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DIAGNOSIS AND TREATMENT OF ACUTE ADRENAL CRISIS IN THE SETTING OF THE EMERGENCY DEPARTMENT - A LITERATURE REVIEW

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ABSTRACT

Introduction and objective: Acute adrenal crisis (AAC) is a life-threatening condition, often under-recognized due to its rarity. Over the years, technological advances have occurred across many branches of medicine, including new solutions for diagnosing and treating AAC. However, they remain fragmented across the literature. In this review, we sought to systematically evaluate and summarize contemporary innovations that may help emergency medicine practitioners to be more confident in their diagnoses and, therefore, make more confident under-pressure clinical decisions.
Review Methods: We searched the PubMed and Google Scholar databases, focusing on papers published between 2020 and 2025.
Brief description of knowledge: Currently, AAC is treated empirically with hydrocortisone. Quick tests for cortisol levels are not widely available; diagnosis is based mainly on clinical symptoms and electrolyte disturbances.
Summary: Developments in diagnostic approaches, such as saliva-based, aptamer-based point-of-care cortisol assays, may aid differential diagnosis of AAC in emergency departments (EDs) and reduce time to hydrocortisone administration.

KEYWORDS

Adrenal Gland, Acute Adrenal Crisis, Corticosteroid, Emergency Medicine

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Introduction

Acute adrenal crisis (AAC) is a medical emergency characterized by absolute or relative glucocorticoid deficiency. When not recognized on time, it may lead to massive hypotension, electrolyte disturbances, hypoglycemia, and shock. According to the existing guidelines, AAC should be diagnosed based on the patient's symptoms. In practice, in an emergency medicine setting, it imposes many difficulties due to AAC's often nonspecific clinical presentation. Mortality rates remain high when diagnosis and corticosteroid administration are delayed. Traditional management of AAC has relied on empirical hydrocortisone administration and supportive care, but recent years have seen significant advances in rapid diagnostics and steroid delivery systems.

Methodology

To prepare this publication, a thorough search of scientific papers was conducted, focusing on the most recent and up-to-date data on this topic. The literature search strategy was carried out using the PubMed and Google Scholar databases.

Epidemiology

Adrenal gland diseases are composed of rare genetic disorders of adrenal insufficiency - Addison's disease, adrenal cancer, and more common adrenal incidentalomas. A life-threatening disease of the adrenal gland is the acute adrenal crisis, which occurs in general in people with previously diagnosed primary or secondary adrenal insufficiency, less often in patients with no prior history of adrenal insufficiency. (Elshimy, Chippa, Kaur & Jeong 2025) Approximately 6 to 8 % of patients with previously diagnosed primary and secondary adrenal insufficiency experience an adrenal crisis each year. (Hahner et al. 2010) Disturbingly, acute adrenal crisis is characterized by a mortality rate of 0.5 per 100 patients per year, and that indicates that it is a significant cause of death in patients with adrenal insufficiency. (Hahner et al. 2015; Rushworth et al. 2018)

Pathophysiology

Adrenal insufficiency can be primary, when cortisol deficiency is due to adrenal gland impairment, or secondary, when cortisol production is blocked by improper pituitary or hypothalamus anatomy or function. (**Table 1**)

The adrenal glands are small endocrine glands that play a critical role in maintaining whole-body homeostasis. Each gland has a cortex and medulla. In this review, we focus primarily on the adrenal cortex. The cortex has three main zones: zona glomerulosa (which produces aldosterone), zona fasciculata (which produces steroids), and zona reticularis (which produces androgens).

Cortisol, secreted by the zona fasciculata, significantly affects the circulatory system by increasing vascular bed sensitivity to catecholamines. When cortisol levels are too low, it leads to massive vasodilation. (Chambers et al.,2019) Low levels of aldosterone are associated with hyponatremia, hyperkalemia, and volume depletion, and, in the long term, metabolic acidosis. These mechanisms explain why AAC often presents as refractory shock unresponsive to fluids and vasopressors until steroids are administered. Regarding the causes of AAC, we can identify 3 basic groups of patients who may develop this condition:

