# Management of adrenal crisis in emergency department: Review

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## Abstract:

The aim of this review is give general information about epidemiology and definition of Adrenal Crisis, risk factors and emphasizes the clinical presentation as well as highlight the management in emergency case. In MEDLINE/PubMed, Cochrane Library, Embase and Web of Science databases search was performed for all studies published throughout the past 3 decades up to December 2017. This search was without language restriction, and involving articles with human subject discussion. Although adrenal insufficiency is a treatable illness in the 21st century, failing to recognize an adrenal crisis and institute appropriate and timely treatment has led to preventable deaths. Present glucocorticoid therapy cannot replicate the physical needs during times of stress. For this reason, all doctors need to be familiar with increased dosages needed in disease or stress. It is essential to identify that patients might not respond to oral treatment, and in those circumstances, early parenteral hydrocortisone administration and referral to an emergency department is warranted. Adrenal crisis continues to be an actual and constant risk to all patients with adrenal insufficiency throughout their life time. Because there is greater than adequate availability of necessary health care in most countries, we

need to aim to eliminate death from adrenal crisis. Every emergency physician must be familiar with adrenocortical insufficiency, which is a possibly life-threatening entity. The initial diagnosis and decision to manage are presumptive and are based upon history, physical examination, and, sometimes, laboratory findings. Delay in therapy while attempting to confirm this medical diagnosis can result in bad patient outcomes.

## Introduction:

Acute adrenal insufficiency is a rare yet life threatening condition that establishes as a result of insufficient adrenal steroid production. In primary adrenocortical insufficiency, glucocorticoid and mineralocorticoid properties are lost; however, in secondary adrenocortical insufficiency (ie, additional to condition or reductions of the hypothalamic-pituitary axis), mineralocorticoid function is preserved. Early diagnosis is essential for effective and life-saving therapy of the affected patients. The main clinical attributes are non-specific, therefore often leading to misdiagnosis and intrusive diagnostic develop, specifically in patients with previously unidentified disease [1]. Adrenal crisis in patients with well-known chronic adrenal insufficiency is nowadays rare, however can only be prevented by structured patient education on stress-related glucocorticoid dose adjustment. Outcome of adrenal crisis is most importantly determined by the physician's clinical competence and instant initiation of particular treatment.

The aim of this review is give general information about epidemiology and definition of Adrenal Crisis, risk factors and emphasizes the clinical presentation as well as highlight the management in emergency case.

## Methodology:

We conducted literature search through the electronic PUBMED, MEDLINE (Ebsco), and COCHRANE databases, for all publications up to December, 2017. Search strategy did not involve language restriction, and involving articles with human subject discussion. We used following MeSH terms: "Adrenal crisis", "Adrenal insufficiency", "emergency department", "management AND treatment". We search for relevant articles which were concerning the adrenal crisis management in emergency department.



## Discussion:

- **DEFINITION AND EPIDEMIOLOGY**

In 1855, Thomas Addison initially described patients with chronic adrenal insufficiency [2].Most of those patients had primary adrenal failure as a result of tuberculosis, although autoimmune adrenal disease has superseded it as the most constant reason for primary adrenal insufficiency in the developed globe. Causes of adrenal insufficiency can be classified as primary, additional, or glucocorticoid-induced adrenal insufficiency (from chronic exogenous glucocorticoid exposure) [3].Of note, metastasis to the adrenal glands rarely triggers adrenal insufficiency, and takes place only if metastatic illness is reciprocal, with considerable damages to the adrenal glands [4]

Without adequate steroid replacement treatment, this was an inevitably fatal problem during Addison, with almost all patients dying within the first 5 years of medical diagnosis. The exploration of cortisone by Hench, Kendall, and Reichstein in the late 1940s boosted the expectation on patients with adrenal insufficiency significantly, and initial data recommended that life span was normalized [5].Nonetheless, during an acute anxiety event, these patients are not able to place a regular physiological response with increased endogenous cortisol production. Failing to raise their dose of exogenous glucocorticoids appropriately can bring about acute adrenal insufficiency, or adrenal crisis.

