

SOCIETY FOR ENDOCRINOLOGY
ENDOCRINE EMERGENCY GUIDANCE

Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients

Wiebke Arlt^{1,2} and the Society for Endocrinology Clinical Committee³

¹Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

²Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK

³The Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol, UK

Correspondence
should be addressed
to W Arlt
Email
w.arlt@bham.ac.uk

Introduction

Acute adrenal insufficiency, also termed **adrenal crisis**, is a life-threatening endocrine emergency brought about by a lack of production of the adrenal hormone cortisol, the major glucocorticoid. Identifying patients at risk and prompt management can save lives. This guideline aims to take the non-specialist through the initial phase of assessment and management.

Underlying conditions

Primary adrenal insufficiency is caused by loss of function of the adrenal gland itself, for example due to autoimmune-mediated destruction of adrenocortical tissue or surgical removal of the adrenal glands or due to inborn disruption of adrenal cortisol production in congenital adrenal hyperplasia.

Secondary adrenal insufficiency is caused if the regulation of adrenal cortisol production by the pituitary is compromised, this can be the consequence of tumours in the hypothalamic–pituitary area. However, pituitary regulation of cortisol production is also switched off in patients who receive **chronic exogenous glucocorticoid treatment** with doses ≥ 5 mg prednisolone equivalent for more than 4 weeks. This may also be caused by long-lasting glucocorticoid injections into joints or chronic application of glucocorticoid cream or inhalers.

In primary adrenal insufficiency cortisol deficiency is aggravated by a lack of adrenal aldosterone production,

a hormone important for blood pressure and electrolyte regulation. This puts primary adrenal insufficiency patients at a somewhat higher risk of adrenal crisis.

Clinical presentation

Clinical signs and symptoms:

- Fatigue, lack of energy, weight loss
- Low blood pressure, postural dizziness and hypotension (≥ 20 mmHg drop in BP from supine to standing position), dizziness, collapse, in severe cases hypovolaemic shock
- Abdominal pain, tenderness and guarding, nausea, vomiting (in particular in primary adrenal insufficiency), history of weight loss
- Fever
- Confusion, somnolence, in severe cases delirium or coma
- Back and leg cramps/spasms are commonly reported and can be distracting if not recognised for what they are (electrolyte derangement in large muscles?)
- In **primary** adrenal insufficiency: generalised skin hyperpigmentation, in particular in areas exposed to mechanical shear stress (palmar creases, nipples, scars, inside of oral mucosa)
- In **secondary** adrenal insufficiency: alabaster-like, pale skin; dependent on underlying conditions also signs and symptoms of other pituitary axis deficiencies



Lab findings:

- Hyponatraemia (in primary and secondary adrenal insufficiency)
- Hyperkalaemia (in primary adrenal insufficiency)
- Pre-renal failure (increased serum creatinine due to hypovolaemia)
- Normochromic anaemia, sometimes also lymphocytosis and eosinophilia
- Hypoglycaemia (primarily in affected children; can cause long-term neurological deficits, if not promptly treated)

Investigations for suspected adrenal crisis in patients not already known to have adrenal failure

- **Adrenal insufficiency should be ruled out in any acutely ill patient with signs or symptoms potentially suggestive of acute adrenal insufficiency**
- **Assess blood pressure and fluid balance status;** if clinically feasible, measure blood pressure from supine to standing to check for postural drop
- **Take drug history (glucocorticoids?)**
- **Bloods:**
 - Sodium, potassium, urea, creatinine
 - Full blood counts
 - TSH, fT₄ (hyperthyroidism can trigger adrenal crisis; acute adrenal insufficiency can increase TSH due to loss of inhibitory control of TRH release, do not replace with thyroxine if TSH ≤ 10 mU/L)
 - **Paired serum cortisol and plasma ACTH**
- **Diagnostic measures should never delay prompt treatment of a suspected adrenal crisis!** There are no adverse consequences of initiating life-saving hydrocortisone treatment and diagnosis can be safely and formally established once the patient has clinically recovered
- If the patient is haemodynamically stable, consider performing a **short Synacthen test** (serum cortisol at baseline and 30 min after i.v. injection of 250 micrograms ACTH_{1–24}); however, if the patient is severely ill, confirmation of diagnosis can be safely left until after clinical recovery following implementation of emergency dose hydrocortisone treatment
- Serum/plasma aldosterone and plasma renin (aldosterone will be low and renin high in primary adrenal

insufficiency; observe special sample collection and transport conditions; can be left to confirmation of diagnosis after clinical recovery)

