The Clinical Manifestations, Diagnosis, and Treatment of Adrenal Emergencies

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KEYWORDS

- Adrenal emergencies • Primary adrenal insufficiency (Addison disease)
- Secondary adrenal insufficiency • Tertiary adrenal insufficiency • Adrenal crisis
- Pheochromocytomas

KEY POINTS

- Adrenal insufficiency occurs because of a disruption in the hypothalamic-pituitary-adrenal axis. The resultant hormonal deficiencies cause a myriad of nonspecific symptoms, complicating the clinical picture and delaying diagnosis.
- The hallmark of adrenal crisis is hypotension and shock refractory to fluid resuscitation and vasopressors. Adrenal crisis is a life-threatening condition and treatment should not be delayed for confirmatory testing.
- Hydrocortisone is the drug of choice for treating cases of adrenal crisis or insufficiency because of its glucocorticoid and mineralocorticoid effects.
- Pheochromocytoma is a rare, catecholamine-secreting tumor of the adrenal medulla, which may precipitate life-threatening hypertension and lead to multiorgan system failure.

INTRODUCTION

With his perfectly tanned, boyish good looks, athleticism, intelligence, and wit, John F. Kennedy (JFK) was the picture of vitality. Even 50 years after his assassination, his presidential administration, still referred to as Camelot, embodies the hopes, dreams, and exuberant idealism of many Americans. Yet beneath the facade, JFK was plagued by the myriad of health problems seen in patients with adrenal insufficiency and those on chronic steroids. JFK's medical records reveal that he was diagnosed with adrenal insufficiency in 1947 and hypothyroidism in 1955. Experts now believe that JFK suffered from autoimmune polyendocrine syndrome type 2. Unlike the participants of more recent political campaigns, JFK's health issues remained largely hidden from the public domain. Decades later, we know that JFK's physicians prescribed him

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numerous medications but the extent to which his illness impacted his presidential decision-making and the course of American history remains largely unknown.[1,2]

Emergency medicine physicians should be able to identify and treat patients whose clinical presentations including key historical, physical examination, and laboratory findings are consistent with diagnoses of primary, secondary, and tertiary adrenal insufficiency, adrenal crisis, and pheochromocytoma. Failure to make a timely diagnosis leads to increased morbidity and mortality. As great mimickers, adrenal emergencies often present with a constellation of nonspecific signs and symptoms that can lead even the most diligent emergency physician astray. As discussed in this article, the emergency physician must include adrenal emergencies in the differential diagnosis when encountering such clinical pictures.

EMERGENCIES OF THE ADRENAL CORTEX

Primary Adrenal Insufficiency (Addison Disease)

Epidemiology

In the United States, the prevalence of Addison disease is 40 to 60 cases per 1 million population. Internationally, the occurrence is equally rare. The reported prevalence in countries where data are available is 39 cases per 1 million population in Great Britain, 60 cases per 1 million population in Denmark, and 144 cases per million in Norway.[3,4] It is more common in women and diagnosis peaks during the fourth to sixth decades of life. In the United States, roughly 80% of cases are caused by autoimmune disorders.[5] These autoimmune disorders can occur as an isolated process or as part of an autoimmune polyendocrine syndrome known as the polyglandular autoimmune syndrome types I and II. Type I polyglandular autoimmune syndrome is associated with candidiasis, hypoparathyroidism, and adrenal failure. Type II polyglandular autoimmune syndrome consists of Addison disease plus either an autoimmune thyroid disease or type 1 diabetes mellitus associated with hypogonadism, pernicious anemia, celiac disease, or primary biliary cirrhosis.[6] Causes of Addison disease are shown in **Table 1**.

Anatomy and physiology

The adrenal glands are encapsulated, retroperitoneal organs comprised of an outer cortex and an inner medullary zone. The cortex is subdivided into three zones: the zona fasiculata and zona reticularis, which secrete glucocorticoids and androgens, and the zona glomerulosa, which produces mineralocorticoids.[7] The most clinically important glucorticoid produced by the adrenal cortex is cortisol. Aldosterone and dehydroepiandrosterone acetate (DHEA) are the most clinically important mineralocorticoid and androgen, respectively. Aldosterone functions in the setting of hypovolemia and regulates blood pressure by acting on the distal tubules and collecting ducts of the nephron to cause the conservation of sodium, secretion of potassium, which leads to increased water retention and blood pressure. DHEA acts as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids.[7] **Table 2** reviews the actions of the adrenal hormones and the target systems they affect. The inner medullary zone produces catecholamines including epinephrine and norepinephrine. Adrenal function and secretion of hormones is maintained by the body until approximately 80% to 90% of the glands are destroyed.

