# What is Adrenal Insufficiency?

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Introduction

Adrenal insufficiency is a rare endocrine (or hormonal) disorder that occurs when the adrenal glands cease to produce any or not enough glucocorticoids (the hormone cortisol or cortisone) and, in some cases, mineralocorticoids (the hormone aldosterone) and androgens. There are different types of adrenal insufficiency, only one of which is Addison’s disease.

Cortisol, produced in the adrenal glands, is a steroid hormone which is essential for a wide range of processes throughout the body including metabolism and the immune response. It also has a very important role in helping the body respond to stress. Failure of the adrenal glands therefore requires lifelong, continuous cortisol replacement therapy.

Adrenal insufficiency occurs in all age groups and afflicts men and women alike. Among one million people, between 82-144 are diagnosed with primary and 150-280 with secondary adrenal insufficiency.

If a sudden emotional or physical stress (e.g. an accident/trauma or fever/infection) occurs, the disease can, despite correct and constant replacement therapy, quickly progress to a condition called an Addisonian crisis, adrenal crisis or acute adrenal insufficiency. This is a potentially life-threatening situation and requires immediate emergency treatment.

The onset of symptoms is often very gradual and may include fatigue, dizziness, weight loss, low blood pressure, muscle weakness, mood changes and sometimes (in primary adrenal insufficiency only) darkening of the skin in both sun-exposed and non-exposed parts of the body.

Because the condition is rare and presents a broad range of nonspecific symptoms its diagnosis is often delayed. Once diagnosed, people should consult an endocrinologist (specialist for hormonal diseases) as adrenal insufficiency can be associated with other hormone deficiencies.
Anatomy and Physiology

The Adrenal Glands

The adrenal glands (also called suprarenal glands) are situated on top of each kidney. They are small but powerful and look like two little upside down acorns. They secrete steroid and catecholamine hormones directly into the blood.

Each adrenal gland has an outer cortex which produces steroid hormones and an inner medulla. The adrenal cortex itself is divided into three zones: zona glomerulosa, zona fasciculata and zona reticularis which produce the three main types of steroid hormones: mineralocorticoids, glucocorticoids and androgens.
What is Cortisol?

Cortisol is a steroid hormone, also known as glucocorticoid, and is produced in the cortex of the adrenal glands. Cortisol is released into the blood and transported all around the body. Almost every cell contains receptors for cortisol, and the cell type determines which effect the cortisol has. These effects, among many others, include:

- controlling the body’s blood sugar levels and thus regulating metabolism;
- acting as an anti-inflammatory;
- influencing memory formation;
- regulating blood pressure.

Regulation of Cortisol Release: HPA Axis

The secretion of cortisol is mainly controlled by three inter-communicating regions of the body: the hypothalamus, the pituitary gland (both in the brain) and the adrenal gland. Together they form our central stress response system and are commonly referred to as the hypothalamic-pituitary-adrenal axis (HPA axis).
Normally, when blood cortisol levels are low, a group of cells in a region of the brain called the hypothalamus releases corticotropin releasing hormone (CRH) which then causes the pituitary gland to secrete the hormone ACTH (adrenocorticotropic hormone, also called corticotropin, adrenocorticotrophin) into the bloodstream.

High blood levels of ACTH are detected in the adrenal glands and stimulate the secretion of cortisol, causing blood levels of cortisol to rise. As the cortisol levels rise they start to block the release of (more) CRH from the hypothalamus and ACTH from the pituitary gland. As a result ACTH blood levels start to drop which then leads to a drop in cortisol levels. This is called a negative feedback loop.

**Circadian Rhythm of Cortisol Release**

The hypothalamus also acts as the body’s “central clock”. In healthy people the production of cortisol follows a daily rhythm, with the highest peak around wake-up time and two smaller peaks around noon and late afternoon. The blood levels are lowest in the evening and early part of the night. In addition, extra cortisol is released in response to stress to help the body to cope and respond appropriately.
GOOD TO KNOW

Soon after waking in the morning, cortisol blood levels rise to the highest levels of the day. People living with adrenal insufficiency usually have low levels of morning cortisol, and getting out of bed can be difficult. They should take their first hydrocortisone dose right after waking up, or even half an hour before getting out of bed.

One of the challenges in the treatment of adrenal insufficiency is to mimic the normal rhythm of cortisol release as closely as possible. So far, conventional oral medication (tablets/pills taken by mouth) such as immediate-release hydrocortisone is not capable of fully replicating the physiological cortisol circadian rhythm, even when given twice or thrice daily.

Interesting fact: In people who work at night the cortisol release pattern is reversed, which shows that the release of cortisol is linked to daily activity patterns.

What is Aldosterone?

Aldosterone, a mineralocorticoid, helps maintain the blood pressure in the body by helping the kidneys retain sodium and excrete potassium. When aldosterone production falls too low, the kidneys are not able to regulate the salt and water balance, causing blood volume and blood pressure to drop.

Whereas all adrenal insufficient people need cortisol replacement, those with secondary and tertiary adrenal insufficiency usually still produce aldosterone and androgens. Therefore, typically only people living with primary adrenal insufficiency need to replace those hormones as well.
Types of Adrenal Insufficiency

The failure to produce sufficient levels of cortisol can occur for different reasons. Depending on the underlying mechanism, the problem may be due to a disorder of the adrenal glands themselves (primary adrenal insufficiency or PAI), inadequate secretion of ACTH by the pituitary gland (secondary adrenal insufficiency or SAI) or impaired production or action of CRH from the hypothalamus (tertiary adrenal insufficiency or TAI).

Primary Adrenal Insufficiency (Addison’s Disease)

Primary adrenal insufficiency develops in about 4 of 100,000 persons annually (= incidence), and studies report between 82-144 cases per one million of the population (= prevalence). It occurs in all age groups and about equally in each sex.

