INTRODUCTION

Background: Adrenal crisis and severe acute adrenocortical insufficiency are often elusive diagnoses that may result in severe morbidity and mortality when undiagnosed or ineffectively treated.

Although more than 50 steroids are produced within the adrenal cortex, cortisol and aldosterone are by far the most abundant and physiologically active. In primary adrenocortical insufficiency, glucocorticoid and mineralocorticoid properties are lost; however, in secondary adrenocortical insufficiency (ie, secondary to disease or suppression of the hypothalamic-pituitary axis), mineralocorticoid function is preserved.

Although suppression of the hypothalamic-pituitary axis from chronic exogenous steroid use is the most common cause of secondary adrenal insufficiency, the possibility of hypopituitarism due to hypothalamic-pituitary disease must be considered. With acute hypopituitarism, other hormone deficiencies must be identified and treated in addition to treating adrenal insufficiency with corticosteroids. For instance, if a patient with pan-hypopituitarism from Sheehan syndrome (postpartum pituitary infarction) is only treated for adrenal crisis, severe cardiovascular compromise from the untreated associated hypothyroidism will probably occur. Death can result if the hypothyroid state is not diagnosed.

Every emergency physician should be familiar with adrenocortical insufficiency—a potentially life-threatening entity. The initial diagnosis and decision to treat are presumptive and are based on history, physical examination, and, occasionally, laboratory findings. Delay in treatment while attempting to confirm this diagnosis can result in poor patient outcomes.

Pathophysiology: Adrenal medullae normally secrete 80% epinephrine and 20% norepinephrine. Sympathetic stimulation results in secretion.

The adrenal cortex produces cortisol, aldosterone, and androgens. Cortisol is produced from 2 hydroxylations of 17alpha-hydroxyprogesterone. Cortisol, also known as hydrocortisone, is 90-93% protein bound (primarily by corticosteroid-binding globulin).

Physiologic effects of glucocorticoids

Glucocorticoids are nonspecific cardiac stimulants that activate release of vasoactive substances. In the absence of
corticosteroids, stress results in hypotension, shock, and death. Glucocorticoids act as follows to:

- Stimulate gluconeogenesis and decrease cellular glucose use
- Mobilize amino acids and fatty acids
- Inhibit the effects of insulin
- Give rise to ketone bodies in metabolism (ketogenesis)
- Elevate RBC and platelet levels
- Exhibit anti-inflammatory effects, including the following:
  - Maintenance of normal vascular response to vasoconstrictors
  - Opposition to increases in capillary permeability
  - Inhibition of interleukin-2 (IL-2) production by macrophages
  - Stimulation of polymorphonuclear neutrophil (PMN) leukocytosis
  - Reduction of adherence of macrophages to endothelium
  - Depletion of circulating eosinophils and lymphocytes
  - Reduction of circulating lymphocytes (primarily T cells)

**Physiologic effects of aldosterone**

Aldosterone is produced by multiple hydroxylations of deoxycorticosterone and is normally 60% protein bound. The renin-angiotensin system stimulates aldosterone release. Increased potassium stimulates aldosterone production, and decreased potassium inhibits production. Chronic adrenocorticotropic hormone (ACTH) deficiency may inhibit production. The primary actions of aldosterone cause the kidneys, gut, and salivary/sweat glands to affect electrolyte balance. The primary targets are the kidneys; these organs stimulate reabsorption of sodium and secretion of potassium and hydrogen ions. The kidneys’ effect on sodium and potassium depend on the intake of these cations (ie, increased sodium intake = increased potassium secretion). The effects on hydrogen probably can occur independently.

Persistent aldosterone excess results in atrial natriuretic factor release and renal hemodynamic changes for compensation. Congestive heart failure (CHF) and cirrhosis with ascites are exceptions that cause progressive sodium retention. Excess aldosterone results in sodium retention, hypokalemia, and alkalosis. Aldosterone deficiency results in sodium loss, hyperkalemia, and acidosis. Hyperkalemia stimulates aldosterone release to improve potassium excretion. Aldosterone is the first-line defense against hyperkalemia.

**Primary adrenal insufficiency**

Primary adrenal insufficiency, which can be acute or chronic, may be caused by the anatomic destruction of the gland. This destruction can have various causes, including tuberculosis (TB) or fungal infection, other diseases infiltrating the adrenal glands, and hemorrhage. However, the most frequent cause is idiopathic atrophy, which is probably autoimmune in origin.