Released during periods of stress including trauma and infection, cortisol is vital to the body's response and impacts immune function; vascular tone; and lipid, protein, and carbohydrate metabolism. Its release is regulated by the hypothalamic-pituitary-adrenal (HPA) axis (**Fig. 1**). Signals from the body (eg, cytokine release, tissue injury, pain, hypotension, hypoglycemia, hypoxemia) are sensed by the central nervous

Table 1
Causes of primary adrenal insufficiency

Disorders in the Adrenal Gland	Examples
Autoimmune (80% of cases)	Polyglandular autoimmune syndrome type I and II, isolated adrenal insufficiency
Adrenal hemorrhage or thrombosis	Coagulation disorders Overwhelming sepsis (Waterhouse-Friderichsen syndrome) Necrosis caused by meningococcal sepsis
Associated endocrinopathies	Hypoparathyroidism Hepatitis Type 1 diabetes mellitus Hypogonadism Hypothyroidism
Drugs	Ketoconazole Suramin Aminogluthimide Etomidate (in children)
Infections	Disseminated tuberculosis Cytomegalovirus Histoplasmosis Cryptococcus Toxoplasmosis HIV Candidiasis
Infiltrative disorders	Amyloidosis Sarcoidosis Hemochromatosis Metastatic disease
Surgery and trauma	Bilateral adrenalectomy Adrenal trauma
Genetic diseases	Congenital adrenal hyperplasia Neonatal and X-linked adrenoleukodystrophy Familial glucocorticoid deficiency

Table 2
Key actions of adrenal hormones

Target System	Action
Cardiovascular	Increases contractility and the vascular response to vasoconstrictors
Endocrine	Inhibits insulin secretion, promotes peripheral insulin resistance Increases epinephrine synthesis
Inflammatory	Causes demargination of granulocytes, suppresses adhesion Reduces circulating eosinophils and lymphocytes Decreases production of inflammatory cytokines
Metabolism	Stimulates gluconeogenesis Promotes lipolysis Induces muscle protein catabolism Increases plasma glucose during stress
Renal	Increases the glomerular filtration rate; pharmacologic doses act at mineralocorticoid receptors

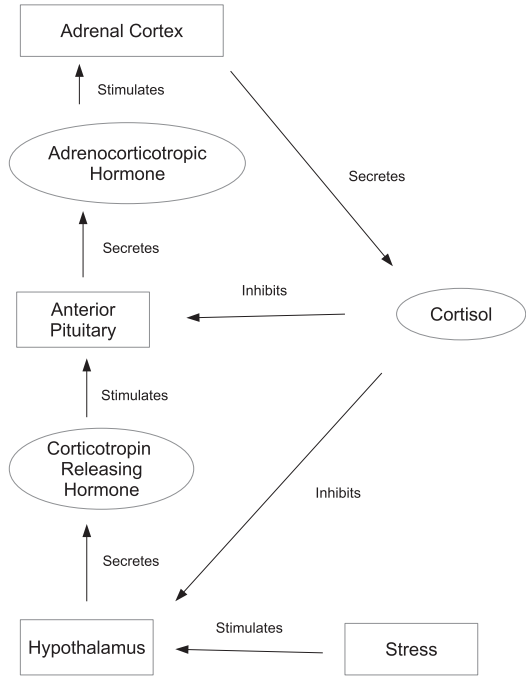

Fig. 1. Hypothalamic-pituitary-adrenal axis.

system and transmitted to the hypothalamus. The hypothalamus integrates these signals and increases or decreases the release of corticotropin-releasing hormone (CRH). CRH circulates to the anterior pituitary gland, where it stimulates the release of adrenal corticotropin hormone (ACTH), which in turn circulates to the adrenal cortex where it stimulates the release of cortisol.

Figs. 1 and **2** illustrate the feedback loop of cortisol and the HPA axis and aldosterone and the renin-angiotensin system. Cortisol levels have a negative and positive feedback effect on the hypothalamus and the anterior pituitary.

Aldosterone acts at the renal tubules to maintain Na+, K+, and water balance by way of the renin-angiotensin system, which is illustrated by **Fig. 2**. The renin-angiotensin system regulates aldosterone production.[7]

Clinical presentation

Patients with Addison disease generally have chronic, vague, and nonspecific complaints. As a result, they may be misdiagnosed with various psychiatric and gastrointestinal diseases.[8,9] Indeed, one study found that up to 20% of patients had symptoms for more than 5 years before they were diagnosed.[8] A recent analysis in Poland found that 54% of patients were only diagnosed after presenting with adrenal crisis.[10] Fulminant presentations may also occur with adrenal hemorrhage. The type and severity of clinical symptoms depends largely on the extent of the patient's hormonal deficiency, the rate at which the deficiency developed, and the underlying cause of the patient's condition.

Signs and symptoms of chronic primary adrenal insufficiency (PAI) and their frequencies are listed in **Box 1**. **Box 2** reports laboratory findings associated with PAI and the frequency for each laboratory result.