GOOD TO KNOW

The difference between incidence and prevalence:
Incidence and prevalence are commonly used terms in describing epidemiology of diseases. Incidence is the rate of new (or newly diagnosed) cases of the disease within a period of time (e.g. per month or year). Prevalence is the actual number of cases during a period or at a particular date in time.
Approx. 80% of cases of primary adrenal insufficiency in developed countries are caused by autoimmune adrenalitis, also called Addison’s disease. An autoimmune disease occurs when a person’s immune system produces antibodies that attack the body’s own tissues or organs and slowly destroys them. In the case of Addison’s, this leads to the gradual destruction of the adrenal cortex (the outer layer of the adrenal glands. Symptoms of adrenal insufficiency occur when at least 90% of the adrenal cortex has been destroyed. As a result, often both glucocorticoid and mineralocorticoid hormones are lacking.

Tuberculosis (TB) accounts for about 10-15% of cases of primary adrenal insufficiency in developed countries (the percentage in developing countries or among immigrant populations is much higher). When adrenal insufficiency was first described by Dr. Thomas Addison in 1849 tuberculosis was found at autopsies in 70% to 90% of cases. As treatment options improved, the incidence of adrenal insufficiency due to this infectious disease greatly decreased.

Further causes of primary adrenal insufficiency are other chronic infections such as AIDS, syphilis or fungal infections, tumours/metastases, acute haemorrhage in both adrenal glands, amyloidosis or the removal of both adrenal glands due to other conditions.

It is important to note that the percentage of the various causes of primary adrenal insufficiency in children differs substantially from that in the adult population. In children, the genetic forms are more common: congenital adrenal hyperplasia accounts for approx. 70% of adrenal insufficiency, other genetic disorders for approx. 6% and autoimmune disease for only 10-15%.

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency occurs more frequently than primary adrenal insufficiency, with a prevalence of 150–280 per one million of the population.

Secondary adrenal insufficiency can be traced to a lack of ACTH which is produced in the pituitary gland and causes a drop in the adrenal glands’ production of cortisol (but not aldosterone). Any condition that affects the pituitary gland or its production of ACTH can therefore result in secondary adrenal insufficiency:

- removal of parts of the pituitary gland due to a benign (non-cancerous) ACTH-producing tumour. In this case, the source of ACTH production is suddenly removed and replacement cortisone must be taken,
- shrinking of the pituitary gland or decreased production of ACTH due to tumours or infections of the area, loss of blood flow to the pituitary or radiation for the treatment of pituitary tumours,
- removal of the pituitary gland during neurosurgical procedures with the goal to treat other conditions,
- traumatic brain injury.
Suppression of HPA Axis due to Steroid Therapy

The most common cause of an induced adrenal insufficiency is the long-term use of steroids to treat other chronic conditions such as asthma, rheumatoid arthritis or ulcerative colitis. The high doses of prescribed steroids (such as prednisone or dexamethasone) suppress CRH and ACTH production in the otherwise healthy hypothalamus and pituitary gland which in turn leads to a suppression of the body’s own cortisol production (see also: HPA, negative feedback loop) in the adrenal glands.

**DO NOT FORGET**

If a person who has been taking long-term steroids abruptly stops or interrupts taking the prescribed steroids and their adrenals have stopped producing sufficient levels of cortisol, they can go into adrenal crisis.

A slow and gradual reduction in steroid dosage under medical supervision is needed to give the adrenal glands time to resume normal functioning (weaning / tapering).

The amount of time it takes to taper off the steroid medication depends on the condition being treated, the dose and duration of use and other medical considerations. It is important to know that the suppression of cortisol production cannot always be reversed, therefore leading to permanent secondary adrenal insufficiency.

**Tertiary Adrenal Insufficiency**

Tertiary adrenal insufficiency results from the impaired production or action of CRH from the hypothalamus which in turn inhibits the secretion of ACTH from the pituitary gland. As mentioned above, tertiary adrenal insufficiency can also be caused by long-term steroid therapy.

**GOOD TO KNOW**

Because the hypothalamus and pituitary gland are part of our brain (also called central nervous system) secondary and tertiary adrenal insufficiency are sometimes referred to as “central adrenal insufficiency” or “central hypoadrenalism”.
Comparison of Primary, Secondary and Tertiary AI

Adrenal Insufficiency (AI)

Endocrine Glands Involved in AI

Hypothalamic Pituitary Adrenal (HPA) Axis – central stress response system

Types of AI

Tertiary AI

Secondary AI

Primary AI
(If autoimmune cause = Addison’s Disease)

GOOD TO KNOW

Primary versus secondary and tertiary adrenal insufficiency at a glance

<table>
<thead>
<tr>
<th>Adrenal Insufficiency (AI)</th>
<th>Primary AI</th>
<th>Secondary AI</th>
<th>Tertiary AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected glands:</td>
<td>Adrenal glands</td>
<td>Pituitary gland</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Affected hormone levels:</td>
<td>Cortisol low</td>
<td>Cortisol low</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td></td>
<td>ACTH high</td>
<td>ACTH low</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other hormone deficiencies such as hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Affected blood levels:</td>
<td>Sodium low</td>
<td>Sodium and potassium are relatively normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potassium high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replacement required:</td>
<td>Cortisol</td>
<td>Cortisol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Symptoms

Symptoms of adrenal insufficiency are mostly nonspecific and could be caused for a variety of reasons. They begin and progress slowly and are usually overlooked for a long time; the average time from symptom onset to diagnosis is 5 years.

Not every person experiences the same symptoms, and (depending on the cause of the adrenal insufficiency) a variety of other symptoms may be present.

Table 2: Most common symptoms of adrenal insufficiency

<table>
<thead>
<tr>
<th>Caused by lack of cortisol:</th>
<th>Observed by approx.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Severe fatigue, lack of energy or stamina, weakness</td>
<td>95 – 100%</td>
</tr>
<tr>
<td>- Loss of appetite, weight loss (in children failure to thrive)</td>
<td>75 – 95%</td>
</tr>
<tr>
<td>- Anorexia progressing to nausea, vomiting, diarrhoea</td>
<td>20%</td>
</tr>
<tr>
<td>- Stomach, muscle and/or joint pains</td>
<td>34%</td>
</tr>
<tr>
<td>- Hypoglycaemia (low blood sugar)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caused by lack of aldosterone (only in primary adrenal insufficiency):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Low blood pressure, dizziness, blackouts / fainting</td>
<td>75 – 85%</td>
</tr>
<tr>
<td>- Salt craving</td>
<td></td>
</tr>
<tr>
<td>- Tachycardia (fast heartbeat)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caused by excess ACTH (only in primary adrenal insufficiency):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Skin hyperpigmentation (areas of dark tanning, covering exposed and non-exposed parts of the body, mostly around skin folds, joints (elbows, knees, knuckles), lips and mucous membranes.)</td>
<td>90%</td>
</tr>
</tbody>
</table>

Adrenal insufficiency can also cause irritability, lack of concentration, memory impairment, confusion, apathy and depression, which are often attributed to stress or other pre-existing conditions. People living with adrenal insufficiency are often diagnosed and treated for other chronic conditions (e.g. other autoimmune disorders, asthma, depression) which may mask the symptoms.