1. Patients with undiagnosed adrenal insufficiency as a prodromal condition.
2. Patients with diagnosed and treated adrenal insufficiency, who are exposed to a very stressful situation without additional hydrocortisone therapy, or who cannot absorb their medication correctly, due to a temporary GI infection with symptoms like severe diarrhea, vomiting.
3. Patients with previously normal secretory function of the adrenal glands, in whom adrenal malfunction appeared due to sudden and massive damage to the adrenals (due to trauma, sepsis, hemorrhage, or pregnancy eclampsia), or hypothalamic-pituitary-adrenal axis dysfunction, in the critical phase of severe diseases. (Gajewski, 2019)

Table 1. Causes of adrenal insufficiency: primary and secondary
(Penman et al., 2020; Lewis et al., 2023)

Primary adrenal insufficiency	Secondary adrenal insufficiency
- **Autoimmune**: Isolated adrenal insufficiency (Addison's disease), Autoimmune polyendocrine syndromes (APS)1 - **Infections**: Tuberculosis, HIV/AIDS - **Genetic**: Adrenoleukodystrophy, congenital adrenal hyperplasia - **Vascular**: Adrenal infarction/haemorrhage (Waterhouse-Friedrichsen syndrome in meningococcal sepsis) - **Infiltrative**: Metastasis, lymphoma, amyloidosis, haemachromatosis, sarcoidosis - **Iatrogenic**: Surgical adrenalectomy or drug-induced (e.g. metyrapone, etomidate, ketoconazole)	- **Tumour**: Pituitary macroadenoma, other tumour (craniopharyngioma, meningioma) - **Iatrogenic**: Pituitary irradiation, drug-induced (e.g., opioids, glucocorticoids, immunotherapy) - **Vascular**: Apoplexy, Sheehan's syndrome - **Infiltrative**: Tuberculosis, sarcoidosis, histiocytosis X, granulomatosis with polyangiitis, lymphocytic hypophysitis - **Trauma** - **Genetic**

Symptomatology

Acute Adrenal Crisis can manifest as symptoms across multiple organ systems. (**Table 2**) The clinical picture of AAC includes prodromal, upcoming crisis, and crisis symptoms.

Prodromal symptoms include loss of appetite, nausea, muscle pain, and malaise. Progressing weakness, influenza-like muscle pain, abdominal pain, nausea, a gradual drop in blood pressure, and a possible increase in body temperature indicate an upcoming crisis. If no measures are undertaken, a full-scale crisis will occur, presenting as severe weakness, fluctuating consciousness, vomiting, diarrhea, low blood pressure, and tachycardia, resulting in a distributive shock, also known as vascular shock (Gajewski, 2019)

Table 2. Signs&Symptoms of Acute Adrenal Crisis (Penman et al., 2020)

System	Signs&symptoms
Overall symptoms	Overall malaise Fatigue Hypotension with possible vascular shock Fever
Biochemical	Hyponatremia Hyperkalemia Hypoglycemia Hypercalcemia
Gastrointestinal	Nausea Vomiting Diarrhea
Musculoskeletal	Muscle pain

Diagnosis and new diagnostic strategies

Acute Adrenal Crisis is present mostly in patients with already existing adrenal conditions. If symptoms suggestive of adrenal insufficiency are present, a physician should perform tests to confirm the suspicion. Cortisol and ACTH measurements are basic diagnostic tools for establishing the correct diagnosis. ACTH serum levels help determine whether adrenal insufficiency is primary or secondary. In general, a low baseline cortisol level, along with a raised ACTH level, is sufficient to diagnose primary adrenal insufficiency. While the insulin tolerance test is the gold standard for diagnosing secondary adrenal insufficiency, this tool is limited by contradictions such as heart disease, seizures, or severe hypothyroidism, and in those with baseline cortisol levels <100 nmol/L.

More complex adrenal testing comprises the glucagon stimulation test or metyrapone suppression test. (Lewis, Thant, Aslam, Aung & Azmi 2024)

These are validated diagnostic tools, yet not always suitable for emergency department settings. Acute Adrenal Crisis is a life-threatening condition, so immediate treatment is required. Proper in-depth diagnosis is

needed, yet in such cases, it is often postponed after emergency procedures. Nevertheless, it is advised that a blood sample be obtained for diagnostic testing, especially basal serum cortisol and ACTH levels, before treatment. (Bornstein et al. 2016) Mentioned challenges raise the question of developing rapid and reliable diagnostic methods, particularly in emergency settings, where staff are often limited and overextended by high patient volumes. Moreover, quick recognition of AAC may be challenging because its clinical presentation may overlap with hypovolemia, septic shock, and that may lead to frequent delays in steroid administration (Ducker et al. 2020). Recent technological advances have focused on developing rapid, reliable diagnostic tools to help emergency physicians more efficiently distinguish AAC from other life-threatening conditions.