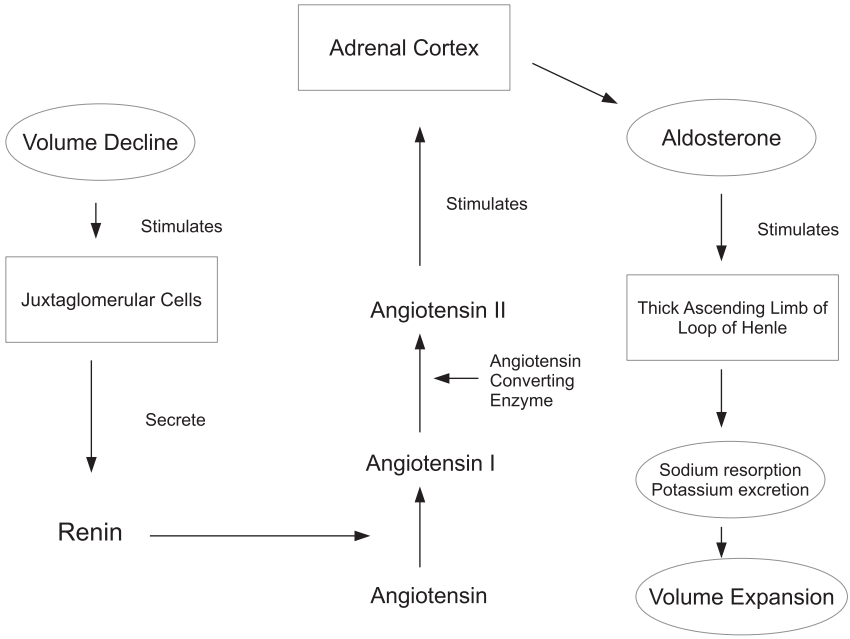

Fig. 2. Effect of volume decline on adrenal cortex and renin-angiotensin-aldosterone system.

Secondary Adrenal Insufficiency

Epidemiology

Secondary adrenal insufficiency (SAI) occurs when the integrity of the HPA axis is lost (see **Fig. 1**) because of pituitary disease. The causes of SAI are listed in **Table 3** but in each instance, secretion of ACTH is diminished and cortisol production is reduced. The lack of ACTH stimulation can eventually result in adrenal atrophy. Aldosterone release, sex hormone release, and catecholamine synthesis are usually normal.[14]

Anatomy and physiology

The pituitary gland, also known as the hypophysis, is a pea-sized gland that sits in a protective bony enclosure called the sella turcica. It is divided into the anterior pituitary, which produces several hormones, and the posterior pituitary, which secretes vasopressin, also known as antidiuretic hormone, and oxytocin.

Clinical presentation

SAI is a chronic disease process and patients may present with many of the same signs and symptoms as PAI. Fulminant presentations may be caused by pituitary hemorrhage or necrosis.

Clinical signs and symptoms of SAI are summarized in **Box 3**. There are some notable clinical and laboratory differences between PAI, SAI, and tertiary adrenal insufficiency (TAI; see **Boxes 1** and **3**, **Table 5**). Patients with Addison disease typically have hyperpigmented skin, particularly of sun-exposed areas, axillae, palmar creases, and mucous membranes. The cause of hyperpigmentation in Addison disease is believed to reflect increased stimulation of melanocyte receptors by ACTH.[15] Patients with SAI, however, do not manifest this finding because the anterior pituitary produces only low levels of ACTH. In addition, in Addison disease, the mineralocorticoid

Box 1
Clinical signs and symptoms of primary adrenal insufficiency

Weight loss, 25%–100%

Hyperpigmentation, 76%–94%

Vitiligo, 10%–20%

Hypotension (systolic blood pressure <110 mm Hg), 88%–94%

Shock, 5%

Auricular calcification, 5%

Amenorrhea, 25%

Infertility and premature ovarian insufficiency, 6%

Constitutional symptoms including weakness, fatigue, 100%

Anorexia, 100%

Nausea, 25%–86%

Vomiting, 25%–75%

Constipation, 33%

Abdominal pain, 31%

Diarrhea, 16%

Salt craving, 16%

Postural dizziness and syncope, 12%–20%

Musculoskeletal complaints including myalgias and arthralgias, 6%–37%

Psychiatric complaints including depression, apathy, psychosis, and pseudodementia

Data from Refs.[10–13]

Box 2
Laboratory abnormalities seen with primary adrenal insufficiency

Hyponatremia, 57%–88%

Hyperkalemia, 64%–85%

Hypercalcemia, 6%–33%

Azotemia, 55%

Mild hypoglycemia, 67%

Hypochloremia and acidosis

Anemia, 40%

Eosinophilia, 17%

Vitamin B_{12} deficiency, 10%

Type 1 diabetes, 12%

Data from Taub YR, Wolford RW. Adrenal insufficiency and other adrenal oncologic emergencies. Emerg Med Clin North Am 2009;27:273; and Erichsen MM, Husebye ES, Michelsen TM, et al. Sexuality and fertility in women with Addison's disease. J Clin Endocrinol Metab 2010;95(9):4354–60.