Because the symptoms progress slowly, they are often overlooked until a stressful event such as an acute illness (fever, diarrhoea, flu) or an accident causes them to become suddenly more pronounced. This is called an Addisonian crisis, adrenal crisis or acute adrenal insufficiency.
Testing and Diagnosis

Due to the combination of nonspecific symptoms, a slow onset of those symptoms and the fact that adrenal insufficiency is considered a rare condition, diagnosis is often delayed, on average up to 5 years.

There are no routinely checked lab parameters that would easily point towards the diagnosis. Although a high percentage of patients show low blood levels of sodium and glucose as well as high blood levels of potassium at the time they are diagnosed with primary adrenal insufficiency, the findings are often borderline and do not necessarily raise a “red flag”.

Proof or diagnosis of adrenal insufficiency depends entirely on demonstrating that the adrenal glands produce no or only minimal cortisol. The initial testing is simple and labs can be ordered by any physician.

The confirmation of the clinical diagnosis of adrenal insufficiency includes three steps:

1. Demonstrating an inappropriately low cortisol secretion.
2. Evaluating of the HPA axis
3. Confirming / excluding a cause of the primary disorder

Lab Tests

The **morning serum cortisol** checks baseline adrenal cortisol production. It should be drawn between 8 and 9am.

The HPA axis is evaluated by determining whether the cortisol deficiency is a) dependent on or independent of corticotropin (ACTH) production and b) the mineralocorticoid secretion in patients without ACTH deficiency.

The **baseline ACTH** test evaluates pituitary corticotropin (ACTH) production. It should be drawn simultaneously with the morning cortisol sample.

The morning cortisol and the baseline ACTH are sampled and interpreted together and should indicate the direction for further testing and/or referral to a specialist.

The **ACTH stimulation** test (also called corticotropin or Synacthen test) evaluates the stimulated adrenal cortisol response. ACTH is given as an intramuscular (IM) or intravenous (IV) injection to test the stress response of the adrenal glands. The blood cortisol concentrations are measured at the time of the injection (=baseline) as well as 30 min and 60 min later.
Healthy adrenal glands are expected to respond to the ACTH injection with a drastic increase of blood cortisol levels. People with non-functioning adrenal glands do not show this response and the increase of blood cortisol is minimal (if some adrenal function remains) or missing.

**GOOD TO KNOW**

**The ACTH stimulation test**
Wrongly, the ACTH stimulation test is often ordered first. It is important to request that the baseline ACTH is sampled BEFORE the injection for the ACTH stimulation test. If the problem originates in the pituitary or hypothalamus, it can go undetected by the ACTH stimulation test alone, leading to misdiagnosis: A lack of an appropriate response may indicate adrenal atrophy in patients with chronic secondary adrenal insufficiency.

An adequate response to the ACTH stimulation test does **not** eliminate the possibility of secondary or tertiary adrenal insufficiency.

The Metyrapone and the Insulin Tolerance Test (ITT), are used to measure stimulated pituitary ACTH production if secondary or tertiary adrenal insufficiency is suspected. Choice of which test to use is based on patient profile. Current recommendations favour the Metyrapone test. It is more accurate, less expensive, and easier to administer than the ITT.

**GOOD TO KNOW**

**Pre-testing considerations:** The following hormones or drugs may interfere with accurate test results.

- Glucocorticoids or corticosteroids in any form, including topical, inhaled, injected, and oral tablets/capsules.
- Birth control or other estrogens, including soybean food products and menopause formulas.
- Drugs that inhibit cortisol biosynthesis, such as etomidate, ketoconazole, fluconazole, metyrapone, and suramin.
- Drugs that accelerate the metabolism of cortisol and most synthetic glucocorticoids by inducing hepatic mixed-function oxygenase enzymes, such as phenytoin, barbiturates, mitotane, and rifampin.
- High dose progestins or chronic administration of opiates.

**Imaging Tests**

Imaging tests such as a CT Scan or MRI are used to confirm or exclude any infiltrative process of the adrenals or hypothalamic and pituitary regions of the brain that would compromise normal hormone production.

Patients with no associated autoimmune disease should undergo a CT (computer tomography) scan of the adrenal glands to find the underlying cause. In developing countries and immigrant populations tuberculosis should be ruled out as a cause. A CT scan can also be helpful to detect rare causes such as bilateral adrenal lymphoma, adrenal metastases, sarcoidosis or amyloidosis.

If secondary or tertiary adrenal insufficiency is suspected an MRI of the hypothalamic and pituitary regions should be done. It can reveal pituitary tumours such as adenomas, meningiomas, metastases, sarcoidosis or other disease.
Treatment of Adrenal Insufficiency

SUSPECTING AN ADRENAL CRISIS?

If a person presents in an adrenal crisis (a potentially life-threatening condition), treatment should not be delayed while waiting for test results!

In the majority of cases, adrenal insufficiency is a chronic and irreversible condition that requires life-long hormone replacement therapy. There is no cure available. Treatment requires the replacement or substitution of the hormones that the adrenal glands ceased to produce and should begin as soon as the diagnosis is confirmed.

Cortisol replacement

The preferred treatment of adrenal insufficiency is oral hydrocortisone which is the most physiological option for cortisol replacement available today. The patient’s well-being usually dramatically improves within 24 hours after the first dose is taken.

