# Diagnosis and management of adrenal insufficiency

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ABSTRACT

**Adrenal insufficiency is the inadequate secretion of glucocorticoid and/or mineralocorticoid secretion from the adrenal cortex. Primary adrenal insufficiency is the result of failure of the adrenal gland and secondary adrenal insufficiency is due to a lack of stimulation via pituitary adrenocorticotropic hormone or hypothalamic corticotropin-releasing hormone. Adrenal insufficiency may cause non-specific symptoms. Early detection and testing based on clinical suspicion may prevent subsequent presentation with adrenal crisis. Once identified, a low baseline cortisol (often <100 nmol/L) alongside raised adrenocorticotropic hormone (ACTH) can be enough to diagnose primary adrenal insufficiency. However, confirmatory testing can be done using the cosyntopin (Synacthen®) stimulation test or the insulin tolerance test, which is the gold standard for secondary adrenal insufficiency. The underlying cause of adrenal insufficiency can often be identified via a strategic approach to investigation. Adrenal crisis is a life-threatening medical emergency which must be treated immediately if there is strong clinical suspicion with fluids and corticosteroids otherwise can be fatal. Patients must be educated and empowered to take control of their own medical management.**

## Introduction

Adrenal insufficiency is characterised by inadequate secretion of glucocorticoid and/or mineralocorticoid secretion from the adrenal cortex. This can be classified as primary adrenal insufficiency, due to failure of the adrenal gland itself, or secondary, due to a lack of stimulation via pituitary adrenocorticotropic hormone (ACTH) or hypothalamic corticotropin-releasing hormone (CRH). Glucocorticoid production is regulated via negative feedback within the hypothalamo–pituitary–adrenal (HPA) axis, whereas mineralocorticoid production is mainly stimulated by the renin–angiotensin–aldosterone system and plasma potassium levels.

The prevalence of primary adrenal insufficiency is estimated to be 93–140 per million. In the Western world, autoimmune adrenalitis accounts for more than 70% of all cases of primary adrenal insufficiency. Secondary adrenal insufficiency is more common than primary, with a prevalence rate of 150–280 per million.[1,2] It has been suggested that exogenous glucocorticoid use is the most common cause of secondary adrenal insufficiency with up to 2.5% of the population taking them for inflammatory or immune-mediated conditions. This leaves them vulnerable to steroid deficiency if the medication is stopped suddenly.[3]

Regardless of the cause, adrenal insufficiency was invariably fatal until 1949, when cortisone was first synthesised and glucocorticoid replacement treatment became available. Despite this breakthrough, the diagnosis and management of patients with these disorders remains challenging and is often delayed, resulting in a presentation with adrenal crisis.[4] Clinical

### Key points

Adrenal crisis is an endocrine emergency associated with increased mortality and morbidity. Therefore, appropriate early treatment is fundamental, without any delay while waiting for the diagnosis confirmation.

Adrenal insufficiency may cause non-specific symptoms. Early detection and testing based on clinical suspicion may prevent subsequent presentation with adrenal crisis.

The underlying cause of adrenal insufficiency can often be identified via a strategic approach to investigation and helps determine long-term follow up/screening for associated conditions.

Patient education is paramount in the management of adrenal insufficiency and patients need to be empowered to take control of their own medical management. All patients should be equipped with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat adrenal crisis and the need of immediate parenteral steroid treatment in the event of an emergency.

Patients taking 5 mg prednisolone or equivalent for longer than 4 weeks are at risk of HPA axis suppression and adrenal crisis if physiologically stressed.

**KEYWORDS:** Adrenal insufficiency, adrenal crisis, glucocorticoid, pituitary

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**Box 1. Clinical presentation of acute adrenal insufficiency**

**Symptoms**
- Abdominal pain
- Nausea
- Myalgia
- Weight loss
- Fatigue
- Dizziness

**On examination**
- Hypotension/shock
- Fever
- Skin hyperpigmentation (primary adrenal insufficiency only)

**Biochemistry**
- Hyponatraemia
- Hyperkalaemia
- ↑Urea
- Metabolic acidosis
- ↑TSH
- Hypercalcaemia (uncommon)
- Hypoglycaemia (more common in children)
- Lymphocytosis
- Eosinophilia

presentation of acute adrenal insufficiency (adrenal crisis) is characterised by the findings listed in Box 1. Many patients report a longer history with a more insidious onset of symptoms including fatigue, reduced strength, anorexia and weight loss. Investigation should be considered in these circumstances.

## Causes of adrenal insufficiency

Adrenal insufficiency can be genetic or non-genetic in aetiology. Genetic causes can be sporadic or inherited and may present as part of a wider syndrome. They tend to present early in life, but some may also manifest atypically in adolescence or early adulthood. Non-genetic causes include autoimmune, neoplastic, infective, infiltrative and vascular diseases, which are summarised in Box 2. Knowledge of the underlying cause is important to allow holistic treatment and screening for other associated features, such in autoimmune polyendocrine syndromes (APS).

