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Recognizing and Managing Adrenal Disorders in the Emergency Department

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Abstract

Primary and secondary adrenal insufficiency are underrecognized conditions among emergency department patients, affecting an estimated 10% to 20% of critically ill patients. The signs and symptoms of cortisol deficit can be nonspecific and wide-ranging, and identification and swift treatment with stress-dosing of hydrocortisone is vital to avoid life-threatening adrenal crisis. Laboratory evaluation focuses on identification of electrolyte abnormalities typical of adrenal insufficiency, and while additional testing may depend on the type and severity of symptoms, it should not delay corticosteroid replacement. This issue provides recommendations on effective management of patients presenting with adrenal insufficiency, with particular attention to the management of critically ill and septic patients, pregnant patients, and children.

Case Presentations

A 56-year-old man presents complaining of a productive cough, fatigue, and shortness of breath. A chest x-ray demonstrates a left lower lobe infiltrate, and he is diagnosed with community-acquired pneumonia. His blood pressure, which was 119/67 mm Hg upon arrival, has decreased to 83/52 mm Hg on reassessment after the chest x-ray. You order antibiotics, and he is given a 30 mL/kg bolus of IV fluids. His blood pressure remains low, at 82/40 mm Hg. You arrange admission to the ICU, and initiate a norepinephrine infusion titrated to a mean arterial pressure of 65 mm Hg, as well as an additional IV fluid bolus. Despite the 30 mcg/min norepinephrine infusion, the patient's MAP is still < 60 mm Hg. You perform a focused bedside ultrasound and note that his inferior vena cava measures 2.2 cm, with minimal respiratory variation. You wonder if you should just add on an additional vasopressor, or if there is something else you should consider…

A 24-year-old woman presents with complaint of nausea with vomiting and diarrhea for 3 days. She has not been able to keep anything down, including any of her medications, for the last 36 hours. A review of her chart reveals that she has primary adrenal insufficiency. Her triage vital signs include mild hypotension of 81/48 mm Hg and tachycardia, at 120 beats/min. Two liters of IV normal saline (0.9% sodium chloride) are ordered, and antiemetics are administered. Her tachycardia begins to improve, but her blood pressure remains low, with systolic blood pressure in the low 80s. You wonder: What is the best way to replace steroids, and is there any indication for obtaining cortisol levels or ACTH stimulation testing?

A 15-day-old full-term infant girl with no prenatal care presents to the ED for poor feeding and lethargy. Her vital signs include a heart rate of 185 beats/min; respiratory rate, 35 breaths/min; blood pressure, 62/40 mm Hg; temperature, 37°C; and oxygen saturation, 98% on room air. Examination reveals a lethargic infant with poor tone and weak cry. Her head is normocephalic and atraumatic, she has a sunken fontanelle, no meningismus, dry mucous membranes, and there is no rash. The lungs are clear and the heart has a regular rate with no murmurs. The abdomen is soft and nontender, and her labia are enlarged and hyperpigmented. You know something is wrong, but you're not quite sure what…

Introduction

First described over 150 years ago, adrenal insufficiency remains a rare, but important, endocrine disorder that is underrecognized among emergency department (ED) patients. Adrenal emergencies occur for a number of reasons and can affect patients of any age and gender. Primary adrenal insufficiency (PAI), historically associated with tuberculosis, is now more commonly caused by autoimmune disorders[1] and is more often seen in women between the ages of 30 and 50 years.[2] Secondary adrenal insufficiency (SAI) is more common than PAI, and is classically seen in an older patient population that uses chronic steroids. Congenital adrenal hyperplasia (CAH) can be diagnosed at birth, but it can also present in older children. Due to its many confounders, adrenal disease can be challenging to diagnose, and once diagnosed, can be challenging to treat efficiently.

Adrenal crisis is the most dramatic and life-threatening manifestation of adrenal disease. Diagnosing adrenal crisis in a patient without known adrenal insufficiency can be difficult because it is nonspecific and often mimics other common diseases. Even in patients with known adrenal insufficiency, adrenal crisis can be difficult to prevent[3] and treat in a timely manner.[4] In a 2015 prospective study, Hahner et al described 364 patients with known PAI or SAI who were followed for 2 years. There were 64 episodes of adrenal crisis, with 4 deaths attributed to adrenal crisis.[5] The same author found in a patient-survey-based study that 42% of patients with known adrenal insufficiency reported at least 1 crisis.[4] Hahner et al examined the time to treatment in patients with known adrenal insufficiency and found that the gravity of the condition and need for timely treatment was underappreciated by clinicians, considering the delay observed in time to glucocorticoid administration in healthcare facilities.[4]

The adrenal system plays an integral role in the body's response to critical illnesses, such as in severe sepsis and post–cardiac arrest syndrome. For patients with underlying adrenal disease, the diagnosis of adrenal crisis can be easy to miss, but it remains a high-stakes diagnosis to make. Once suspected, the treatment pathway is clear and potentially life-saving if administered in a timely manner. When treating critically ill patients, knowledge of the controversies and supporting evidence for use of corticosteroids can help optimize management. For all emergency clinicians, a basic understanding of the pathophysiology of the adrenal axis and treatment can have a substantial impact on patients suffering from acute adrenal diseases. This issue of *Emergency Medicine Practice* reviews the subtle and often-missed signs of adrenal disease, the evidence-based pharmacologic treatments, and the management of adrenal insufficiency in critically ill patients.

Selected Abbreviations

ACTH	Adrenocorticotropic hormone
CAH	Congenital adrenal hyperplasia
CI	Confidence interval
CIRCI	Critical-illness-related corticosteroid insufficiency
ECG	Electrocardiogram
ED	Emergency department

HPA Hypothalamic-pituitary-adrenal
OR Odds ratio
PAI Primary adrenal insufficiency
RR Relative risk
SAI Secondary adrenal insufficiency

Critical Appraisal of the Literature

A broad search for literature published over the past 10 years was performed, using the key words: *adrenal crisis, primary adrenal insufficiency, secondary adrenal insufficiency,* and *adrenal hyperplasia*. These yielded a pool of 2679 articles that were surveyed. Several key topics were identified, which resulted in additional searches for the following topics with no date restriction: etomidate + adrenal, cardiac arrest + steroids. Investigation into relevant cited literature was also performed. This resulted in a total of 132 articles with relevance to emergency medicine practice, 50 of which have been cited here.

Review of the available literature demonstrates an overall consensus in the diagnosis and treatment of adrenal crisis that has changed very little over the past 50 years. Several clinical practice guidelines and consensus statements exist that address the basic tenets of diagnosis and treatment.[6-11] A few high-quality randomized controlled trials and cohort studies exist; however, these primarily address the controversial aspects and special populations that are encountered in adrenal emergencies.

Etiology and Pathophysiology

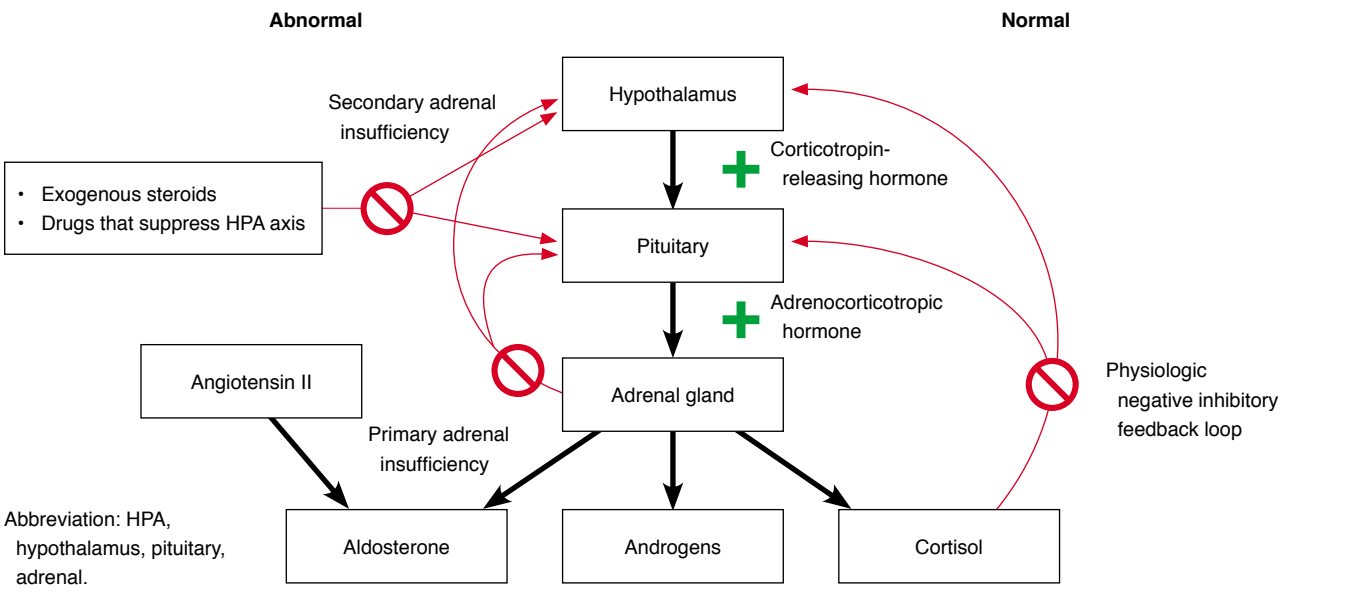
The adrenal glands, which sit atop each kidney, are composed of 2 anatomic segments: the medulla and the cortex. The medulla secretes epinephrine and norepinephrine in response to sympathetic stimulation. The cortex secretes aldosterone, cortisol, and androgens. The cortex responds to stimulation from adrenocorticotropic hormone (ACTH), which is secreted by the anterior pituitary gland as part of the hypothalamic-pituitary-adrenal (HPA) axis. **(See Figure 1.)** The cortex has 3 distinct zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis. The zona glomerulosa secretes aldosterone primarily in response to angiotensin II (part of the renin-angiotensin system) but also in response, to a lesser degree, to ACTH. Aldosterone acts as a mineralocorticoid to help regulate fluid and electrolyte balance via water and sodium resorption and potassium excretion by the renal tubular epithelial cells. The zona fasciculata secretes cortisol, the primary glucocorticoid produced in the human body. Cortisol helps regulate carbohydrate, protein, and lipid metabolism. The zona reticularis secretes androgens, which are sex steroids.