<table>
<thead>
<tr>
<th></th>
<th>hydrocortisone per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary adrenal insufficiency:</td>
<td>20–25 mg</td>
</tr>
<tr>
<td>Secondary adrenal insufficiency:</td>
<td>15–20 mg</td>
</tr>
</tbody>
</table>

The daily hydrocortisone dose should be given in two to three doses, with half to two thirds of the total daily dose in the morning. The goal should be to mimic the circadian rhythm of the physiological cortisol production as closely as possible.

Figure 7: Comparison of physiological cortisol levels in healthy people and levels reached under hydrocortisone replacement
Since every person with adrenal insufficiency has a different residual function of their adrenal glands and a different metabolism, fixed dosage recommendations are not available. Dosing needs to be adjusted to meet the needs of each individual. It is highly recommended to have an endocrinologist oversee and manage dosage and necessary adjustments.

Unfortunately, there are no reliable or “easy tests” to assess how effective the replacement therapy is. Some clinicians prefer to use cortisol day curves for treatment monitoring and dose titration whereas others rely on the clinical symptoms reported by their patients to adjust and optimise dosing.

**GOOD TO KNOW**


<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrocortisone</td>
<td>Hysone</td>
</tr>
<tr>
<td>cortisone acetate</td>
<td>Cortate</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>Dexethsone, Ozurdex, Maxidex</td>
</tr>
<tr>
<td>prednisone</td>
<td>Panaf cort, Predsone, Panaf cort, Sone, Redipred, Predmix, Predsol</td>
</tr>
<tr>
<td>prednisolone</td>
<td>Panaf cortelone, Predsolone, Solone</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>Solu Medrol, Depo Medrol</td>
</tr>
<tr>
<td>hydrocortisone sodium succinate</td>
<td>Solu-Cortef</td>
</tr>
</tbody>
</table>

**GOOD TO KNOW**

**Outlook – Novel treatment options under development**

Research has shown that it is possible to better mimic the physiological circadian rhythm of cortisol with special “modified-release” hydrocortisone preparations. A number of drugs are currently under clinical investigation and a few have recently been introduced in some European countries:

**Plenadren** is a once-daily dual-release hydrocortisone tablet taken in the morning. It contains a rapid-release coating and a timed-released inner core of hydrocortisone. Plenadren currently enjoys orphan status as a licensed treatment for adrenal insufficiency by the European Medicines Agency (EMA).

**Chronocort** offers a delayed and sustained release of the hormone. When taken at bedtime, it maintains low cortisol levels during midnight with an early morning peak. Its manufacturer Diurnal is committed to conduct more clinical studies in the US in the future.

Future studies will show whether these new preparations stand up to the promise of improving cardiovascular risk factors, glucose metabolism and quality of life.
**GOOD TO KNOW**

**Not all people respond well to oral hydrocortisone**
Some people metabolise oral hydrocortisone very quickly and require a more continuous hydrocortisone supply that mimics the normal circadian cortisol rhythm. This can be achieved, for instance, by using a subcutaneous infusion or “pump”, similar to insulin pumps used by diabetic patients. So far, pumps are rarely used in patients with adrenal insufficiency but can be a good option for people who are doing poorly on oral steroids.

“I am now on a pump because I rapidly metabolise oral medication, and my adrenal insufficiency has much improved since commencing the pump.” – Desley

**GOOD TO KNOW**

**Most common symptoms of hormone under- and over-replacement**

<table>
<thead>
<tr>
<th><strong>Under-replacement of cortisol</strong> <em>(given dose of hydrocortisone is too low)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>- severe fatigue, weakness</td>
</tr>
<tr>
<td>- nausea, loss of appetite, weight loss</td>
</tr>
<tr>
<td>- hyperpigmentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Over-replacement of cortisol</strong> <em>(given dose of hydrocortisone is too high)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>- inappropriate hunger, weight gain</td>
</tr>
<tr>
<td>- fatigue</td>
</tr>
<tr>
<td>- easy bruising</td>
</tr>
<tr>
<td>- muscle weakness</td>
</tr>
<tr>
<td>- mood swings</td>
</tr>
<tr>
<td>- red face</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Under-replacement of fludrocortisone</strong> <em>(primary adrenal insufficiency only, given dose of fludrocortisone is too low)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>- dizziness on standing, low blood pressure</td>
</tr>
<tr>
<td>- salt craving</td>
</tr>
<tr>
<td>- muscle cramps</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Fludrocortisone excess</strong> <em>(primary adrenal insufficiency only, given dose of fludrocortisone is too high)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>- high blood pressure</td>
</tr>
<tr>
<td>- ankle swelling</td>
</tr>
<tr>
<td>- headache under exertion</td>
</tr>
</tbody>
</table>

* Not all patients experience all symptoms. As a rule of thumb, the symptoms of under-replacement are most likely those experienced before diagnosis. (Adapted from: Margulies / NADF)

**DO NOT FORGET**

**The difference between replacement therapy and steroid treatment of other conditions**
It is important to understand that there is a difference between replacing a hormone that is no longer produced by the body and taking high(er) doses of cortisone to treat another condition such as asthma. The feared side effects associated with cortisone treatment such as osteoporosis, weight gain, glaucoma, or mood changes are not to be expected when replacing cortisol in adrenal insufficiency.
Aldosterone replacement

In primary adrenal insufficiency mineralocorticoid (aldosterone) replacement therapy is necessary to stabilise blood pressure (prevent sodium loss, intravascular volume depletion and hyperkalaemia).

Aldosterone is given in the form of fludrocortisone (fludrocortisone acetate, Florinef) in a dose of 0.05–0.20 mg daily, taken in the morning. The dose may have to be increased in the summer under medical supervision, especially if temperatures are high.

Signs of mineralocorticoid under-replacement are a drop in blood pressure after standing up, weight loss, and dehydration (blood test: plasma renin level increased, hyponatraemia). Signs of an over-replacement are weight gain and increased blood pressure (blood test: hypernatraemia, suppressed plasma renin activity).

GOOD TO KNOW

Aldosterone replacement
Is not needed if the daily hydrocortisone dose exceeds 50 mg,
People living with secondary or tertiary adrenal insufficiency normally produce enough aldosterone and do not require replacement therapy.

