Adrenal Insufficiency Coalition
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# Daily Management of Adrenal Insufficiency

## The importance of adequate baseline and flexibility with doses to prevent adrenal crisis.

Conventional glucocorticoid (GC) replacement for patients with adrenal insufficiency (AI) is often inadequate. Patients with AI continue to have increased mortality, morbidity, and compromised quality of life despite treatment and monitoring. The increased demand for corticosteroids during periods of stress can result in a life-threatening adrenal crisis (AC) in a patient with adrenal insufficiency. [1]

For several years, the life expectancy of patients with adrenal insufficiency who received conventional glucocorticoid replacement therapy and adequate follow-up was considered normal. However, it has recently been determined that patients with adrenal insufficiency have a more than twofold increased standardized mortality ratio (SMR) mainly due to cardiovascular and infectious diseases. [2,3]

In addition to decreased life expectancy, patients with adrenal insufficiency on current replacement therapy also have a significantly compromised quality of life, irrespective of the origin of adrenal insufficiency or concomitant disease. [4,5] Establishing a correct daily baseline, learning to recognize the early signs of an impending adrenal crisis, and learning how to treat it appropriately, can improve the quality of life for patients and reduce the number of adrenal crises.

Optimization and individualization of glucocorticoid replacement remains a challenge partly because available therapies do not mimic physiological cortisol patterns. While increased mortality and morbidity appear related to inadequate glucocorticoid replacement, there are no objective measures to guide dose selection and optimization. Physicians must rely on experience to recognize the clinical signs of inadequate treatment, which are not unique to adrenal insufficiency. [1]

There are also wide variations in treatment needs among patients. Some manage well on a regular baseline amount and rarely have an adrenal crisis. Others have daily fluctuations in their cortisol needs and frequently experience an adrenal crisis. Successful management of adrenal insufficiency requires tailoring the glucocorticoid replacement therapy to the needs of each patient.

**To prevent an adrenal crisis there are three areas to be considered:**

1) the daily maintenance dose,
2) the need for extra cortisol during an intercurrent illness or non-illness-related event, such as exercise or psychological stress,
3) and the patient's Quality of Life, (QoL).

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## ESTABLISHING A DAILY BASELINE

It is generally recommended to use the lowest dose of hydrocortisone (HC) that relieves symptoms of glucocorticoid deficiency**. This advice in current guidelines remains true only when QoL is adequately considered in determining the appropriate dose for the individual patient.** Results from a 2015 randomized controlled trial show that a higher HC substitution dose will improve patient well-being:

> *"On the higher dose of HC, patients reported a better HRQoL on various domains as compared to the lower dose of HC. The fact that a higher dose of HC may improve patient well-being should be taken into consideration when individualizing the HC substitution dose."* [6]

**We recommend starting with 20mg hydrocortisone, divided into three doses, with the higher dose in the morning.** Timing of steroid doses directly affects daily function. The circadian rhythm achieves a high "peak" between the hours of 6 am and noon, after which it falls steadily to a low point, or "trough" between 6 pm and midnight. It begins to rise again around 1 am. Mimicking this peak and trough with medication is a challenge. It is possible to be over-replaced and under-replaced on the same day by being above or below the optimal amount at any point in the 24-hour period.

**Low, but not zero, levels of cortisol are necessary for REM sleep.** [7] Waking in the early morning hours feeling unwell is a clear sign of inadequate coverage. Patients may need an additional dose, either before bedtime or during the night to prevent an adrenal crisis. Some patients may benefit from a small dose of longer-acting steroid overnight.

**Taking glucocorticoid replacement affects thyroid levels.** A thyroid panel should be drawn three to four weeks after the beginning of treatment.

**It can take time for the patient to adjust to the glucocorticoid treatment.** Physicians and nursing staff need to be available to the patient during this adjustment period. If the patient is still unwell after ten days of treatment, the dose may be inadequate and dose adjustment is recommended.