Primary Adrenal Insufficiency (Addison Disease)

PAI, also known as Addison disease, is characterized by a deficiency of glucocorticoid and/or mineralocorticoid production by the adrenal glands, causing deficiency in both cortisol and aldosterone.[6] To be considered PAI, there must be an intact HPA axis with sufficient ACTH production. Addison disease is rare, with a prevalence of 100 to 140 cases per million people and an incidence of 4:1,000,000 people per year.[8]

Symptoms related to cortisol deficiency include weakness, fatigue, weight loss, and mental status changes; gastrointestinal symptoms include nausea, vomiting, and abdominal pain. Aldosterone deficiency can result in salt-craving and orthostatic

Figure 1. Hypothalamic-Pituitary-Adrenal Axis and Feedback Loops



Abbreviation: HPA, hypothalamus, pituitary, adrenal.

hypotension or syncope from dehydration. Excess amounts of ACTH cause hyperpigmentation of the skin or mucous membranes. Deficiencies in androgens cause reduction in axillary and pubic hair. Autoimmune disorders (most commonly autoantibodies to 21-hydroxylase autoantibody) are the most common causes of PAI in developed countries.[7,12] Other etiologies include adrenal hemorrhage or infarction, infections such as tuberculosis or AIDS-related diseases, cancer, sarcoidosis, genetic disorders, and medication side-effects. See **Table 1** for a more complete list of etiologies.[2]

Congenital Adrenal Hyperplasia

PAI in children occurs most commonly as a result of CAH. CAH is a group of autosomal recessive disorders that result in inborn errors of the cortisol biosynthesis pathway, occurring in approximately 1 per 10,000 to 20,000 births.

Classic CAH comprises 95% of cases and is due to a mutation in the CYP21A2 gene, which results in 21-hydroxylase deficiency.[13] This enzyme is responsible for conversion of steroid precursors into cortisol and aldosterone. Reduced expression of this enzyme causes these precursors to be converted to androgens. Additionally, the lack of the negative cortisol loop feedback on the pituitary gland results in increased corticotropin-releasing hormone levels, stimulating further steroid biosynthesis and more androgen production. Patients with classic CAH have cortisol and aldosterone deficiencies as well as androgen excess that manifest as adrenal insufficiency, precocious puberty, and varying degrees of salt wasting.

Classic CAH is divided into 2 forms, based on severity: salt-wasting CAH and simple virilizing CAH. The severity of disease is determined by the degree of aldosterone deficiency that correlates with salt wasting. Salt wasting can be fatal in infants if not treated promptly. Adrenal crisis and salt-wasting symptoms are nonspecific and include decreased activity, altered mental status, poor feeding/weak suck, nausea/vomiting, and abdominal pain. Virilizing symptoms depend on the age and sex. In infants, clinicians should look for hyperpigmentation of the labia or scrotum. There may also be enlargement of the clitoris or penis. Older children may have early appearance of axillary and pubic hair, acne, and early growth.

Nonclassic CAH encompasses the remaining 5% of cases and is generally late in onset. It is due to excessive androgens without cortisol deficiencies. Complaints in these patients may include early puberty, short stature (from early epiphyseal closure and advanced bone age), cystic acne, hypertension, insulin resistance, and, in females, oligomenorrhea/amenorrhea.[14]

Table 1. Causes of Primary Adrenal Insufficiency[2,6,7,12]

Etiology	Example
Autoimmune	• Isolated autoimmunity to adrenocortical cells • Polyglandular autoimmune syndrome type I or II
Infectious	• Tuberculosis • Bacterial sepsis (meningococcus and *Haemophilus influenzae*) • Systemic viral infection (HIV/AIDS, herpes simplex, cytomegalovirus)
Adrenal hemorrhage	• Antiphospholipid syndrome • Coagulation disorders • Complications of anticoagulation therapy • Disseminated intravascular coagulation • Waterhouse-Friderichsen syndrome
Infiltrative	• Amyloidosis • Hemochromatosis • Bilateral adrenal metastasis • Lymphoma • Xanthogranulomatosis
Medications that inhibit adrenal enzymes	• Ketoconazole (Nizoral®, Xolegel®, Extina®) (chronic use) • Etomidate (Amidate®) (transient effect) • Mitotane (Lysodren®) • Metyrapone (Metopirone®®)
Medications that affect cortisol metabolism	• Barbiturates • Certain antiepileptics • Topiramate (Topamax®, Qudexy XR®, Trokendi XR®)
Genetic	• Congenital adrenal hyperplasia • Adrenoleukodystrophy (X-linked) • Hypogonadotropic hypogonadism (X-linked) • Familial glucocorticoid deficiency • Kearns-Sayre syndrome (mitochondrial)
Other	• Bilateral adrenalectomy • Cushing syndrome

Secondary Adrenal Insufficiency

SAI is distinguished from PAI by a lack of corticotropin-releasing hormone or ACTH production. The adrenal gland still functions, but due to a lack of hormonal stimulation, there is a lack of glucocorticoid production; this can be secondary to hypothalamic or pituitary malfunction. The most common cause of SAI is withdrawal of exogenous glucocorticoid use once the HPA axis has been suppressed; however, other etiologies exist.[12] **(See Table 2, page 5.)** Nonpharmacologic causes include cancer, sarcoidosis, pituitary necrosis, pituitary hemorrhage (apoplexy) and traumatic brain injury. One distinguishing factor between SAI and PAI is that, in patients with SAI, aldosterone secretion is maintained.

Adrenal Crisis

Cortisol affects many different functions throughout the body, including the inflammatory response, vascular tone, gluconeogenesis, response to vasopressors, and endothelial integrity.[16] In patients with adrenal insufficiency, a lack of the cortisol response leads to severe symptoms, such as shock and confusion, due to the inability of the body to respond normally to a stressor or illness. This results in what is known as *adrenal crisis*, when the body cannot maintain vascular tone, and the patient can succumb to shock. The risk of adrenal crisis in patients with PAI is between 5 and 10 episodes per 100 patient-years. Patients can present in adrenal crisis as their first sign of PAI.[17-19]

There are no pathognomonic findings for adrenal crisis. The symptoms are similar to those of adrenal insufficiency, only more severe. Because there is no universally accepted definition of adrenal crisis, experts in endocrinology have proposed the following definition:[5,19]

1. Major impairment of general health, with at least 2 of the following signs/symptoms:
   - Hypotension (systolic blood pressure < 100 mm Hg)
   - Nausea or vomiting
   - Severe fatigue
   - Fever
   - Somnolence
   - Hyponatremia (≤ 132 mmol/L) or hyperkalemia
   - Hypoglycemia
2. Occurrence of clinical improvement following parenteral glucocorticoid administration.

Critical-Illness-Related Corticosteroid Insufficiency

Inflammatory cytokines released during illness lead to cortisol production. During critical illness, these inflammatory cytokines appear to overwhelm the glucocorticoid response and disrupt the HPA axis. This has been described as critical-illness-related corticosteroid insufficiency (CIRCI).[9] CIRCI—also referred to as *relative adrenal insufficiency* or *functional adrenal insufficiency*—is defined as inadequate corticosteroid activity relative to a patient's severity of illness.[20]

In CIRCI, the HPA axis is disrupted in several ways. Decreased production of corticotropin-releasing hormone, ACTH, and cortisol have been observed. Additionally, dysfunction of the receptors for these hormones leads to peripheral glucocorticoid resistance via fewer tissue glucocorticoid receptors as well as a lowering of their affinity for glucocorticoids.[16] Some patients may also have direct damage to the adrenal glands from the underlying illness. Due to the multiple ways for dysfunction of the HPA axis to develop in critical illness, some patients have low cortisol levels and some have a functional cortisol insufficiency despite normal serum cortisol levels. This makes the diagnosis of adrenal insufficiency during severe illness complex.

It is estimated that 10% to 20% of critically ill patients have some degree of adrenal insufficiency.[9] This phenomenon can present during any critical illness, although it is most commonly seen in patients with sepsis.[9] Cortisol is normally over 90% bound to corticosteroid-binding globulin and albumin.[20] The remaining 10% is free cortisol, which is the active form. During severe illness, corticosteroid-binding globulin and albumin levels decrease. Due to the changes in protein binding, cortisol levels may not increase despite increased levels of free cortisol.[16] CIRCI typically manifests as hypotension refractory to fluids.[20] It should be considered in all patients requiring vasopressors, especially in those in whom multiple vasopressors are required.

Table 2. Causes of Secondary Adrenal Insufficiency[12,15]

Etiology	Example
Medications	• Cessation of prolonged glucocorticoid therapy
Brain tumor	• Pituitary tumor • Hypothalamic tumor • Craniopharyngioma
Infiltrative	• Sarcoidosis • Hemosiderosis • Hemochromatosis • Histiocytosis X • Metastatic cancer • Lymphoma • Wegener granulomatosis
Infectious	• Tuberculosis • Meningitis • Fungal infection • HIV/AIDS
Pituitary injury or bleeding	• Pituitary or brain surgery • Severe head trauma • Pituitary irradiation • Sheehan syndrome (postpartum pituitary necrosis) • Pituitary hemorrhage (apoplexy)

Differential Diagnosis

Many patients suffering from adrenal crisis will present with hypotension and altered mental status. A key component of ED management is evaluating for alternative causes of common presenting complaints of adrenal crisis. **(See Table 3.)** Often, patients will have concomitant diagnoses that may have precipitated the adrenal crisis. Maintaining a high index of suspicion is paramount to diagnosing adrenal crisis and distinguishing it from other diseases seen more commonly in the ED.

