

Adrenal Insufficiency

Prohibited Substances: Glucocorticoids and Mineralocorticoids

1. Introduction

Adrenal insufficiency is a complex condition affecting the different cortical areas of the adrenal glands with corresponding aberrations in endocrine functions. There are a number of different causes that may result in significant morbidity and mortality if undiagnosed, untreated, or inadequately treated. It is an often elusive condition that requires awareness, knowledge of symptoms and signs, and endocrinological expertise to be correctly diagnosed and adequately treated. Adrenal insufficiency occurs with a frequency of 110–120 cases per million persons. The exact prevalence among athletes is not known, but for some causes, a more frequent occurrence is documented (see below).

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

Chronic Adrenal Insufficiency

a. Chronic primary adrenal insufficiency^{1,2}

This condition describes dysfunction of the adrenal glands from congenital or acquired causes. In primary adrenal insufficiency, there is an anatomical loss or severe structural damage to all three adrenal cortical zones. Clinical features relate principally to cortisol and aldosterone deficiency, with superadded androgen excess resulting from androstenedione excess (and its subsequent metabolism to testosterone and oestradiol) in Congenital Adrenal Hyperplasia (CAH).

Congenital disease may result from adrenal hyperplasia or, far less often, hypoplasia. CAH is the commonest form of primary adrenal insufficiency in children, resulting from autosomal recessive mutations of a gene encoding an enzyme required for the synthesis of cortisol.¹ 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) that is subdivided into salt-losing and simple virilizing types and a non-classic form without cortisol deficiency (manifested only in late childhood to adulthood).^{3,4,5,6,7}

The most common type of acquired primary adrenal insufficiency with adult onset is autoimmune adrenal insufficiency due to immune destruction of the adrenal cortex (Addison's disease).^{1,2} Less frequently, mycobacterial, bacterial, viral, and fungal infections or hemorrhage may cause adrenal insufficiency by destroying active glandular tissue. In developing countries, tuberculosis is the major cause of adrenal insufficiency.¹

b. Chronic secondary adrenal insufficiency

This is also known as “central” or “partial” adrenal insufficiency, where the cortical zone (“zona fasciculata”) of the adrenals is structurally intact but functionally inhibited by reduced pituitary adrenocorticotrophic hormone (ACTH) secretion.⁸

Secondary adrenal insufficiency is most commonly iatrogenic, caused by suppression of the hypothalamic-pituitary-adrenal (HPA) axis due to exogenous glucocorticoid use.⁸ This cause is particularly relevant in an athletic population due to the frequent use of glucocorticoids and their unpredictable uptake into the circulation and HPA axis suppression.⁸ Local treatment of musculoskeletal disease with potent glucocorticoids, such as long-acting betamethasone, triamcinolone, or dexamethasone, generally inhibits the HPA axis, and daily oral use may suppress the HPA axis within days.

Iatrogenic secondary adrenal insufficiency is likely to recover over time if glucocorticoid use can be discontinued, with the duration of the requirement for replacement corresponding to the dose and duration of the glucocorticoid used. Generally, prolonged recovery occurs only after glucocorticoid use of at least 2–4 weeks duration.

Another important consideration in athletes is that secondary adrenal insufficiency may occur months or even years after traumatic brain injury due to pituitary damage. Other reasons for central adrenal insufficiency include hypopituitarism from other forms of hypothalamic-pituitary disease, most notably pituitary tumors and their treatment.⁸

A number of medications (e.g., azole antifungals such as ketoconazole, miconazole, fluconazole, itraconazole) may inhibit adrenal steroidogenesis and precipitate adrenal insufficiency usually, but not always, in individuals with underlying undiagnosed adrenal insufficiency.

Secondary adrenal insufficiency results in cortisol deficiency, but aldosterone secretion is preserved. Hence, hyperkalemia does not occur, and fludrocortisone replacement is not required.