Table 3
Causes of secondary adrenal insufficiency

Reason for Dysfunction of HPA Axis	Examples
Sudden cessation of prolonged glucocorticoid therapy (most common)	Chronic use of steroid inhibits ACTH production
Brain tumors	Pituitary tumor Local invasion (craniopharyngioma)
Medications (eg, megesterol, medroxyprogesterone, opioids)	Progestin binds to glucocorticoid receptor resulting in some glucocorticoid activity leading to decreased response to ACTH Opioids impacts diurnal release of cortisol, diminishes response to exogenous ACTH
Pituitary irradiation Pituitary surgery Head trauma involving the pituitary gland	Disrupts ACTH production capacity in HPA axis
Pituitary necrosis or bleeding	Postpartum pituitary necrosis (Sheehan syndrome)
Infiltrative disorders of the pituitary or hypothalamus	Sarcoidosis Amyloidosis Hemosiderosis Hemochromatosis Histiocytosis X Metastatic cancer Lymphoma
Infectious diseases	Tuberculosis Meningitis Fungus HIV

Box 3
Clinical signs and symptoms of secondary adrenal insufficiency

Weight gain

Thin axillary and/or pubic hair

Decreased libido

Infertility, amenorrhea

Auricular calcification

Constitutional symptoms including weakness, fatigue, weight gain, cold intolerance

Anorexia

Headache and visual disturbance

Gastrointestinal complaints including abdominal pain, nausea, vomiting, diarrhea, constipation

Musculoskeletal complaints including myalgias and arthralgias

Psychiatric complaints including depression, apathy, psychosis, and pseudodementia

deficiency often produces significant salt craving, and evidence in laboratory analysis, including hyperkalemia and hyponatremia.[15] Because mineralocorticoids are not primarily affected by ACTH, patients with SAI are not hypokalemic, hypernatremic (aldosterone functioning), or hyponatremic (because of water retention). Pathology of the anterior pituitary gland produces clinical manifestations of adrenal insufficiency in addition to the effects that are seen with deficiencies of the other hormones produced by the anterior pituitary.

Tertiary Adrenal Insufficiency

Epidemiology

TAI occurs secondary to hypothalamic disease. CRH secretion is diminished, leading to minimal ACTH and cortisol production. As with SAI, the lack of ACTH stimulation can lead to adrenal atrophy. Aldosterone release, sex hormone release, and catecholamine synthesis are usually normal.[14]

The most common cause of TAI is long-term, high-dose glucocorticoid therapy (eg, prednisone, hydrocortisone, and dexamethasone) for autoimmune and inflammatory conditions. Exogenous steroid administration suppresses CRH synthesis and secretion, which also leads to decreased ACTH production. Adrenal atrophy is the result of this long-term therapy with levels of ACTH being suppressed. Recovery of the HPA axis may take a few months to 1 year after cessation of long-term glucocorticoid therapy. A summary of causes of TAI is listed in **Table 4**.

Anatomy and physiology

The hypothalamus is located below the thalamus, just above the brainstem and is roughly the size of an almond. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system by the pituitary gland. It synthesizes and secretes certain neurohormones, often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones (see **Fig. 1**).

Table 4
Causes of tertiary adrenal insufficiency

Reason for Dysfunction of HPA Axis	Examples
Exogenous high-dose glucocorticoid use	Chronic use of steroid inhibits CRH, ACTH production
Brain tumors	Hypothalamic tumor
Isolated CRH deficiency (rare)	Idiopathic
Cushing syndrome cure	Removal of pituitary tumor or other tumor that secretes ACTH or cortisol
Infiltrative disorders of the pituitary or hypothalamus	Sarcoidosis Amyloidosis Hemosiderosis Hemochromatosis Histiocytosis X Metastatic cancer Lymphoma
Infectious diseases	Tuberculosis Meningitis Fungus HIV

Clinical presentation

TAI is a chronic disease process and patients may present with many of the same signs and symptoms as PAI and SAI.

Differentiating PAI, SAI, and TAI

It can be difficult for practitioners to tease out differences in clinical presentation between PAI, SAI, and TAI. The key differences in signs and symptoms and noteworthy laboratory findings are listed in **Table 5**.

Differential Diagnosis

The differential diagnoses of neoplasia, acute appendicitis, cardiac dysrhythmias, subarachnoid hemorrhage, and acute coronary syndrome must be considered in patients with this disease. The nonspecific constellation of signs and symptoms, such as headache, visual changes, fatigue, generalized weakness, weight loss, abdominal pain, nausea and vomiting, syncope, and postural dizziness, often makes chronic adrenal insufficiency an elusive diagnosis for practitioners.

Table 5
Differences in clinical presentation and laboratory findings between primary, secondary, and tertiary adrenal insufficiency

	Primary Adrenal Insufficiency	Secondary Adrenal Insufficiency	Tertiary Adrenal Insufficiency
Signs and Symptoms			
Cushingoid features including abdominal striae and central obesity, humpback	Absent	May be present (if caused by long-term glucocorticoid use)	May be present (if caused by long-term glucocorticoid use)
Volume depletion and hypotension	Marked	Absent or mild (caused by decreased vascular tone)	Absent or mild (caused by decreased vascular tone)
Axillary hair loss, decreased libido, amenorrhea	Present	Present	Present
Hyperpigmentation	Present	Absent	Absent
Laboratory Findings			
Aldosterone deficiency	Present	Absent	Absent
Serum potassium level	Hyperkalemia	Normal or hypokalemia	Normal or hypokalemia
Serum sodium level	Hyponatremia (caused by salt wasting)	Hypernatremia (aldosterone functioning) or hyponatremia (caused by water retention)	Hypernatremia (aldosterone functioning) or hyponatremia (caused by water retention)
Serum chloride	Hypochloremia	Normal	Normal
Blood-urea-nitrogen	Mildly elevated	Normal	Normal
Serum glucose	Mild hypoglycemia	Marked hypoglycemia	Marked hypoglycemia

Adrenal Crisis

Epidemiology

Most cases of adrenal crisis occur in a person with Addison disease caused by mineralocorticoid deficiency but can be seen in patients with SAI or TAI and who are under severe physiologic stress, such as sepsis, trauma, burns, surgery, and myocardial infarction. Severe physiologic stress rapidly depletes the patient's already limited cortisol reserves, making the patient unable to mount an adequate stress response.

