



ADRENAL INSUFFICIENCY (ADDISON'S DISEASE)

1. Medical Condition

Introduction

Adrenal insufficiency is a complex condition with a number of different causes that may result in considerable morbidity and mortality if left undiagnosed/untreated. It is an often elusive diagnosis that requires awareness, knowledge of symptoms and signs and endocrinological expertise to be correctly diagnosed and adequately treated. The condition occurs with a frequency of 110-120 cases per million persons, with the exact incidence among athletes not known, but for some causes more frequent occurrence is documented (s. below).

Primary adrenal insufficiency is due to:

Dysfunction of the adrenal glands which may be congenital or acquired. Congenital disease may result from adrenal hypoplasia or hyperplasia. Congenital adrenal hyperplasia (CAH) results from a deficiency of one of several enzymes required for synthesis of cortisol. The most prevalent CAH disorder is steroid 21-hydroxylase (OH)-deficiency (1: 10,000-18,000 births) which exists in a classic form (manifested in early childhood) subdivided into salt-losing and simple virilising, and a nonclassic form (manifested only in late childhood to early adulthood). The most common type of acquired primary adrenal insufficiency is idiopathic adrenal insufficiency mostly due to autoimmune destruction of the adrenal cortex. In developing countries, tuberculosis is another major cause, while other infections may also destroy the active gland tissue.

Secondary adrenal insufficiency:

(also "central" adrenal insufficiency) is most commonly iatrogenic, caused by suppression of the hypothalamic-pituitary axis due to exogenous glucocorticosteroid use. This cause is particularly relevant in an athletic population due to the frequent use of non-systemically applied glucocorticosteroids and unpredictable uptake into the circulation. Local treatment of musculoskeletal disease can in fact inhibit the axis. With daily oral treatment, suppression of the axis may occur within as little as two weeks treatment. Important to consider in athletes, too, is the fact that adrenal insufficiency may occur months or even years after brain trauma due to pituitary damage. Other reasons include hypopituitarism in any kind of hypothalamic-pituitary disease.

The diagnostic and therapeutic work-up in adrenal insufficiency of whatever cause differs depending on the presentation as either an acute crisis or with slowly evolving chronic disease.

For the purpose of this Medical Information, diseases and differential diagnoses that render a patient too impaired to be able to exercise and compete (e.g. polyendocrine disorders) are not presented, but focus is on conditions likely to be encountered in athletes at different levels.

2. Diagnosis

A. Medical history

History taking has to confirm the time of onset, acute onset/crisis or chronic disease.

Congenital disease

Females with classic 21-OH deficiency may present with ambiguous, virilised genitals at birth. Males might go undiagnosed until they present with a salt-wasting crisis within one to three weeks of age, reflecting the degree of mineralocorticosteroid deficiency. Males without salt loss present with precocious puberty (pubic hair, accelerated growth at 2-4 years of age). Females with non-classic form of CAH show signs of hyperandrogenism from late puberty onwards whereas males may be oligosymptomatic.

In acute crisis, history is of particular importance and together with findings on examination represents the main pillar of a presumptive diagnosis necessitating treatment that is started immediately after securing blood samples as any delay in order to confirm diagnosis by more extensive laboratory investigations may result in poor outcome.

Acute crisis

Acute crisis results from exacerbation of chronic insufficiency due to e.g. severe infection, sepsis, disseminated intravascular coagulation or surgery. Another important cause, particularly in athletes, might be abrupt steroid withdrawal. The patient is severely ill, may be dehydrated, hypotensive, hypoglycemic and of altered mental status.

Chronic insufficiency

Chronic insufficiency may manifest itself as chronic fatigue, weakness, tiredness, anorexia, weight loss, nausea, abdominal pain, diarrhea or constipation and orthostatic hypotension with dizziness or even syncopal episodes. After withdrawal of glucocorticosteroid therapy, patients typically feel cold, have difficulties in concentrating, have bone and muscle pain or headache. In chronic adrenal insufficiency in athletes, poor performance might be observed but compensated by rigid training schedules. Episodes of salt-craving are typical for primary adrenal insufficiency.