Adrenal dilemma may be specified as an acute wear and tear in a patient with adrenal insufficiency. The major indication of adrenal crisis is hypotension or hypovolemic shock, but various other signs and signs such as weak point, anorexia, nausea, abdominal discomfort, high temperature, throwing up, tiredness, electrolyte abnormalities, confusion, coma, and marked laboratory problems can also take place, which requires prompt therapy [3].Nonetheless, use variable definitions in various researches has caused trouble in approximating truth occurrence of adrenal crisis happening in patients with known adrenal insufficiency, along with the danger of death from adrenal crisis.



Initial studies in patients with both secondary [6] and primary adrenal insufficiency [7] utilized information registries and revealed that they were at raised death threat, with some suggesting that endocrine and transmittable reasons added to this [7]. Ultimately, in a Swedish study12 of patients with hypopituitarism, all 15 situations of fatality from infections occurred in patients with hypocortisolism. 8 of these patients had actually a documented adrenal crisis, and 7 of these 8 died at home or upon arrival to the medical facility. Premature death occurring in young patients with adrenal insufficiency was noted in 2 other researches, [8] with adrenal dilemma a

likely reason in > 50%, and oftentimes associated with minor infections [8].This highlights the significance of prevention and early treatment.

The danger of adrenal crisis happening in a patient with adrenal insufficiency has been approximated to be regarding 6-10 adrenal crises each 100 patient years (PYs) [9].These quotes were based on retrospective studies using questionnaires, and restricted by reporting predisposition. A recent potential research [10] found 64 episodes of adrenal situation in 423 patients with primary and second adrenal insufficiency (8.3 adrenal crises/100 PYs), and, amazingly, 4 adrenal crisis-related fatalities were noted over a follow-up period of 2 years (0.5 adrenal crisis-related deaths each 100 PYs). Of concern, these situations took place despite the fact that the patients enlisted in this research had received, at standard, patient education and learning with created instructions on corticosteroid dosage modifications throughout stress, health problem, and self-treatment with injectable hydrocortisone, which most doctors think about as adequate preventive measures.



- **CLINICAL PRESENTATION**

There need to be a high degree of uncertainty in all patients with well-known adrenal insufficiency or danger aspects for any of the root causes of adrenal insufficiency. Adrenal crisis can be the initial discussion of patients with adrenal insufficiency, taking place in up to 50% of patients with Addison's condition [11].The diagnosis could be postponed, as the majority of the signs and symptoms and indications of adrenal insufficiency happen insidiously and are nonspecific, such as anorexia, fatigue, nausea, high temperature, sleepiness, and orthostatic hypotension (Table 2). Patients providing with adrenal situation are often in hypotensive shock, and could have altered sensorium. They frequently have gastrointestinal signs and symptoms like

abdominal discomfort, nausea or vomiting, vomiting and looseness of the bowels, resulting in a wrong diagnosis of an acute abdominal area or gastroenteritis.

Hypotension happens secondary to hypovolemia, however additionally as a result of hypocortisolism, as glucocorticoids exert a liberal impact on catecholamine action [12].Otherwise recognized, it could be refractory to fluids and inotropes. In second adrenal insufficiency, hyponatremia happens as a result of failure to suppress vasopressin and impaired electrolyte-free water excretion in the kidneys [13].In primary adrenal insufficiency, hyponatremia is because of concomitant aldosterone deficiency, which results in natriuresis, volume deficiency, and hyperkalemia. Various other biochemical features include hypoglycemia and, rarely, hypercalcemia, which is because of lowered kidney excretion of calcium and enhanced bone resorption [3] (Table 1).



**Table 1.**Clinical Features of Chronic Adrenal Insufficiency (AI) and Adrenal Crisis (AC)

| | **Chronic Adrenal Insufficiency** | **Adrenal Crisis (Acute Adrenal Insufficiency)** |
|---|---|---|
| **Symptoms** | Fatigue, anorexia, weight loss, myalgia, arthralgia<br>Dizziness<br>Nausea, vomiting, diarrhea<br>Salt craving (in primary AI only) | Severe weakness<br>Acute abdominal pain, nausea, vomiting<br>Altered sensorium |
| **Signs** | Orthostatic hypotension<br>Fever<br>Hyperpigmentation of the skin creases and buccal mucosa (in primary AI only) | Hypotension<br>Fever<br>Abdominal tenderness or guarding<br>Reduced consciousness |
| **Biochemical** | Hyponatremia<br>Hyperkalemia (primary AI)<br>Hypoglycemia<br>Hypercalcemia<br>Mild normocytic anemia, lymphocytosis, eosinophilia | Hyponatremia<br>Hyperkalemia (primary AI)<br>Hypoglycemia<br>Hypercalcemia |