Management of adrenal crisis

- **Hydrocortisone (immediate bolus injection of 100 mg hydrocortisone i.v. or i.m. followed by continuous intravenous infusion of 200 mg hydrocortisone per 24 h** (alternatively 50 mg hydrocortisone per i.v. or i.m. Injection every 6 h)
- **Rehydration with rapid intravenous infusion of 1000 mL of isotonic saline infusion** within the first hour, followed by further intravenous rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients)
- **Contact an endocrinologist** for urgent review of the patient, advice on further tapering of hydrocortisone, investigation of the underlying cause of disease including diagnosis of primary vs secondary adrenal insufficiency
- Tapering of hydrocortisone can be started after clinical recovery guided by an endocrinologist. In patients with primary adrenal insufficiency, mineralocorticoid replacement needs to be initiated (starting dose 100 micrograms fludrocortisone once daily) as soon as the daily glucocorticoid dose is below 50 mg hydrocortisone/24 h

Precipitating factors

- In more than half of patients with adrenal insufficiency the diagnosis of adrenal failure is only established after presentation with an acute adrenal crisis
- However, patients with established adrenal insufficiency and those receiving chronic exogenous supraphysiological glucocorticoid treatment (e.g. for asthma or autoimmune disease) are at permanent risk of adrenal crisis. Most frequent causes are:
 - Chronic glucocorticoid intake is suddenly stopped
 - Failure to observe **Sick Day Rule 1:** the need to double daily oral glucocorticoid dose during intercurrent illness with fever that requires bed rest and/or antibiotics
 - Failure to observe **Sick Day Rule 2:** the need to administer glucocorticoids per i.v. or i.m. injection

or iv infusion during prolonged vomiting or diarrhoea, during preparation for colonoscopy or in case of acute trauma or surgery requiring general anaesthesia

times and showing it to any health care professional they are dealing with

- Provide them with emergency phone numbers and contact details for the patient self-help groups

After emergency care: how to prevent an adrenal crisis

- **Regular review of the patient by an endocrinologist**, initially monthly, in the long-term every 6–12 months
- **Education of patients and partner/parents** regarding symptom awareness and the correct adjustment of glucocorticoid replacement dose:
 - **Sick Day Rule 1:** the need to double daily oral glucocorticoid dose during illness with fever that requires bed rest and/or antibiotics
 - Ensure they have an additional supply of hydrocortisone tablets so that they can double their dose for at least 7 days
 - **Sick Day Rule 2:** the need to administer glucocorticoids per i.v. or i.m. injection during prolonged vomiting or diarrhoea, during preparation for colonoscopy or in case of acute trauma or surgery
 - Teach the patient and partner/parents how to self-administer and inject hydrocortisone and provide them with a **Hydrocortisone Emergency Injection kit** (100 mg hydrocortisone sodium succinate for injection; hyperlink to ADSHG and Pit foundation where there are picture tutorials on using this); check regularly that their kit is up to date
- Provide the patient with a **Steroid Emergency Card** www.endocrineconnections.org/adrenal-crisis and encourage them to wear medical alert bracelets, in addition to keeping the steroid emergency card with them at all

Further information

The document should be considered as a guideline only; it is not intended to determine an absolute standard of medical care. The doctors concerned must make the management plan for an individual patient.



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Sources

- 1 Wass JA & Arlt W. How to avoid precipitating an acute adrenal crisis. *British Medical Journal* 2012 **345** e6333. (doi:10.1136/bmj.e6333)
- 2 Husebye ES, Allolio B, Arlt W, Badenhop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting AL, Kasperlik-Zaluska A, *et al.* Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. *Journal of Internal Medicine* 2014 **275** 104–115. (doi:10.1111/joim.12162)
- 3 Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M & Allolio B. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 407–416. (doi:10.1210/jc.2014-3191)
- 4 Bancos I, Hahner S, Tomlinson JW & Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes & Endocrinology* 2015 **3** 216–226.
- 5 Allolio B. Extensive expertise in endocrinology: adrenal crisis. *European Journal of Endocrinology* 2015 **172** R115–R124. (doi:10.1530/eje-14-0824)
- 6 Bornstein S, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye E, Merke DP, Murad MH, Stratakis CA, *et al.* Management of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 364–389. (doi:10.1210/jc.2015-1710)

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