# ADRENAL INSUFFICIENCY AND ADRENAL CRISIS

**STEROID HORMONES ARE SYNTHESISED IN THE ADRENAL CORTEX AND CATECHOLAMINES IN THE MEDULLA**

**ADRENAL INSUFFICIENCY REFERS TO A STATE OF DEFICIENCY OF HORMONE PRODUCTION, WHEREAS ADRENAL CRISIS IS A LIFE-THREATENING EXACERBATION OF ADRENAL INSUFFICIENCY DUE TO INCREASED PHYSIOLOGIC DEMAND (E.G. INFECTION) OR DECREASED SUPPLY (E.G. DISCONTINUATION OF STEROID THERAPY) OF CORTISOL.**

**CRISIS NORMALLY OCCURS IN RESPONSE TO MAJOR STRESS AND THE ADSRENAL GLAND FAILS TO MOUNT A STRESS RESPONSE VIA INCREASING CIRCULATING CORTISOL LEVELS**

**THE MOST FREQUENT IATROGENIC CAUSE OF CRISIS IS RAPID WITHDRAWAL OF STREOIDS IN PATIENTS WITH ADRENAL ATROPHY SECONDARY TO LONG-TERM STEROID ADMINISTRATION**

## PATHOPHYSIOLOGY:

- PRIMARY ADRENAL INSUFFICIENCY → AKA ADDISON DISEASE → due to intrinsic adrenal gland dysfunction. ~90% of the gland must be destroyed for adrenal insufficiency to develop
    - Causes include infection (TB, HIV), drugs, adrenal haemorrhage (warfarin, sepsis, trauma), autoimmune disorders, metastases and congenital adrenal hyperplasia
- SECONDARY ADRENAL INSUFFICENCY → due to hypothalamic-pituitary dysfunction causing inadequate ACTH production → cortisol deficiency
    - Causes include prolonged steroid therapy, pituitary disease, head trauma, post-partum pituitary necrosis (Sheehan syndrome)

**Table 225-1 Causes of Primary Adrenal Insufficiency**

| Primary Adrenal Insufficiency (disorders in the adrenal gland) | Examples |
|---|---|
| Autoimmune | Isolated adrenal insufficiency or associated with polyglandular insufficiencies (polyglandular autoimmune syndrome types I or II) |
| Adrenal hemorrhage or thrombosis | Necrosis caused by meningococcal sepsis |
| | Coagulation disorders |
| | Overwhelming sepsis (Waterhouse-Friderichsen syndrome) |
| Drugs | Adrenolytic agents |
| | Metyrapone |
| | Aminoglutethimide |
| | Mitotane |
| | Ketoconazole |
| Infections involving adrenal glands | Tuberculosis |
| | Fungal, bacterial sepsis |
| | Acquired immunodeficiency syndrome involving adrenal glands |
| Infiltrative disorders involving adrenal glands | Sarcoidosis |
| | Hemochromatosis |
| | Amyloidosis |
| | Lymphoma |
| | Metastatic cancer |
| Surgery | Bilateral adrenalectomy |
| Hereditary | Adrenal hypoplasia |
| | Congenital adrenal hyperplasia |
| | Adrenoleukodystrophy |
| | Familial glucocorticoid deficiency |
| Idiopathic | — |

| Table 225-2 Causes of Secondary Adrenal Insufficiency | |
|---|---|
| **Secondary Adrenal Insufficiency (hypothalamic-pituitary dysfunction)** | **Examples** |
| Sudden cessation of prolonged glucocorticoid therapy | Chronic use of steroid inhibits ACTH production |
| Pituitary necrosis or bleeding | Postpartum pituitary necrosis (Sheehan syndrome) |
| Exogenous glucocorticoid administration | Causes decreased production of ACTH at pituitary |
| Brain tumors | Pituitary tumor |
| | Hypothalamic tumor |
| | Local invasion (craniopharyngioma) |
| Pituitary irradiation | Disrupts corticotropin-releasing hormone and ACTH production capacity in hypothalamic-pituitary axis |
| Pituitary surgery | |
| Head trauma involving the pituitary gland | |
| Infiltrative disorders of the pituitary or hypothalamus | Sarcoidosis |
| | Hemosiderosis |
| | Hemochromatosis |
| | Histiocytosis X |
| | Metastatic cancer |
| | Lymphoma |
| Infectious diseases involving organs away from adrenal | Tuberculosis |
| | Meningitis |
| | Fungus |
| | Human immunodeficiency virus |

- Secondary adrenal deficiency normally has normal aldoosterone levels because of both renin-angiotensin axis and hyperkalaemia
- Most common cause of secondary adrenal insufficiency is long0term therapy with glucocorticoids
    - Although this is often related to duration of treatment and total cumulative dose, there is no strict correlation with either of these factors
    - Can also be attributed to the potency of the glucocorticoid and the time of day that it is taken → greater suppression when taken in the morning

