Adrenal Insufficiency and Addison's Disease

See related separate article Adrenal Crisis.

Description
Adrenal insufficiency is a condition in which there is destruction of the adrenal cortex and subsequent reduction in the output of adrenal hormones, ie glucocorticoids (cortisol) and/or mineralocorticoids (aldosterone). There are two types of adrenal insufficiency:

- **Primary insufficiency (Addison's disease)** - there is an inability of the adrenal glands to produce enough steroid hormones. The most common cause for this in the developed world is autoimmune disease.
- **Secondary insufficiency** - there is inadequate pituitary or hypothalamic stimulation of the adrenal glands.

Epidemiology

- **Primary insufficiency** - this is a relatively rare condition. The annual incidence is about 1 in 10,000 people, with a prevalence in the UK of about 8,400. Across Europe, prevalence is estimated as 93-144 per million. All age groups can be affected but the most common onset is between 30 and 50 years. More women than men are affected.
- **Secondary insufficiency** - bearing in mind the many factors that can lead to suppression of the hypothalamic-pituitary axis (of which the most common is exogenous steroid use) it is not surprising that this is a relatively common condition. Estimated prevalence is 150-280 per million, with women more affected than men and a peak age of onset between 50 and 60 years.

Aetiology

Addison's disease is the term used to describe primary adrenal insufficiency but it can have many causes. In Western Europe, 85% of cases of Addison's disease now have an autoimmune basis. Tuberculosis (TB) was the most common cause in the first half of the 20th century and remains a common cause elsewhere in the world.

Autoimmune adrenal destruction is isolated in 40% of cases, and part of an autoimmune polyendocrinopathy syndrome in 60%. There is progressive destruction of the adrenal glands via immune mechanisms. Antibodies against steroid 21-hydroxylase can be found in about 85% of patients. Clinical and biochemical insufficiency only occurs once >90% of the gland is destroyed.

Administration of exogenous steroids is the most common cause of secondary insufficiency.
Causes of adrenal insufficiency

Primary adrenal insufficiency

**Anatomic destruction of the gland (acute or chronic):**
- Addison's disease (autoimmune; 85% of cases).
- Surgical removal.
- Trauma.
- Infections - eg, tuberculosis (TB), histoplasmosis, cryptococcosis, HIV, syphilis.
- Haemorrhage - eg, anticoagulants, Waterhouse-Friderichsen syndrome.
- Infection - eg, antiphospholipid syndrome.
- Invasion - eg, neoplastic, sarcoidosis, amyloidosis, haemachromatosis.

**Hypothalamic-related:**
- Congenital.
- Corticotropin-releasing hormone (CRH) deficiency.
- Trauma - eg, fracture of the skull base.
- Radiotherapy.
- Surgery.
- Neoplasm, primary or metastatic.
- Infiltration or infection - eg, sarcoidosis, haemachromatosis, lymphocytic hypophysitis, TB, meningitis.

**Metabolic failure in hormone production:**
- Congenital adrenal hyperplasia - eg, 21-hydroxylase deficiency, 3-beta-hydroxysteroid dehydrogenase deficiency, lipoid hyperplasia.
- Enzyme inhibition - eg, ketoconazole, fluconazole, etomidate and metapyrone.
- Accelerated hepatic metabolism of cortisol - eg, phenytoin, barbiturates, rifampicin.
- Adrenocorticotropic hormone (ACTH) or glucocorticoid resistance.
- Cytotoxic agents.

**Other causes:**
- ACTH-blocking antibodies.
- Mutation in ACTH receptor gene.
- Adrenal hypoplasia congenita.
- Familial adrenal insufficiency.
- Metabolic disorders - eg, Smith-Lemli-Opitz syndrome, Wolman's disease, adrenal leukodystrophy.
- Mitochondrial disorders - eg, Kearns-Sayre syndrome.

Secondary adrenal insufficiency

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Children and adrenal insufficiency

- Adrenal insufficiency is rare in children.
- Presentation is nonspecific and thus there is often delay in diagnosis.
- The most common causes are congenital adrenal hyperplasia (72% of cases), adrenoleukodystrophy (15% of cases) and autoimmune adrenalitis (13% of cases). [4]

See separate Congenital Adrenal Hyperplasia article for more details.

AIDS patients [5]

- Can have cytomegalovirus (CMV) necrotising adrenalitis; also, *Mycobacterium avium-intracellulare* and cryptococcal infection.
- Adrenal tests are commonly abnormal in patients with HIV.
- These abnormalities may be due to drug interactions - eg, phenytoin, ketoconazole.

