



Continuing Education

# Adrenal insufficiency: Considerations for the prehospital provider

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Photo by Ryche Guerrero.

## Abstract

*Adrenal crisis and severe acute adrenocortical insufficiency are often elusive diagnoses that may result in severe morbidity and mortality when undiagnosed or ineffectively treated.<sup>1</sup> Approximately six million persons in the United States are considered to have undiagnosed adrenal insufficiency, which is clinically significant only during times of physiologic stress.<sup>1</sup> Signs and symptoms may be nonspecific; therefore, the diagnosis may not be suspected early in the course of treatment. Because of the increasing frequency of secondary adrenal insufficiency and the prevalence of undiagnosed disease, the prehospital provider should be aware of the clinical presentation of patients suffering from adrenal insufficiency. Effective and emergent management of adrenal insufficiency requires an appreciation of its etiology, pathophysiology, clinical presentation, populations at risk and treatment. A fundamental understanding of*

*this rare but critical medical condition will enable prehospital providers to identify, treat and prevent the potentially deadly sequelae of adrenal insufficiency. This article will attempt to provide its readers with the basic knowledge required to recognize and effectively manage patients with adrenal insufficiency.*

## Introduction

Adrenal crisis and severe acute adrenocortical insufficiency are often elusive diagnoses that may result in severe morbidity and mortality when undiagnosed or ineffectively treated.<sup>1</sup> If unrecognized, adrenal insufficiency may present with life-threatening cardiovascular collapse.<sup>2</sup> The challenge, as is often the case with medical patients, is that the clinical picture is muddled by vague and somewhat universal signs and symptoms of illness. Altered mental status, weakness, nausea/vomiting, abdominal pain, hypotension and hypoglycemia are all somewhat non-helpful signs and complaints.

Astute providers should be able to ask the right questions and probe deeper into the patient's history as well as sense subtleties in their physical assessment in an effort to identify an emergent patient. The potentially critical nature of the aforementioned symptoms may portend ominous outcomes and therefore may necessitate a call to EMS. Effective and emergent management of adrenal insufficiency requires an appreciation of its etiology, pathophysiology, clinical presentation, populations at risk and treatment. A fundamental understanding of this rare but critical medical condition will enable prehospital providers to identify, treat and prevent the potentially deadly sequelae of adrenal insufficiency.

### **Etiology**

Thomas Addison first identified the syndrome that now bears his name, characterized by wasting and hyperpigmentation associated with adrenal gland destruction 150 years ago.<sup>2</sup> Once invariably fatal, the disorder is now highly treatable with the advent of corticosteroid replacement therapy in the 1950s; thus, a patient's outlook is quite favorable.<sup>3</sup> Adrenal insufficiency may be categorized as primary or secondary and congenital or acquired. Adrenocortical insufficiency is an uncommon disorder with an incidence in Western populations near five cases per 100,000 persons with three patients suffering from secondary adrenal insufficiency, one from primary adrenal insufficiency due to autoimmune adrenalitis and one from congenital adrenal hyperplasia.<sup>4,1</sup> Secondary adrenocortical insufficiency due to steroid withdrawal is much more common with the advent of widespread corticosteroid use.<sup>1</sup> Although primary adrenocortical insufficiency affects men and women equally, women are affected two to three times more often by the idiopathic autoimmune form of adrenal insufficiency. More important for the prehospital provider, approximately six million persons in the United States are considered to have undiagnosed adrenal insufficiency, which

is clinically significant only during times of physiologic stress.<sup>1</sup> Signs and symptoms may be nonspecific; therefore, the diagnosis may not be suspected early in the course of treatment.