Androgen replacement

In women, the adrenal cortex is the main source of androgen production. Treatment with dehydroepiandrosterone (DHEA) may improve mood and general wellbeing and may be considered in people whose wellbeing is greatly impaired despite optimal glucocorticoid and mineralocorticoid replacement. Discuss this with your endocrinologist.

DO NOT FORGET

For people living with adrenal insufficiency, it is important to understand that:
- Hormone replacement is essential for life.
- Tablets need to be taken every day, at the right and same time of day. They may be taken on an empty stomach.
- Never abruptly stop taking your medication.
- Always carry extra medication and an emergency kit containing Solu-Cortef, syringes and needles.
- Dosage requirements may change over time.
Stress dosing and Sick day Management

People living with adrenal insufficiency need to take extra hydrocortisone in addition to their daily doses when they are sick, injured and before any kind of surgery. This is called stress dosing or sick day dosing.

Guidelines for stress and sick day dosing

Healthy adrenal glands are able to quickly release cortisol into the blood stream to help the body cope with occurring stress situations. People living with adrenal insufficiency require additional cortisol in times of emotional, medical or surgical stress, with doses proportionate to severity of the stress event.

Table 5: Guidelines for stress and sick day dosing (examples below for people taking Hysone)

<table>
<thead>
<tr>
<th>Stress</th>
<th>Some individuals take a small dose of hydrocortisone for these events, but it is not universally required. The precise dosing is not known, but it should not exceed 4-10mg hydrocortisone*.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild injury</td>
<td></td>
</tr>
<tr>
<td>Exhausting, strenuous physical exercise if a person is not used to it (e.g. hiking, mountain climbing for several hours).</td>
<td></td>
</tr>
<tr>
<td>Minor emotional or mental stress (eg: before an important exam)</td>
<td></td>
</tr>
<tr>
<td>Major emotional or mental stress (eg: death of a close relative, witnessing a traumatic event)</td>
<td></td>
</tr>
<tr>
<td>Take an additional daily dose</td>
<td></td>
</tr>
<tr>
<td>Infection / Fever</td>
<td>Note: Infections are the most frequent cause of adrenal crisis, including gastroenteritis. Maintain the extra doses until recovery, then reduce to the standard doses within 1–2 days.</td>
</tr>
<tr>
<td>Fever of more than 38°C / 100.4°F</td>
<td>Double normal daily dose(s)</td>
</tr>
<tr>
<td>Fever of more than 39°C / 102.2°F</td>
<td>Triple normal daily dose(s)</td>
</tr>
<tr>
<td>Severe infections (eg: pneumonia)</td>
<td>If you are diagnosed with a severe infection, a hospital admission may be required and your doctor will initiate treatment or advise you how to stress-dose. The recommendations are: Initial 100mg hydrocortisone injection (by a physician) IV* Followed by 50mg every 6 hours until condition stabilises, then 2 or 3x normal dose</td>
</tr>
<tr>
<td>Vomiting / Diarrhoea</td>
<td>Note: Vomiting and diarrhoea pose a particularly high risk as the absorption of hydrocortisone is compromised while the demand for cortisol is increased.</td>
</tr>
<tr>
<td>Any illness that includes vomiting and/or diarrhoea</td>
<td>Triple normal daily dose(s), sip rehydration/electrolyte fluids. If vomiting persists and medication cannot be kept down, use emergency injection kit (100mg IM/SC hydrocortisone**). Then call a doctor / go to the nearest emergency department.</td>
</tr>
<tr>
<td>Severe sudden illness or injury</td>
<td>Note: Go to the nearest emergency department for hydrocortisone injection and fluids.</td>
</tr>
<tr>
<td>Severe illness or injury</td>
<td>Use emergency injection kit (100mg IM/SC hydrocortisone**). Then call a doctor / go to the nearest emergency department.</td>
</tr>
</tbody>
</table>

* Example brands for hydrocortisone are: Cortef, Hysone
** Example brands for soluble hydrocortisone are: Solu-Cortef, Solu-Medrol
DO NOT FORGET

Keep your stress dosing guidelines handy and review them regularly
A recent study showed that more than half of the people living with adrenal insufficiency who were previously educated on the topic of stress dosing were not able to adjust the dose of hydrocortisone in hypothetical situations of physical and mental stress. The authors gave the following reasons: unaware of the seriousness of the described condition, ineffective coping strategies, the lack of experience with self-management skills and misconceptions. The same study identified repetition of education, the use of guidelines, learning from experience and optimising social support as important to improve those results.

Surgery and Special Diagnostic Procedures (planned and emergency)

People living with adrenal insufficiency should always inform their doctor, dentist or any specialist of their condition before undergoing procedures. This includes invasive diagnostic tests such as a colonoscopy or barium enema, dental treatment or minor outpatient surgery.

If general anaesthesia is required, stress dosing is needed before surgery begins. Usually IV injections of hydrocortisone and saline are given which may begin on the evening before the procedure (requiring an overnight stay at hospital) and continue until the patient is fully awake after surgery and able to take medication by mouth.

Ensure your surgical team is aware of your need for extra cortisol/medication and that they have checked the surgical guidelines for stress dosing.

Pregnancy

Women with primary adrenal insufficiency who become pregnant are treated with standard replacement therapy but require special monitoring. If nausea and vomiting in early pregnancy interfere with oral medication, injections of hydrocortisone may be necessary. At the onset of labour and if undergoing a caesarean section, the hydrocortisone dose has to be increased, and hydrocortisone can be given IM or IV.