Primary adrenal insufficiency also may be caused by metabolic failure (eg, insufficient hormone production). This failure may be a result of congenital adrenal hyperplasia, enzyme inhibitors (eg, metyrapone), or cytotoxic agents (eg, mitotane). Primary adrenocortical insufficiency is rare and it occurs at any age. The male-to-female ratio is 1:1.

**Secondary adrenal insufficiency**

Secondary adrenal insufficiency may be caused by hypopituitarism due to hypothalamic-pituitary disease, or it may result from suppression of the hypothalamic-pituitary axis by exogenous steroids or endogenous steroids (ie, tumor).

Secondary adrenocortical insufficiency is relatively common. Extensive therapeutic use of steroids has greatly contributed to increased incidence.

**Acute adrenocortical insufficiency**

Adrenal crisis may result from an acute exacerbation of chronic insufficiency, usually caused by sepsis or surgical stress. Acute adrenal insufficiency also can be caused by adrenal hemorrhage (eg, usually septicemia-induced Waterhouse-Friderichsen syndrome [fulminant meningococcemia]) and anticoagulation complications. Steroid withdrawal is the most common cause of acute adrenocortical insufficiency, and it almost exclusively causes a glucocorticoid deficiency.

**Frequency:**
In the US: Primary adrenocortical insufficiency is an uncommon disorder with an incidence in Western populations near 50 cases per 1,000,000 persons. With the advent of widespread corticosteroid use, however, secondary adrenocortical insufficiency due to steroid withdrawal is much more common. Approximately 6,000,000 persons in the US are considered to have undiagnosed adrenal insufficiency, which is clinically significant only during times of physiologic stress.

Primary adrenocortical insufficiency has multiple etiologies; however, 80% of cases in the US are caused by autoimmune adrenal destruction. Glandular infiltration by tuberculosis is the second most frequent etiology.

In patients with primary adrenocortical insufficiency due to idiopathic autoimmune lymphocytic infiltration, the presence of other associated endocrine disorders must be entertained. Consider polyglandular autoimmune disorders (PGAs) such as Schmidt syndrome.

Schmidt syndrome (PGA type II) includes adrenal insufficiency, autoimmune thyroid disease, and, occasionally, insulin-dependent diabetes mellitus. Adrenal insufficiency usually occurs in these patients when they are older than 20 years. In approximately 40-50% of patients with PGA II, the first manifestation of the syndrome is adrenal insufficiency.

PGA type I includes hypoparathyroidism and mucocutaneous candidiasis in conjunction with adrenal insufficiency. The full triad may manifest in approximately 30% of patients with PGA type I.

Mortality/Morbidity:

Acute adrenocortical insufficiency is a difficult diagnosis to make. The disorder rarely occurs without concomitant injury or illness. Many of the presenting signs and symptoms are nonspecific. For instance, a postoperative fever may presumptively be treated as infection or systemic inflammatory response syndrome when it may be a subtle indicator of adrenal insufficiency.

Left untreated, a patient with acute adrenal insufficiency has a dismal prognosis for survival. Therefore, treatment upon clinical suspicion is mandatory. Any delay in management while waiting for diagnostic confirmation cannot be justified.

Sex: Although primary adrenocortical insufficiency affects men and women equally, women are affected 2-3 times more often by the idiopathic autoimmune form of adrenal insufficiency.

Age: In idiopathic autoimmune adrenal insufficiency, the diagnosis is most often discovered in the third to fifth decades of life; however, it is particularly important to recognize that adrenocortical insufficiency is not limited to any specific age group.

**History:**

- Weakness (99%)
- Pigmentation of skin (98%)
- Weight loss (97%)
- Abdominal pain (34%)
- Salt craving (22%)
- Diarrhea (20%)
- Constipation (19%)
- Syncope (16%)
- Vitiligo (9%)

**Physical:**

- Physical findings in patients with adrenal insufficiency are subtle and nonspecific.
- Patients with mineralocorticoid insufficiency may show signs of sodium and volume depletion (eg, orthostatic hypotension, tachycardia).
- Evidence of hyperpigmentation is observed, particularly in areas exposed to the sun or areas subject to friction or pressure.