## CLINICAL FEATURES:

- A high index of suspicion for adrenal crisis in any case of UNEXPLAINED HYPOTENSION → especially in those who are high risk for HIV?AIDS, prior steroid therapy, those with known autoimmune disease or those with history of chronic fatigue and hyperpigmentation, severe head trauma
- Differentiating between primary and secondary adrenal insufficiency can be challenging, but suspect secondary when there are symptoms related to pituitary lesions (headache, visual change and glaactorrhoea)

| Table 225-3 Difference between Primary and Secondary Adrenal Insufficiency | | |
|---|---|---|
| **Points of Difference** | **Primary Adrenal Insufficiency** | **Secondary Adrenal Insufficiency** |
| Aldosterone deficiency | Present | Absent |
| Volume depletion and hypotension | Marked | Not as severe unless crisis is present |
| Serum potassium | Hyperkalemia | Hypokalemia |
| Serum sodium | Hyponatremia (due to salt wasting) | Hypernatremia (aldosterone functioning) or hyponatremia (due to water retention) |
| Cushingoid | Absent | May be present (if due to long-term glucocorticoid use) |
| Symptoms of other pituitary hormone deficiencies (hypothyroidism and amenorrhea) | Absent | May be present (depends on the hypothalamic-pituitary site of lesion) |

- **Cortisol deficiency** → weight loss, lethargy, weakness
- **Aldosterone deficiency** → dehydration, syncope, hypotension (usually with orthostatic)
- Primary adrenal insufficiency → hyponatraemia, hyperkalaemia due to aldosterone deficiency
    - Secondary → hypernatramia (aldosterone mediated sodium reabsorption) or hypnatraemia (following water retention) and hypokalaemia
- Hypoglycaemia due to cortisol deficiency
- Mild metabolic acidosis due to tissue hypoxia
- ADRENAL CRISIS → severe hypotension refractory to fluid and vasopressors with dehydration, weakness, circulatory collapse, delirium with (in some cases) severe abdominal pain

**TREATMENT:**

- BEGIN THERAPY IMMEDIATELY AS PROGNOSIS IS RELATED TO SPEED OF TREATMENT ONSET
- Dextrose-containing IV fluids initiated early
- HYDROCORTISONE IS DUR OF CHOICE FOR ADRENAL CRISIS OR INSUFFICIENCY → provides both glucocorticoid and mineralocorticoid effects
- Vasopressors administered after steroid therapy in patients unresponsive to fluid resuscitation (noradrenaline preferred)
- Patients may subsequently need lifelong glucocorticoids with or without mineralocorticoid supplementation → increased during periods of stress
    - Mineralocorticoid usually unnecessary if salt and water replacement is adequate
    - 100mg hydrocortisone has equivalent mineralocorticoid activity as 0.1mg of fludrocortisone
- TREAT PRECIPITATING OR COMORBID CAUSES

| **Table 225-4 Treatment Guide for Adrenal Insufficiency** |
|---|
| Begin therapy immediately in any suspected case of adrenal crisis (prognosis is related to rapidity of treatment delivery). |
| ↓ |
| **Administer IV fluids** |
| 5% dextrose in normal saline is the fluid of choice to correct both hypoglycemia and hyponatremia. |
| ↓ |
| **Steroids** |
| Hydrocortisone (100-milligram bolus) is the drug of choice for cases of adrenal crisis or insufficiency (provides both glucocorticoid and mineralocorticoid effects). |
| *or* |
| Dexamethasone, 4-milligram bolus (for accuracy of rapid adrenocorticotropic hormone stimulation test results). |
| ↓ |
| **Vasopressors** |
| Administered after steroid therapy in patients unresponsive to fluid resuscitation [norepinephrine, dopamine, or phenylephrine (Neo-Synephrine®) preferred]. |
| ↓ |
| **Supplementation** |
| Patients may require lifelong glucocorticoids ± mineralocorticoid supplementation. |
| ↓ |
| **Maintenance** |
| Increased maintenance doses of chronic steroids are required during periods of stress (e.g., illness, surgery, trauma, etc.) to satisfy increased physiologic need for cortisol. |

- Because the hypothalamic-pituitary-adrenal axis recovers within one month after the last dose of steroids, it is reasonable to consider steroid supplementation for 3-4 weeks in patients who have received oral steroids in the preceding 12 months
    - Those who receive steroids by topical, intranasal, inhalational or PR routes are not thought to be at risk for axis suppression

**Table 225-6 Glucocorticoid Preparations***

| | Estimated Potency | |
|---|---|---|
| **Commonly Used Name** | **Glucocorticoid** | **Mineralocorticoid** |
| Short-acting | | |
| Hydrocortisone† | 1 | 1 |
| Cortisone | 0.8 | 0.8 |
| Intermediate-acting | | |
| Prednisone | 4 | 0.25 |
| Prednisolone | 4 | 0.25 |
| Methylprednisolone | 5 | <0.01 |
| Triamcinolone | 5 | <0.01 |
| Long-acting | | |
| Paramethasone | 10 | <0.01 |
| Betamethasone | 25 | <0.01 |
| Dexamethasone | 30–40 | <0.01 |