A. Serum analysis of
- Sodium, potassium, and HCO_3
- Plasma cortisol[a]
- Plasma sample for corticotropin, renin, and aldosterone

B. Corticotropin stimulation test
- 250 μg administered intravenously with additional cortisol measurement 30 minutes later[a]

Interpretation

Adrenal insufficiency crisis is highly unlikely if
1. Basal total cortisol is greater than 20 μg/dL
2. Postcorticotropin cortisol is greater than 20 μg/dL

[a] Normal morning total cortisol levels are between 10 and 20 μg/dL (6:00–8:00 AM) if CBG is normal. Values less than 3 μg/dL (80 nmol/L) are highly suggestive of adrenal insufficiency, and values less than 10 μg/dL (275 nmol/L) certainly require further adrenal evaluation.

Data from Oelkers W. Adrenal insufficiency. N Engl J Med 1996;335(16):1206–12; and Grinspoon SK, Biller BMK. Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 1994;79(4):923–31; and Grinspoon SK, Biller BMK. Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 1994;79(4):923–31.

diagnosis of acute adrenal crisis

symptoms of adrenal insufficiency

- usually present slowly over time with nonspecific symptoms of chronic fatigue, weakness and lethargy, anorexia and weight loss, postural hypotension, abdominal complaints (eg, nausea, vomiting, diffuse abdominal pain), and loss of libido as well as loss of axillary and pubic hair in women.
- Hyperpigmentation (attributable to excess proopiomelanocortin and melanocyte-stimulating hormone), especially of non-sunlight-exposed skin areas, is an imported clinical hallmark for the attentive and suspicious physician.
- Abnormal serum electrolytes with low sodium, high potassium, and, occasionally, hypercalcemia and fasting hypoglycemia, and especially this combination are highly suspicious for adrenal insufficiency.
- Acute adrenal insufficiency (adrenal crisis) is mainly attributable to mineralocorticoid deficiency; thus, the clinical presentation is dominated by hypotension or hypotensive shock.

adrenocortical insufficiency [created by Paul Young 03/12/07]

treatment

- If adrenal insufficiency is confirmed or highly likely based on the acute screening results, replacement therapy should be continued by the intravenous or intramuscular route (at 150-300 mg/d for 2 to 3 days) until full clinical recovery. High dose cortisol replacement has major mineralocorticoid effects therefore no additional mineralo-corticoid therapy is needed in the acute phase.
- The 150- to 300-mg/d replacement dose of hydrocortisone is frequently considered to be a physiologic stress dosage. However, serum cortisol levels measured after such so-called "acute replacement" dosages exceed several times the maximal stress cortisol levels found in healthy or even critically ill patients thereby questioning the need for maintaining such high acute emergency replacement dosages.
- In contrast to the rather generous replacement dosage used in emergency situations, the chronic replacement dosage for patients with adrenal insufficiency should be as low as possible with clear instructions for dosage adjustments in case of stress or acute emergencies.
- Detailed information about and education of the patient and of his or her family and a medical emergency alert card as well as appropriate follow-up should be initiated.

Drug	Equivalent dose (mg)	Sodium-retaining activity	Plasma half-life (h)	Duration of action (h)
Cortisone	25	1	1.5	8–12
Hydrocortisone (cortisol)	20	1	+1.5	8–12
Prednisone, prednisolone	5	0.8	>3	>24
Methylprednisolone	4	0.5	>3	>24
Dexamethasone	0.75	0	>3	>36

Indication	Hydrocortisone dose (or equivalent)	Timing
Low dose maintenance (e.g. 5 mg prednisolone/day)	Consider omitting	
Minor stress (e.g. hernia repair)	25 mg i.v. stat	Taper over 1–2 days
Moderate stress (e.g. abdominal hysterectomy)	50–75 mg i.v. stat	Taper over 1–2 days
Major stress (e.g cardiac surgery)	100–150 mg i.v. per day	Maintenance for 1–3 days then taper over 1–2 days
Critically ill patients	50–100 mg i.v. 6–8-hourly	Maintenance for 3–7 days and then gradual taper

The contents of the table represent a consensus view from limited data.

epidemiology

- Primary and secondary adrenal insufficiency (excluding critical illness adrenal insufficiency and adrenal insufficiency secondary to acute interruption of chronic glucocorticoid therapy) are rare diseases, affecting less than 0.1% of the population

physiology

- The adrenal gland is a mixture of the steroid hormone-producing adrenal cortex and the adrenal medulla, which is responsible for the secretion of catecholamines.
- The secretion of cortisol and aldosterone is controlled by different mechanisms, whereby the pituitary axis (corticotropin-releasing hormone [CRH] or corticotropin) is vital for cortisol secretion and the renin-angiotensin system is vital for aldosterone secretion.
- Cortisol regulates a wide variety of genes involved in energy metabolism (eg, glucose-protein-fatty acid metabolism), mineral homeostasis, and immune function and influences many more cellular functions.
- Aldosterone has a more focused action on mineral homeostasis

aetiology

Primary adrenal insufficiency
- Autoimmune diseases (isolated or associated with polyglandular insufficiencies)
- Adrenal infections and inflammation (eg, tuberculosis, fungal diseases, AIDS)
- Bilateral metastasis
- After adrenalectomy[a]
- Adrenal enzyme deficiency
- Adrenal hemorrhage or necrosis caused by (meningococcal) sepsis or coagulation disorders[a]
- Idiopathic
- Drug-induced
- Adrenoleukodystrophy and other congenital disorders

Secondary adrenal insufficiency
- **Pituitary or hypothalamic tumor (including craniopharyngioma)**
- **Pituitary irradiation**
- **Pituitary surgery[a]**
- **Pituitary/brain trauma[a]**
- **Infections or inflammatory/autoimmune disorders in pituitary region (eg, sarcoidosis, hypophysitis)**
- **Pituitary necrosis or bleeding (eg, postpartum Sheehan syndrome)[a]**
- **Acute interruption of prolonged pharmacologic glucocorticoid therapy[a]**
- **Causes of adrenal insufficiency with increased risk for presentation as acute adrenal crisis[a]**

[a] Adrenal insufficiency with increased risk for presentation as acute adrenal crisis.

- Although adrenal insufficiency has been known as a clinical syndrome for a long time, new risk groups have been identified, because as many as 20% of AIDS patients eventually develop adrenal insufficiency. Moreover, patients with head trauma develop pituitary insufficiency much more frequently than previously recognized.

pathophysiology

- adrenal insufficiency is a hormone deficiency syndrome attributable to primary adrenal diseases or caused by a wide variety of pituitary-hypothalamic disorders.
- if such diseases evolve gradually over time, they rarely cause an abrupt-onset adrenal insufficiency crisis, whereas acute destruction of the adrenal or pituitary gland or acute interruption of glucocorticoid therapy is more likely to cause an acute onset adrenal failure crisis.
- there is increasing attention to relative adrenal insufficiency in patients with acute (nonadrenal or pituitary) critical illness. Such patients still secrete cortisol (and corticotropin in the early phases of critical illness) but less than expected during acute stress, and the survival of such patients can be improved by pharmacologic doses of glucocorticoids.