Acute Adrenal Insufficiency (adrenal crisis)

In a previously undiagnosed patient, acute adrenal insufficiency may be the initial presentation.^{9,10} Acute adrenal insufficiency is usually a presentation of complete primary adrenal failure and may be a life-threatening emergency.² Acute crisis or exacerbation in secondary adrenal insufficiency due to the use of exogenous glucocorticoids is rare, but cases where structural causes have rendered the patient cortisol-deficient, may present with adrenal crisis. Although efforts should be made to ascertain the cause of the adrenal crisis, treatment should not be delayed.⁸

2. Diagnosis

a. Medical history

Adrenal insufficiency symptoms are mostly non-specific and include fatigue, weakness, weight loss, nausea and vomiting, postural dizziness, syncope, disturbed mood, concentration or delirium, and in primary adrenal insufficiency only, skin darkening.¹ The rate of onset and severity of adrenal insufficiency symptoms may help establish the chronology of the disease.

Adrenal crisis may be defined as an acute deterioration in health in association with absolute or relative hypotension and symptomatic improvement after IV hydrocortisone and standard fluid resuscitation.

Chronic adrenal insufficiency and adrenal crisis are often missed, sometimes with fatal outcomes.⁹ Triggers to diagnosis may include salt hunger and skin darkening (primary adrenal insufficiency only) and hyperkalaemia.¹ Reduced athletic performance is expected. Some cases are misdiagnosed as eating disorders such as anorexia nervosa.

In congenital disease, females with classic 21-OH deficiency (a primary adrenal insufficiency) may present with ambiguous, virilized genitals at birth. Males might go undiagnosed in countries where newborn screening is not performed until they present with a salt-wasting crisis within one to three weeks of age, reflecting the degree of mineralocorticoid deficiency. Males without salt loss may present with precocious pseudopuberty (pubic hair, accelerated growth at 2–4 years of age). Rarely, an athlete with classic 21-OH-deficiency might remain asymptomatic (other than rapid growth as a child with premature linear growth cessation and being of short stature as an adult) and may not present themselves to a physician at all or be incidentally diagnosed in adult life (e.g., during fertility investigations or after detection of adrenal masses).^{5,6} Children with a non-classic form of CAH show signs of hyperandrogenism (early pubarche and body hair development, accelerated growth). Females continue to experience hyperandrogenemia from late puberty onwards, whereas adult males are usually asymptomatic.⁵

Distinguishing between primary and secondary adrenal insufficiency

The clinical distinction between primary and secondary insufficiency is important because primary adrenal insufficiency includes mineralocorticoid deficiency, which renders athletes more vulnerable to crises. Secondary adrenal insufficiency usually involves additional pituitary deficiencies, except for the iatrogenic suppression caused by glucocorticoid administration.

b. Diagnostic criteria

The diagnosis of adrenal insufficiency demands the synthesis of medical history with physical examination, substantiated by appropriate laboratory measurements and tests.^{1,8}

Physical examination

- Weight loss: Universally present in primary adrenal insufficiency
- Blood pressure: Hypotension, especially postural hypotension
- Pigmentation: Chronic hyperpigmentation (sun-exposed skin, skin creases, mucus membranes in primary adrenal insufficiency).²

Laboratory measurements^a

- Electrolytes: hyponatremia is commonly found in primary adrenal insufficiency, occasionally in secondary, hyperkalemia implies primary adrenal insufficiency.
- Fasting blood glucose: hypoglycemia, particularly in athletes during/after exercise and in children.
- 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 (83 nmol/L). Cortisol concentrations fall by approximately 30 nmol/L after this time and nadir at midnight. Values below 14 µg/dL (400 nmol/L) in the presence of markedly elevated ACTH and plasma renin concentrations are very suggestive of primary adrenal insufficiency and require further investigation by provocative testing (cosyntropin). Values above 14 µg/dL (400 nmol/L) generally rule out adrenal insufficiency. In rare cases of circulating binding protein disorders, lower serum cortisol values can be normal.
- Plasma ACTH concentration: When serum cortisol is low, ACTH can be decreased or inappropriately normal (secondary adrenal insufficiency) or increased at least two-fold¹ (primary adrenal insufficiency).
- Plasma renin and aldosterone concentration: considered in conjunction with concurrent evaluation of blood pressure (including postural), extracellular fluid volume (hydration status) and electrolytes. High plasma renin with low aldosterone and extracellular fluid volume depletion is characteristic of untreated primary adrenal insufficiency.

