

UNDERSTANDING THE DISEASE



Understanding adrenal crisis

Karin Amrein^{1*} , Gennaro Martucci² and Stefanie Hahner³

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Incidence and mortality

Approximately 5–17 cases of adrenal crisis (AC) occur per 100 patient years in patients with primary or secondary adrenal insufficiency (AI) [1, 2]. The mortality rate is estimated to be between 0.5% and 2%. Norwegian data indicate that overall, 1 in 7 patients with Addison's disease eventually dies from AC. It is estimated that AC will account for 5500–10,600 excess deaths in the European Union in the next decade [3]. Often, these are preventable deaths in relatively young patients in the emergency department (ED) or intensive care unit (ICU) occurring from cardiorespiratory arrest in hypovolemic shock after delayed or insufficient steroid replacement, contributing to the excess mortality in patients at risk.

Adequate treatment of AC using stress-dose intravenous steroids is often delayed, even when AI is known and patients present their emergency card to EDs or retrieval services (European Steroid Emergency Card www.endocrinology.org/adrenal-crisis) [4].

Causes and patients at risk

The main triggers for AC include interruption of glucocorticoid intake, infections, surgery, gastroenteritis, and stress; the most important predictor is a history of AC (OR 2.85) [5, 6].

Primary adrenal insufficiency (PAI) and secondary adrenal insufficiency (SAI) caused by panhypopituitarism or pituitary corticotrophic insufficiency may lead to AC. By far the largest group of patients at risk, however,

are those with chronic steroid medication (up to 3% of the population) who often develop adrenal suppression over time and therefore may not be able to increase their endogenous cortisol levels sufficiently during acute stress/illness [7]. In critically ill patients, more specific causes include Waterhouse–Friderichsen syndrome and hemorrhagic adrenalitis in sepsis/coagulopathy.

PAI may be caused by autoimmune (Addison's disease), surgical, hemorrhagic, ischemic, or metastatic etiology.

SAI is caused by traumatic brain injury, tumors, and hemorrhagic/ischemic lesions of the hypothalamic-pituitary axis but also by chronic glucocorticoid treatment lasting more than 3–4 weeks, even including topical administration such as aerosols for asthma and COPD or creams used for skin problems [8]. The latter category likely represents the largest group of patients in the ICU, when infection triggers only an insufficient increase of cortisol levels because of SAI (e.g., transplant recipients on a glucocorticoid-based immunosuppression, or COPD patients with pneumonia). A novel patient group where AC should always be considered are cancer patients on checkpoint inhibitor immunotherapy (including ipilimumab and nivolumab) that may cause severe hypophysitis or adrenalitis [9]. Moreover, several medications interact with steroid metabolism and may cause AC, including antiepileptic drugs, barbiturates, etomidate, antituberculosis and antifungal drugs (fluconazole, ketoconazole, voriconazole) [10].

*Correspondence: karin.amrein@medunigraz.at

¹ Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria
Full author information is available at the end of the article

ADRENAL CRISIS

Trigger ⇒ Restricted availability of cortisol ⇒ Adrenal Crisis

PATIENTS AT RISK

1. Adrenal OR pituitary insufficiency (e.g. infections, Addison's disease)
2. Adrenalectomy *
3. Chronic corticosteroid therapy
4. Hypophysitis / adrenalitis in cancer patients receiving immuno therapy
5. NEW ONSET of unknown 1.

* in case of bilateral adrenalectomy OR unilateral adrenalectomy for adrenal Cushing's disease (pituitary /adrenal suppression)

TRIGGERS

- Gastrointestinal infection
- Other infection
- Malcompliance
- Stress (physical, emotional)
- Surgery
- Other

SIGNS AND SYMPTOMS

**Major health deterioration
2 or more of the following:**

- Nausea/vomiting
- Fever
- Altered consciousness
- Hypotension < 100mmHg systolic
- Hyponatraemia < 132 mmol/l
- Hyperkalaemia
- Hypoglycaemia
- (Hypercalcaemia)

TREATMENT

**NEVER DELAY FOR DIAGNOSIS
KEEP ONE SERUM SAMPLE BEFORE
TREATMENT
ALWAYS IV WHEN VOMITING OR
DIARRHEA IS PRESENT**

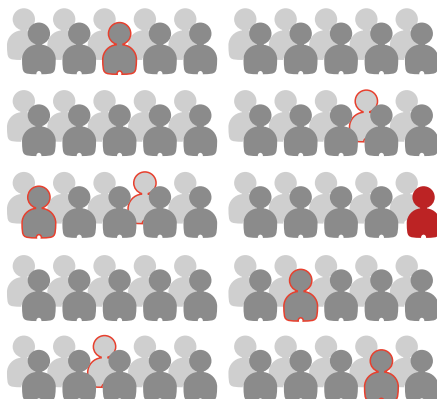
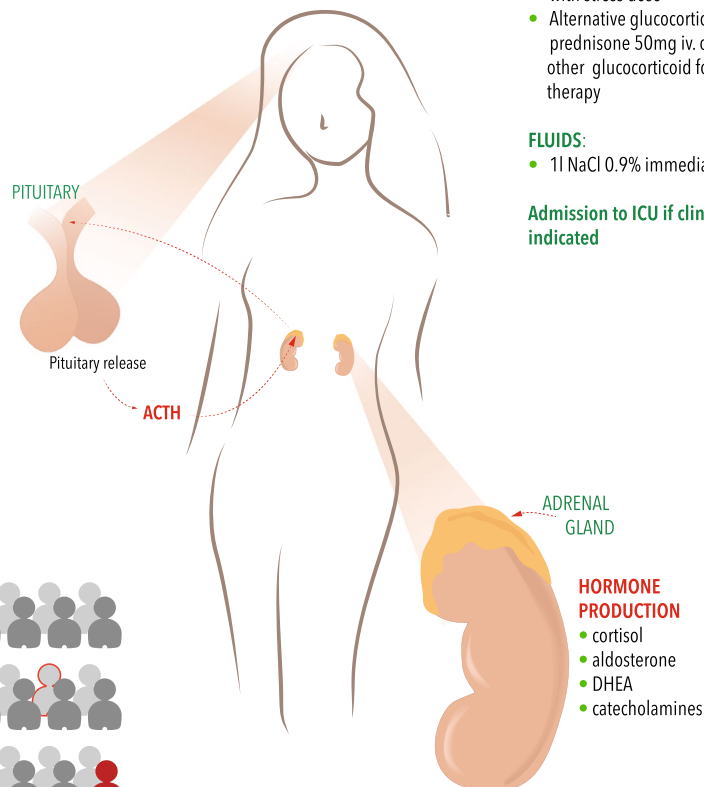
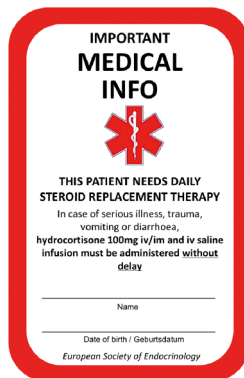
STEROIDS:

- Hydrocortisone 100mg immediately iv., followed by 200mg/24h
- Consider im, io if venous access delayed (not po)
- Mineralocorticoids not necessary with stress dose
- Alternative glucocorticoids: prednisone 50mg iv. or any other glucocorticoid for first-line therapy

FLUIDS:

- 1l NaCl 0.9% immediately

Admission to ICU if clinically indicated



100 people ⇒ 8 adrenal crises ⇒ 1 death per year

Glossary:

- HPA** ... hypothalamic-pituitary-adrenal axis
ACTH ... adrenocorticotropic hormone
DHEA ... dehydroepiandrosterone
im ... intramuscular
io ... intraosseous
po ... peroral

Definition and diagnosis

The definition of AC remains debated, but commonly it is defined as a major acute health deterioration and at least two of the following: hypotension—absolute (systolic blood pressure less than 100 mmHg) or relative (systolic blood pressure reduction greater than 20 mmHg), acute abdominal symptoms, nausea or vomiting, altered mental state, fatigue, fever and laboratory abnormalities (hyponatremia, hyperkalemia, hypoglycemia, rarely hypercalcemia) [11]. In pregnancy, diagnosis of AI is complicated because of endocrine and metabolic changes. AC should be suspected when symptoms are out of proportion in relation to the gestational state and include weight loss, salt-craving, hypoglycemia, and hyponatremia [12].

In the ED or ICU setting, the diagnostic criteria are particularly unsatisfactory, as other serious diseases such as sepsis or cardiogenic shock may well mimic these features or contribute to them, and classic signs (hyperpigmentation in PAI or axillary/pubertic hair loss in SAI) may not be present; consequently the diagnosis may be suspected when there is high suspicion level in the context of an “undifferentiated shock”. The medication history has a pivotal role in this syndrome. Further complicating the picture, relative adrenal insufficiency (RAI) or critical illness related corticosteroid insufficiency (CIRCI) may also be present in the context of severely ill patients with multiple end-organ failure, and in such cases, total cortisol level measurement may not be reliable [13] in a context of altered corticosteroid binding protein release and corticosteroid degradation [14].

If AC is possible, a sample for later cortisol/adrenocorticotropic hormone (ACTH) analysis should be stored but this must never delay treatment. Also, the sensitivity and specificity of total or calculated bioavailable fraction of cortisol are still unknown reflecting the active cellular mediator. The short Synacthen test, a diagnostic tool used under stable conditions (measurement of serum cortisol at baseline and 30 min after i.v. injection of ACTH 250 µg) is of little use in the emergency setting and would unnecessarily delay treatment [15].

Treatment

When recognized, treatment is simple, straightforward, and not different from less severe AC in patients admitted to the ward:

- Rapid infusion of 0.9% saline or balanced solutions.
- Supraphysiologic doses of i.v. hydrocortisone as soon as possible (initially 100 mg followed by 200 mg over 24 h).
- 5% glucose may be needed in case of hypoglycemia.

Above a daily dose of 50 mg hydrocortisone, no additional mineralocorticoid replacement is necessary. Usually, the clinical response is rapid and some authors even include an improvement of hypotension within 1 h in the definition of AC.

Summary and suggestions

More often than not, definitive and timely diagnosis of AC is *not* possible in the ED/ICU because of out-of-hours presentation, unspecific signs/symptoms, and unreliable/unavailable specific laboratory tests.

Given the large number of patients at risk, the poor outcomes when untreated, and the low risk of short-term hydrocortisone treatment in patients without AC, we suggest the following for EDs and ICUs:

- Actively consider AC in all acutely ill patients presenting to the ED or the ICU.
- Use a low therapeutic threshold to give 100 mg hydrocortisone i.v., especially when hypotension and hyponatremia are present.
- If venous access is delayed, use an immediate intraosseous infusion.
- In known PAI or SAI, a “show emergency card-to-steroid injection time” < 15 min should be implemented.
- When an underlying disease is unknown, keep a serum/plasma sample and consult with endocrinology when possible.
- Perform standard testing after complete recovery from critical illness.

Patients with AI must not die from adrenal crisis. It is time we all take the possibility of adrenal crisis dead seriously.

Author details

¹ Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria. ² Department of Anesthesia and Intensive Care, IRCCS-ISMETT, Palermo, Italy. ³ Division of Endocrinology and Diabetology, Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany.

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