Androgen insufficiency in females is a controversial subject. As women carry androgen receptors and certain clinical syndromes, namely primary and secondary adrenal insufficiency lead to decreased binding of androgen with associated symptoms / complaints, the clinical term may be applied. It has been shown that women with adrenal insufficiency have lower than normal androgen levels and may suffer symptoms such as sexual dysfunction. However, defining and confirming such condition is too complex an undertaking and posing several diagnostic problems (assays, questionnaires) to be applied to athletes. Significant impairment to health if treatment with androgens were withheld cannot be established and the borders between therapeutical use and abuse in sports are too close to allow for adequate monitoring. Therefore, this medical information does not include the diagnosis and treatment of such conditions in women as the granting of therapeutic use exemptions in female athletes should not be considered. For androgen insufficiency in males, refer to the Medical Information "Male hypogonadism".

B. Diagnostic criteria (s. annex)

The diagnosis of adrenal insufficiency demands the synthesis of medical history with physical examination, substantiated by appropriate laboratory measurements and tests.

The physical findings in chronic adrenal insufficiency are subtle. Hyperpigmentation is present in primary adrenal insufficiency (often in areas unexposed to the sun such as palmar creases, axillae, etc., also pigmentary lines in the gum), but does not occur in secondary (central) adrenal insufficiency due to chronic suppression of CRH and ACTH by exogenous corticosteroids.

In acute insufficiency, dehydration, hypotension, hypoglycemia, and altered mental status are present. With mineralocorticoid deficit, the patient might be hypovolemic, hypotensive, tachycardiac. Orthostatic hypotension is frequently seen.

Laboratory measurements¹

- Complete blood count: Relative lymphocytosis and neutropenia, eosinophilia
- Blood urea nitrogen, creatinine
- Electrolytes: hyponatremia with or without hyperkalemia is commonly found in primary adrenal insufficiency, occasionally in secondary

¹ This information mentions limit values for parameters though these are not all scientifically proven and will be difficult to apply in a clinical setting where the effect of the hormones needs to be considered. Threshold values provide some guidance in the case of athletes.

- Fasting blood glucose: hypoglycemia particularly in children or in athletes during/after exercise
- **Serum cortisol**
Diagnosis is confirmed if serum cortisol level measured between 8.00 am and 9.30 am after an overnight fast (basal cortisol) is less than 3 µg/dL. Values below 18 µg /dL in the presence of a markedly elevated ACTH and plasma renin concentrations are very suggestive of adrenal insufficiency and require further investigation by provocative testing (cosyntropin, CRH, insulin). Values above 18 µg /dL rule out adrenal insufficiency.
- Plasma adrenocorticotrophic hormone concentration (ACTH): ACTH can be decreased or normal (central adrenal insufficiency) or increased (peripheral adrenal insufficiency)
- Plasma renin and aldosterone concentration
- 17-hydroxyprogesterone level: marked elevation (>242.4 nmol/L; normal value <8.9 nmol/L) is a diagnostic indicator of classic 21-OH- or 11β-OH-deficiency. Elevated early morning values can be used for screening of the non-classic form, but are not diagnostic.

Testing²

It is not within the scope of this document to provide the full details of each test. These tests should be undertaken by an endocrinologist in an established laboratory. All test results need to be interpreted in the context in which they were obtained.

Cosyntropin testing

Adrenal insufficiency is likely if serum cortisol level is less than 18 µg/dL 30-60 minutes after administration of 250 µg cosyntropin (synthetic ACTH; dose to be adapted in children). If response to cosyntropin is subnormal but ACTH concentration is not elevated, central (secondary) adrenal insufficiency is likely.

Corticotropin-releasing hormone (CRH) stimulation test

This test is superior to cosyntropin testing in individuals with short-term (less than 3 months) secondary adrenal insufficiency, e.g. after glucocorticosteroid treatment). Cut-off values are the same as for the cosyntropin test.

Insulin-tolerance testing or metyrapone stimulation

These tests are the reference tests for establishing the integrity of the hypothalamic-pituitary-adrenal axis, for example when secondary insufficiency should definitely be ruled out.

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Antibody tests

If adrenal insufficiency is confirmed, antiadrenal antibodies may confirm an autoimmune disorder. They might help when cortisol levels are low and ACTH elevated. Negative results do not exclude autoimmune adrenalitis, however useful where other causes such as tuberculosis, adrenal hemorrhage or adrenoleukodystrophy need to be excluded.