Critically ill patients [2, 6, 7]

- Patients who are critically ill are increasingly recognised to be at risk of adrenal dysfunction. It is also known as critical illness-related corticosteroid insufficiency (CIRCI). [8]
- Conditions where adrenal insufficiency may occur include:
  - Sepsis.
  - Severe pneumonia.
  - Adult respiratory stress syndrome (ARDS).
  - Trauma.
  - HIV infection.
  - After treatment with etomidate.

- The pathophysiology of this is not yet clear. It involves reduction in the production of glucocorticoids as well as reduced effect.
- Diagnosis should be suspected in critically ill people who do not respond to measures to treat hypotension, particularly where sepsis is present.
- Diagnosis is by cortisol levels either with or without prior administration of corticotropin.
- A trial of steroids may be indicated, but has only been proven to be beneficial in those with septic shock and ARDS.
Diagnosis is often difficult and delayed if symptoms are mild and nonspecific.

Presentation in part depends on the rapidity of loss of adrenal function:

- **Acute**: presentation may be as a crisis precipitated by infection, surgery or trauma. In these situations, features include hypotension, hypovolaemic shock, acute abdominal pain, low-grade fever and vomiting. Sudden onset of insufficiency, such as the Waterhouse-Friderichsen syndrome (infarction secondary to septicaemia - eg, meningococcal) presents with collapse and shock.
- **Chronic**: symptoms develop insidiously and may be mild.

Persistent nonspecific symptoms which should provoke consideration of a diagnosis of adrenal insufficiency include:

- Fatigue and weakness (common feature).
- Anorexia.
- Nausea.
- Vomiting.
- Weight loss.
- Abdominal pain.
- Diarrhoea.
- Constipation.
- Cravings for salt and salty foods such as soy sauce or liquorice (primary insufficiency).
- Muscle cramps and joint pains.
- Syncope or dizziness (due to hypotension).
- Confusion.
- Personality change.
- Irritability.
- Loss of pubic or axillary hair in women, delayed puberty in children.

**Signs**

- Hyperpigmentation - look at buccal mucosa, lips, palmar creases, new scars and in areas subject to pressure such as elbows, knuckles and knees. (Not present in secondary adrenal insufficiency.)
- Hypotension.
- Postural hypotension.

Other situations which should provoke consideration of Addison's disease include:

- People with hypothyroidism in whom symptoms get worse when thyroxine treatment is commenced.
- Unexplained recurrent episodes of hypoglycaemia in people with type 1 diabetes. (Hypoglycaemia can be the presenting symptom in children.)
- Presence of other autoimmune diseases.
- Low sodium and high potassium levels. (Not necessarily present but common in established Addison's disease.)

**Investigations**

In the early period of adrenal insufficiency, investigations may be normal; however, patients have no reserve when faced with stress.

**Laboratory abnormalities in adrenal insufficiency**

- **Sodium**: reduced in 90% of newly diagnosed cases of primary adrenal insufficiency.
- **Potassium**: raised in 50% of newly diagnosed cases of primary adrenal insufficiency.
- **Calcium**: raised in 10-20% of newly diagnosed cases of primary adrenal insufficiency.
- **FBC**: there may be anaemia, mild eosinophilia and lymphocytosis.
- **Glucose**: often low in children.
- **LFTs**: may be raised liver transaminases.
- **Cortisol**: usually reduced:
  - Levels are highest between 8 am and 9 am when blood test should be taken.
  - Specialist advice should be sought in interpreting results for people on shift work (diurnal variation may be altered), people taking oestrogen (can increase cortisol-binding globulin production by the liver), pregnant women and people on long-term steroids.
  - Different assays are used so refer to local reference ranges. Generally levels of <100 nmol/L should prompt urgent investigation or admission, and levels of 100-500 nmol/L require referral to an endocrinologist for further investigation.
  - Salivary cortisol has been used for diagnosis, but not yet fully validated.

- **ACTH** (also known as corticotropin) - when measured together with cortisol allows differentiation of primary vs secondary insufficiency:
  - Levels are raised in primary insufficiency.
  - Levels are low or low normal in secondary insufficiency.
- Plasma **renin and aldosterone levels** - will give an indication of mineralocorticoid activity. (Renin is often high and aldosterone low in Addison’s disease. Usually unaffected in secondary insufficiency.)