Ensure your doctor and medical team is aware of your need for extra cortisol/medication and that they have checked the surgical guidelines for stress dosing, see table above.
Table 6: Surgical guidelines for stress dosing

<table>
<thead>
<tr>
<th>Type of Procedure</th>
<th>Perioperative needs (before surgery begins)</th>
<th>Postoperative needs (after surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major surgery</strong></td>
<td>100mg hydrocortisone IV with induction (at time the anesthetic is given)</td>
<td>Continue 50mg hydrocortisone IV every 6 hours for 24 hours. Taper to normal dose over 2-3 days</td>
</tr>
<tr>
<td>with long recovery time e.g., cardiothoracic surgery, oesophagectomy, Whipple’s procedure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate surgery</strong></td>
<td>100mg hydrocortisone IV with induction</td>
<td>Hydrocortisone 25mg IV 8-hourly for 24 hours. Then return to normal oral dose.</td>
</tr>
<tr>
<td>e.g., open cholecystectomy, total joint replacement, hysterectomy, caesarean section. Includes dental surgery under general anesthesia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minor surgery</strong></td>
<td>One-time dose of 25mg hydrocortisone IV or 20mg oral with induction / immediately prior to onset procedure.</td>
<td>Continue with normal dose.</td>
</tr>
<tr>
<td>e.g., cataract surgery, hernia repairs, laparoscopy with local anesthetic, endoscopy. Includes dental surgery with &gt;1hr and local anesthetic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Labour and vaginal birth</strong></td>
<td>25mg hydrocortisone IV at onset of labour, then every 6 hours until delivery. 100mg IV at the time of delivery.</td>
<td>Double oral dose for 24-48 hours after delivery.</td>
</tr>
<tr>
<td><strong>Invasive bowel procedures requiring laxatives</strong></td>
<td>Hospital admission overnight with IV fluids and 100mg hydrocortisone IV during preparation.</td>
<td>Hydrocortisone 20mg oral/by mouth 8-hourly for 24 hours then return to normal dose.</td>
</tr>
<tr>
<td>e.g. colonoscopy, barium enema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Example brands for hydrocortisone are: Cortef, Hysone
** Example brands for soluble hydrocortisone are: Solu-Cortef, Solu-Medrol
Adrenal Crisis, Acute Adrenal Insufficiency or Addisonian Crisis

**DO NOT FORGET**

An adrenal crisis is a potentially life-threatening medical emergency that requires immediate medical attention and management in a hospital or emergency department.

An adrenal crisis is caused by an extreme or sudden physical or emotional stress such as surgery, trauma, accident or an acute infection. It can occur frequently in people who already receive standard replacement therapy but can also be the first presentation of adrenal insufficiency.

**DO NOT FORGET**

People with chronic adrenal insufficiency cannot produce cortisone as a response to stress. While a fixed daily dose of hydrocortisone should be sufficient to maintain all bodily functions under normal circumstances, it may not be high enough to cover acute stress situations. Therefore any stress that, for a healthy person, seems minor or easily manageable (e.g. a stomach bug), requires taking additional hydrocortisone (also called “stress dosing” or may otherwise potentially lead to an adrenal crisis.

The threshold to progressing to an adrenal crisis differs from person to person and situation to situation.

**Incidence**

Retrospective studies consistently show that 5 – 10 % of all people with known and treated adrenal insufficiency will experience at least one adrenal crisis per year. 1 in 200 of those patients will die from an adrenal crisis.

There is an uneven distribution in the occurrence of crises, as some people do not experience a single adrenal crisis for decades, while others do so recurrently. However, the incidence of an adrenal crisis increases with age, especially above 50 years of age.

**GOOD TO KNOW**

Incidence of an adrenal crisis among diagnosed people

The largest analysis so far was conducted via postal survey by the UK Addison’s Disease Self Help Group. The results from 841 participants from the UK, Canada, Australia and New Zealand indicate an incidence of eight crises per 100 patient years (or 8% of patients per year).

A recent Australian study identified an increase in adrenal crisis hospital admission rates over 13 years. It suggested that people with adrenal insufficiency today are at a greater risk because they have less of a “cushion” of cortisol with a standard daily dose of approx. 20-25 mg hydrocortisone compared with the old-fashioned standard dose of 30 mg. However, taking more hydrocortisone than necessary over a long time can increase the susceptibility to infection and thereby increase the risk of adrenal crisis. Therefore it seems sensible to take daily doses as low as possible and stress dose when needed rather than over-replacing on a continuous basis.
Symptoms of Adrenal Crisis

In addition to the symptoms of the triggering cause (e.g. stomach or respiratory flu, accident), typical symptoms of an adrenal crisis are:

- Severe drop in blood pressure causing dizziness, lightheadedness and possibly loss of consciousness (patient is in danger of hypovolaemic shock)
- Nausea and vomiting
- Confusion and lethargy
- Muscle weakness, joint pains, cramps, headache

GOOD TO KNOW

Many people with secondary adrenal insufficiency do not present with electrolyte abnormalities when in crisis due to their still functioning aldosterone production. Some even experience an increase of blood pressure before the expected sudden drop.

The onset of measurable serum electrolyte abnormalities in patients with primary adrenal insufficiency depends on how quickly the crisis progresses. For instance, it will be faster for patients with an acute gastrointestinal event than those experiencing an injury.

Causes and Development

The most frequent causes of adrenal crises in people with already diagnosed chronic adrenal insufficiency are infections, particularly gastroenteritis (“stomach flu” with diarrhoea and vomiting), pneumonia / lower respiratory tract infections and urinary tract infections. In addition, surgery, strenuous exercise, emotional stress and accidents can contribute and lead to an adrenal crisis.

The development of an adrenal crisis usually takes several hours. However, a survey of 37 patients who had experienced a crisis showed a substantial variation, with the median time from first symptoms to contacting health professionals being 135 minutes with a range of 5 minutes to 7 days.

Treatment

Treatment of an adrenal crisis should not be delayed under any circumstances.

DO NOT FORGET

Every person diagnosed with adrenal insufficiency should carry an emergency kit and know how to give him- or herself an intra muscular (IM) or sub cutaneous (SC) injection of Solu-Cortef in case medical attention is delayed or his or her condition is deteriorating quickly.
Hospital or emergency department treatment is simple and highly effective, consisting of immediate intravenous administration of 100 mg hydrocortisone and rapid rehydration with normal saline infusion, followed by 100mg IV or IM every 6 hours (as per NSW emergency protocols) or continuous hydrocortisone infusion of 200mg over 24 hours until the patient stabilises. (Usually, mineralocorticoid replacement (in primary adrenal insufficiency) is not necessary if the daily hydrocortisone dose is > 50mg.)