In primary adrenal insufficiency, glucocorticoid and, frequently, mineralocorticoid hormones are lost. Primary adrenocortical insufficiency has multiple etiologies; however, 80 percent of cases in the United States are caused by autoimmune adrenal destruction. Glandular infiltration by tuberculosis is the second most frequent etiology.<sup>1</sup> In secondary adrenocortical insufficiency; there is lack of corticotropin-releasing hormone (CRH) secretion from the hypothalamus and/or adrenocorticotropic hormone (ACTH) secretion from the pituitary, which results in hypofunction of the adrenal cortex and thus insufficiency and subsequent clinical manifestation.<sup>2</sup>

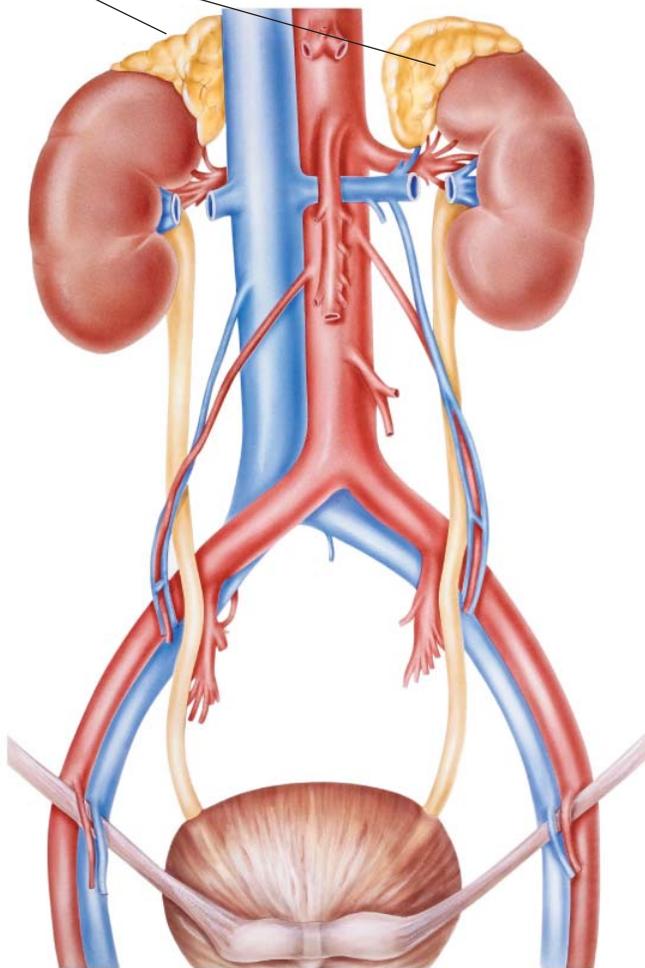
The two adrenal glands are located on top of the kidneys (ad meaning *above* and renal meaning *kidney*). They consist of the outer portion, called the cortex, and the inner portion, called the medulla. The cortex produces three types of hormones, all of which are called corticosteroids.<sup>5</sup> While more than 50 steroids are produced within the adrenal cortex, cortisol and aldosterone are by far the most abundant and physiologically active. Cortisol is a glucocorticoid, a corticosteroid that helps regulate blood glucose, suppresses the immune response, and is released as part of the body's response to stress.<sup>5</sup> Cortisol is essential for life. Its production is regulated by the pituitary gland. The pituitary gland releases ACTH, causing the adrenal glands to release cortisol. Aldosterone is produced in the zona glomerulosa and is controlled primarily by the renin-angiotensin system, serum potassium levels and ACTH. The primary target of aldosterone is the kidney, where it stimulates reabsorption of sodium and secretion of potassium and hydrogen ions. Aldosterone deficiency results in hyperreninemia, hyperkalemia, hyponatremia and mild acidosis. Mineralocorticoid deficiency is present in primary adrenal insufficiency only; the renin-



angiotension-aldosterone system in patients with hypothalamic-pituitary disease and intact adrenals is usually preserved.<sup>1,2</sup>