Hahner and colleagues[16] investigated the frequency, precipitating conditions, and risk factors for adrenal crisis in patients with chronic adrenal insufficiency. They found that 47% and 35% experienced at least one crisis in patients with PAI and SAI, respectively. Precipitating factors were fever (24% in PAI, 15% in SAI), gastrointestinal illness (33% in PAI, 22% in SAI), surgery (7% in PAI, 16% in SAI), and strenuous activity. Risk factors for adrenal crisis included nonendocrine comorbidities for PAI and female gender and diabetes insipidus for patients with SAI.

Clinical presentation The hallmark of adrenal crisis is hypotension and shock refractory to fluid resuscitation and vasopressors. As with adrenal insufficiency, patients have nonspecific symptoms including abdominal pain, nausea, vomiting, fever, lethargy, malaise, weakness, and confusion. The frequency of clinical signs and symptoms are listed in **Box 4**.

Emergency Department Management of Adrenal Insufficiencies and Adrenal Crisis

Treatment before diagnostic testing

Emergency physicians should begin empiric treatment of patients with suspected adrenal crisis before receiving the results of any confirmatory laboratory testing. **Table 6** serves as a treatment guide for adrenal crisis.

Hydrocortisone is the drug of choice for cases of adrenal crisis or insufficiency (provides both glucocorticoid and mineralocorticoid effects).[17,18] Although not necessary in the acute phase, fludrocortisone, 0.1 mg, is often part of a daily maintenance regimen. Although still controversial, DHEA may also be considered because of its reported improvement in patient quality of life.[19]

A thorough search for a precipitating cause should be undertaken. Empiric antibiotics may be given based on the patient's clinical presentation. Reversal of coagulopathy, if present, should be attempted with fresh frozen plasma. Patients with primary failure of the HPA axis may have concurrent clinical hypothyroidism and require

Box 4
Clinical signs and symptoms of adrenal crisis

Hypotension and shock, 90%

Fever, 66%

Abdominal rebound tenderness or rigidity, 22%

Anorexia, nausea, and vomiting, 47%

Abdominal pain, flank pain, back pain, lower chest pain, 86%

Neuropsychiatric complaints (confusion, disorientation), 42%

Data from Rao RH, Vagnucci AH, Amico JA. Bilateral massive adrenal hemorrhage: early recognition and treatment. Ann Intern Med 1989;110(3):227–35.

Table 6
Treatment guide for adrenal crisis

Treatment	Adult	Pediatric
Fluids	5% dextrose in normal saline or normal saline boluses may be used	Shock and hypotension is addressed with standard fluid resuscitation measures: 20 mL/kg normal saline boluses up to a maximum of 60 mL/kg over 1 h
Vasopressors	May be necessary if shock is refractory	May be necessary if shock is refractory
Steroids	Hydrocortisone, 100 mg bolus Followed by daily doses of 100 mg divided two to three times per day	Hydrocortisone Infants and toddlers to age 3: 25 mg IV Children ages 3–12: 50 mg IV Adolescents older than 12: 100 mg IV
Glucose	D50 may be used as necessary	Infants and children to age 12: 2.5 mL/kg of 10% dextrose Adolescents older than 12: 1 mL/kg of 25% dextrose

thyroxine supplementation. Hyperkalemia must be addressed in adult patients but is generally well tolerated in pediatric populations and resolves with normal saline infusions.[18]

Guillamondegui and colleagues,[20] in their retrospective review, found that compared to their untreated counterparts, trauma patients promptly identified and treated for acute adrenal insufficiency had an almost 50% reduction in mortality, spent less time in the intensive care unit and on ventilators and had shorter overall hospital stays.

Table 7 provides a summary of current maintenance recommendations for patients with chronic adrenal insufficiency.

Confirmatory diagnostic testing

Patients with all forms of adrenal insufficiency exhibit a deficiency of cortisol. In the outpatient setting, patients are generally screened with an early morning plasma cortisol level.[21] Readings lower than 3 μg/dL confirm adrenal insufficiency and values higher than 13 to 15 μg/dL make the diagnosis highly unlikely.[22]

The second step is to establish whether the cortisol deficiency is caused by ACTH or CRH deficiency. Adrenal function testing begins with the administration of 250 μg of synthetic ACTH (Cosyntropin). A rise in serum cortisol to greater than 8 μg/dL within 30 minutes is considered a normal response. Such a finding excludes PAI but does not evaluate the HPA axis–related causes of SAI. To differentiate between PAI and

Table 7
Management of chronic adrenal insufficiency

Treatment	Primary	Secondary
Glucocorticoid	20–25 mg hydrocortisone per 24 h divided in two to three doses	15–20 mg hydrocortisone per 24 h divided in two to three doses
Mineralcorticoid	0.1 mg per day	Not required
Androgen	May consider DHEA 25–50 mg and using transdermal testosterone	Not required

Data from Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003;31(1):141–5; and Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab 2009;94(4):1059–67.