## Risk Factors

It is important to be familiar with conditions that boost the risk of adrenal crisis in patients with adrenal insufficiency . Patients with primary adrenal insufficiency might go to greater threat of adrenal crisis compared to patients with additional adrenal insufficiency, because of the absence of mineralocorticoids and better threat of dehydration and hypovolemia [10].The true threat of adrenal crisis in patients with glucocorticoid-induced adrenal insufficiency is difficult to identify, as they form a heterogeneous team and just minimal case reports are offered [14].It is essential, however, to recognize that the most usual cause of adrenal insufficiency is use exogenous steroids, and these patients are likewise at risk of adrenal crisis. Sudden, and frequently unintentional, withdrawal of steroids could result in adrenal crisis. For this reason, a detailed medication history is important, particularly for surreptitious use of steroids. Use glucocorticoids in the forms of topical, inhaled, nasal, injectable, intraarticular, intradermal (eg, keloid), paraspinal, or rectal preparations have all been defined to create suppression of the hypothalamus-pituitary-adrenal axis. Megestrol and medroxyprogesterone additionally have substantial glucocorticoid action at medicinal doses [15].Concomitant use of steroids with itraconazole [16] or ritonavir [17] (which prevent hepatic CYP3A metabolic process of steroids) could raise this risk. Usually, longer duration, higher dosages, and oral and intraarticular prep work raise the danger of adrenal suppression. However, there is no dosage, duration, or management form that could forecast adrenal insufficiency, and doctors should work out a high level of suspicion [18].

In undiagnosed patients with adrenal insufficiency, cytochrome P-450 enzyme inhibitors like ketoconazole or fluconazole could reduce endogenous adrenal production and precipitate adrenal crisis.28 Levothyroxine could accelerate the outer metabolism of cortisol, and precipitate adrenal

crisis in patients with undiagnosed adrenal insufficiency or those currently on replacement,2 which matters, as patients with type 2 autoimmune polyglandular syndrome could have concomitant thyroid and adrenal deficiency [19].Cytochrome P-450 enzyme inducers (phenytoin, rifampicin, phenobarbitone) might similarly speed up an adrenal dilemma [20].Therefore, in patients with tuberculosis-associated adrenal failure being launched on rifampicin, glucocorticoid doses must be appropriately boosted [21].

Diabetes insipidus was likewise associated with greater danger of adrenal dilemma in patients with secondary adrenal insuffi- ciency, which could be as a result of the higher danger of dehydration, or the lack of V1-receptor moderated vasoconstriction throughout serious stress. Other medical problems (eg, type 1 and kind 2 diabetes mellitus, hypogonadism) were related to higher threat of adrenal crisis in some studies, although the device is not clear [22].



The life-time threat of adrenal crisis in a patient with adrenal insufficiency has to do with 50%, and those with previous adrenal crisis seem at greater risk of succeeding episodes [10].While some patients could experience life without an episode of adrenal situation, the very first might be fatal, as held true in 3 of 4 patients in a recent prospective research study, highlighting the have to be vigilant in handling all patients with adrenal insufficiency [10].