Sepsis

Sepsis is one of the most common and lethal causes of shock in ED patients. Infection is also a common precipitating factor in patients with adrenal crisis. Septic patients require early intervention to improve mortality, including administration of intravenous (IV) fluids and antibiotics. If there is any question that a patient with adrenal crisis may have sepsis, early empiric antibiotics are indicated.

Diabetic Ketoacidosis

Diabetic ketoacidosis and adrenal crisis have many symptoms in common. In both conditions, patients can present with weakness, vomiting, and abdominal pain. Patients may appear dehydrated and have low blood pressure. Both conditions can lead to sodium and potassium abnormalities. The key to distinguishing between these conditions is the level of glucose as well as detection of ketone production. Treatment of both conditions consists of fluid and electrolyte replacement. Patients with diabetic ketoacidosis will also require insulin, while patients in adrenal crisis need glucocorticoid replacement.

Table 3. Differential Diagnosis for Common Presenting Complaints of Adrenal Crisis

- **Acute Myocardial Infarction**
- **Heat Exhaustion**
- **Sepsis**
  - Pneumonia
  - Meningitis
  - Urinary tract infection
  - Other systemic infections
- **Diabetes Complications**
  - Diabetic ketoacidosis
  - Hyperosmolar hyperglycemic state
- **Ingestions**
  - Antihypertensive agents
  - Insulins or oral hypoglycemic agents
  - Sedative/hypnotics
- **Thyroid disorders**
  - Thyroid storm
  - Myxedema coma
- **Shock From any Cause**
  - Cardiogenic
  - Obstructive
  - Distributive
  - Hypovolemic
- **Malignancy**
- **Panhypopituitarism**
- **Electrolyte Disorders**
  - Hypoglycemia
  - Hyponatremia
  - Hyperkalemia
  - Hypercalcemia
- **Dehydration**
  - Gastrointestinal illness with volume depletion
  - Inadequate oral intake
- **Neuropsychiatric Disorders**
  - Anorexia nervosa
  - Psychogenic polydipsia
  - Delirium
  - Dementia
- **Gastrointestinal Disorders**
  - Celiac disease
  - Cyclical vomiting syndrome
- **Pregnancy Complications**
  - Nausea and vomiting of pregnancy
  - Hyperemesis gravidarum

Ingestions

Presentations of adrenal emergencies do not consistently mimic a single toxidrome; however, the common findings of altered mental status, hypotension, electrolyte disturbances, and gastrointestinal symptoms require that toxic ingestions be considered as part of the differential, as they can also present in this manner. Medications such as sedative-hypnotics (benzodiazepines, ethanol, sleep aids) and psychiatric medications (antipsychotics, antidepressants), when taken in overdose, may cause coma or sedation and mild hypotension. Tricyclic antidepressants are well recognized to cause altered mental status and significant hypotension through their actions on sodium channels. Exogenous potassium ingestions, though rare, can cause hyperkalemia, especially in the patient with compromised renal function. Insulin or sulfonylurea overdoses commonly cause hypoglycemia. Antihypertensives such as beta blockers and calcium-channel blockers can cause hypotension and mental status changes when central nervous system perfusion is affected by low blood pressures. Salicylate overdoses can present with altered mental status, nausea and vomiting, and mild hypoglycemia. Ethylene glycol ingestions can cause sedation or altered mental status, along with acute kidney injury, which can then result in hyperkalemia.

Attempting to obtain a history from friends or family is important in assessing the possibility of overdose in a patient who cannot contribute a history of present illness. It is important to know which medications a patient may have access to in the home. If there is concern for overdose, checking for aspirin and acetaminophen levels and discussing the case with the poison control center is recommended.

Prehospital Care

Prehospital treatment of adrenal crisis should focus on resuscitating the unstable patient and the identification and treatment of life-threatening hypoglycemia. IV fluid resuscitation is critical for hypotensive patients in adrenal crisis. Prehospital care should focus on obtaining IV access and initiating normal saline (0.9% sodium chloride). Additionally, a point-of-care glucose check should be performed, and if required, glucose should be given promptly. Full medication histories can be challenging in the prehospital environment, especially if the patient is critically ill. Emergency medical services personnel should transport any medications the patient is or

has been taking to allow rapid review by emergency clinicians. Some patients will have medications for home stress-dosing, and these should be specifically asked about if a history of adrenal disease or chronic steroid use is revealed. There are no studies that guide prehospital provider treatment of adrenal insufficiency/adrenal crisis, but given the universal nature of the interventions, there is little controversy.

Emergency Department Evaluation

History

Patients with adrenal insufficiency will often present with nonspecific symptoms, so emergency clinicians must maintain a high index of suspicion for this condition. Diagnosis can be straightforward in patients with known adrenal disease, known recent cessation of long-term corticosteroid use, or hyperpigmentation. However, in most cases, the symptoms, historical features, and physical examination findings are not likely to contain unique or pathognomonic features. **(See Table 4.)** Common symptoms include fatigue, weight loss, dizziness, anorexia, nausea, vomiting, and abdominal pain.[6] Patients with PAI may also report salt-craving. Some patients may even present with primary psychiatric complaints such as depression.[19] PAI is rare in children, but can present similarly.[21]

When reviewing a patient's past medical history, autoimmune disorders place the patient at higher risk for having PAI. Common concomitant autoimmune disorders include thyroid disease, gastritis with vitamin B_{12} deficiency, type 1 diabetes mellitus, vitiligo, and celiac disease.[7] Determining whether the patient is taking any medications that can affect the HPA axis is important. Patients who chronically take exogenous corticosteroids are at risk for adrenal crisis if they abruptly stop taking them. Medications and foods that affect the enzyme CYP3A4 may affect steroid metabolism (eg, rifampin, phenytoin, carbamazepine [Tegretol®, Carbatrol®, Epitol®], St. John's wort, grapefruit juice, and ritonavir [Norvir®]).[6,7] Initiating or discontinuing these agents in these patients may lead to clinical symptoms due to changes in cortisol metabolism. Medications such as the antineoplastic adrenal enzyme mitotane (Lysodren®), cortisol synthesis-blocking agent metyrapone (Metopirone®), or chronic use of ketoconazole may induce a significant cortisol deficit.[6]

A clue to diagnosis in patients without a known history of adrenal disease is that they can appear more ill than their chief complaint would classically dictate. They can also seem less responsive to traditional treatments. For example, presentations of adrenal crisis could include the following:

- Persistent hypotension after appropriate volume replacement in patients with vomiting or diarrhea
- Greater-than-expected altered mental status in a patient on chronic corticosteroids diagnosed with diabetic ketoacidosis
- New hyperkalemia associated with hyponatremia and hypoglycemia in a patient who appears ill
- Refractory hypotension in septic shock patients despite adequate IV fluid resuscitation and IV vasopressor support

If there is suspicion for adrenal crisis, the emergency clinician must evaluate the patient for a precipitating factor of the crisis. Gastrointestinal illness is the most common cause.[18] Other common causes include any type of infection or other stressors, such as surgery or trauma. Another common

Table 4. History and Physical Examination Elements to Aid Diagnosis of Adrenal Emergencies

Symptoms
- Abdominal pain
- Confusion
- Fatigue
- Constitutional symptoms consistent with infection (fever, chills, rigors)
- Nausea, vomiting, or diarrhea
- Decreased appetite
- Salt-craving
- Skin pigmentation changes
- Syncope
- Weakness
- Weight loss

Past Medical History
- Addison disease
- Adrenal disease
- Autoimmune diseases
- Prior head trauma leading to pituitary disorder
- Steroid use (prescribed or illicit[23])

Physical Examination Findings
- Altered mental status
- Dry mucous membranes
- Hyperpigmentation
- Hypotension
- Alopecia in axillae/genital area
- Abdominal pain
- Tachycardia

Important Precipitating Factors
- Recent medication changes
- Cessation of corticosteroid therapy
- Recent surgery (major, minor, or dental)
- Recent or current illness (most commonly gastrointestinal illness with significant nausea, vomiting, or diarrhea)
- Current pregnancy (first trimester and labor/delivery are periods of highest risk)
- Traumatic injury

cause is medication noncompliance. If patients are not prophylactically prescribed stress-doses of glucocorticoids, the physiological stress caused by even minor surgery (such as dental work) can result in an adrenal crisis.[22]

Physical Examination

The most characteristic physical examination finding is hyperpigmentation of the skin and mucous membranes. **(See Figures 2 and 3.)** This is caused by excess ACTH production, which stimulates melanin production.[24] Hyperpigmentation tends to be most obvious on sun-exposed areas, skin creases, mucous membranes, and scars. Women can also have alopecia in the axillary and pubic regions. Patients taking long-term exogenous glucocorticoids can present with Cushing syndrome, which consists of moon facies (round face secondary to lateral facial fatty deposits), increased fat between the shoulders (buffalo hump), thin extremities, and pink or red stretch marks on the skin. Patients may also have evidence of poor wound healing, hypertension, acne, or prior evidence of fractures due to bone-density loss.

Patients in adrenal crisis are often ill-appearing and hypotensive on presentation. These patients can have a lower baseline blood pressure, so determining their normal blood pressure is important. A hypotensive patient with altered mental status is concerning for poor cerebral perfusion. There may be signs of dehydration, such as dry mucous membranes and poor skin turgor. Occasionally, patients may present with severe abdominal pain, which can mimic signs of an acute abdomen.

Pediatric patients with severe forms of salt-wasting CAH can present with signs of dehydration, poor tone, poor feeding, decreased activity, altered mental status, nausea, vomiting, and abdominal pain. Further evaluation may reveal ambiguous genitalia, although this is not always present. Males may have phallic enlargement, and females can have clitoral enlargement, labial fusion, and urogenital sinuses. Hyperpigmentation of genitalia in both men and women is also seen.