SAI, basal corticotropin (ACTH) levels must be obtained. Levels are high in primary adrenal disorders (>100 pg/mL) and low or normal in SAI.

Early morning cortisol testing followed by ACTH stimulation testing in the emergency department is impractical and alternative testing algorithms have been sought. For critically ill patients, random serum cortisol levels above 34 μg/dL generally exclude a diagnosis of adrenal insufficiency and levels below 15 μg/dL in a patient with severe sepsis or shock suggest adrenal crisis.[23] Care must be taken in interpreting cortisol measurements in critically ill patients because those with hypoproteinemia may have low serum cortisol but normal free cortisol levels.[24]

Laboratory testing and imaging should also seek to establish whether the patient's adrenal insufficiency is caused by a treatable condition, such as infection. Computed tomography (CT) of the abdomen may reveal calcifications (associated with tuberculosis), adrenal hemorrhages, or metastatic infiltration. In cases of SAI, a head CT scan may show destruction of the pituitary gland (ie, empty sella syndrome).

In summary, serum cortisol levels are low in PAI, SAI, and TAI. ACTH levels are high in PAI, whereas they are low or normal in SAI and TAI. The ACTH stimulation test has no effect on cortisol in PAI but restores normal cortisol production in SAI and TAI. There is absent or minimal ACTH response to the CRH stimulation test in SAI but an exaggerated ACTH release in TAI.

Disposition

All patients with adrenal crisis should be admitted to an intensive care unit for resuscitation, and electrolyte and hemodynamic monitoring. Inpatient teams should continue to search for the inciting event that precipitated the patient's crisis (eg, infections, acute coronary syndrome). Patients with the more classically indolent and chronic presentations of PAI or SAI may be managed on an outpatient basis.

EMERGENCIES OF THE ADRENAL MEDULLA

Pheochromocytomas

Epidemiology

Pheochromocytomas are neuroendocrine tumors that secrete excess catecholamines and may cause life-threatening hypertensive crises. Pheochromocytomas account for only 0.05% to 0.2% of hypertensive individuals. Pheochromocytomas occur in people of all races but are less commonly diagnosed in blacks. Pheochromocytomas may occur in persons of any age, but the peak incidence is from the third to the fifth decades of life. An estimated 500 to 1600 cases occur with an annual prevalence between 1:2500 and 1:6500.[25] The true incidence of pheochromocytoma in the United States is difficult to determine because of the number of patients with asymptomatic cases found incidentally at autopsy. Indeed, one retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy.[26]

Traditional teachings regarding pheochromocytoma include the Rule of 10s (**Box 5**). The tumor is malignant in 10% of cases. However, surgical removal is often curative. Approximately 10% of pheochromocytomas are discovered incidentally.[27] Approximately 10% occur in children. Fifty percent of pheochromocytomas in children are solitary intra-adrenal lesions, 25% are present bilaterally, and 25% are extra-adrenal.

Pheochromocytomas occur in certain familial syndromes and are inherited in an autosomal-dominant manner. These include multiple endocrine neoplasia, neurofibromatosis (von Recklinghausen disease), and von Hippel-Lindau disease.

Box 5
Rule of 10s

10% Bilateral

10% Malignant (higher in familial cases)

10% Extra-adrenal (most commonly in the sympathetic chain in the thorax, abdomen, and pelvis)

10% Familial (now estimated to be as high as 24%)

Anatomy and physiology

The inner zone of the adrenal gland is the medulla. It consists of chromaffin cells that produce mainly the catecholamines norepinephrine, epinephrine, and a small amount of dopamine. The catecholamines are secreted in response to stimulation by sympathetic preganglionic neurons and receptors for catecholamines are widely distributed throughout the body. The physiologic effects of catecholamines are well known and include increased heart rate and blood pressure, blood vessel constriction in the skin and gastrointestinal tract, smooth muscle (bronchiole and capillary) dilation, and increased metabolism. Pheochromocytomas can occur anywhere along the sympathetic chain, although 85% to 90% are discovered within the adrenal gland.

Clinical presentation

Pheochromocytoma classically presents with paroxysmal "spells" wherein the afflicted patient experiences headaches, palpitations, diaphoresis, and severe hypertension. These spells may occur monthly, weekly, daily, or multiple times per day, and the duration may vary from seconds to hours. Typically, they worsen with time, occurring more frequently and becoming more severe with tumor progression.