## Diagnosis of adrenal insufficiency

Once suspected, testing is carried out to confirm adrenal failure and then further investigations are required to determine the aetiology. In adrenal crisis, diagnostic tests should never delay hydrocortisone treatment; formal diagnosis may be take place after clinical recovery. In many cases a low baseline cortisol (often <100 nmol/L) alongside raised ACTH can be enough to diagnose primary adrenal insufficiency.

### Confirming the diagnosis

Cosyntropin stimulation testing can be used to confirm the diagnosis. It is a measure of adrenal reserve and the HPA axis. Serum cortisol is collected at baseline and 30 or 60 minutes after cosyntopin (Synacthen®) 250 microgram (IV or IM) injection.

**Box 2. Causes of adrenal insufficiency**

**Primary adrenal insufficiency**
- **Autoimmune:** Isolated adrenal insufficiency (Addison's), APS1 (adrenal insufficiency + hypoparathyroidism + mucocutaenous candidiasis), APS2 (adrenal insufficiency + thyroid disease [Schmidt's syndrome] + Type 1 diabetes [Carpenter's syndrome])
- **Infections:** Tuberculosis, fungal infiltration, AIDS
- **Genetic:** Adrenoleukodystrophy, congenital adrenal hyperplasia, adrenal hypoplasia congenita
- **Vascular:** Adrenal infarction / haemorrhage (Waterhouse-Friedrichson syndrome in meningococcal sepsis)
- **Infiltrative:** Metastasis, lymphoma, sarcoidosis, amyloidosis, haemachromatosis
- **Iatrogenic:** Surgical adrenalectomy or drug induced (eg mitotate, etomidate, ketoconazole, immunotherapy)

**Secondary adrenal insufficiency**
- **Tumour:** Pituitary macroadenoma, other tumour (craniopharyngioma, meningioma)
- **Iatrogenic:** Pituitary irradiation, drugs (opioids, glucocorticoids, immunotherapy)
- **Vascular:** Apoplexy, Sheehan's syndrome
- **Infiltrative:** Tuberculosis, sarcoidosis, histiocytosis X, granulomatosis with polyangiitis, lymphocytic hypophysitis
- **Trauma**
- **Genetic**

APS = autoimmune polyendocrine syndromes.

Concerns have been raised about false positive diagnoses of adrenal insufficiency if relying on 30-minute cortisol values in isolation and clinical judgement is required when interpreting the results, taking into account pre-test probability.[5,6] This can be used to determine primary adrenal insufficiency and secondary pituitary causes which lead to adrenal atrophy because of inadequate ACTH production. It is important to note that this test is not reliable in diagnosing secondary adrenal insufficiency within 2 weeks of pituitary surgery. Baseline ACTH helps to differentiate between primary and secondary adrenal insufficiency. In sepsis or severe illness, the interpretation of cortisol levels should take into account the underlying stress.

Insulin tolerance test is the gold standard for identifying secondary adrenal insufficiency, if suspected. However, its use is limited as it is contraindicated in those with heart disease, seizures or severe hypothyroidism and in those with baseline cortisol <100 nmol/L. Alternatives include glucagon stimulation test or metyrapone suppression test.

Prior to any of these tests certain, medications should be withheld. Oral oestrogen should be discontinued 6 weeks beforehand. No oral steroid medications should be administered 24 hours prior to the test. Steroid creams and inhalers should ideally also be avoided if possible.

## Identifying a causative aetiology

### Medication review

For patients taking topical, intra-articular or oral corticosteroid medications, secondary adrenal insufficiency is the most likely diagnosis.


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### Measurement of 21-hydroylase autoantibodies

In primary adrenal insufficiency, high 21-hydroxylase autoantibody titres indicate autoimmune adrenalitis (Addison's disease). If positive, patients should be screened for other related conditions such as autoimmune thyroid disease, coeliac disease, pernicious anaemia and type 1 diabetes. If neither family history nor antibody titre suggest autoimmune aetiology, additional testing is needed. Some patients become antibody-negative once autoimmune damage progresses; thus testing may prove negative later in the disease course and a negative result does not exclude autoimmune adrenal failure.

### Adrenal imaging

Antibody-negative patients benefit from adrenal imaging. This may indicate infiltration, infection, or hematoma/haemorrhage. Bilateral solid organs metastases may cause adrenal insufficiency, so further relevant imaging may be warranted in the presence of an adrenal mass. If adrenal imaging is negative infiltration should still be considered and further tests organised dependent on clinical suspicion.

### Pituitary testing for secondary adrenal insufficiency

In secondary adrenal insufficiency, a pituitary hormone profile (IGF-1, LH, FSH, TSH, free T4, prolactin, testosterone or oestradiol) should be assessed looking for other hormone deficiency or excess. A pituitary MRI scan should be organised to confirm or exclude a structural cause of secondary adrenal insufficiency (eg tumour, infiltration, apoplexy).

## Management of adrenal insufficiency

### Adrenal crisis

This is a life-threatening emergency which must be treated immediately if there is strong clinical suspicion, rather than waiting for confirmatory test results. Bloods should be taken urgently for electrolytes, glucose in addition to cortisol and ACTH.