Aptamer-based point-of-care cortisol assays

In 2020, Dlirirad et al. reported an aptamer-based point-of-care (POC) cortisol detector. Although the aim of this study wasn't to diagnose AAC, we considered it worthwhile to evaluate this type of innovation in this specific condition. Saliva testing is time-efficient and can be performed in any setting.

Aptamers – synthetic oligonucleotides with high binding specificity – have enabled the development of rapid, disposable lateral-flow biosensors for saliva-based cortisol detection. They provide a clinically relevant detection range and yield results within minutes, making them suitable for emergency settings where diagnostic speed is essential. The cortisol range assessed by this test is 0-15 ng/mL, and results are ready within 15 minutes. (Dalirirad et al., 2020). Because saliva collection is quick and noninvasive, aptamer-based assays have the potential to facilitate early screening for AAC even when venous sampling is delayed. (Panfilova, 2021) Broader validation of portable cortisol devices has been achieved through research evaluating handheld POC analyzers. A 2020 study by Ducker K.J et al. showed that a point-of-care salivary cortisol assessment produced reliable results with strong agreement compared with standard laboratory immunoassays, thereby confirming its usefulness in time-sensitive environments such as emergency departments (Ducker et al., 2020). Although the saliva-testing strategy may serve as a useful clinical tool, it appears more useful for differential diagnosis than for diagnostic confirmation.

Treatment

Adrenal insufficiency treatment requires corticosteroid substitution therapy. Moreover, the treatment of adrenal insufficiency should always include consideration of AAC treatment, as the incidence of adrenal crisis is increasing due to the growing prevalence of secondary, tertiary, and iatrogenic adrenal insufficiency in modern clinical practice. (Martel-Duguech et al. 2024)

When AAC is suspected, most studies recommend administering an immediate IV dose of 100 mg hydrocortisone, followed by continuous hydrocortisone infusions or frequent IV boluses to maintain stable hormone levels during the crisis. New studies recommend continuous IV GKS infusions rather than boluses, based on the hypothesis that they may provide more physiologic cortisol coverage and better hemodynamic stability in critically ill patients. (Pokrzywa, Kusz & Ambroziak,;Mushtaq et al., 2023; Mortensen et al., 2023; Lewis et al., 2023). The management comprises aggressive fluid resuscitation, prompt steroid replacement, correction of electrolyte disturbances, and management of precipitating triggers as immediate priorities in the emergency department (Lewis et al., 2023).

In recent years, medicine has increasingly focused on disease prevention as a relevant component of disease treatment. Modern medicine emphasizes the importance of a trust-based relationship with patients, thereby improving adherence to prescribed medical treatment. (Wu et al., 2022) AAC typically develops in patients with preexisting adrenal disease, and rarely in previously healthy patients (Szczeklik, Interna Szczeklika 2019, Medycyna Praktyczna). This fact highlights the strong potential for AAC prevention. Prevention entails educating patients and their families about the disease and the symptoms that may precede a crisis. Patient education should also include the ability to recognise AAC risk factors, such as common illnesses, and to apply "sick-day rules," and, if needed, to administer a hydrocortisone injection. (Çamtosun et al., 2025). Patients should play a significant role in disease treatment, becoming active participants rather than passive recipients. This change in attitude facilitates patient empowerment and control over the course of the disease; in the case of AAC, it can significantly reduce time to steroid administration, thereby improving overall health outcomes. The need for further education in patients was presented in a 2025 study analyzing an online survey of 657 individuals, including both patients and caregivers, which reported concerning findings. While up to 58% of patients and caregivers reported the need for an emergency glucocorticoid injection, more than one-third were unable to administer it. (Hover et al., 2025) The most common reason for failed medication administration was the severity of the crisis itself, the present symptoms, leading to confusion and a need for

assistance to prepare the injection. Similar challenges were also confirmed in another cross-sectional study, which listed the following setbacks as defining difficulties for patients: the complexity of the multi-step hydrocortisone injection process, challenges in accessing the correct hydrocortisone formulation or equipment, and inadequate support for managing adrenal crisis (Llahana et al., 2025).