This treatment usually brings rapid improvement. After the patient has improved and can take fluids and medications by mouth the amount of hydrocortisone is decreased until a maintenance dose is achieved. The length of hospitalisation may be hours to days and will depend on the severity of the crisis and any underlying precipitating factors, such as infection, as well as overall health.

Unfortunately, some cases are fatal due to delayed treatment, especially in previously undiagnosed persons.

Reducing the Risk of Adrenal Crises: Knowledge is Key

Not all triggers for an adrenal crisis (such as accidents) can be prevented.

To reduce the risk of an adrenal crisis,
people with diagnosed adrenal insufficiency should
- never stop taking their medication
- know, recognise and act upon symptoms of under-replacement
- regularly review their stress dose/sick day management plan
- follow up with an endocrinologist on an annual basis
- get the flu vaccine each year
- maintain hydration and electrolytes especially in hot weather

To be prepared to deal with the onset of an adrenal crisis,
people with diagnosed adrenal insufficiency (and their relatives/friends) should know:
- and recognise the symptoms of the beginning of an adrenal crisis. (This is easier said than done; It has been commonly reported that people who are in general well informed about their condition fail to recognise the signs in themselves.)
- what circumstances may trigger an adrenal crisis and therefore require stress dosing (fever, diarrhoea, vomiting, flu or cold, injury, medical procedures / surgery).
- how (and when) to give an emergency injection
- when to notify medical staff about their condition (e.g. before undergoing planned or emergency surgical or invasive diagnostic procedures)

To ensure that emergency personnel recognise the condition as quickly as possible
people with diagnosed adrenal insufficiency should:
- wear a medical alert bracelet
- carry a medical treatment letter from their endocrinologist
- carry an emergency kit with Solu-Cortef, syringes and needles
Quality of Life and Risks

Before being diagnosed, people often have been suffering for months or years. When finally treated, their condition usually improves within 24 hours. This initial improvement in wellbeing led expert physicians to believe that treated patients can lead a normal life with a normal life expectancy. Only in recent years it became evident that in some patients the restoration of wellbeing remains incomplete. The reasons are not yet fully understood, but may be linked to the disturbed circadian rhythm of blood cortisol levels and the lack of DHEA.

People living with chronic adrenal insufficiency who receive standard replacement therapy also show an increased mortality. Recent studies have shown that imbalances in blood cortisol may lead to a higher prevalence of coronary heart disease and cardiovascular events. Adrenal crisis also contributes to the increased mortality in people with diagnosed and treated adrenal insufficiency, 1 in 200 patients will die from an adrenal crisis.

Other Conditions and Drugs

Often, people diagnosed with adrenal insufficiency also suffer from other conditions or diseases that require treatment.

Drug Interactions

Drug interactions occur when a drug interacts or interferes with another drug. This can alter the way the drug(s) act(s) in the body (e.g. by increasing or decreasing the effect of one or both of the drugs) or cause unexpected side effects.

For people with adrenal insufficiency, taking drugs that influence the glucocorticoid metabolism may require an adjustment of their daily hydrocortisone dose.

Some drugs, such as antiretroviral drugs, delay metabolism and therefore lead to an increased glucocorticoid concentration in the blood. Other drugs accelerate glucocorticoid metabolism and therefore reduce their effect. Examples for those are anticonvulsants / antiepileptica (eg. phenytoin, carbamazepine), antituberculosis medicine (eg. rifampicin) and antifungals (eg. ketoconazole).

Other drugs (NSAIDs, some antidepressants and some antibiotics) influence electrolyte levels and blood pressure and may require an adjustment of the fludrocortisone dose.

Diuretics and acetazolamide should be avoided unless clearly indicated.
Autoimmune Diseases / Polyendocrine Deficiency Syndrome

In 40% of people living with Addison’s disease (autoimmune adrenalitis/primary adrenal insufficiency) only the adrenal glands have ceased hormone production. More often, other glands are affected as well. This is called polyendocrine deficiency syndrome and classified into two separate forms, referred to as type I and type II.

Type I typically occurs in children and adrenal insufficiency may be accompanied by underactive parathyroid glands, slow sexual development, pernicious anaemia, chronic candida infections, chronic active hepatitis, and, in very rare cases, hair loss.

Type II is often called Schmidt’s syndrome and affects adults in the 3rd to 4th decade of life. Symptoms may include an underactive thyroid gland, slow sexual development, diabetes mellitus and/or vitiligo (a loss of pigment on areas of their skin).

Schmidt’s syndrome is believed to be inherited because frequently more than one family member tends to have one or more (but not always the same) endocrine deficiencies.

More information on Autoimmune Polyendocrine Syndrome Type II can be found on the Website of the National Organization for Rare Disorders, Inc. (USA, information last updated in 2007).

Steroid Therapy and Adrenal Suppression

Over the past decades, an increase in the total number of people diagnosed with adrenal insufficiency has been observed and attributed to the long-term use of steroids to treat chronic conditions (= secondary adrenal insufficiency, see also types of adrenal insufficiency)

Although considered rare in the past, the number of people with secondary adrenal insufficiency is rising rapidly and now outweighs the incidence of primary adrenal insufficiency (Addison’s) by 2:1.

Steroids (usually prednisone) are commonly used to treat conditions such as rheumatoid arthritis, asthma or ulcerative colitis. Although essential in the treatment of those disorders, taking any steroids for longer than two weeks may lead to a suppression of cortisol production (see also HPA, negative feedback loop) in the adrenal glands, eventually causing adrenal insufficiency.

Short-term treatments, e.g. steroids given over 3 days, do not pose a significant risk.

Every person on long-term steroid treatment needs to know that any acute illness (e.g. a fever), accident, procedure (e.g. colonoscopy) or surgery require taking additional cortisone (“Stress-dosing”) to avoid an adrenal crisis. They also need to be able to recognise low
cortisol symptoms and should never abruptly discontinue steroid treatment, as this can lead to an adrenal crisis.

Instead, a gradual reduction in dosage (tapering/weaning off) **under medical supervision** may give the adrenal glands time to resume their normal function. How long it will take to taper off depends on the condition being treated, the dose and duration of use and other medical considerations. A full recovery can take anywhere from a week to several months or even years. Unfortunately, the suppression of endogenous cortisol production cannot always be reversed, therefore leading to secondary adrenal insufficiency.