Imaging studies

CT scanning is the study of choice. A CT of the abdomen helps to identify hemorrhage, calcification or infiltration of the adrenal glands. In secondary adrenal insufficiency, a head CT may show destruction or mass lesion of the pituitary.

C. Relevant medical information

In chronic disease, symptoms of the patient in the course of treatment over time should be documented and reported by the treating physician, e.g. any exacerbation (acute crisis), required adaptation of doses of glucocorticosteroids and mineralocorticosteroids. Genetic analyses in congenital disease may confirm diagnosis.

3. Medical best practice treatment

The mainstay of any treatment for adrenal insufficiency is substitution with glucocorticosteroids. Patients with additional mineralocorticosteroid deficiency might require fludrocortisone acetate.

Emergency situations with sufficient clinical suspicion require treatment prior to definitive laboratory confirmation or consultation of an endocrinologist but after securing blood samples. This needs to be considered in any case of retroactive TUE application for emergency treatment.

In case of an acute crisis, the underlying problem precipitating the crisis also requires treatment.

In women with non-classic 21-OH-deficiency, glucocorticosteroids, a contraceptive pill containing a gestagen with antiandrogenic effects is frequently used.

Males with non-classic 21-OH-deficiency do not usually require treatment.

In athletes with adrenal insufficiency due to withdrawal from previous glucocorticosteroid therapy, glucocorticosteroids are required to stabilise the athlete until symptom-free prior to careful tapering over weeks to months (even years), depending on the duration of initial therapy.

A. Name of prohibited substances

Glucocorticosteroids

- Hydrocortisone: drug of choice in emergency treatment and in children (less influence on growth; effective in controlling androgen production (in higher than physiological doses); easy to titrate, mineralocorticosteroid activity.
- Prednisone: in adults, agent is inactive and needs to be metabolized to **active** prednisolone; conversion might be impaired in liver disease.
- Prednisolone, methylprednisolone: in adults.
- Dexamethasone: alternative to hydrocortisone to avoid interference with testing.
- Fludrocortisone: partial replacement therapy for primary, usually not secondary, adrenal insufficiency; not needed unless glucocorticosteroid with low mineralocorticosteroid activity is used (e.g. dexamethasone); only orally applicable.

Testosterone, gestagens with androgenic activity

Note: Supplementation of patients with primary adrenal insufficiency with dehydroepiandrosterone has not proven generally beneficial though some studies showed improved quality of life and bone mass density in women. Supplementation is therefore not an established therapy.

Spirolactone

In combination with birth control pill and glucocorticosteroid in females with hypertensive forms of CAH

B. Route

- Intravenous in emergency situation;
- Oral for permanent treatment once patient is stable and in chronic treatment;
- Intramuscular, e.g. in emergency treatment prior to admission in acute crisis or to surgical intervention.

C. Frequency

Daily oral medication with timing in the morning and second dose in late afternoon is important though physiological secretion cannot be imitated.

After emergency treatment, intravenous doses of corticosteroids need to be tapered and may be discontinued once symptoms resolve, depending on the cause of the crisis. Maintenance of glucocorticosteroid and mineralocorticosteroid (only in primary insufficiency) level with oral medication. The athlete should be treated with the lowest possible glucocorticosteroid dose to avoid symptoms of adrenal insufficiency.

Immediately prior to a surgical intervention, patients require stress doses (triple the normal dosage) of glucocorticosteroids and additional doses should be continued throughout the procedure.

D. Recommended duration of treatment

Lifetime in primary adrenal insufficiency, but with regular clinical and laboratory evaluation. Balance between too little and too much glucocorticosteroids is vital and requires continuous surveillance.

Patients need to be advised to increase cortisol dosage in times of physical stress (e.g. operations, infections, but also major endurance competitions). Normal exercise does not require stress doses of glucocorticosteroids.

Secondary adrenal insufficiency due to oral (or local) glucocorticosteroids may last for weeks to months and even years, depending on the dose and duration of initial exposure. These patients require treatment (hydrocortisone) with regular monitoring of basal cortisol levels, ideally together with ACTH and DHEAS (not in CAH) and relative lymphocyte count (s. annex). DHEAS is more sensitive than cortisol and relative lymphocyte counts reflect long-term glucocorticosteroid action.