Glucocorticoids are nonspecific cardiac stimulants that activate release of vasoactive substances. In the absence of corticosteroids, stress results in hypotension, shock and death.<sup>1</sup> Glucocorticoids have effects on all body tissues. The overall metabolic action of glucocorticoids is catabolic, promoting protein and lipid breakdown and restraining protein synthesis in muscle, connective tissue,

Adrenal glands



*Illustration from iStockphoto.*

adipose tissue and lymphoid cells. These effects are antagonistic to those of insulin, increasing the concentration of glucose by stimulating gluconeogenesis. Cortisol decreases glucose use by muscle and promotes lipolysis in adipose tissue. Amino acids and

glycerol released by the catabolic action of cortisol on protein and fat are used as gluconeogenic substrates.<sup>1</sup> The net effect is increased production and conservation of glucose for use by essential tissues, such as the brain and red blood cells, at the expense of less essential tissues during times of stress or starvation. Moreover, cortisol contributes to the maintenance of normal blood pressure through several mechanisms. Under non-stressful conditions, cortisol increases urine flow by stimulating glomerular filtration rate and decreasing water resorption; however, at high concentrations, cortisol can act like a mineralocorticoid, promoting sodium and water retention. Also in high concentrations, cortisol increases angiotensinogen synthesis by the liver and increases the vascular reactivity to vasoconstrictors. In the adrenal medulla, cortisol is required for the enzymatic activity of phenylethanolamine *N*-methyltransferase, which converts norepinephrine to epinephrine.<sup>6</sup> Epinephrine stimulates cardiac output as well as hepatic glucose production. Cortisol prevents life-threatening hypotension by decreasing capillary permeability and the production and activity of nitrous oxide and the vasodilatory kinin and prostaglandin systems during stress.<sup>6</sup> In the absence of these effects patients become symptomatic and require emergency intervention to maintain blood pressure and the homeostatic mechanisms that ensure end organ perfusion.

### **Clinical presentation**

Symptoms of adrenal insufficiency may be nonspecific like fatigue, anorexia, vomiting and abdominal pain but may also lead to a life-threatening adrenal crisis accompanied by shock.

As previously mentioned, the presentation of adrenal insufficiency can mimic many other diseases. Acute adrenal insufficiency is frequently associated with

other pathology and comorbidities, therefore confounding the physical and history of the critically ill patient. Adrenal crisis occurs when the adrenal gland is damaged (Addison's disease, primary adrenal insufficiency) or the pituitary gland is injured (secondary adrenal insufficiency) and it cannot release ACTH.<sup>5</sup> Risk factors for adrenal crisis include: dehydration, infection and other physical stress, injury to the adrenal or pituitary gland, stopping treatment with steroids such as prednisone or hydrocortisone quickly or too early, surgery and trauma.<sup>6</sup> Mineralocorticoid deficiency is reflected by arterial hypotension and deranged potassium and sodium, and also by intravascular volume depletion. These are common findings in Addison patients. Hyponatremia is observed in about 80 percent of acute cases whereas less than half present with hyperkalemia.

Unlike adrenal crisis, primary adrenal insufficiency (Addison's disease) often develops insidiously.<sup>7</sup> Addison's disease remains clinically silent until some 90 percent of the adrenal cortices have been destroyed. Chronic insufficiency of corticosteroids can lead to a number of health problems, including an inability to recover from even a minor infection. Complications such as protracted weakness, shock or death may result.<sup>3</sup> Delay in treatment while attempting to confirm this diagnosis can result in poor patient outcomes.

