST).
* Other tests to determine **etiology** are plasma ACTH test; (adrenal, chest, or abdominal) CT scans and CRH stimulation test.

**Treatment:**

Goals of therapy include return the patient to a normal functional state by removing the source of hypercortisolism while minimizing pituitary or adrenal deficiencies.

**Non-pharmacological therapy:**

* Treatment of choice for both ACTH-dependent & independent Cushing syndrome is **surgical** resection of offending **tumors**. Trans-sphenoidal resection of the pituitary tumor is recommended.
* Pituitary irradiation provides clinical improvement in about 50% of patients within 3 to 5 years, but pituitary hormone deficiencies (hypopituitarism) can occur.
* Laparoscopic **adrenalectomy** may be preferred in patients with unilateral adrenal adenomas or for whom trans-sphenoidal surgery or pituitary radiotherapy have failed or cannot be used.

**Pharmacotherapy:**

Pharmacotherapy is generally used as:

1. Secondary treatment in preoperative patients, or
2. Adjunctive therapy in postoperative patients awaiting response.
3. Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

The therapeutic agents include:

1- **Steroidogenic inhibitors**

1. **Metyrapone:** inhibits 11β-hydroxylase, thereby inhibiting cortisol synthesis. Initially, patients can demonstrate increased plasma ACTH concentrations because of a sudden drop in cortisol. This can increase androgenic and mineralocorticoid hormones, resulting in hypertension, acne, and hirsutism. Other side effects include vertigo, headache, abdominal discomfort, and allergic rash.

Metyrapone is currently available through the manufacturer only for compassionate use.

1. **Ketoconazole:** inhibits hepatic 11β-hydroxylase& 17α-hydroxylase. It is effective in lowering serum cortisol levels after several weeks of therapy. It also has **antiandrogenic** activity, which may be beneficial in women but can cause gynecomastia and decreased libido in men.

The most common adverse effects are reversible elevation of hepatic transaminases. Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole’s antiandrogenic actions may offset the androgenic potential of metyrapone.

1. **Etomidate:** is an imidazole derivative similar to ketoconazole that inhibits 11β-hydroxylase. Because it is only available in a **parenteral** formulation, use is limited to patients with acute hypercortisolemia requiring **emergency** treatment.
2. **Aminoglutethimide:** inhibits cortisol synthesis and should be coadministered with another steroidogenic inhibitor (usually metyrapone) due to **high relapse rates** with aminoglutethimide monotherapy.

2- **Adrenolytic agents**

* **Mitotane** is a **cytotoxic** drug that inhibits the 11-hydroxylation & **reduces synthesis** of cortisol. It takes weeks to months to exert beneficial effects.
* Mitotane damages cells within the zonafasciculata and reticularis.
* Nausea & diarrhea are common at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering it with food.

3- **Neuromodulators of ACTH release**

ACTH secretion is **mediated by neurotransmitters** such as serotonin, acetylcholine and catecholamines. Consequently, agents that target these transmitters have been proposed for treatment of Cushing disease, including cyproheptadine, bromocriptine, cabergoline, octreotide & rosiglitazone.

1. **Cyproheptadine** can decrease ACTH secretion in some patients. However, sedation and weight gain significantly limit its use.
2. **Pasireotide** is a somatostatin analogue that activates somatostatin receptors, thereby inhibiting ACTH secretion. It is approved for treatment of adults for whom pituitary surgery is not an option or has not been curative.

**4-Glucocorticoid Receptor Blocking agents:**

**Mifepristone** (RU-486) is a progesterone- and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in **normal subjects**.

Evidence suggests that mifepristone is highly effective in **reversing** the manifestations of **hypercortisolism**. Its use for treatment of Cushing syndrome remains investigational.

**Pheochromocytoma**

* Pheochromocytoma is a rare, **catecholamine-secreting tumor** derived from chromaffin cells.
* Typically, there is elevation in the secretion of norepinephrine and epinephrine. Dopamine is found to be produced by some tumors.
* Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening **hypertension** or cardiac **arrhythmias**.
* If pheochromocytoma is found, it is potentially curable.
* About **85%** of pheochromocytomas are located **within the adrenal glands**.
* When tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas, or **paragangliomas**.
* Common locations for extra-adrenal pheochromocytomas include bladder wall, heart & mediastinum.
* Approximately 10% of pheochromocytomas and 35% of extra-adrenal pheochromocytomas are malignant.

Clinical presentation

Headache, diaphoresis, palpitations, tremor, nausea, anxiety, epigastric pain, constipation & weight loss.

Diagnosis

Pheochromocytoma is diagnosed by measuring elevated levels of metanephrines (catecholamine metabolites) in blood or urine. CT scanning or MRI is performed to specify the location of the tumor.

Treatment

* Surgical resection of the tumor is the treatment of choice for pheochromocytoma and usually results in cure of the hypertension.
* Careful preoperative management is required to control blood pressure and heart rate, to correct fluid volume, and to prevent intraoperative hypertensive crises.
* Laparoscopic adrenalectomy should be performed for small adrenal pheochromocytomas, while open resection reserved for very large or invasive pheochromocytomas.
* Alpha blockers, beta blockers, calcium channel blockers, and angiotensin receptor blockers all are recommended to **control hypertension prior to surgery**. Start alpha blockade with phenoxybenzamine **10-14 days** preoperatively to allow for **expansion** of blood volume. Initiate a beta blocker only **after** adequate alpha blockade (usually, 2 days). If beta blockade is started prematurely, unopposed alpha stimulation could precipitate a hypertensive crisis. Administer the last doses of oral alpha and beta blockers on the morning of surgery.
* Postoperatively; high-sodium diet is combined with fluid intake to prevent severe hypotension after removal of the tumor. Blood pressure, heart rate, and glucose levels should be **monitored immediately** after surgery.