**DO NOT FORGET**

**Any long-term steroid treatment can cause adrenal insufficiency!**
Taking prednisone or other steroids as tablets is not the only way to develop adrenal insufficiency. Inhaled or locally injected steroids as well as creams are equally potent and may suppress cortisol production in the adrenal glands (HPA, negative feedback loop).

- Hydrocortisone / prednisone tablets
- Inhaled asthma steroids eg. Symbicort, Seretide
- Intravenous steroids eg. methylprednisolone
- Joint and muscle steroid injections
- Steroid creams for skin conditions

There is a chance of causing adrenal suppression by taking as little as 5mg of prednisone, or 20mg of hydrocortisone, for 3 or more weeks. The longer the steroids are taken, or the higher the dose, the greater the chance.
Long-term Management: Educate yourself!

Seek the help of a specialist

In addition to seeing a primary care physician (GP) regularly, people diagnosed with adrenal insufficiency should consult with an endocrinologist (a specialist for hormone disorders) on a regular basis. They should request that the endocrinologist

- Prescribes an emergency injection kit (Solu-Cortef 100mg with syringe and needles) and demonstrates its use.
- Provides a letter that describes the condition and importance of immediate medical attention and treatment in case of an adrenal crisis. (see: Sample letter, under development).
- Explains the need for taking extra hydrocortisone in the case of an illness, accident, acute trauma or before a surgical procedure (“stress-dosing”), how to prevent and prepare for an adrenal crisis.

Patients should also inform their doctor/specialist if they are prescribed any new drugs as those may influence the cortisol metabolism and may require adjusting of the daily hydrocortisone dose. A pharmacist may also be able to address any concerns.

In primary adrenal insufficiency of autoimmune origin, the doctor should enquire about symptoms and signs of other autoimmune disorders and undertake relevant testing every 6–12 months if needed.

Be your own advocate

Remember: Adrenal insufficiency is a rare condition.

Not every health care professional has encountered a patient with adrenal insufficiency during his or her career and therefore may not be up-to-date on treatment guidelines and / or protocols. Everyone diagnosed with adrenal insufficiency should play an important part in the management of this chronic condition to ensure his/her own wellbeing.

Every person living with adrenal insufficiency and their family and friends should know and understand:

- Continuous (life-long, daily) rigorous cortisol replacement therapy is essential for life.
- Medication requirements can change and doctors should monitor for any new symptoms which might require adjustment of doses.
- During physical or mental stress, the usual cortisol dose may need to be increased.
- Stress dosing is required in circumstances such as accident, injury, fever, diarrhoea, vomiting, influenza or extreme emotional stress to prevent an adrenal crisis.
- Symptoms of under-replacement and the beginning symptoms of an adrenal crisis.
- When and how to give an emergency injection of Solu-cortef.
- Medical staff must always be notified when undergoing planned or emergency surgical procedures.

**Adrenal Crisis: Don’t stress, but be prepared**

Approx. 8 – 10% of all people living with adrenal insufficiency will experience at least one adrenal crisis per year. Therefore, everyone diagnosed should:

- Always carry a medical alert bracelet and an emergency letter from their doctor explaining their condition and including the contact information of their GP and endocrinologist
- Always carry spare medication (tablets).
- Always carry an emergency kit consisting of Solu-Cortef, syringes and needles for injection
- Order repeat prescriptions in plenty of time – ideally maintaining a month’s reserve supply – to ensure they do not run out of essential medication.
- Take an extra supply of medication (e.g. double what they would normally need) when travelling or on holidays plus the injection kit.
- Carry the medication and injection kit in their hand luggage when travelling by plane, along with a doctor’s note explaining why they need to carry medications, needles and syringes.

**DO NOT FORGET**

**Once-a-quarter checklist**

- Make sure your emergency bracelet is still readable and your emergency letter is up-to-date.
- Read up about stress dosing/sick day management – especially if you haven’t needed it recently.
- Check your Solu-Cortef emergency self-injection kit for the expiration date and request a new prescription when needed.

**DO NOT FORGET**

**SC or IM?**
People seem to prefer subcutaneous (under the skin, SC) over intramuscular (into the muscle, IM) injections. The ease of an SC injection far outweighs the short delay of about 11 min for the injected hydrocortisone to reach efficient serum concentrations.

**Practice injecting!**
Use expired Solu-Cortef to practice an emergency situation by injecting it into an orange, apple or potato. To increase the impact, gather your family and friends for the demo!
Suggested Reading

The following articles may give the interested reader a broader understanding of the topic.

Allolio B:
Adrenal crisis

Gargya A, Chua E, Hetherington J, Sommer K, Cooper M:
Acute adrenal insufficiency: an aide-memoire of the critical importance of its recognition and prevention
*Internal Medicine Journal, 2016 Royal Australasian College of Physicians*

Nenke MA, Torpy DJ:
Addison’s disease: Managing ‘sick days’ to avoid crises
*Endocrinology Today* FEBRUARY 2014, VOLUME 3, NUMBER 1

Quinkler M, Hahner S:
What is the best long-term management strategy for patients with primary adrenal insufficiency?
*Clin Endocrinol (Oxf) 2012; 76: 21–25*

Rushworth RL, Torpy DJ:
A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections
*Endocrine Disorders 2014, 14:79*

Rushworth RL, Torpy DJ, Falhammar H:
Adrenal crises: perspectives and research directions
Literature/References

This document is based on an extensive study and review of current clinical research on adrenal insufficiency.


Grossman AB: The Diagnosis and Management of Central Hypoadrenalism J Clin Endocrinol Metab, November 2010, 95 (11): 4855–4863


Hahner S, Allolio B: Therapeutic management of adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2009 Apr;23(2):167-79


Nenke MA, Torpy DJ: Addison’s disease: Managing ‘sick days’ to avoid crises. Endocrinology Today FEBRUARY 2014, VOLUME 3, NUMBER 1


Rushworth RL, Torpy DJ: Adrenal insufficiency in Australia: is it possible that the use of lower dose, short-acting glucocorticoids has increased the risk of adrenal crisis? Horm Metab Res 2015; 47: 427–32.