Most commonly used emergency kits (**Table 3**) include vials of hydrocortisone, needles, and syringes for 2-3 emergencies, along with step-by-step instructions for preparing the medication. While most recommendations mention an adrenal insufficiency emergency kit, they do not provide specific information on its exact composition. The ingredients in the kit depend on the country and the local pharmacy's availability. Internet sites of self-help groups for patients with adrenal insufficiency disease can be a source of helpful information, and patients should be informed about them upon hospital discharge. According to a UK self-help group of patients with Addison's disease (www.addisonsdisease.org.uk), there are 3 possible emergency kits.

1. Hydrocortisone in the form of an already prepared solution.
2. Hydrocortisone in the form of a powder in one vial, with an extra vial containing the needed solvent.
3. Hydrocortisone in the form of a powder in a capsule situated over a vial with the needed solvent.

All these kits, when acquired, include a leaflet describing the multiple-step process of preparing the syringe with the proper medication. Most commonly, patients with an adrenal insufficiency diagnosis are educated by medical professionals. Nevertheless, the adequate preparation of hydrocortisone may impose difficulties. A solution to this adversity may be a new form of steroid dosing. In case of an anaphylactic shock, a dose of adrenaline is administered with a ready-to-use EpiPen, which facilitates rapid responses in emergencies. Similarly, in AAC, an easy-to-use injector of a life-saving medication is needed. Therefore, an EpiPen-like solution may revolutionize AAC treatment. In one study (Llahana et al., 2025), 97% of participants expressed a preference for a hydrocortisone autoinjector to enhance their self-injection capability. A response to that demand is TwistJect, a prefilled, single-use device (similar to an EpiPen) developed by SOLUtion Medical. Their research program aims to create two products: a 3-step prefilled syringe and a 2-step autoinjector. In a 2024 interview, the founder stated that the company is in the process of preparing supply chains, finalizing manufacturing processes, ensuring regulatory compliance, and conducting clinical trials. The SOLUtion Medical's TwistJect device is not yet FDA-approved (Food & Drug Administration), so its wide availability is a long way off.

Table. 3 Comparison of Classical kits and the new Corticosteroid autoinjectors

Characteristic	Classical kits	Corticosteroid autoinjectors
Availability	Widely available	Currently under development
Need for education and practice	A longer time is needed to educate patients properly, and regular refreshments are required	A possible reduction in education time, and a lower need for instruction refreshment
Complexity	Multiple-step preparation of the injection kit	No need for preparation of the injection kit
Composition	Vial with already dissolved corticosteroids or powder form with an attached solvent, syringes, and needles	Prefilled syringe or an autoinjector

Discussion

Acute adrenal crisis may present with nonspecific symptoms. Rational pharmacotherapy and rapid diagnosis are essential for improved patient outcomes. Every doctor should consider AAC when they have a patient who presents with hypotension of unknown cause, with hyperkalemia, hypoglycemia, and hyponatremia in blood tests, especially if a patient has a recent history of steroid therapy. The AAC diagnostic process may be limited within the Emergency Department to symptom-based diagnosis. Therefore, advances such as saliva analyzers may objectify the diagnostic process and accelerate ED procedures. However, more studies designed to test the efficacy of cortisol saliva-based tests should be conducted, and appropriate cut-off points should be developed. In terms of therapy, portable cortisol Epipen-like injectors that are currently under development, in the future, may be recommended and widely used among high-risk patients, e.g., in those who have Addison's disease.

Conclusions

Proper diagnosis of acute adrenal crisis may be difficult, as present symptoms may overlap with those of other conditions. Modern advances in AAC diagnosis and treatment indicate a shift toward more consistent, evidence-based emergency protocols focused on rapid intervention, improved steroid delivery strategies, and proactive prevention. Saliva analyzers enable quick, non-invasive measurement of cortisol levels, while advances in delivery systems, which are currently in trials as EpiPen-like solutions, ensure proper drug delivery and reduce hospital admissions by resolving problems in pre-hospital care, often at home. Technology development is essential; however, appropriate patient education is key and should remain at the center of patient treatment. With expansions of awareness and changes in treatment approaches becoming increasingly targeted and standardized, emergency physicians will be better dequipped to manage patients and prevent fatalities associated with acute adrenal crisis.

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