**Other investigations**
- An ACTH stimulation (Synacthen®) test may be required to confirm the diagnosis. ACTH is administered IV or IM, and cortisol levels subsequently measured. The normal response is a rise in cortisol level; in adrenal insufficiency this does not occur.
- An insulin tolerance test is occasionally used to confirm a diagnosis of secondary adrenal insufficiency - hypoglycaemia is induced by an insulin infusion and the cortisol response is monitored; this is not regularly performed due to safety issues.
- Investigations are required to establish the cause of the adrenal malfunction, as this will obviously influence management. This will depend on presentation, and whether it appears to be a primary or secondary insufficiency, but may include:
  - Adrenal autoantibodies - if negative, consider investigating for other causes (eg, TB).
  - CXR - to exclude lung neoplasms.
  - Abdominal X-ray - any adrenal calcification which may indicate previous TB infection.
  - CT scan of the adrenal glands if autoantibodies are negative.
  - MRI scan of hypothalamus and pituitary where central causes of adrenal insufficiency are suspected.
  - Tests of other hormones of the hypothalamic-pituitary axis - eg, TSH, prolactin, FSH/LH.
  - Screening for adrenoleukodystrophy (males only, X-linked condition) by measuring very long-chain fatty acids in a serum sample.

**Associated diseases**[^10]

Because most cases of primary adrenal insufficiency are autoimmune in origin, comorbidity with other autoimmune conditions is common. Other autoimmune illnesses which may also be present include thyroid disorders, diabetes mellitus, pernicious anaemia, vitiligo and premature ovarian failure. In these patients it is important to consider the possibility of polyglandular autoimmune syndromes. In these conditions, Addison’s disease is predominant. At least 40-50% of those with Addison’s disease will develop an associated endocrine abnormality.[^11]

<table>
<thead>
<tr>
<th>Polyglandular autoimmune syndrome[^1, 12]</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset:</strong></td>
<td>Children.</td>
<td>Childhood to adult.</td>
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<tr>
<td><strong>Prevalence:</strong></td>
<td>Rare.</td>
<td>More common than type 1.</td>
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<tr>
<td><strong>Main features:</strong></td>
<td>Triad of the following:</td>
<td>Autoimmune adrenal insufficiency and:</td>
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<tr>
<td></td>
<td>Adrenal insufficiency.</td>
<td>Autoimmune thyroid disease; and/or</td>
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<tr>
<td></td>
<td>Chronic hypoparathyroidism.</td>
<td>Type 1 diabetes mellitus.</td>
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<td></td>
<td>Chronic candidiasis.</td>
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<tr>
<td><strong>Other features:</strong></td>
<td>Include:</td>
<td></td>
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<tr>
<td></td>
<td>Type 1 diabetes mellitus.</td>
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<td></td>
<td>Pernicious anaemia.</td>
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<td></td>
<td>Thyroid disorders.</td>
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<td></td>
<td>Immunoglobulin A deficiency.</td>
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<td>Chronic active hepatitis.</td>
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<td></td>
<td>Alopecia.</td>
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<td>Vitiligo.</td>
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<td>Keratoconjunctivitis.</td>
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<td>Chronic atopic dermatitis.</td>
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<td></td>
<td>Hypogonadism.</td>
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<td>Premature ovarian deficiency.</td>
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<td></td>
<td></td>
<td>Vitiligo.</td>
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<tr>
<td></td>
<td></td>
<td>Chronic atopich gastritis and vitamin B12 deficiency.</td>
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<td></td>
<td></td>
<td>Coeliac disease.</td>
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<tr>
<td></td>
<td></td>
<td>Hypoparathyroidism.</td>
</tr>
<tr>
<td><strong>Inheritance:</strong></td>
<td>Autosomal recessive.</td>
<td>Complex genetic factors. Links to HLA DR3 and DR4.</td>
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**Management[^1, 2]**

Initiation and adjustment of treatment is done by an endocrinologist, but patients need to be educated about managing their condition and repeat prescriptions and changes during intercurrent illness will involve GPs.

