Adrenal crisis

February 13, 2017 by Josh Farkas

CONTENTS

- Physiology (#physiology)
- Epidemiology: at-risk populations (#epidemiology_at-risk_populations)
- Presentation (#presentation)
- Testing (#testing_in_patient_with_suspected_adrenal_insufficiency)
- Clinical definition of adrenal crisis (#clinical_definition_of_adrenal_crisis)
- Treatment (#treatment)
- Prevention (#prevention)
- Podcast (#podcast)
- Questions & discussion (#questions_discussion)
- Pitfalls (#pitfalls)

physiology

/TOC/
impaired suppression of inflammation

- Normally, cortisol inhibits pro-inflammatory cytokines (via mechanisms including depression of nuclear factor kappa b, i.e. NF-kB).
- Release of this inhibition increases systemic inflammation.
- Clinical manifestations may include fever, malaise, and anorexia ([Rushworth 2019](https://www.nejm.org/doi/full/10.1056/NEJMra1807486)).

hemodynamic effects

- Cortisol normally functions synergistically with catecholamines to cause vasoconstriction.

metabolic effects

- Cortisol is generally a catabolic hormone, which stimulates the production of numerous fuels in times of stress:
  - (a) Cortisol stimulates gluconeogenesis in the liver
  - (b) Cortisol promotes production of free fatty acids
  - (c) Cortisol promotes the release of amino acids
- Adrenal crisis may lead to low levels of these fuels (particularly hypoglycemia, which can be detected clinically).

renal effects

- Aldosterone is deficient only in cases involving failure of the entire adrenal gland (e.g. Addison's disease).
Deficiency of aldosterone causes wasting of sodium, with retention of positively charged ions (K+ and H+). This leads to hyperkalemia and non-anion-gap metabolic acidosis (NAGMA).

### epidemiology: at-risk populations

- Common causes of chronic adrenal insufficiency
  - Addison's disease
  - Chronic steroid therapy (the most frequent cause of adrenal suppression).
- Adrenal crisis is precipitated by any acute stressor, such as:
  - Infection (especially gastroenteritis, but be careful – symptoms of adrenal crisis from other causes may mimic gastroenteritis)
  - Trauma/surgery
  - Volume depletion
  - Pregnancy
  - Psychological stress, exercise
  - Reduced steroid dose (either due to non-adherence or steroid tapering)
  - Initiation of carbamazepine, etomidate, ketoconazole/fluconazole, phenytoin, rifampin, St. John's Wort, or thyroid hormone (any drug which induces cytochrome P-450 3A4 will increase hydrocortisone metabolism)

### acute adrenal insufficiency (less common)

- This generally occurs in context of another illness:
  - Waterhouse-Friedrichson syndrome (adrenal infarction due to disseminated intravascular coagulation).
  - Pituitary apoplexy (pituitary infarction, often postpartum or due to disseminated intravascular coagulation).
  - Cancer patients receiving checkpoint-inhibitor immunotherapy may experience acute failure of the adrenal and/or pituitary gland.

### presentation
signs and symptoms of adrenal crisis

- Hallmarks
  - Hypotension, vasodilatory shock (often refractory to fluid and vasopressors)
  - Nausea/vomiting, abdominal pain/tenderness
  - Fever

- Other findings
  - Delirium
  - Features of the trigger of the crisis (e.g. trauma, surgery, etc.).

- Additional clues that might be present in patients with chronic adrenal insufficiency:
  - Cutaneous hyperpigmentation or vitiligo
  - History of chronic fatigue, anorexia, vomiting, and weight loss.

basic laboratory findings

- Electrolyte abnormalities due to mineralocorticoid deficiency:
  - These occur in primary adrenal insufficiency (e.g. Addison's disease), but not in secondary insufficiency (e.g. pituitary dysfunction).
  - Mineralocorticoid deficiency causes a type-4 renal tubular acidosis, leading to hyperkalemia and non-anion-gap metabolic acidosis.

- Electrolyte abnormalities which can be seen regardless of the type of adrenal insufficiency:
  - Hyponatremia
  - Hypoglycemia
  - Hypercalcemia
Unfortunately, absence of these abnormalities cannot exclude crisis – especially in complex patients receiving various fluids and medications.

**Eosinophilia**
- Normally, physiologic stress (e.g. sepsis) stimulates cortisol production, which decreases eosinophil counts.
- Normal or increased eosinophil counts in a critically ill patient raise the possibility of adrenal crisis.

---

**testing (in patient with suspected adrenal insufficiency)**

It’s important to determine whether or not the patient has underlying adrenal insufficiency, as this will impact subsequent care. One exception to this is the patient on chronic steroids (who very likely has temporary suppression of the adrenal gland by exogenous steroid).

### #1. start with random cortisol level

- Cortisol >20 ug/dL excludes adrenal insufficiency.
- Cortisol <20 ug/dL is nonspecific, requiring an ACTH stimulation test. However, a cortisol level below 5-7 ug/dL in the context of physiologic stress strongly suggests adrenal insufficiency.