The clinical symptoms and signs and their frequencies (when available) of pheochromocytoma are listed in **Boxes 6** and **7**, respectively. The most common sign of pheochromocytoma, found in upward of 95% of patients, is hypertension.[28] Approximately 50% of patients have sustained hypertension, 45% present with the "classic picture" of paroxysmal hypertension, and the remainder is normotensive.[29] One recent review noted, however, that approximately 30% of patients with pheochromocytoma or paraganglioma are normotensive or have orthostatic hypotension.[30]

Box 6
Clinical symptoms of pheochromocytoma

Headache, 82%

Palpitations, 48%

Diaphoresis

Anxiety, 35%

Dizziness, 18%

Abdominal pain, flank pain

Myalgias, arthralgias

Data from Anderson NE, Chung K, Willoughby E, et al. Neurologic manifestations of phaeochromocytomas and secretory paragangliomas: a reappraisal. J Neurol Neurosurg Psychiatry 2013;84(4):452–7.

Box 7
Clinical signs of pheochromocytoma

Weight loss
Pallor
Fever
Hypertensive crisis
Paroxysmal hypertension
Malignant hypertension
Orthostatic hypotension
Frank shock
Diaphoresis
Tachycardia and arrhythmias
Acute coronary syndrome
Cardiomyopathy
Acute heart failure
Myocarditis
Dissecting aortic aneurysm
Acute respiratory distress syndrome
Hypertensive retinopathy
Seizure, 7%
Hemiplegia
Tremors, 15%
Melena
Hematochezia
Café au lait spots
Neurofibromas
Hematuria
Pain
Pallor
Paresthesias
Rales
Pulmonary edema

Data from Anderson NE, Chung K, Willoughby E, et al. Neurologic manifestations of phaeochromocytomas and secretory paragangliomas: a reappraisal. J Neurol Neurosurg Psychiatry 2013;84(4):452–7.

Cerebrovascular accidents are frequently responsible for neurologic symptoms in patients with pheochromocytoma.[31,32] Intracranial and subarachnoid hemorrhages have been reported during paroxysmal attacks of hypertension and may be seen in connection with seizures. Patients may also present with generalized seizures secondary to cerebral ischemia and vasospasm.[33]

Adrenal tumor hemorrhages or necrosis can present as severe abdominal pain, nausea, and vomiting. The destruction of the adrenal medulla by either process may result in the excretion of vast quantities of catecholamines and precipitate a hypertensive crisis, cardiovascular collapse, and shock.[34] Moreover, emergency surgery or angiographic embolization by interventional radiology may be required to stop associated arterial bleeding with hemorrhage. Emergency surgery may also be indicated if a catecholamine surge induces vasoconstriction or spasms of the mesenteric arteries resulting in bowel ischemia.

Pheochromocytoma multisystem crisis is the most severe presentation of a pheochromocytoma that an emergency physician may encounter in practice. Patients with this condition may present with temperatures exceeding 40°C, encephalopathy, hypertension or hypotension, and multisystem organ failure. Mortality rates can exceed 85%.[35] Treatment with imipramine, metoclopramide, and glucocorticoids including dexamethasone have been reported to precipitate acute crises.[36–41]

Pheochromocytoma in pregnancy also warrants special consideration. Up to 65% of practitioners fail to diagnose pheochromocytoma in their pregnant patients before delivery despite the high maternal and fetal morbidity and mortality rates (40.3% and 56%, respectively).[42]

Hypertension complicates an estimated 8% of pregnancies and is classically divided into four categories: (1) chronic/essential hypertension, (2) preeclampsia, (3) preeclampsia complicated by chronic hypertension, and (4) transient hypertension of pregnancy.[43–45] Diagnosis of pheochromocytoma during pregnancy is complicated by the similarities in its clinical presentation with preeclampsia. The key differences are hypertension is generally not seen until 20 weeks after gestation in preeclampsia but may be seen at anytime during the pregnancy with pheochromocytoma. Edema and proteinuria are present in preeclampsia but are usually absent in pheochromocytoma.

Differential diagnosis

Also known as the great mimicker, patients with pheochromocytoma may present to the emergency department with a wide range of signs and symptoms, as seen in **Boxes 6** and **7**. Screening for pheochromocytoma should be done in children and young adults without any other explanation for hypertension and in older adults that are hypertensive and refractory to any medication regimens.

Surgical and Medical Management of Pheochromocytoma

Treatment of hypertension associated with pheochromocytoma depends in part on the clinical severity. Surgery is the only curative measure.

The indications for emergency surgery in the context of pheochromocytoma multisystem crisis are controversial with some advocates stating that emergent surgical resection may be the only means to halt disease progression, and others that medical stabilization followed by elective or urgent surgery is the best course of action.[46] Scholten and colleagues[47] conducted a retrospective cohort study enrolling 137 patients with pheochromocytoma, including 25 who presented in crisis. None of the crisis patients underwent emergent surgery and those who received urgent surgery had a higher rate of complications and longer intensive care unit stays and overall hospital admission compared with patients who received elective surgery. Their literature review found that emergency resection of pheochromocytoma resulted in higher intraoperative and postoperative surgical morbidity and mortality. They concluded that pheochromocytoma crisis should be treated with medical stabilization and elective or urgent surgery rather than emergency surgery.