**Patient education**
- Information about the condition.
- Medical emergency identification bracelet or similar.
- Steroid card.
Importance of not missing steroids and not stopping them abruptly.
Intercurrent illness - if tolerating oral medication then the dose should be doubled until better. If the patient is so unwell that they are unable to take the medication orally then they will need to take it parenterally - thus, they will need to be given IM hydrocortisone and be taught how to administer it.
Seek medical help if requiring parenteral therapy.
Medication is free of charge in the UK, via application by medical exemption form FP92A.
Advice for travel - carrying extra medication, and an emergency self-injection kit, along with specific instructions. The Addison's disease self-help group website offers a proforma for a letter to carry when travelling.\[13\]

Hormone replacement
Both glucocorticoid and mineralocorticoid replacement are required.

- **Glucocorticoid replacement** - hydrocortisone is the mainstay of treatment; usually 15-30 mg in three divided doses with the highest dose in the morning (thus stimulating the normal diurnal adrenal rhythm). Twice daily regimens are also used, although opinion on their benefit varies. A modified-release once-daily preparation is also now available and licensed for use, and is still being evaluated.
- During minor illness or minor surgery, glucocorticoid doses may be increased up to three times their normal dose to avoid adrenal crisis, and up to ten times for major illness or major surgery.
- If there is co-existent thyroid deficiency then thyroid hormones should not be replaced before glucocorticoids, as a crisis may be precipitated.

- **Mineralocorticoid replacement** - this is usually required in primary adrenal insufficiency. Fludrocortisone is used and the usual adult dose is 50-300 micrograms per day, depending on activity levels, weight and metabolism.
- Assessing adequacy of therapy involves monitoring symptoms and signs, measuring blood pressure and looking for postural hypotension and normalising of serum electrolytes (Na and K).
  - Signs of over-replacement include raised blood pressure, thin skin, striae, easy bruising, glucose intolerance, hyperglycaemia and electrolyte abnormalities.
  - Signs of under-replacement are the symptoms of Addison's disease persisting, ie fatigue, postural hypotension, nausea, weight loss, and salt craving.

Ongoing monitoring
History and examination should occur at least annually to ascertain whether therapy is adequate. This should include:

- Questions about symptoms - eg, energy and appetite.
- Checking understanding regarding increasing dose of steroids during intercurrent illness and when to seek medical advice.
- Weight.
- Blood pressure - sitting and standing.
- Examination of skin for pigmentation.
- Blood tests for electrolytes.

Because of the high incidence of other autoimmune disease, those with an autoimmune cause should be screened annually with:

- TFTs.
- Glucose and Hba1c.
- FBC.
- Vitamin B12.
- Coeliac screen if symptoms suggest.

Management of adrenal crisis
This is covered in the separate article Adrenal Crisis.

Management involves admission to hospital, often to a critical care unit for intensive monitoring. The condition is managed with high-dose hydrocortisone parenterally and IV fluids.

People treated for adrenal insufficiency should be prescribed, and shown how to use, an emergency hydrocortisone self-injection kit, particularly for use when travelling or when medical care is not immediately available.

Complications\[1\]

- Adrenal crisis. Despite being preventable, this is common. In one study across four countries, 8% of people with Addison's disease surveyed had annual admissions for adrenal crisis.\[14\] If not promptly treated, adrenal crisis can be fatal.
- Reduced quality of life. This is caused by ongoing symptoms of fatigue, causing an inability to manage normal daily activities including work. Loss of libido and recurrent admissions for adrenal crisis may contribute.
- Osteoporosis. On lower doses of hydrocortisone, this should not be a risk, but may occur when other steroids or regular high doses are required for management. It is also possible that low adrenal androgen levels may increase the risk of osteoporosis. Studies have contradictory findings.\[15\]
Prognosis

Untreated, adrenal insufficiency is fatal, and indeed this was invariably the case until the advent of synthetic cortisone in 1949. Treatment of Addison's disease is lifelong. The prognosis for any patient with adrenal insufficiency will depend on the underlying cause. In those patients in whom the prognosis is not affected by the underlying pathology, replacement therapy should result in a return to health. However, a Norwegian study found an excess of mortality in patients diagnosed with Addison's disease at a young age, associated with acute adrenal failure, infection and sudden death. [16]

History

Thomas Addison (1793-1860) first described the syndrome in 1855. He was a student of medicine in Edinburgh (1812-1815) and went on to be one of the three 'giants' of Guy's Hospital (together with Richard Bright (1789-1858) and Thomas Hodgkin (1798-1866)). Life-saving replacement therapy only became available following the synthesis of cortisone (Kendall, Sarett and Reichstein in 1949).

Further reading & references


1. Addison's disease; NICE CKS, May 2014 (UK access only)
13. Addison's Disease Self Help Group

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