**Patients should be educated about and instructed what to do if they suspect that they are having an adrenal crisis.** Patients also need an emergency injection prescription and instructions about how to administer emergency medication. Patient education resources can be found at www.adrenalinsufficiency.org

**In the absence of a meter to test cortisol levels, the patients' symptoms must guide treatment.** Physicians should discuss symptoms in detail with the patient and be alert for over or under-replacement symptoms:

| Signs of over-replacement | Signs of under-replacement |
|---|---|
| Food cravings | Lack of appetite |
| Weight gain | Weight loss |
| Thin skin/bruising | Extreme fatigue/unable to function daily |
| Hot flushes | Chills/temperature fluctuations |
| Edema | Nausea |
| Stretch marks | Headaches |
| Extreme fatigue | Insomnia |
| Depression | Anxiety |
| Round face | Reoccurring adrenal crisis |

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**Patients may need to keep a journal** to record their dosage times and amounts, as well as blood pressure (BP) throughout the day. They should also record sick periods with symptoms and BP, and if extra steroids were taken. Physicians need to be flexible during this period.

**Withholding adequate steroids can result in an adrenal crisis.** Short term fluctuations in steroid amounts will not contribute to over-replacement provided a correct baseline is established within a few months. Patients who have regular unwell periods throughout the day, or who wake up feeling sick may need more frequent dosing, a different dosing schedule, a higher baseline, or a longer acting steroid. It may take time to determine which one is appropriate.

**The correct daily maintenance amount is one that the patient can wake up and function throughout the day, (possibly with rest periods) and obtain adequate sleep at night.**

## DEFINITION OF ADRENAL CRISIS

The early detection of an impending adrenal crisis is often complicated by the lack of consensus on its definition. The Endocrine Society guidelines on the diagnosis and treatment of Primary Adrenal Insufficiency (PAI) defines an adrenal crisis as a medical emergency with hypotension, abdominal symptoms and laboratory abnormalities requiring emergency treatment. However, this definition addresses only PAI patients with Aldosterone deficiency who experience hypotension. Secondary Adrenal Insufficient (SAI) patients often have hypertension.

Allolio and colleagues describe an adrenal crisis as a major impairment of general health in addition to the demonstration of a clinical improvement following parenteral glucocorticoids. [8] They also proposed a grading system using levels of hospitalization to denote adrenal crisis severity ranging from grade 1 (outpatient care only) to grade 4 (death from adrenal crisis), with or without parenteral glucocorticoid administration.

Definitions also differ among research studies. Puar et al. [9] defined an adrenal crisis as an acute deterioration in a patient with adrenal insufficiency, whereas Smans and colleagues defined adrenal crisis as an acute impairment of general health requiring hospitalization and administration of IV saline and gluco-corticoids in patients with adrenal insufficiency. [10] More recently, Rushworth et al. proposed a definition that the authors feel will increase the likelihood that true adrenal crisis events are identified and that other, less-severe episodes of illness are not classified as an adrenal crisis but a milder form of illness [11]. The wide variation of proposed definitions highlights the individual nature of an adrenal crisis and the symptoms preceding it.

**For this paper, we identify an adrenal crisis as a sudden deterioration of general health, consisting of three or more symptoms (listed below) that requires administration of steroids to stabilize.**
The goal is to recognize the symptoms early and treat promptly to PREVENT an adrenal crisis.
The early administration of steroid tablets can often avoid the need for an emergency injection later.

Symptoms of an impending adrenal crisis

| | | |
|---|---|---|
| Nausea/abdominal pain | Chills/sweats | |
| Headache | Body aches | Flank pain/leg pain |
| Extreme fatigue/weakness | Confusion/anxiety | Sadness/weepy |
| Tachycardia/Bradycardia | Hypotension | Hypertension |

**Each person is unique. Not all symptoms may be present. A profound worsening of health condition constitutes an emergency for an adrenal insufficient patient.**

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It is important that patients, caregivers, and family members are aware of the symptoms of an impending crisis. It should be reinforced to patients to have a low threshold to administer a hydrocortisone emergency injection and seek urgent medical care if they develop severe symptoms. Patients are encouraged to pack extra hydrocortisone when travelling abroad, including a letter from their endocrinologist to allow the emergency kit to go through customs. [1] It is recommended that patients always wear an emergency medical bracelet with instructions for steroid treatment.

## Causes of an adrenal crisis

In retrospective and prospective studies, the most frequent precipitating causes of adrenal crisis are gastroenteritis (35–45%) and fever (17–24%), but other stressful events such as trauma, surgery, dental procedures, and major psychological distress can cause adrenal crisis.