Fluid:

- Resuscitate with 0.9 % normal saline. Often 4–6 L is required in the first 24–48 hours to reverse volume depletion and sodium deficiency. However, fluid should be replaced cautiously where there has been chronic hyponatraemia. If plasma sodium is <120 mmol/L at presentation, aim to correct by no more than 10 mmol/L in the first 24 hours to avoid central pontine myelinolysis.

Glucocorticoid:

- Bolus dose of intravenous 100 mg hydrocortisone followed by 50 mg IM or IV 6-hourly for 24–48 hours until the patient can take oral therapy. Alternatively, a 200 mg/24h continuous infusion may be used after the initial bolus dose.
- Specific mineralocorticoid replacement is not required in acute setting as the high dose of glucocorticoid has sufficient mineralocorticoid effects (40 mg hydrocortisone equivalent to 100 microgram fludrocortisone).
- Dexamethasone is not a suitable replacement glucocorticoid as it lacks mineralocorticoid activity.

Following initial treatment with fluid and glucocorticoid, it is necessary to investigate and treat the precipitant.

### Long-term treatment

#### *Glucocorticoid replacement*

Hydrocortisone is the treatment of choice for replacement therapy, as it is reliably and predictably absorbed and allows biochemical monitoring of levels. It is administered three times a day (or occasionally twice daily), eg 10 mg immediately on waking, 5 mg at midday, and 5 mg at teatime, or 15 mg on waking and 5 mg at midday. Try to avoid giving this too late as it may cause insomnia.

#### *Mineralocorticoid replacement*

Fludrocortisone is required in primary adrenal insufficiency and given at a dose of 100–150 micrograms daily. Adjust both hydrocortisone and mineralocorticoid dose on clinical grounds. If there is a poor response, suspect an associated autoimmune disease (thyroid, type 1 diabetes, coeliac disease, myasthenia gravis).

#### *Annual assessment*

**Clinical** – Be mindful for signs of glucocorticoid excess, eg weight gain, hypertension or poor glycaemic control. Hypertension and oedema may suggest excessive mineralocorticoid replacement, whereas postural hypotension and salt craving suggest insufficient treatment. Timing of glucocorticoid doses may need varying if patients describe symptoms of insufficiency at certain points in the day.

**Biochemical** – Cortisol day curves (salivary cortisone or serum cortisol) can be used to assess glucocorticoid adequacy if there are concerns about frequent crisis or symptoms despite adequate dosing regimes. Patients who have autoimmune adrenal disease should be screened for other manifestations of commonly associated autoimmune diseases.

**Prevention** – annual influenza vaccination should be offered and pneumococcal vaccination for those age >60.

### Special circumstances

**Pregnancy** – Cortisol rises during the third trimester so patients with adrenal insufficiency may require dose increases. Progesterone has anti-mineralocorticoid effects so some also need an increase in fludrocortisone.[7]

**Drug interactions** – CYP3A4 enzyme inducers may reduce cortisol availability, necessitating in higher or more frequent dosing regimens.

**Steroid withdrawal in secondary adrenal insufficiency due to exogenous steroids** – Patients taking 5 mg or more of prednisolone for more than 4 weeks are at risk of HPA axis suppression and secondary adrenal insufficiency. Many of these patients will be able to recover adrenal function with slow tapering of glucocorticoid dose, either using prednisolone or hydrocortisone. Patients may require further short cosyntopin tests over time to confirm whether adrenal insufficiency persists. Use of salivary cortisone assays to guide steroid weaning may prove useful and more convenient as a measure in future.[8]

## Patient and healthcare professional education

Mortality is increased in patients with adrenal failure and often this relates to episodes of adrenal crisis. Education of both patients

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### Box 3. Sick day rules

- For moderate illness (eg fever, infection requiring antibiotics, surgical procedure under local anaesthetic), usual oral steroid dose can be doubled up. In patients with suspected or proven COVID-19 infection, high doses of gluccocorticoid supplementation (equivalent to hydrocortisone 20 mg four times daily) should be used.
- To cover severe illness, eg persistent vomiting, pneumonia, trauma or acute surgery, patients should receive an initial bolus of 100 mg IV hydrocortisone followed by 50 mg (IM or IV) hydrocortisone 6-hourly or 200 mg / 24 hour IV infusion until resolution of the illness.
- For moderate elective procedures or investigations, eg endoscopy or angiography, patients should receive a single dose of 100 mg hydrocortisone before the procedure.

and healthcare professionals regarding steroid safety is perhaps the single intervention most likely to reduce the incidence of adrenal crisis in those with established adrenal insufficiency. Cortisol requirements increase during severe illness or surgery and delay in getting appropriate treatment can be life-threatening. Patients should be taught never to miss a dose and to follow 'sick day rules' when unwell (Box 3). All patients should be provided with a steroid emergency card (www.endocrinology.org/adrenal-crisis) or encouraged to wear a medical alert identifier. ■

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