**Causes:**

- Surgery
- Anesthesia (eg, etomidate)
Volume loss
- Trauma
- Asthma
- Hypothermia
- Alcohol
- Myocardial infarction
- Fever
- Hypoglycemia
- Pain
- Psychoses or depression
- Exogenous steroid withdrawal

### DIFFERENTIALS

Anorexia Nervosa
Gastroenteritis
Hypercalcemia
Hyperkalemia
Hypoglycemia
Hyponatremia
Hypopituitarism
Hypothyroidism and Myxedema Coma
Metabolic Acidosis

### WORKUP

**Lab Studies:**
- Complete blood count
- Electrolytes
- Blood urea nitrogen
- Creatinine
- Cortisol level
- Serum calcium
- Thyroid function tests (possibly performed in ED but unlikely to influence immediate management)

**Imaging Studies:**
- Chest radiograph
- CT scan
  - A CT scan of the abdomen may show hemorrhage in the adrenals, calcification of the adrenals (seen with TB), or metastasis.
  - In cases of secondary adrenal insufficiency, a head CT scan may show destruction of the pituitary (ie, empty sella syndrome) or a pituitary mass lesion.

**Other Tests:**
- Adrenocorticotropic hormone stimulation test
  - Note: In emergent situations, do not delay treatment of presumed adrenal insufficiency during diagnostic testing. Treatment with dexamethasone allows ACTH stimulation testing without affecting or interfering with the measurement of serum cortisol levels.
  - Obtain baseline serum cortisol and ACTH levels.
  - Administer 0.25 mg (250 mcg) of cosyntropin (synthetic ACTH) IV/IM.
  - Repeat cortisol levels every 30 minutes (some authors recommend 60 min) and 6 hours after ACTH
Adrenal Insufficiency and Adrenal Crisis from Emergency Medicine / Endocrine And Metabolic 

administration.

- Normal response is indicated when the cortisol level doubles in response to ACTH stimulation.
- In adrenal insufficiency, serum cortisol levels fail to rise after ACTH administration.

- Electrocardiograph (ECG): Elevated peaked T waves may indicate hyperkalemia.
- 24-hour urinary cortisol: Use only in nonemergent situations.

TREATMENT

Emergency Department Care:

- Maintain airway, breathing, and circulation.
- Employ coma protocol (ie, glucose, thiamine, naloxone).
- Use aggressive volume replacement therapy (dextrose 5% in normal saline solution [D5NS]).
- Correct electrolyte abnormalities as follows:
  - Hypoglycemia (67%)
  - Hyponatremia (88%)
  - Hyperkalemia (64%)
  - Hypercalcemia (6-33%)
- Use dextrose 50% as needed for hypoglycemia.
- Administer hydrocortisone 100 mg IVP q6h. During ACTH stimulation testing, dexamethasone (4 mg IV) can be used instead of hydrocortisone to avoid interference with testing of cortisol levels.
- Administer fludrocortisone acetate (mineralocorticoid) 0.1 mg qd.
- Always treat the underlying problem that precipitated the crisis.

Consultations:

- Endocrine consultation following admission is beneficial. If no endocrinologist is available, a general internist can manage the process. Emergency management should be implemented in the ED prior to consultation when sufficient clinical suspicion for this diagnosis exists.
- ICU admission is necessary for most patients with acute adrenal insufficiency and adrenal crisis.

MEDICATION

One of the goals in treating adrenal insufficiency is glucocorticoid replacement. Electrolyte and metabolic abnormalities, as well as hypovolemia, also must be corrected. In addition, address the event precipitating abrupt decompensation.