Despite the controversies surrounding emergent versus urgent versus elective operative resection, pharmacotherapy is essential to preoperative and perioperative management. Pharmacotherapy is the mainstay of treatment of inoperable metastatic disease.

There is no consensus with respect to the ideal preoperative medical management. α-Blockers, calcium channel blockers, β-blockers, and angiotensin-receptor blockers have all been used by practitioners. Local practice patterns and drug shortages can complicate pharmacologic choices.[48]

The most common preoperative drug regimen used in the United States is phenoxybenzamine, 10 mg taken twice daily for 10 to 14 days. Shorter courses have also been used successfully and there is no universally recommended treatment duration.[49] The dose is titrated to symptom resolution by an irreversible, noncompetitive, α-adrenergic blockade. α-Blockers are typically started to control blood pressure and prevent a hypertensive crisis triggered by the high levels of circulating catecholamines that stimulate α-receptors and cause vasoconstriction.

β-Blockers are often included in preoperative regimens to treat the tachyarrhythmias that occur with α-blockade. However, β-blockade should not be used as a lone therapy and should not be started before initiation of the α-blockade because unopposed β-blockade potentiates the α-agonist effects of epinephrine and may precipitate a hypertensive crisis. Both noncardioselective β-blockers, such as propranolol or nadolol, and cardioselective agents, such as atenolol and metoprolol, may be used. The use of labetolol and carvedilol is controversial. Although both agents have α- and β-antagonist activity at a ratio of approximately 1:7, their use has been associated with paradoxic episodes of hypertension thought to be secondary to incomplete α-blockade.

Calcium channel blockers have also successfully been used preoperatively particularly in patients who are unable to tolerate the side effects of α-blockade.

A tyrosine analog, metyrosine, is sometimes used as an adjunct to α-blockade to inhibit catecholamine synthesis by inhibiting tyrosine hydroxylase.[50] This therapy may be beneficial to patients with refractory hypertension despite α-blockade and those patients with a high tumor burden or biochemically active tumors.[51,52]

There are also no consensus guidelines for intraoperative management of pheochromocytomas and this condition often presents significant challenges to our anesthesia colleagues because of the rapid hemodynamic shifts often seen in such cases. Tumor manipulation during surgery can result in bursts of catecholamine activity and hypertensive spikes. So called background infusions of nitroprusside or nitroglycerin can be used to prevent and address such spikes. Similarly, nicardipine has been used to prevent and treat hypertensive spikes.[53] Treatment with magnesium sulfate boluses (20–40 mg/kg) and infusions (1–2 mg/h) has also gained popularity in the

Table 8
Sensitivity and specificity of laboratory testing in pheochromocytomas

Diagnostic Test	Sensitivity and Specificity
Plasma metanephrine testing	96% sensitivity, 85% specificity
24-h urinary collection for catecholamines and metanephrines	87.5% sensitivity, 99.7% specificity

Data from Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2010;95(5):2023–37; and Sheps SG, Jiang NS, Klee GG, et al. Recent developments in the diagnosis and treatment of pheochromocytoma. Mayo Clin Proc 1990;65(1):88–95.

Table 9
Sensitivity and specificity of imaging modalities in pheochromocytomas

Test	Sensitivity (%)	Specificity (%)
Abdominal CT scan	93	95
Magnetic resonance imaging	86–100	93
I-MIBG scintigraphy	90	100

Data from Luster M, Karges W, Zeich K, et al. Clinical value of (18)F-fluorodihydroxyphenylalanine positron emission tomography/computed tomography ((18)F-DOPA PET/CT) for detecting pheochromocytoma. Eur J Nucl Med Mol Imaging 2010;37(3):484–93; and Ilias I, Pacak K. Diagnosis, localization and treatment of pheochromocytoma in MEN 2 syndrome. Endocr Regul 2009;43(2):89–93.

last 15 years because of magnesium's anti-arrhythmic properties and its ability to decrease catecholamine stores and cause arteriolar vasodilation.[54–62]

Confirmatory Diagnostic Testing

Biochemical tests including 24-hour collection of urinary metanephrines and vanillylmandelic acid and plasma metanephrines are used to confirm a diagnose of pheochromocytoma. The sensitivity and specificity of these tests are listed in **Table 8**.

CT, magnetic resonance imaging, and scintigraphy scans are generally reserved to assist with planning operative course and are not part of the emergency department evaluation. The sensitivity and specificity of each imaging modality for diagnosing pheochromocytoma are provided in **Table 9**.

Disposition

Postoperatively, patients should be monitored closely for 24 hours in an intensive or immediate care unit. Hypotension and hypoglycemia are the most common postoperative complications.

Incidentalomas

Patients presenting to the emergency department increasingly receive CT scans of their chest, abdomen, or pelvis to evaluate for a myriad of complaints. Incidental adrenal masses are found in up to 4% of these scans.[63] Patients being discharged from the emergency department should be directed to follow up with their primary care provider in a timely manner to ascertain whether these masses are benign, nonfunctioning, hormonally active, malignant, or metastatic.

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