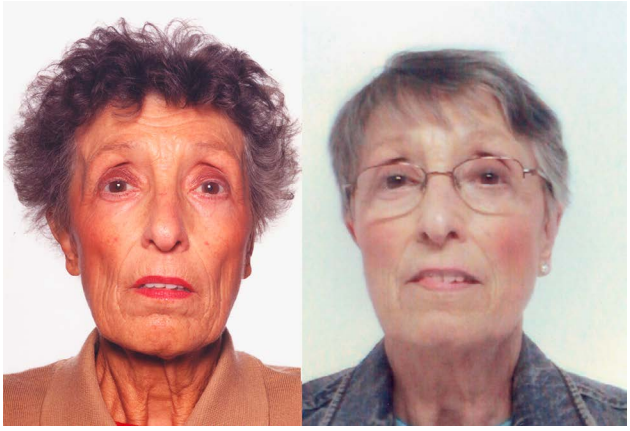
Patients with less severe cases of CAH often present through outpatient primary care providers; however, complaints of hypertension, urinary tract infections, fatigue, or other complaints may bring them to the ED. CAH in school-aged children, adolescents, or young adults frequently involves hirsutism, acne, short stature, and Tanner staging more advanced for age.

Diagnostic Studies

Laboratory Testing

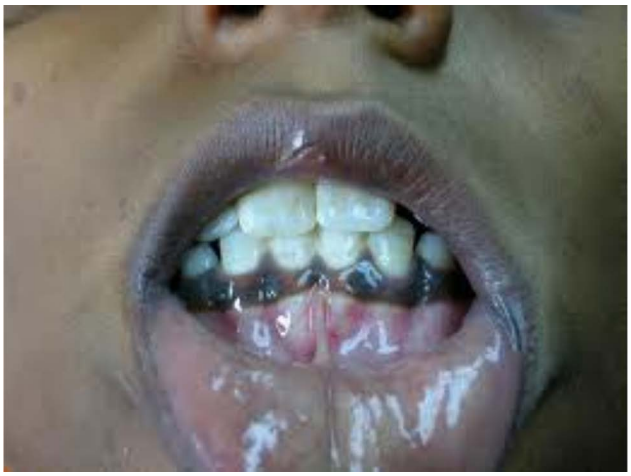
The diagnostic evaluation of patients with suspected adrenal crisis should include measurement of glucose and electrolytes, creatinine and transaminase testing, and a search for possible underlying stressors. **Table 5 (page 9)** includes a list of recommended tests in the ED and rationale for ordering. Recommended tests include complete blood cell count with differential, complete metabolic panel, magnesium, phosphorus, urinalysis, pregnancy test in reproductive-age women, and electrocardiogram (ECG). Additional tests for suspected underlying infection may include infection-specific cultures, polymerase chain reaction, or imaging studies, depending on the predicted source.

Figure 2. Hyperpigmented Skin



Left photo, before treatment; right photo, after treatment. Source: Perros P (2005) A 69-year-old female with tiredness and a persistent tan. *PLoS Med* 2(8): e229.
DOI: https://doi.org/10.1371/journal.pmed.0020229

Figure 3. Hyperpigmentation in Addison Disease



Source: *Dermatology Online Journal*. http://dermatology.cdlib.org/

The classic electrolyte disorder combination seen in PAI is hyponatremia, hypoglycemia, and hyperkalemia. Hyponatremia is very common and present in 90% of new diagnoses of PAI.[7] Nonetheless, serum sodium levels may be only marginally decreased from normal values, making its presence easy to overlook. Hyperkalemia is seen in about 50% of newly presenting patients. Hyponatremia and acidosis can be seen in PAI patients if they have profound nausea and vomiting, due to gastrointestinal losses. SAI does not present with hyperkalemia, as it is a glucocorticoid deficiency without mineralocorticoid deficiency.[7] Profound hypoglycemia is more likely in the pediatric population. The combination of hyponatremia, hypoglycemia, and hyperkalemia should raise suspicion for PAI; however, its presence or absence is not a reliable laboratory indicator of adrenal insufficiency or crisis.

Adrenal Function Testing

Laboratory evaluation of adrenal function in the ED is limited, often time-consuming, and difficult to interpret. There is no role for adrenal function testing in the ED for patients with known adrenal insufficiency. The emergency clinician should focus on detection and diagnosis of the underlying cause of adrenal crisis and on identifying and correcting any electrolyte disorders and/or hypoglycemia. Decisions made for the management of adrenal crisis should not depend on or be delayed for laboratory results; they should be based on history, vital signs, physical examination, clinician judgment, and response to parenteral stress-dose glucocorticoid treatment.[6,7,9] A verified diagnosis of adrenal crisis, or even adrenal insufficiency, is highly unlikely during the ED visit, though consulting and referring physicians can gain benefit from more-specific testing. As such, collecting additional blood for later testing prior to steroid administration can assist the endocrinology evaluation and should be done routinely in cases of suspected new-onset adrenal insufficiency.

Table 5. Recommended Testing for Adrenal Disease in the Emergency Department

Test	Rationale
Complete blood cell count with differential	• Leukocytosis, leukopenia, or bandemia suggestive of infection • Eosinophilia can be found in cases of adrenal insufficiency[7]
Complete metabolic panel	• Assessment of electrolytes • Evaluation for severity of dehydration • Evidence of organ dysfunction
Magnesium	• Assessment of electrolytes
Phosphorus	• Assessment of electrolytes
Urinalysis	• Evaluation for severity of dehydration • Evaluation for urinary tract infection
Urine pregnancy test	• Confirmation of pregnancy
Electrocardiogram	• Assess for acute myocardial infarction • Rapid screen for electrolyte disorders
Blood, urine, sputum, cerebrospinal fluid cultures	• As indicated for suspected source of infection

Testing for Cortisol or ACTH

There are no ED-specific guidelines for cortisol or ACTH testing. Emergency clinicians may be asked by admitting or consulting physicians to order definitive testing for adrenal insufficiency. In these circumstances, it is important to be familiar with the initial tests.

Cortisol Testing

Emergency testing for cortisol levels is not generally recommended due to the variability of cortisol levels and the associated difficulty of interpreting the results. Cortisol levels follow a circadian rhythm, creating a broad range for the "normal" level. Acute illness and stressed states cause even greater variability in cortisol levels than the expected circadian pattern. Random cortisol levels can also be confounded by exogenous steroid use. In some patients, cortisol levels may appear to be within normal limits, but in reality, they may be inappropriately low, given a physiologic stress. It is generally accepted that a cortisol level < 10 mcg/dL is highly suggestive of CIRCI and a level of < 3 mcg/dL is virtually diagnostic of CIRCI;[9] however, this level is not always found in patients with true adrenal crisis.[20]

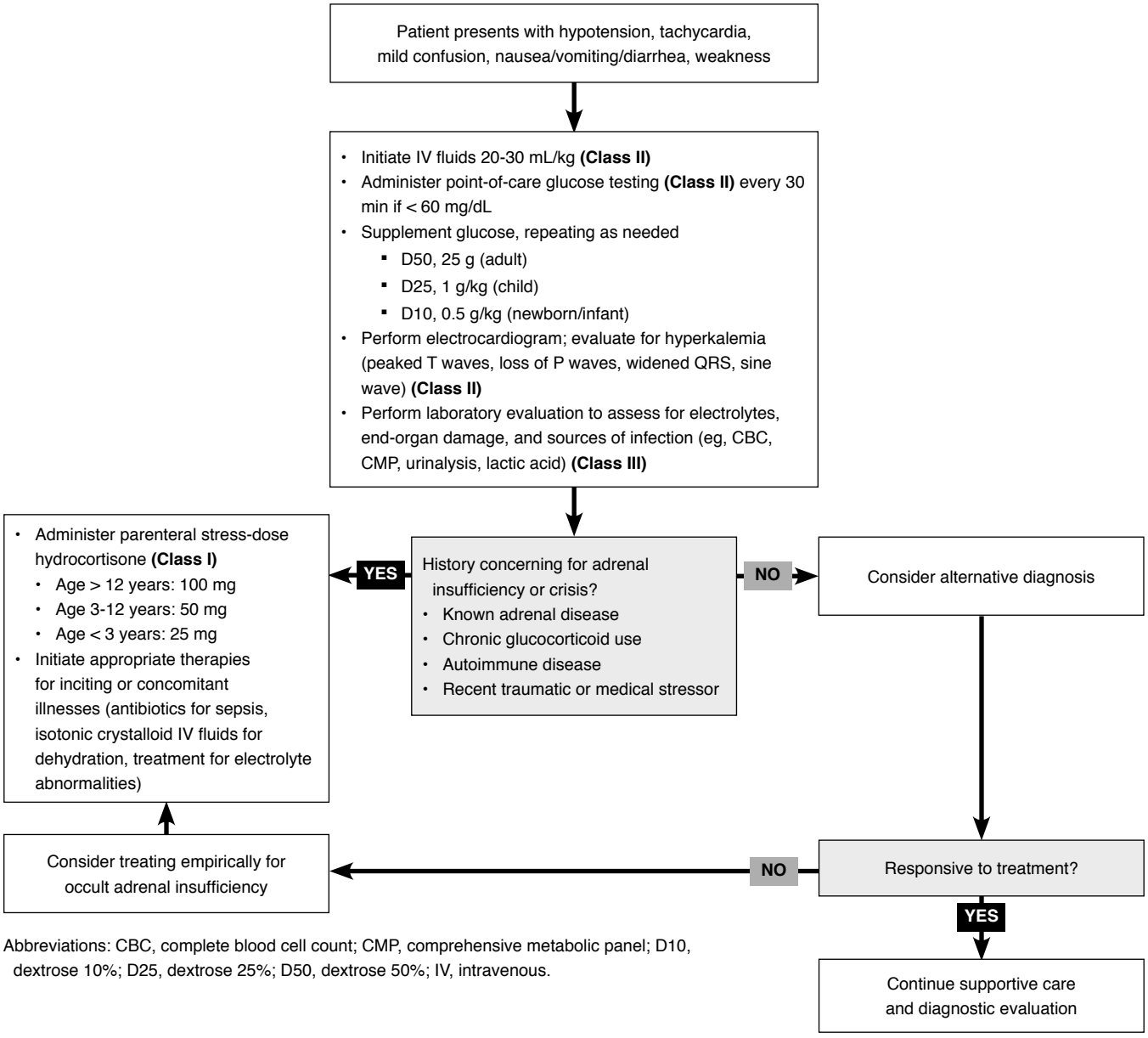
There are 2 versions of the cortisol level test. The commonly available random cortisol test measures both protein-bound and free cortisol. Only free cortisol is biologically active; thus, the test that reports a total cortisol can overestimate the biologically active component. The free cortisol test may be a more accurate assessment of active hormone, but is not widely available and does not have defined normal values.[9] Because most institutions do not have ready access to a free cortisol level, the commonly assessed laboratory test is the total cortisol test.