Drug Category: **Corticosteroids** - Used primarily to correct glucocorticoid deficiencies. DOCs are hydrocortisone, cortisone, and prednisone.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Hydrocortisone (Cortef, Solu-Cortef)- DOC because of mineralocorticoid activity and glucocorticoid effects.</th>
</tr>
</thead>
</table>
| Adult Dose| 100 mg IV bolus; follow by 100 mg q8h continuous infusion for 24-48 h  
|           | Once patient is stable, PO hydrocortisone may be started at 50 mg q8h for another 48 h; may taper dose until dosage is 30-50 mg/d in divided doses  
|           | Taper dose over 14 d; discontinue once symptoms resolve  |
| Pediatric Dose| <12 years: 1-2 mg/kg IV bolus; follow by 25-150 mg/d divided q6-8h  
<p>|              | &gt;12 years: 1-2 mg/kg IV bolus; follow by 150-250 mg/d divided q6-8h  |
| Contraindications| None for this emergency  |
| Interactions| None for this emergency  |
| Pregnancy| C - Safety for use during pregnancy has not been established.  |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Cortisone acetate (Cortone Acetate)- Considered the DOC by some prescribers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>25-300 mg/d PO/IM divided q12-24h</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>25-300 mg/d PO/IM divided q12-24h; 0.25-0.35 mg/kg/d IM qd or 12.5 mg/m²/d</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None for this emergency</td>
</tr>
<tr>
<td>Interactions</td>
<td>None for this emergency</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>May lower serum potassium levels; complications of hypokalemia (eg, digitalis toxicity) may ensue; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications of glucocorticoid use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Prednisone (Deltasone, Liquid Pred)- Treats various diseases including adrenocortical insufficiency. Agent is inactive and must be metabolized to active metabolite prednisolone. Conversion may be impaired in patients with liver disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>5-60 mg/d PO qd or divided bid/qid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>4-5 mg/m²/d PO; alternatively, administer 1-2 mg/kg PO qd; taper over 2 wk as symptoms resolve</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None for this emergency</td>
</tr>
<tr>
<td>Interactions</td>
<td>None for this emergency</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dexamethasone (Decadron, AK-Dex, Alba-Dex, Dexone)- Alternative to hydrocortisone to avoid interference with testing of cortisol levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>4 mg IV; repeat q2-6h if necessary</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>0.03-0.15 mg/kg/d IV divided q6-12h</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None for this emergency</td>
</tr>
<tr>
<td>Interactions</td>
<td>None for this emergency</td>
</tr>
</tbody>
</table>
### Pregnancy

| Pregnancy | C - Safety for use during pregnancy has not been established. |

### Precautions

| Precautions | May lower serum potassium levels; complications of hypokalemia (eg, digitalis toxicity) may ensue; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications of glucocorticoid use |

### Drug Name

| Drug Name | Fludrocortisone acetate (Florinef Acetate)- Partial replacement therapy for primary and secondary adrenocortical insufficiency. |

#### Adult Dose

| Adult Dose | 0.1 mg PO qd |

#### Pediatric Dose

| Pediatric Dose | 0.05-0.1 mg PO qd |

### Contraindications

| Contraindications | Documented hypersensitivity; systemic fungal infections |

### Interactions

| Interactions | Antagonizes effects of anticholinergics; rifampin, hydantoins, and barbiturates decrease effects of fludrocortisone; decreases salicylate levels |

### Pregnancy

| Pregnancy | C - Safety for use during pregnancy has not been established. |

### Precautions

| Precautions | Taper dose gradually when therapy is discontinued; caution in Addison disease, potassium loss, and sodium retention |

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**FOLLOW-UP**

### Further Inpatient Care:

- Employ supportive measures as necessary.
- Correct electrolyte abnormalities.
- Perform judicious volume resuscitation.
- Continuously monitor and administer glucose.
- Once the patient stabilizes, usually by the second day, the corticosteroid dose may be reduced and then tapered. Oral maintenance usually can be achieved by the fourth or fifth day.
- Mineralocorticoid administration is not needed unless a corticosteroid with low mineralocorticoid activity (eg, dexamethasone) is used, or cortisol/corticosteroid administration has been reduced to near maintenance levels. Mineralocorticoid administration usually is not necessary for treatment of secondary adrenocortical insufficiency.
- Pursue and manage precipitating factors of adrenal crisis or insufficiency. Infectious etiologies commonly precipitate adrenal crisis. Recognition and treatment of causative factors are crucial aspects of managing adrenal hypofunction.

### Further Outpatient Care:

- Maintenance of cortisol levels may be achieved by administering hydrocortisone 15-20 mg PO every morning and 5-10 mg PO between 4:00-6:00 PM every afternoon.
- Maintenance mineralocorticoid levels may be achieved by administering 9alpha-fluorocortisol 0.05-0.1 mg every morning. (This treatment is necessary only for primary adrenocortical insufficiency.)
- Periodically assess blood pressure, body weight, and electrolytes.
- Advise patients to increase their cortisol dosage during times of physical stress.

### MISCELLANEOUS

**Medical/Legal Pitfalls:**

- Failure to diagnose due to ambiguous presentations or comorbidity
- Failure to identify missed mineralocorticoid deficiency

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file:///D|/X. SOLER/BIBLIO2/Adrenal crises.htm (7 de 8) [18/09/2001 20:23:40]
Failure to identify missed associated endocrine abnormalities

Failure to administer steroids before tetraiodothyronine (thyroxine T4)

Failure to administer glucose before steroids

**Special Concerns:**

- Dexamethasone
  - Administer 4 mg q6h during ACTH stimulation test.
  - This agent is 100 times more potent than cortisone but does not alter cortisol levels.

**BIBLIOGRAPHY**