A detailed and careful history is imperative to proper identification and treatment of adrenal crisis. The following are important elements in the history of patients with adrenal crisis or adrenal insufficiency: weakness (99%), pigmentation of skin (98%), weight loss (97%), abdominal pain (34%), salt craving (22%), diarrhea (20%), constipation (19%), syncope (16%) and vitiligo (9%).<sup>1</sup> The features of acute adrenal crisis include hypotension (particularly postural hypotension), shock and hyponatremia in 90 percent of patients. Hyperkalemia is also a feature in 65 percent of patients.<sup>8</sup> Sometimes mild metabolic acidosis or hypercalcemia can also be observed, the latter mostly in the context of coincident hyperthyroidism. Medication

history is a powerful tool if the patient is unable to act as a reliable historian secondary to their condition. Serum glucose may be low; however, significant hypoglycemia as a presenting sign plays a more important role in childhood adrenal insufficiency where it can result in significant brain damage.<sup>4</sup>

Acute adrenocortical insufficiency is a difficult diagnosis to make. The disorder rarely occurs without concomitant injury or illness. Many of the presenting signs and symptoms are nonspecific. And while adrenal insufficiency may occur at any age and affects both sexes equally, acute adrenal crisis is rare in childhood and adolescence.<sup>1</sup>

Patients with acute adrenal insufficiency generally present with acute dehydration, hypotension, hypoglycemia or altered mental status. Conversely, patients with chronic adrenal insufficiency usually complain of chronic fatigue, anorexia, nausea, vomiting, loss of appetite, weight loss and recurring abdominal pain. Symptoms may mimic gastrointestinal illness or psychiatric disorder, in particular, behavior changes or depression. Gastrointestinal infections, a frequent cause of crisis, may require parenteral hydrocortisone administration.<sup>4</sup> Although increased skin pigmentation may be noted, it is not always clinically obvious. Salt craving is common in chronic primary adrenal insufficiency, whereas hyperpigmentation and salt craving are not observed in patients with secondary adrenal insufficiency.<sup>1</sup>

Unless there is a history of recent pharmacologic glucocorticoid therapy, secondary adrenal insufficiency is usually associated with signs of other pituitary hormone deficiencies such as growth failure, delayed puberty, secondary hypothyroidism and/or diabetes insipidus (polyuria and polydipsia).<sup>1</sup> Treatment courses with corticosteroids for as brief as two weeks may result in transient suppression of endogenous cortisol production.<sup>1</sup>

Left untreated, a patient with acute adrenal insufficiency has a dismal prognosis for survival.<sup>1</sup> Fatal but avoidable Addisonian crisis is the second most common cause



of death in patients with known Addison's disease, accounting for 15 percent of deaths in patients with this disease.<sup>8</sup> Classical features of adrenal failure such as anorexia, lethargy and weight loss with deranged plasma electrolytes, hypotension, hyperpigmentation and vitiligo are present in Addisonian crisis.<sup>7</sup> The majority of states in the United States are currently performing newborn screening, as are many other countries. Infant screening programs have markedly decreased the time to diagnosis, theoretically decreasing morbidity.<sup>1</sup>

### Special populations

As with other diseases, the presence of existing pathology, demographic classification and comorbid conditions affect the physical manifestation of adrenal insufficiency. A brief discussion of several of these subgroups, in particular, patients on inhaled corticosteroids, critically ill patients, type I diabetics, patients with infection, trauma and post-surgical patients, is clinically germane and can serve a vigilant provider well in the assessment of these patients.

For instance, a postoperative fever may presumptively be treated as infection or systemic inflammatory response syndrome when it may be a subtle indicator of adrenal insufficiency. Addison's disease is rare, with a reported incidence of about five cases per million population per year and a prevalence of 110 per million, although it is at least five times more common in the diabetic population. In patients with type 1 diabetes who develop unexplained recurrent hypoglycemia, the development of an associated endocrinopathy, such as Addison's disease, should be considered.<sup>7</sup> An unexplained reduction of total insulin requirement of more than 15 to 20 percent (in response to recording frequent low blood glucose values) should arouse suspicion of adrenocortical insufficiency. This may precede the clinical features.<sup>7</sup>