- **INVESTIGATIONS**

In patients with well-known adrenal insufficiency presenting with signs and symptoms normal of adrenal dilemma, treatment must be set up promptly immediately. In patients where the medical diagnosis has not yet been made, therapy must also not be postponed for the purpose of diagnostic examinations (eg, adrenocorticotropic hormone [ACTH] -excitement examination) in a patient that is clinically unstable.3 Serum cortisol, ACTH, aldosterone,

dehydroepiandrosterone-sulfate, and renin can be taken just before hydrocortisone management and may be useful in the medical diagnosis of adrenal insufficiency. A high cortisol degree of > 20 mg/dL (550 nmol/L) could exclude the diagnosis, [24] while a low cortisol level of > 20 mg/dL (550 nmol/L) can leave out the medical diagnosis, [24] while a low cortisol degree of <5 mg/dL (138 nmol/L) done in the early morning or in a state of stress, strongly sustains the medical diagnosis of adrenal insufficiency [23].A concomitant high ACTH degree exists in cases of primary adrenal insufficiency, [3] while low or inappropriately regular ACTH follows secondary or tertiary adrenal insufficiency. In all situations of unpredictability, glucocorticoid therapy need to be proceeded up until the patient has recouped, after which an analysis examination such as an ACTH-stimulation examination can be carried out safely. This test must be done as early as possible, since prolonged glucocorticoid therapy can influence the activity of the hypothalamic-pituitary-adrenal axis.



- **MANAGEMENT OF ADRENAL CRISIS**

The concepts of therapy are fluid resuscitation and steroid replacement. Intravenous fluid resuscitation with isotonic sodium chloride 0.9% will certainly deal with the hypovolemia and hyponatremia, while intravenous dextrose could additionally be needed to correct hypoglycemia. One liter of saline 0.9% should be given over the first hr, and further replacement fluids must be led by frequent hemodynamic monitoring and dimension of serum electrolytes [24].Cortisol substitute could generate water diuresis and reduce antidiuretic hormone (in secondary adrenal insufficiency), which along with sodium replacement could result in fast correction of hyponatremia, and osmotic demyelination disorder. Hence, caution needs to be worked out to correct sodium by<10 mEq over the first 24 hours[13].

Parenteral hydrocortisone, which can be administered at home intramuscularly, before arriving at a hospital, is fundamental to avert further clinical deterioration. In the hospital, hydrocortisone can be given intravenously or intramuscularly 100 mg as a bolus, followed by 100-300 mg per day for another 2 to 3 days, either as boluses every 6 hours or as continuous infusion until full recovery[24]. At hydrocortisone doses of>< 10 mEq over the very first 24 hrs [13].Parenteral hydrocortisone, which can be administered at home intramuscularly, prior to reaching a hospital, is fundamental to prevent further scientific degeneration. In the hospital, hydrocortisone can be given intravenously or intramuscularly 100 mg as a bolus, followed by 100-300 mg daily for an additional 2 to 3 days, either as boluses every 6 hrs or as constant infusion until complete recovery [24].At hydrocortisone doses of > 50 mg/day, there is sufficient activity at the mineralocorticoid receptor, and it is generally approved that added mineralocorticoid treatment is not called for [24].With subsequent tapering of the dosages, fludrocortisone must be begun in patients with primary adrenal insufficiency, with a dose of 50-200 mg each day sufficient in most patients [25].



## Emergency Help

If a patient with adrenal insufficiency becomes unconscious, it is essential that appropriate medical aid is administered. Patients should be reminded to wear or carry a MedicAlert bracelet or emergency situation card at all times [26].A significant worry is the reluctance of some healthcare specialists to treat the problem even after it is presented to them, as illustrated in a current survey of 46 patients. While 86% of patients were promptly attended to by a health care professional within 45 mins of a distress call, just 54% obtained glucocorticoid administration within 30 minutes of arrival [27].This may be due to the fact that it is an uncommon problem with which healthcare experts are commonly strange. The intro of a pan-European Emergency

card with clear directions on the requirement of early treatment will hopefully encourage allied health care service providers and medical professionals to institute therapy [28].For physicians who are much less familiar with this unusual problem, it is prudent to hear patients and their households that typically do know best, and in times of unpredictability, note patients' requests for more hydrocortisone [29].Increased glucocorticoid doses in the short term are normally safe, while the repercussions of inadequate doses can be tragic. Nevertheless, in the long-lasting management of a patient with adrenal insufficiency, it is additionally vital to review the frequency of anxiety doses used by the patient. Regular usage might show overzealous action to minor ailment (which requires added counseling concerning sick day rules), or a demand for adjustments in basal regimens.