Some guidelines advocate for initial screening for suspected adrenal insufficiency by measuring paired cortisol and ACTH levels.[6] Ideally drawn early in the morning to improve accuracy, both the cortisol and ACTH tests are drawn at the same time. A low cortisol level (< 5 mcg/dL) combined with a high ACTH level (twice the normal value) raises concerns for PAI.[6]

ACTH Stimulation Testing

The recommended evaluation for PAI is the ACTH stimulation test. This involves administration of 250

Clinical Pathway for Emergency Department Treatment of Suspected Adrenal Crisis



Abbreviations: CBC, complete blood cell count; CMP, comprehensive metabolic panel; D10, dextrose 10%; D25, dextrose 25%; D50, dextrose 50%; IV, intravenous.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

mcg of corticotropin with measurement of cortisol levels before administration, then again 30 and 60 minutes after administration. The advantage of this test is that corticotropin can be administered intramuscularly or intravenously, so the test can be performed on an outpatient basis. A low-dose version of this test using 1 mcg of corticotropin is also available. The low-dose test was believed to be a more accurate test when it was developed, as the dose of corticotropin used more closely resembles plasma ACTH levels. However, it requires dilution of the corticotropin correctly prior to administration and must be given intravenously, making it more difficult to administer. Both the high-dose and low-dose tests can be used to diagnose PAI.[6,7] If the adrenal system is functioning normally, there should be a rise in the cortisol level following ACTH stimulation.

Evaluation of SAI is much more complicated. The gold-standard testing is the insulin tolerance test or the overnight metyrapone test. These tests are time-intensive, require monitoring, and in some instances can precipitate adrenal crisis, so are therefore impractical in the ED setting. Most providers will attempt to diagnose SAI with an ACTH stimulation test.[25]

Imaging Studies

Radiological studies should be ordered to help refine the differential diagnosis and identify potential inciting factors for adrenal crisis. Additional radiography, ultrasound, or other advanced imaging may be clinically indicated, based on the patient's presenting complaints. For example, chest radiography can serve as a rapid screen for pulmonary infections. Adrenal imaging for new-onset adrenal insufficiency is not indicated in the ED.[6,7,19]

Treatment

The care of the patient in adrenal crisis begins with good symptomatic and supportive care, as it does for every critically ill patient. This includes adequate IV fluid resuscitation and abnormal electrolyte correction. For unstable patients with known PAI (eg, Addison disease), or those in whom SAI is possible, given available history (eg, the chronic corticosteroid user with abrupt cessation), treatment with stress-dose corticosteroids should be given immediately. The more subtle presentations of acute adrenal insufficiency require the emergency clinician to make a judgment call based on the presentation, any known risk factors, lack of response to traditional treatment, and ranking of other competing diagnoses.

Corticosteroid effects occur in 3 categories: (1) anti-inflammatory, (2) glucocorticoid (mimicking cortisol), and (3) mineralocorticoid (mimicking aldosterone). Different corticosteroids have different proportions of activity in these different categories. Additionally, this must be balanced with the negative effects of chronic use, which includes growth retardation and androgen suppression, among others.[26]

Table 6 illustrsates the anti-inflammatory, glucocorticoid, and mineralocorticoid profiles of the available corticosteroid supplementation options. Hydrocortisone is the baseline steroid, and the relative potency of each effect is expressed as a factor compared to it. For example, dexamethasone has no mineralocorticoid activity and fludrocortisone has up to a 200-fold mineralocorticoid activity as compared to hydrocortisone. The ideal steroid treatment profile for adrenal crisis is a strong glucocorticoid and mineralocorticoid effect with minimal growth and androgen suppression. Fludrocortisone has a poor glucocorticoid profile, and dexamethasone and methylprednisolone have poor mineralocorticoid activity, making them poor choices for adrenal crisis. Hydrocortisone

Table 6. Glucocorticoid and Mineralocorticoid Comparison

Steroid	Anti-Inflammatory, Glucocorticoid Effect	Growth Retarding, Glucocorticoid Effect, Androgen-Suppressing Effect	Salt Retaining, Mineralocorticoid Effect
Hydrocortisone	1	1	1
Prednisolone	4	5-15[a]	0.8
Prednisone	3.5-4		0.8
Dexamethasone	30	70-100[b]	0
Fludrocortisone	15		200

Relative potency is expressed as a factor compared to hydrocortisone.

Reprinted from *Pharmacology & Therapeutics*, Volume 132, Issue 1. HL Claahsen-van der Grinten, NMML Stikkelbroeck, BJ Otten, ARMM Hermus. Congenital adrenal hyperplasia—pharmacologic interventions from the prenatal phase to adulthood. Copyright 2011, with permission from Elsevier.

[a]Punthakee Z, Legault L, Polychronakos C. Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency. *J Pediatr.* 2003;143(3):402-405.

[b]Rivkees SA, Crawford JD. Dexamethasone treatment of virilizing congenital adrenal hyperplasia: the ability to achieve normal growth. *Pediatrics.* 2000;106(4):767-773.

and prednisolone have both glucocorticoid and mineralocorticoid effect, making them options for treatment of adrenal crisis. Hydrocortisone is the corticosteroid of choice for the treatment of adrenal crisis, as it possesses the most favorable mix of both glucocorticoid and mineralocorticoid activity and is available by IV.[6] Initial stress-doses of hydrocortisone are listed in **Table 7**, with multiple dosing schemes available for pediatric patients based on age or body surface area.

Patients will continue on stress-dose steroids following the initial dose in the ED. A total daily dose divided every 6 hours is recommended as noted in **Table 7**. This dose will be administered for 24 hours following the initial dose. After completion of this, a tapering dose of corticosteroid can be considered. The decision to begin a taper is dependent on clinical improvement and is managed by the admitting physician or consulting endocrinologist. Prednisolone may be used as an alternative medication; however, with no clear recommendations available on dosing, it should be ordered in consultation with an endocrinologist. Dexamethasone has been used as the initial treatment for adrenal crisis, given its lack of interference in ACTH stimulation testing; however, its use is discouraged due to its lack of mineralocorticoid activity, and in one guideline it is listed as the least-preferred alternative to hydrocortisone.[6] Additional supplementation with fludrocortisone for adrenal crisis is not needed, as hydrocortisone has adequate mineralocorticoid activity.

Patients with PAI who are not in crisis but are currently experiencing or will experience a stressor also require an increase in corticosteroid therapy. Severe illness, major surgery, significant trauma, and childbirth mandate stress-dosing. Moderate illness involving fever, nausea, vomiting, and diarrhea will require increases in the daily supplement amount. Mental and emotional stressors, exercise, and minor illness do not require any changes to the baseline corticosteroid supplementation plan.[6,27] **Table 8** shows recommendations for prophylactic corticosteroid dosing for ill patients with adrenal insufficiency who are not in crisis. **Table 9 (page 13)** shows recommended corticosteroid dosing for surgical procedures.

IV fluid resuscitation should be administered to treat hypotension: adults, 1 to 2 L IV bolus; children, 10 to 20 mL/kg. Consider using isotonic crystalloids (such as 0.9% sodium chloride or 5% dextrose in 0.9% sodium chloride) if needed to maintain euglycemia. Vasopressors may be needed in addition to fluids and corticosteroids in patients with hypotension unresponsive to fluid resuscitation.[7] Norepinephrine is the suggested initial vasopressor (8-12 mcg/min or 0.01-0.3 mcg/kg/min). Additional vasopressors can be added based on the response, clinical picture, and other comorbid conditions.

Correction of severe electrolyte abnormalities and hypoglycemia should also be initiated in the ED. Glucose and insulin dysregulation are common during periods of stress, and point-of-care glucose measurements should be monitored every 30 minutes until stabilized. Hyperkalemia can be identified via a screening ECG and laboratory evaluation, and treated promptly if ECG changes are present. Hyponatremia correction begins with IV fluid resuscitation; however, further sodium replacement may be required, especially in children.

Table 8. Hydrocortisone for Adrenal Crisis Prophylaxis During Illness[7,19]

Illness	Recommended Dosing
Fever > 38°C	Double daily dosing orally for duration of illness, and then 1-2 days after
Fever > 39°C	Triple daily dosing orally for duration of illness, and then 2 days after
Gastroenteritis with vomiting and/or diarrhea	100 mg hydrocortisone SC or IM early, then repeat in 6-12 hr
Severe infection (eg, pneumonia with altered mental status)	100 mg hydrocortisone SC or IM early, then repeat in 6-12 hr until recovery

Abbreviations: IM, intramuscular; SC, subcutaneous.
Adapted with permission from Allolio B. Extensive expertise in endocrinology. Adrenal crisis. *European Journal of Endocrinology*. 2015;173(3):R115-R124.

Table 7. Hydrocortisone Stress-Dosing by Age for Adrenal Crisis[6,7,11]

Age		Initial Dose	Continued Inpatient Dosing
Adult		100 mg IV	50 mg IV every 6 hr
Pediatric		50 mg/m^2 IV, max dose 100 mg IV	50 mg/m^2/day, divided every 6 hr
Alternative pediatric	≤ 3 years	25 mg IV	25 mg/day IV divided every 6 hr
	3-12 years	50 mg IV	50 mg/day IV divided every 6 hr
	≥ 12 years	100 mg IV	100 mg/day IV divided every 6 hr

Alternative pediatric dosing reprinted from *Best Practice & Research Clinical Endocrinology & Metabolism*, Volume 29, Issue 3. Emma A. Webb, Nils Krone. Current and novel approaches to children and young people with congenital adrenal hyperplasia and adrenal insufficiency. Pages 449-468. Copyright 2015, with permission from Elsevier.