Inhaled steroids are indispensable in the treatment of chronic asthma, but their prolonged use at doses higher than recommended increases the risk of adrenal suppression. Inhaled corticosteroids (ICS)

given for a long term and in higher doses can cause hypothalamic-pituitary axis suppression because of absorption from the lung and partial clearance at first pass if swallowed.<sup>9</sup> Fluticasone propionate seems to exhibit greater dose-related adrenal suppression greater than other available inhaled corticosteroids, particularly at doses above 0.8 mg/d.<sup>10</sup> Patients presenting with signs and symptoms of adrenal insufficiency with a history of asthma/ICS use should be treated with a high level of suspicion. Excess use of steroids results in negative feedback on the hypothalamic-pituitary-adrenal axis, rendering the body incapable of mounting a stress response in times of increased need. Life-threatening adrenal crisis may be a consequence even at the usual prescribed doses, stressing the importance of using the lowest dose of inhaled steroids needed to control symptoms and being vigilant of side effects.<sup>11</sup>

Elevation in corticosteroid levels to meet physiological needs during acute illness is a protective response. This homeostasis is maintained by the hypothalamic-pituitary-adrenal (HPA) axis. However, inadequate response as a result of corticosteroid insufficiency is common in critically ill patients, especially those with severe sepsis or septic shock. Thus, corticosteroids could be beneficial in the setting of septic shock or severe acute illness.<sup>6</sup> Diagnosis of acute adrenocortical insufficiency must be considered if clinical manifestations are present suggesting septic shock without any obvious infectious cause in patients having undergone considerable intravenous fluid therapy as an initial course of treatment.<sup>12</sup> Adrenal crisis after surgical procedure is a rare but potentially catastrophic life-threatening event. Its manifestations, such as hypotension, tachycardia, hypoxia and fever mimic the other more common postoperative complications. Clinical outcome is dependent upon early recognition of the condition and proper management with exogenous steroid administration.<sup>13</sup> Acute adrenal insufficiency may be triggered by infection or trauma but may also be seen without an obvious



concomitant illness or stress. Hypoglycemia is most common in young children. Altered mental status may occur at any age with or without hypoglycemia.<sup>1</sup>

### Emergency management and treatment

While care for a patient with adrenal insufficiency or adrenal crisis is largely supportive, there are therapeutic decisions specific to the pathophysiology that can decrease morbidity and mortality. By definition, a patient with symptomatic hypotension is inadequately perfusing. Rapid intervention is paramount to successful patient management. Airway, breathing and circulation in patients with adrenal crisis remain the priority. High flow oxygen and airway protection followed by aggressive volume replacement therapy (dextrose 5% in normal saline solution [D5NS]) should be administered rapidly to maintain oxygenation and reestablish blood pressure. Coma protocol (i.e., glucose, thiamine, naloxone) to rule out alternate causes of decreased level of consciousness is indicated. The patient should be monitored for signs and symptoms of electrolyte abnormalities. If protocols or transfer orders indicate, the provider may choose to correct electrolyte derangement. Hypoglycemia should be treated first with dextrose 50 percent followed by hyponatremia, hyperkalemia and hypercalcemia. Longer-term management should include administration of hydrocortisone 100 mg intravenously (IV) every six hours. While clinical condition may necessitate immediate intervention in order to protect life, the provider should always treat the underlying problem that precipitated the crisis.<sup>1</sup>

### Summary

The obscure and vague nature of the presenting symptoms of adrenal crisis and severe acute adrenocortical insufficiency provide fertile ground for missed or misdiagnosis of this potentially fatal condition by prehospital providers. With approximately six million persons in the United States considered to have undiagnosed adrenal

insufficiency, and the increasing use of inhaled corticosteroids, the prevalence of adrenal insufficiency is increasing. A fundamental understanding of the etiology, pathophysiology, clinical presentation, populations at risk and treatment of adrenal insufficiency bestows prehospital providers with an expanding depth and scope of clinical knowledge in the struggle against morbidity and mortality.

**This article is provided for education only. Always consult with your medical director and follow your local protocols in making treatment decisions.**

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