If serum cortisol alone is used, once the morning serum cortisol concentration is $\geq 10\mu\text{g/dL}$ (270 nmol/l) 24 hours after the last dose of hydrocortisone, continuous hydrocortisone therapy is no longer required.

Measurements of ACTH, DHEAS (not in CAH) and provocation tests may be performed to assess the need for further treatment under stress. A cosyntropin test alone is not valid in short-termed secondary adrenal insufficiency. If normal results are obtained for all parameters (for cosyntropin test 60 min plasma cortisol $\geq 18\ \mu\text{g/dL}$ (500 nmol/l)), hypothalamic-pituitary-adrenal function is normal and steroid supplementation *is no longer required during stress*. If it is not, steroids still need to be supplemented *during stress* and all tests should be repeated every month until they yield normal results.

When early morning serum cortisol is $< 10\mu\text{g/dL}$ (270 nmol/l), or cortisol, ACTH and DHEAS levels are subnormal, hydrocortisone therapy is continued and the respective values are re-assessed after four weeks. Stress supplementation needs to be continued. After normalisation of cortisol morning values, the procedure above is followed.

4. Other non-prohibited alternative treatments

In case of confirmed primary adrenal insufficiency, there is no non-prohibited alternative.

To complete treatment in emergency situations, intravenous fluids, dextrose and others might be needed.

In 21-OH-deficiency, bilateral adrenalectomy might be discussed in selected cases (controversial). A new treatment regime combining reduced hydrocortisone doses with an antiandrogen and an aromatase inhibitor has achieved promising results and is currently under evaluation.

Future therapies might include corticotropin-releasing hormone antagonists and gene therapy.

5. Consequences to health if treatment is withheld

Adrenal insufficiency, in particular an acute crisis, is a life-threatening disease that may lead to death if treatment is delayed or insufficient. Death may occur due to hypotension, cardiac arrhythmia or central impairment. This should be considered in applications for retroactive TUEs after emergency treatment without definite confirmation of diagnosis.

Other consequences as in chronic insufficiency are chronic ill health with repetitive decompensation. Underperformance in physical activity and competitive sport may occur.

6. Treatment monitoring

Due to the delicate balance that needs to be maintained between administering the lowest possible dose to achieve sufficient substitution on the one hand and overdosing on the other hand, monitoring by a qualified endocrinologist should be undertaken at least annually in case of stable disease, instable or acute cases require more frequent, sometimes monthly assessment. This may apply to athletes with secondary adrenal insufficiency due to glucocorticosteroid use.

7. TUE validity and recommended review process

The recommended validity of a TUE for an athlete suffering from primary adrenal insufficiency or in case of pituitary disease or surgery is 8 years with annual reviews of clinical status, blood count, creatinine, electrolytes, fasting blood glucose, serum aldosterone, ACTH, cortisol concentration, plasma renin concentration, and further parameters depending on the cause of primary adrenal insufficiency, by an endocrinologist.

In case of anticipated increased physical stress, such as infections, trauma, surgery or endurance competition, an increase of dosage as advised by the treating endocrinologist should be included in the granting without having to apply for a new TUE. The athlete should be advised to note such intermittent increase in dose on the doping control form at the time of testing in case of a doping control in the following months.

In treatment of adrenal insufficiency due to glucocorticosteroid withdrawal, TUEs may be granted for 4-12 weeks, depending on the values of the last cortisol and DHEAS measurements. A new TUE will only be issued after clinical and biological verification of further need due to persistent adrenal insufficiency.

Reference is made to article 4.1 of the International Standard TUE that a TUE should not be granted if the necessity for the use of a Prohibited Substance is the consequence of prior non-therapeutic use of any Prohibited Substance.

8. Any appropriate cautionary matters

- As adrenal insufficiency is potentially life-threatening, any delay of treatment of an acute exacerbation in case of clinical suspicion in order to establish diagnosis by testing is unwarranted. In such case, non- or delayed treatment is more dangerous than treatment.
- With adequate replacement therapy, no restriction in physical activity is required in an otherwise healthy person.
- Given the controversy associated with approval of dehydroepiandrosterone, the opinion of an independent endocrinological expert is strongly recommended.

9. References

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Medical Information to Support the Decisions of TUECs
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Annex:

Diagnostic algorithm in the work-up of a patient/athlete with adrenal insufficiency