Special Circumstances

Pregnancy

Adrenal insufficiency is a rare occurrence during pregnancy, with an incidence of 1:3000 births. Both PAI and SAI have a negative impact on fertility, thus conception in these disease states is difficult. Most pregnant patients with adrenal insufficiency will experience a normal, uneventful pregnancy when treated under the guidance of an endocrinologist.[7] The riskiest periods during pregnancy are the first trimester, followed by labor and delivery. The similarities between symptoms present in a patient with a normal early pregnancy and in a patient with adrenal insufficiency make a new diagnosis of adrenal insufficiency challenging. Complaints of severe and persistent lightheadedness, syncope, nausea, vomiting, salt-craving, weight loss, and hyperpigmentation of skin creases should raise concern for adrenal insufficiency. Laboratory testing can demonstrate hyponatremia and hypoglycemia. Persistence of symptoms past the first trimester can lead to a diagnosis of adrenal insufficiency. Normal physiologic changes in pregnancy result in a reset of the HPA axis. Normal pregnancy is a state of hypercortisolism, thus trimester-specific normal values must be referenced when laboratory testing for adrenal disorders is performed in pregnant patients.[29]

Treatment of adrenal insufficiency during pregnancy requires increased daily dosing of hydrocortisone supplementation to mimic the physiological increase in cortisol during pregnancy. Progesterone is an antimineralocorticoid, so a dosing increase of fludrocortisone is needed during the later stages of pregnancy. The stress of labor and delivery requires stress-dose glucocorticoid administration (100 mg hydrocortisone IV, repeating 50 mg every 6 hours as needed) that should be continued for a few days after delivery.[6,7]

Table 9. Hydrocortisone Prophylaxis Dosing for Surgery and Procedures[7,19,28]

Type of Procedure	Example	Preoperative and Operative Needs	Postoperative Needs
Lengthy major surgery with long recovery time	• Open-heart surgery • Major bowel surgery	100 mg hydrocortisone IV just before anesthesia, **then** 100 mg IV every 6 hr **or** 200 mg/24 hr infusion	Continue 100 mg hydrocortisone IV every 6 hr **or** 200 mg/24 hr infusion until able to tolerate orally, **then** double daily dose orally for 48 hr
Major surgery with rapid recovery	• Cesarean delivery • Joint replacement	100 mg hydrocortisone IV just before anesthesia, **then** 100 mg IV every 6 hr **or** 200 mg/24 hr infusion	Continue 100 mg hydrocortisone IV every 6 hr **or** 200 mg/24 hr infusion for 24-48 hr **or** until able to tolerate orally, **then** double daily dose orally for 24-48 hr
Labor and vaginal birth	• Labor and vaginal delivery	100 mg hydrocortisone IV at onset of active labor, **then** 100 mg IV every 6 hr **or** 200 mg/24 hr infusion until delivery	Double daily dose orally for 24-48 hr
Minor surgery	• Cataract • Hernia repair • Laparoscopic surgery with local anesthesia	100 mg hydrocortisone IM just before anesthesia	Double daily dose orally for 24 hr
Minor procedure	• Skin mole removal	Extra oral dose 1 hr before procedure	Extra oral dose 1 hr after procedure
Invasive bowel procedures requiring laxatives	• Colonoscopy • Barium enema	100 mg hydrocortisone IV **and** hospital admission overnight for IV fluids during preparation, **then** 100 mg hydrocortisone IV just before start	Double daily dose orally for 24 hr
Other invasive procedures	• Endoscopy	100 mg hydrocortisone IM just before starting	Double daily dose orally for 24 hr
Major dental surgery	• Dental extraction with local or general anesthesia	100 mg hydrocortisone IM just before anesthesia	Double daily dose orally for 24 hr
Dental surgery	• Root canal with local anesthesia	Double oral dose 1 hr before surgery	Double daily dose orally for 24 hr
Minor dental procedure	• Filling, scale, and polish	Extra oral dose 1 hr before procedure	Take extra oral dose if symptoms present

Abbreviations: IM, intramuscular; IV, intravenous.

Congenital Screening

Retrospective studies have demonstrated mortality from salt-wasting CAH ranging from 3% to 11%.[30,31] Emphasis on reducing mortality from salt-wasting CAH in the first year of life has resulted in all 50 states in the United States and multiple other countries instituting newborn screening.[31] Several states in the United States have progressed to a second newborn screen at a point between days 8 and 14 to help detect the approximately 30% of CAH cases missed by the primary screen.[32,33] Emergency clinicians should not rely on a negative newborn screen to exclude congenital adrenal hyperplasia as a possible diagnosis. Any ill-appearing infant presenting with poor feeding, decreased activity, and dehydration, along with ambiguous genitalia on examination or hypoglycemia and hyponatremia should raise a concern for adrenal crisis, regardless of the results of a newborn screen. Initiate fluid resuscitation, stress-dose steroids, and glucose control immediately, and admit for further investigation and testing.

Controversies and Cutting Edge

Etomidate Use in Patients With Sepsis

Etomidate is often used to facilitate rapid sequence intubation (RSI) for patients who are hypotensive due to its favorable hemodynamic profile relative to other induction agents.[34] Etomidate reversibly blocks 11-beta-hydroxylase enzyme action for at least 24 hours, thus inhibiting adrenocortical steroid synthesis.[35] Its use has been a topic of debate in the critical care and emergency medicine literature, given the potential clinical effects. A well-known 2008 study of trauma patients randomized to receive etomidate or fentanyl and midazolam for induction for intubation showed that patients who received etomidate had a longer intensive care unit (ICU) length of stay and increased ventilator days.[36]

In a 2009 trial, 655 critically ill patients were randomized to ketamine or etomidate for induction for intubation.[37] There were no differences in mortality, catecholamine usage, mechanical ventilation-free days, or ICU-free days. However, patients given etomidate were more likely to demonstrate evidence of adrenal insufficiency (86% vs 48%, $P < .0001$). In a subgroup analysis of patients with sepsis, there was no difference in mortality, although there were only 76 patients in this subset. A 2010 trial randomized 122 patients with sepsis to receive etomidate or midazolam for RSI for intubation.[35] There were no significant differences in mortality, ICU length of stay, or hospital length of stay.

Multiple meta-analyses evaluating this subject have reached different conclusions. A 2015 Cochrane review on single-dose etomidate in RSI for critically ill patients demonstrated no significant difference in mortality in patients who received etomidate versus other agents (odds ratio [OR], 1.17; 95% confidence interval [CI], 0.86-1.60; 772 participants).[38] There was a small increase in Sequential Organ Failure Assessment (SOFA) score in patients who received etomidate, but there was no difference in duration of mechanical ventilation, duration of vasopressor use, ICU length of stay, or hospital length of stay. Another review came to a similar conclusion.[39] However, a 2012 review on single-dose etomidate use in patients with severe sepsis and septic shock came to a different conclusion.[40] The authors analyzed data from 5 trials, demonstrating that, in 865 septic patients given etomidate versus other induction agents, the relative risk of mortality was 1.20 (95% CI, 1.02-1.42). One trial in the analysis was a prospective observational trial, and 2 trials were subgroups of trials in which septic patients were randomized to hydrocortisone versus placebo. The 2 remaining studies are the 2 aforementioned randomized trials in which there was no statistical difference between etomidate and ketamine in one study and etomidate and midazolam in the other study. In contrast, a 2015 review including randomized as well as observational data showed no difference in mortality in septic patients who were administered etomidate.[41]

Overall, equipoise remains on this subject. There is a limited amount of quality data, and therefore, clinicians can continue to make a patient-by-patient decision on which induction agent to use for patients with sepsis. Ketamine may prove to be an attractive alternative to etomidate. With ketamine, there is no concern for adrenal insufficiency, and in the study comparing etomidate to ketamine, there was a nonsignificant trend toward decreased mortality with ketamine. Further studies are needed to provide a definitive answer.

Adrenal Insufficiency in Sepsis

The body requires an intact HPA axis in order to address infections and maintain homeostasis. Critical illness disrupts the functions of the HPA axis by decreasing production of corticotropin-releasing hormone, ACTH, and cortisol, as well as dysfunction of their receptors via mechanisms that are not clearly understood. Structural damage to the adrenal glands from hemorrhage or infection can also occur.[9] This HPA dysfunction can result in a relative adrenal insufficiency, also known as CIRCI.[20] The rate of CIRCI in patients with septic shock can approach 60%.[9] Adrenal insufficiency can result in increased inflammation and decreased response to catecholamines.[16] Corticosteroid replacement may help to reverse those changes. Based on previous trials, corticosteroids were previously standard therapy for patients

with septic shock.

In 2008, data from the seminal CORTICUS trial was released. In this trial, 499 patients with septic shock were randomized to hydrocortisone versus placebo.[42] There was no difference in mortality between the 2 groups, even when the subgroup of patients with no response to corticotropin was analyzed. Hemodynamics improved more quickly in patients with septic shock randomized to hydrocortisone, but there was also an increased incidence of hyperglycemia and superinfection. In a 2015 Cochrane review, the authors found a lower relative risk of dying at 28 days in patients with septic shock who were given corticosteroids (RR, 0.88; 95% CI, 0.78-0.99).[43] The review noted that studies with lower doses of corticosteroids given for a longer course resulted in the largest benefit, especially in the sickest subset of patients.

In the most recent Surviving Sepsis guidelines, corticosteroids were not recommended in patients with septic shock who are hemodynamically stable after receiving fluid resuscitation and vasopressors.[8] In the subset of patients with vasopressor-refractory shock, IV hydrocortisone is recommended at a daily dose of 200 mg. The usual dosing is a 100 mg IV bolus of hydrocortisone followed by 50 mg IV every 6 hours. (CORTICUS trial dosing: hydrocortisone 50 mg IV every 6 hours for 5 days; 50 mg IV every 12 hours for 3 days; 50 mg IV daily for 3 days.[42]) The guidelines recommend against using an ACTH stimulation test to help identify which patients may benefit from exogenous corticosteroids.[8] Overall, corticosteroids should be reserved for patients with septic shock who are at the greatest risk of mortality. They should not be administered to patients with sepsis without shock.