## Conclusion:



Although adrenal insufficiency is a treatable illness in the 21st century, failing to recognize an adrenal crisis and institute appropriate and timely treatment has led to preventable deaths. Present glucocorticoid therapy cannot replicate the physical needs during times of stress. For this reason, all doctors need to be familiar with increased dosages needed in disease or stress. It is essential to identify that patients might not respond to oral treatment, and in those circumstances, early parenteral hydrocortisone administration and referral to an emergency department is warranted. Adrenal crisis continues to be an actual and constant risk to all patients with adrenal insufficiency throughout their life time. Because there is greater than adequate availability of necessary health care in most countries, we need to aim to eliminate death from adrenal crisis. Every emergency physician must be familiar with adrenocortical insufficiency, which is a possibly life-threatening entity. The initial diagnosis and decision to manage are presumptive and are based upon history,

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## Reference:

1. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. Crit Care Clin 2001;17:27.
2. Bishop PM. The history of the discovery of Addison's disease. Proc R Soc Med. 1950;43(1):35-42.
3. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361(9372): 1881-1893.
4. Lutz A, Stojkovic M, Schmidt M, et al. Adrenocortical function in patients with macrometastases of the adrenal gland. Eur J Endocrinol. 2000;143(1):91-97.
5. Dunlop D. Eighty-six cases of Addison's disease. Br Med J. 1963;2(5362):887-891.
6. Tomlinson JW, Holden N, Hills RK, et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. 2001;357(9254):425-431.
7. Bensing S, Brandt L, Tabaroj F, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol. 2008;69(5):697-704.
8. Erichsen MM, Lovas K, Fougner KJ, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol. 2009;160(2):233-237.
9. Omori K, Nomura K, Shimizu S, et al. Risk factors for adrenal crisis in patients with adrenal insufficiency. Endocr J. 2003;50(6):745-752.
10. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100(2):407-416.
11. Zelissen PM. Addison Patients in the Netherlands: Medical Report of the Survey. The Hague, The Netherlands: Dutch Addison Society; 1994.
12. Allolio B, Ehses W, Steffen HM, Muller R. Reduced lymphocyte beta 2-adrenoceptor density and impaired diastolic left ventricular function in patients with glucocorticoid deficiency. Clin Endocrinol. 1994;40(6):769-775.
13. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-S42.
14. Robati S, Shahid MK, Vella A, Rang S. Importance of a thorough drug history in presurgical patients. BMJ Case Rep. 2014;2014. http://dx. doi.org/10.1136/bcr-2013-202667.
15. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. Endocrinol Metab Clin North Am. 2005;34(2):371-384, ix.
16. Bolland MJ, Bagg W, Thomas MG, et al. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. Ann Pharmacother. 2004;38(1):46-49.

17. St Clair K, Maguire JD. Role of fluconazole in a case of rapid onset ritonavir and inhaled fluticasone-associated secondary adrenal insuffi- ciency. Int J STD AIDS. 2012;23(5):371-372.
18. Broersen LH, Pereira AM, Jorgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(6): 2171-2180.
19. Graves L 3rd, Klein RM, Walling AD. Addisonian crisis precipitated by thyroxine therapy: a complication of type 2 autoimmune polyglandular syndrome. South Med J. 2003;96(8):824-827.
20. Bornstein SR. Predisposing factors for adrenal insufficiency. N Engl J Med. 2009;360(22):2328-2339.
21. Yadav J, Satapathy AK, Jain V. Addisonian crisis due to antitubercular therapy. Indian J Pediatr. 2015;82(9):860.
22. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol. 2010;162(1): 115-120.
23. . Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab. 2008;93(11):4245-4253.
24. Bouillon R. Acute adrenal insufficiency. Endocrinol Metab Clin North Am. 2006;35(4):767-775, ix.
25. . Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104-115.
26. Peacey SR, Pope RM, Naik KS, et al. Corticosteroid therapy and intercurrent illness: the need for continuing patient education. Postgrad Med J. 1993;69(810):282-284.
27. Hahner S, Hemmelmann N, Quinkler M, et al. Timelines in the management of adrenal crisis—targets, limits and reality. Clin Endocrinol. 2015;82(4):497-502.
28. Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol. 2013;169(6):R165-R175.
29. Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. BMJ. 2012;345:e6333.