In their prospective study of PAI patients, Hahner et al., [12] found that emotional stress was identified as a triggering factor in 30% of adrenal crisis, as frequently as gastrointestinal symptoms, or infections (35% and 32%, respectively). The ability for psychological stress to trigger an adrenal crisis is under recognized and patients are often advised that this does not lead to adrenal crisis, which based on the above data is incorrect.
Similarly, in a longitudinal study of patients across all ages with Congenital Adrenal Hyperplasia (CAH), gastrointestinal and upper respiratory tract infections were the two most common precipitating events for adrenal crises and hospitalizations.
A history of a previous adrenal crisis is the most important risk factor for further crises, with approximately threefold higher risk observed in the prospective study by Hahner et al. Non-endocrine comorbidities were also found to increase the risk of an adrenal crisis dramatically. [1, 12]

## Taking additional Glucocorticoids for stress

Patients need to be empowered to make relevant adjustments to their own medication, in the absence of their treating physician, and to adapt their dose according to individual needs. An additional dose of hydrocortisone may be considered in situations of severe and prolonged psychological stress, or prolonged physical exercise. Patients on shift work may need to adapt their hydrocortisone dose according to the time of wakefulness. In the case of a hot climate or strong perspiration, it is necessary to increase the fludrocortisone dose (0.1–0.2mg/ day) or the salt intake to compensate. [1]

Taking small amounts of glucocorticoids when needed, in addition to the daily baseline amount, is part of successful AI management. For healthy people, the body makes minute adjustments of cortisol based on need. If you run to catch a bus, exercise, or have an argument with your spouse, your body will adjust by making more cortisol. Patients with adrenal insufficiency must be guided by their symptoms. Each person will be different. If a patient requires additional glucocorticoids often, they may need a higher daily baseline.

If stress can be anticipated, such as taking an exam or a strenuous hike, it's beneficial to take the additional glucocorticoids BEFORE the event. Waiting until the patient feels unwell can often require more steroids to stabilize.

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In the event of prolonged psychological or physical stress, such as the illness of a spouse, the death of a loved one, or recovery from an injury, a higher daily baseline may need to be established for the duration of the recovery period.

Patients must be alert to possible signs of infection. Infections are the cause of 32% of adrenal crises. Even a common urinary tract infection can precipitate an adrenal crisis. Patients should be instructed to contact their physician if they develop a fever or need to double their dose for more than three days. Stress dosing is not limited to three days. Sick day dosing should continue until the precipitating condition, such as infection or fever, is resolved.

**Patients should be educated about sick day rules. Physicians need to prescribe an extra week of glucocorticoids each month for sick-day and stress dosing.**

## Current recommendations for stress dosing

- **The National Adrenal Disease Foundation, (NADF)**
  Unusual work-related stress or increased hours, travel, overexertion, intensive exercise, positive or negative emotional stress, dependent on individual and circumstance, typically requires extra dose of 5-10 mg hydrocortisone based on symptoms.
  *NADF complete stress dosing guidelines:*
  *https://www.nadf.us/uploads/1/3/0/1/130191972/nadf_stress-dosing_guidelines.pdf*

- **Extensive Expertise in Endocrinology: Adrenal crisis** [8]
  For emotional and physical stress, such as an exam or a strenuous hike: 10 mg hydrocortisone one hour before the event (Abstract).

- **The Dutch Adrenal Network,** www.adrenals.eu
  For moderate mental stress, such as an exam: 2.5 to 5 mg hydrocortisone.
  For a death or other traumatic experience, increase daily baseline temporarily, possibly up to double the regular amount.

- **Sick day rules** [1]
  → Double the daily **<** maintenance dose
  when the patient experiences fever or illness requiring bed rest, when requiring antibiotics for an infection, or before a small outpatient procedure, such as dental work. The physician must ensure that the patient has an adequate supply of hydrocortisone tablets so the regular daily amount can be doubled for at least seven days if required.

  → Inject a glucocorticoid preparation **IM/IV**
  in the case of severe illness, trauma, persistent vomiting, when fasting for a procedure (colonoscopy) or during surgical intervention.

  *For complete stress/illness/surgery guidelines, please see www.nadf.us*

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