Adrenal Insufficiency After Cardiac Arrest

In the cardiac arrest literature, recent attention has been given to the role of adrenal suppression and refractory shock following cardiac arrest. Interest in the use of stress-dose corticosteroids during and post resuscitation resulted from data demonstrating that patients with high cortisol levels following cardiac arrest have higher survival rates.[44-46] This led to hypotheses regarding relative adrenal suppression during cardiac arrest, similar to the phenomenon seen in septic patients. The administration of stress-dose corticosteroids to patients successfully resuscitated from cardiac arrest with refractory hypotension has demonstrated mixed outcomes for short-term survival, survival to discharge, or neurological status.

Tsai et al conducted a prospective, nonrandomized, open-label trial involving administration of stress-dose corticosteroids versus placebo to 97 patients with out-of-hospital cardiac arrest. Results demonstrated that the hydrocortisone group had more patients regain and maintain return of spontaneous circulation; however, there was no difference between the groups regarding short-term survival rates, hospital discharge, or neurologic outcome.[47]

Donnino et al performed a multicenter randomized, blinded, controlled trial involving administration of stress-dose corticosteroids to patients with vasopressor-refractory shock (defined as vasopressor administration for a minimum of 1 hour) following cardiac arrest. This was a study with 50 patients, with 25 randomized to 100 mg IV hydrocortisone versus placebo. Results showed no statistical difference in time to shock reversal, difference in neurological outcomes, achievement of shock reversal, or survival to discharge.[48]

Two studies have demonstrated improvement in survival rates and neurologic outcomes for in-hospital cardiac arrests. Both were small, single-center randomized, blinded, controlled trials evaluating epinephrine plus saline versus epinephrine plus vasopressin plus methylprednisolone during resuscitation. The initial study included 100 patients with in-hospital cardiac arrest and it evaluated for return of spontaneous circulation and survival to hospital discharge in the study groups versus controls.[49] The second study with similar design evaluated 300 patients for neurologic outcomes. Study investigators were blinded and performed interviews and medical record reviews to determine the outcomes. Results showed improved return of spontaneous circulation and survival to hospital discharge, with favorable neurologic outcomes.[49,50]

Overall, there has been limited study on the use of stress-dose corticosteroids in cardiac arrest. Studies involving corticosteroids alone show no significant trend in survival, neurological outcomes, or discharge rates. However, 2 other smaller trials with a treatment group including stress-dose steroids and vasopressin demonstrated improvement in short-term survival and neurological outcome. While further investigation is warranted, the use of steroids in cardiac arrest is not recommended at this time.

Disposition

Ultimately, all patients in adrenal crisis will require admission for continued corticosteroid administration and fluid and electrolyte replacement. The degree of electrolyte abnormality and vital-sign derangement differentiate those patients that require ICU level of care.

Some patients with an exacerbation of adrenal insufficiency that has not progressed to shock or metabolic abnormalities have the potential to be discharged home. These patients can start a 2- to 3-fold increase in daily corticosteroid replacement

Risk Management Pitfalls for Adrenal Insufficiency and Adrenal Crisis

1. **"She had a history of chronic corticosteroid use with pneumonia, but I thought she was hypotensive from sepsis, so I didn't give her corticosteroids."**
   Hypotension may be related to septic shock, cardiac dysfunction, medication side effects, or a host of other causes. However, in the patient on chronic corticosteroids or who has a history of adrenal insufficiency, a single dose of IV hydrocortisone should be administered early in the resuscitation, as adrenal insufficiency/adrenal crisis are of great concern in this population.

2. **"He had a history of chronic corticosteroid use with pneumonia, but I thought he was hypotensive from adrenal crisis, so I didn't give him antibiotics."**
   While administering corticosteroids is key, it should never be done instead of conventional treatments. Antibiotics, IV fluids, vasopressors, or antidotal care should be administered as if the patient was not adrenally insufficient, but it should be done in addition to the IV hydrocortisone.

3. **"I presumed the neonate's poor feeding was the reason for his hyponatremia. He had a normal newborn screen."**
   Newborn screens miss a significant number of children with congenital salt wasting, and relying on that alone to exclude the diagnosis of adrenal crisis with CAH can lead to an incorrect diagnosis. Poor feeding and salt wasting can be presenting complaints of CAH in the neonate.

4. **"I thought he was in adrenal crisis, but I wanted to get his cortisol result back to be sure before giving him steroids."**
   Cortisol or ACTH testing may have a role to assist inpatient workup, but in the acute setting, it should never delay the administration of stress-dose corticosteroids in the patient with adrenal crisis.

5. **"I gave the patient with adrenal insufficiency oral prednisone as his stress-dose, since he could tolerate oral medication."**
   The medication of choice in adrenal crisis or adrenal insufficiency is IV hydrocortisone. It has the proper mix of mineralocorticoid and glucocorticoid function and is preferred over dexamethasone, prednisolone, methylprednisolone, or prednisone.

6. **"The patient told me she took 'herbals,' but I didn't ask which ones."**
   Any history of taking dietary supplements, "natural" remedies, compounded medication, or medications from a foreign country should prompt further questioning. Steroid contamination of these products, purposely or accidentally, may lead to an increased risk of adrenal crisis. As such, a detailed medication history should be obtained, including doses, schedules, compliance, and type of drugs.

7. **"The patient has a history of stopping his corticosteroids. He was altered, but did not improve after we gave him IV hydrocortisone and IV fluids. We are waiting for the chemistry to come back from the lab."**
   Hypoglycemia is a common problem in the adrenal crisis patient. Bedside glucose measurement should be a regular part of evaluating any altered patient, but in the patient with potential adrenal suppression, this is vital.

8. **"The patient gave a good history for adrenal crisis, but he was only hyponatremic, and not hyperkalemic or hypoglycemic, which is why I didn't give him corticosteroids."**
   While the classic laboratory abnormalities are the triad of hyponatremia, hyperkalemia, and hypoglycemia, by no means are they required to make the diagnosis. Hyponatremia is the most common, but approximately 10% of patients do not manifest an abnormal sodium level during periods of acute adrenal crisis.

9. **"The patient was being admitted to the floor for sepsis, so we gave her a dose of hydrocortisone."**
   Corticosteroids for the stable septic patient are not indicated.

10. **"The patient has a history of adrenal insufficiency and has a gastrointestinal illness. As long as he can take his medications by mouth after fluids and antiemetics in the ED, he can take his regular dosing at home."**
    Gastrointestinal illness is the most common reason for adrenal crisis, and as such, stress-dose corticosteroids should be administered promptly after arrival to the ED.

with the possible addition of fludrocortisone and close follow-up. The decision to discharge this subset of patients should be at the discretion of the provider and take into consideration comorbid conditions, access to follow-up, age, and previous history of disease.

Summary

Adrenal insufficiency is categorized as either primary or secondary. In the setting of adrenal insufficiency, when the body is unable to manifest enough corticosteroids during periods of stress, the patient can develop an adrenal crisis that presents with hemodynamic instability, electrolyte dysfunction, and/or alterations in mental status. The symptoms of adrenal crisis mimic many other critical illnesses, and there is no pathognomonic finding to secure the diagnosis. As such, a detailed history and physical examination are required to delineate adrenal crisis from other differentials such as diabetic ketoacidosis or sepsis. Prompt administration of parenteral hydrocortisone is indicated in suspected cases of adrenal insufficiency. Cortisol or ACTH tests are not indicated in the ED; however, in cases of new-onset adrenal insufficiency, providing consultants with access to pre–steroid-administration blood samples can be helpful for future diagnostic studies. Stress-dose corticosteroids should be considered in vasopressor-refractory sepsis. All patients with suspected adrenal crisis should be admitted to the hospital.

Case Conclusions

Despite IV fluids and a norepinephrine infusion, the 56-year-old man with pneumonia remained hypotensive. You ordered a vasopressin infusion to be started, but also gave an IV bolus of 100 mg of hydrocortisone. The patient's MAP stabilized in the upper 60s, and the norepinephrine infusion could be titrated down. He was admitted to the ICU with septic shock, but with a stable blood pressure.

With the initiation of 0.9% sodium chloride IV boluses and antiemetic administration, the 24-year-old female patient with PAI with vomiting and diarrhea was given a stress-dose of hydrocortisone (100 mg) intravenously. Her blood pressure improved during her ED stay. You diagnosed mild hypoglycemia and mild hyperkalemia and treated her with glucose supplementation and rehydration. She was admitted to a telemetry floor for continued observation, electrolyte monitoring, and rehydration.

The lethargic infant's bedside glucose was found to be 54 mg/dL. IV access was established, and a 20 mL/kg bolus of 0.9% sodium chloride and glucose replacement were initiated. Cultures were collected and empiric antibiotic therapy was initiated. Laboratory evaluation was significant for a potassium level of 7.5 mmol/L and a sodium level of 124 mmol/L. A presumptive diagnosis of salt-wasting adrenal hyperplasia was made. Additional blood was drawn for future testing, and the infant was given stress-dose corticosteroids, hydrocortisone 25 mg IV, and admitted to the pediatric ICU. Additional testing following admission confirmed congenital adrenal hyperplasia.

Time- and Cost-Effective Strategies

- **Don't waste time with testing for adrenal function in the emergency department.** Adrenal function testing (cortisol levels, ACTH levels, ACTH stimulation tests) will not help the emergency clinician make decisions on management for adrenal crisis. These tests do not result promptly enough to help make management decisions. Additionally, the results are often complicated and difficult to interpret correctly. Emergency clinicians should rely on history, physical examination, and clinical suspicion, and initiate diagnosis and treatment for suspect adrenal crisis. In certain situations, it may be necessary to order some of the above tests on the admitting orders for these patients if they will not be seen until the next day by the admitting provider.
- **Do not delay hydrocortisone administration if the differential diagnosis includes adrenal crisis.** If you have clinical suspicion for adrenal crisis in an unstable or ill patient, you should initiate corticosteroid therapy immediately. Failure to initiate timely corticosteroids for adrenal crisis carries a higher morbidity and mortality rate.