### #2. ACTH stimulation test

- Give 250 micrograms of intravenous ACTH (trade names COSYNTROPIN or SYNACTHEN).
- Check cortisol at baseline and 60 minutes after ACTH administration.\(^3\)
- If cortisol level doesn’t rise above 20-25 ug/dL, this confirms the diagnosis of adrenal insufficiency.
- This test can be done if the patient is receiving dexamethasone, but administration of other types of steroid renders the results meaningless.

---

**clinical definition of adrenal crisis**

There is no established, formal definition of adrenal crisis. A reasonable definition may be as follows (Rushworth 2019 [https://www.nejm.org/doi/full/10.1056/NEJMra1807486].)

1. Acute deterioration with absolute hypotension (systolic pressure < 100 mm) or relative hypotension (fall in systolic pressure by >20 mm)
2. Resolution within 1-2 hours of intravenous steroid administration

This definition reveals that steroid may play both a diagnostic and therapeutic role here. When in doubt, patients should be trialed with steroid therapy. If hemodynamic instability persists, then alternative etiologies should be sought (see #4 below).

---

**treatment**

### #1 investigation & treatment of trigger

- The trigger of the crisis should be sought and treated.
- For patients with possible infection, it may be reasonable to culture and start empiric antibiotic.

### #2 steroid

- For patient with known adrenal insufficiency:
  - 100 mg hydrocortisone IV STAT as a loading dose. This is followed by 50 mg IV hydrocortisone IV q6hr as a maintenance dose
  - If hydrocortisone isn’t immediately available, may substitute 40 mg IV methylprednisolone daily.
  - Once patient has recovered, steroid may be tapered over 3 days to the patient’s baseline regimen (Rushworth 2019 [https://www.nejm.org/doi/full/10.1056/NEJMra1807486].)
- For patient with suspected adrenal insufficiency:
  - Don't delay steroid administration in suspected adrenal crisis.
• Give dexamethasone 4-6 mg IV once. Dexamethasone is useful because it doesn't interfere with measurement of cortisol levels (unlike most other steroids).
• Test for adrenal insufficiency as described above, with further management depending on these results.
• Dexamethasone has no mineralocorticoid effects, but that generally isn't important (these patients will be receiving lots of IV crystalloid, so increased renal sodium excretion isn't a big deal). For patients with hyperkalemia, supplemental mineralocorticoid may be beneficial (fludrocortisone 0.2 mg orally).

#3 resuscitation

• The overall resuscitative strategy here is similar to a sepsis resuscitation (another type of distributive shock).
  • Provide volume resuscitation based on hemodynamic assessment (patients often depleted due to poor oral intake and vomiting).
  • Early use of vasopressors should be considered, with subsequent weaning based on clinical parameters.
• Treat hypoglycemia with IV glucose as needed.

#4 re-evaluation

• Patients with adrenal crisis should improve rapidly with aggressive resuscitation and steroid.
• Failure to improve suggests missed injury (e.g. occult focus of infection). Re-evaluate and consider further imaging studies.

prevention

• For patients with known adrenal insufficiency, steroid dose should be increased when undergoing physiologic stress to prevent the development of adrenal crisis.
  • 50 mg IV hydrocortisone Q6hr may be reasonable for patients experiencing severe stress (e.g. major surgery, severe infection). This represents roughly eight times the normal physiologic output of steroid (Rushworth 2019 (https://www.nejm.org/doi/full/10.1056/NEJMra1807486).
  • Lesser degrees of stress may be managed by smaller increases in the steroid dose (e.g. doubling or tripling of maintenance steroid dose for patients with fever).4

podcast


The Podcast Episode

Want to Download the Episode?
Right Click Here and Choose Save-As (http://traffic.libsyn.com/bccpodcast/IBCC_EP15_Adrenal_Crisis_Final.mp3)

questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page here (https://emcrit.org/pulmcrit/adrenal-crisis/).
Adrenal insufficiency should be considered in any patient with known chronic steroid use plus acute illness.

For patients without a known diagnosis of adrenal insufficiency, it is important to make a firm diagnosis up-front (e.g. with an ACTH stimulation test).

Don't forget that chronic steroid use is the most common cause of adrenal insufficiency, leaving these patients at risk for adrenal crisis due to acute stress (e.g. severe infection).

Adrenal crisis should be considered in any patient who appears to be septic, but doesn't have an obvious source of infection. This is a classic sepsis-mimic.

Going further:

- Adrenal insufficiency (https://lifeinthefastlane.com/ccc/adrenal-insufficiency/) (Chris Nickson, LITFL)
- Adrenal Crisis (https://wikem.org/wiki/Adrenal_crisis) (WikiEM)
- Adrenal Crisis (https://coreem.net/core/adrenal-crisis/) (Trudi Cloyd, CoreEM)
- Priming to diagnose an atypical case (https://acpinternist.org/archives/2011/07/mindful.htm) (Jerome Groopman and Pamela Hatzband, ACP Internist)