Key Points

- In PAI, the lack of endogenous steroids is secondary to a lack of production by the adrenal glands, whereas in SAI, it is secondary to a lack of hormone stimulation to intact adrenal glands.
- CIRCI is a multifactorial adrenal insufficiency during times of extreme stress on the body.
- Adrenal insufficiency or adrenal crisis may have a nonspecific presentation (hypotension, tachycardia, weakness, nausea) and should be included in the differential when considering sepsis, other endocrine emergencies, ingestions, or dehydration.
- Obtaining a history of any prior adrenal insufficiency and a detailed medication list are key to homing in on the diagnosis of adrenal insufficiency or crisis.
- CAH should be in the differential of any infant with poor feeding or vomiting, especially if there are genital anomalies or hyperpigmented skin.
- The laboratory evaluation of the suspected adrenally insufficient patient should focus on finding electrolyte abnormalities or sequelae of dehydration, such as acute kidney injury.

- While hormonal testing in the ED has little utility, if a patient is suspected of new-onset adrenal insufficiency and hydrocortisone is to be administered, drawing additional blood for future studies can assist the inpatient workup.
- Treatment should focus on early corticosteroid administration, IV fluid resuscitation, and electrolyte/glucose management.
- Hydrocortisone is the preferred agent for treating acute adrenal insufficiency or adrenal crisis in children and adults.
- While CAH screening is done at birth, approximately 30% of cases are missed, so a neonate presenting with symptoms of salt wasting should have CAH in the differential diagnosis.
- There is equipoise on the topic of etomidate as an RSI agent in septic patients, and clinicians should make a patient-by-patient decision on which induction agent to use.
- Administration of corticosteroids in patients in septic shock is not advised, but should be considered for those with vasopressor-refractory shock.
- The use of corticosteroids status post cardiac arrest is not indicated, based on current evidence.
- Patients with adrenal insufficiency or crisis requiring IV fluid resuscitation and corticosteroid administration should be admitted to the hospital for observation, hydration, and continued steroid administration.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study is included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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1. The most common cause of primary adrenal insufficiency (PAI) in developed countries is:
   a. Adrenal infarction
   b. Autoimmune disease
   c. Medication side effects
   d. AIDS-related diseases

2. How is PAI distinguished from secondary adrenal insufficiency (SAI)?
   a. There is an intact hypothalamus-pituitary axis
   b. There is a lack of adrenocorticotropic hormone (ACTH) production
   c. SAI occurs in response to infection
   d. There is no difference

3. With regard to patients with classical congenital adrenal hyperplasia (CAH) which of the following is most accurate?
   a. The degree of aldosterone deficiency correlates with the salt wasting
   b. Delayed puberty is typical
   c. Primary adrenal insufficiency in children is rarely due to CAH
   d. Salt wasting is a rarely associated with CAH

4. What is the most common cause of adrenal crisis?
   a. Trauma
   b. Surgery
   c. Gastrointestinal illness
   d. Medication noncompliance

5. What is the most common electrolyte abnormality identified in adrenal insufficiency and crisis?
   a. Hypoglycemia
   b. Hyperkalemia
   c. Hypokalemia
   d. Hyponatremia

6. Which event requires stress-dose steroids for the patients with PAI?
   a. Exercise
   b. Bronchitis
   c. Uncomplicated childbirth
   d. Emotional stress

7. A 33-year-old man with a history of Addison disease presents with mild confusion and hypotension. His daughter recently had gastroenteritis and he describes similar symptoms of nausea, vomiting, and diarrhea. Which correctly describes the role of hydrocortisone in his treatment?
   a. Laboratory testing for cortisol level should be done, and if the cortisol level is low, aggressive hydrocortisone dosing should be started.
   b. Hydrocortisone should be dosed if he is not responsive to IV fluids and vasopressors.
   c. Hydrocortisone should be administered if the patient has hyponatremia, hyperkalemia, and hypoglycemia.
   d. Hydrocortisone treatment should be administered at 100 mg IV along with initial resuscitation fluids.

8. Which of the following is the correct dose of stress-dose steroids for an adult who presents with adrenal crisis?
   a. 100 mg hydrocortisone IV
   b. 60 mg prednisone orally
   c. 10 mg dexamethasone IV
   d. 0.1 mg fludrocortisone orally

9. Which of the following intubation induction agents may pose a risk for reversible adrenal insufficiency?
   a. Midazolam
   b. Etomidate
   c. Ketamine
   d. Propofol

10. Which patients with sepsis should be given hydrocortisone?
   a. All septic patients
   b. Septic patients with hypotension after a 30 ml/kg IV fluid bolus
   c. Septic patients requiring vasopressors
   d. Septic patients with IV fluid- and vasopressor-refractory shock

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EMERGENCY MEDICINE PRACTICE
POINTS & PEARLS

A Quick-Read Review Of Key Points & Clinical Pearls, July 2017

Identifying Emergency Department Patients With Chest Pain Who Are at Low Risk for Acute Coronary Syndromes

Points

- For the evaluation of suspected acute coronary syndromes (ACS) in the ED, consensus guidelines recommend obtaining basic history, physical examination, electrocardiogram (ECG), cardiac biomarkers, and chest radiography. If these tests are unremarkable, confirmatory tests can be performed, with a focus on diagnosis of atherosclerotic coronary artery disease (CAD).
- History cannot reliably rule in or rule out ACS.
- Features with a higher likelihood of ACS include pain radiating to both arms or shoulders, pain similar to prior ischemia, exertional pain, pain associated with diaphoresis, and a change in pain pattern over the past 24 hours.
- Features with a lower likelihood of ACS include pain described as pleuritic, positional, reproducible with palpation, sharp/stabbing, or non-exertional.
- Women are more likely to present with atypical symptoms and their exercise stress-testing results are less accurate.
- Younger patients are more likely to have low-yield confirmatory testing.
- Elderly patients may be unable to have certain confirmatory testing performed based on medical comorbidities or exercise limitations, but this is not necessarily a contraindication for all testing.
- In patients with chest pain, the physical examination is often normal, and it may be more important for assessing overall hemodynamic function and the likelihood of alternative diagnoses.
- Physical examination features that show a higher likelihood of ACS include hypotension, new mitral regurgitation murmur, and third heart sound.
- An ECG should be obtained within 10 minutes of arrival. STEMI is defined as ST elevation at the J point of ≥ 1 mm (0.1 mV) in ≥ 2 contiguous leads (except in leads V_2-V_3 where ST elevation can be up to 1.5 mm in women, 2 mm in men aged ≥ 40 years, and 2.5 mm in men aged < 40 years).
- Conventional troponin assays can detect myocardial infarction within 3 hours of ED arrival in most patients; they have excellent sensitivity but poor specificity for myocardial infarction.

Pearls

- The 2 most useful scores for the ED evaluation of undifferentiated chest pain for suspected ACS are the TIMI and HEART Scores.
- Women, the elderly, and diabetic patients are more likely to present with atypical symptoms, such as lack of pain, pain outside of the chest, nausea, or dyspnea.
- High-sensitivity troponin assays can shorten detection time, but have decreased specificity.
- Most ED patients with chest pain who are hemodynamically stable, have normal or nondiagnostic serial ECGs, negative serial biomarkers, and low risk, based on a validated clinical score, can be safely discharged.

- If symptoms are suggestive of ACS but initial troponin is negative, a second value should be obtained in 3 to 6 hours.
- Current consensus guidelines recommend that all patients with normal serial ECGs and negative biomarkers undergo confirmatory testing before discharge or within 72 hours. Such testing adds little to no additional benefit for patients at low risk for a major adverse cardiac event (MACE).
- Patients with an unremarkable ED evaluation but who are at intermediate or high risk should be admitted to an observation or inpatient setting.
- Patients with chest pain who are at low risk for ACS or MACE may be candidates for primary prevention and lifestyle modification.

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Table 2. Electrocardiographic Classification and Likelihood of 30-day Major Adverse Cardiac Event[39]

Electrocardiographic Classification	Positive LR for 30-day MACE
Normal	0.4
Nonspecific ST and/or T-wave changes	1.2
Abnormal, but not diagnostic of ischemia	1.2
Ischemia or prior infarction known to be old	2.6
Ischemia or prior infarction not known to be old	9.7
Consistent with acute myocardial infarction	15.8

Major adverse cardiac events include acute myocardial infarction, cardiovascular death, unstable angina, or revascularization.
Abbreviations: LR, likelihood ratio; MACE, major adverse cardiac event.

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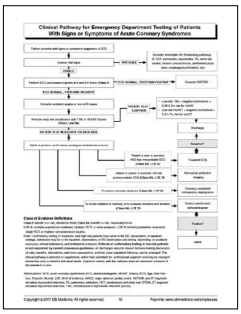

Clinical Pathway for Emergency Department Testing of Patients With Signs or Symptoms of Acute Coronary Syndromes

MDCalc Score Calculators

HEART Score for Major Cardiac Events:
https://www.mdcalc.com/heart-score-major-cardiac-events

TIMI Risk Score for UA/NSTEMI:
https://www.mdcalc.com/timi-risk-score-ua-nstemi

Questions, comments, suggestions?
To write a letter to the editor, email:
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First Responders

What changes do you anticipate making in your practice as a result of this activity?

- Incorporate HEART score to better identify patients who can be safely discharged.
- Use TIMI score and chart this score on all chest pain patients.
- Be more careful with utilizing single troponin to rule out ACS.
- Will likely get more troponin tests on young patients to further characterize them as low risk.
- Will discuss role of confirmatory testing in chest pain patients since there are no good studies to show that it decreases morbidity and mortality.

Most Important References

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