Testing^b

It is not within the scope of this document to provide the full details of each test, and the criteria are for general guidance only. These tests should be chosen and undertaken by an endocrinologist in an established laboratory. The test results need to be interpreted in the specific clinical context.

Cosyntropin testing (also corticotropin stimulation test)^{5,6,7}

Adrenal insufficiency is likely if serum cortisol level is less than 14 µg/dL (400 nmol/L) at 30-60 minutes after administration of 250 µg cosyntropin (synthetic ACTH; dose to be modified in children). Measurement of plasma ACTH determines whether adrenal

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insufficiency is primary or secondary. Elevated ACTH levels indicate primary adrenal insufficiency. If the cortisol response to cosyntropin is subnormal, but ACTH concentration is not elevated, secondary adrenal insufficiency is likely.

CRH stimulation test

This test is not widely used but can be superior to cosyntropin testing in individuals with short-term (less than three months) secondary adrenal insufficiency, e.g., after glucocorticoid treatment. Diagnostic cut-off values are the same as for the cosyntropin test.

Insulin-tolerance testing or metyrapone stimulation⁸

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

Antibody tests

If primary adrenal insufficiency is confirmed, anti-adrenal, mostly 21-hydroxylase antibodies, may confirm autoimmune primary adrenal insufficiency. Negative results should prompt a search for another cause of primary adrenal insufficiency and necessitate adrenal CT imaging and testing for very long-chain fatty acids in males to exclude adrenoleukodystrophy.

Imaging studies

A CT or MRI of the abdomen helps to identify hemorrhage, calcification, or infiltration of the adrenal glands. In secondary adrenal insufficiency, a sella MRI (or, if unavailable, cranial CT) may show destruction or a mass lesion of the pituitary.

c. Other relevant information

The patient's symptoms during the course of treatment over time should be documented and reported by the treating physician, noting any exacerbation (acute crisis) or required adaptation to doses of glucocorticoids and mineralocorticoids. Genetic analyses in congenital disease demonstrate the specific molecular etiology.

d. Likelihood of the medical condition being caused by previous use of glucocorticoids

Secondary adrenal insufficiency may occur with the administration of glucocorticoids by almost any route, not just from sustained oral use. Injectable glucocorticoids, depending on the formulations, may lead to sustained systemic exposure. Topical glucocorticoids (inhaled, intranasal, ophthalmic, dermal) rarely cause any significant systemic exposure but could if used at extremely high doses.⁸ Glucocorticoid-induced HPA axis suppression may last for a highly variable period of time, depending on the dose and duration of systemic exposure to exogenous glucocorticoids. There is considerable interindividual variability in efficacy and HPA axis suppression in response to glucocorticoid therapy.⁸ Adrenal

insufficiency demonstrated by low basal serum cortisol levels has been reported in elite cyclists with a high frequency of glucocorticoid use.¹¹

The TUEC should establish the dosage, frequency, duration, and administration route of previous or ongoing GC use, as well as the existence of any relevant TUEs when evaluating an athlete presenting with secondary adrenal insufficiency.

3. Treatment

The mainstay of treatment for primary adrenal insufficiency is substitution with glucocorticoids. Patients with additional mineralocorticoid deficiency might require fludrocortisone acetate.^{1,8,12}

Prevention of adrenal crises is essential to avoid fatal consequences, especially in those involved in competitive sport. All athletes with adrenal insufficiency need to be thoroughly educated about the steps needed to prevent adrenal crises. These include the use of stress doses of glucocorticoid for high levels of physiological stress, injury, or illness, especially those involving pyrexia. **In athletes with primary and secondary adrenal insufficiency who require life-long treatment, these situations requiring dose increases should be explicitly covered in the conditions of the TUE.**

Emergency situations with sufficient clinical suspicion of an adrenal crisis require treatment prior to definitive laboratory confirmation or consultation of an endocrinologist, but ideally after securing blood samples. This needs to be considered in any case of a retroactive TUE application for emergency treatment. In case of an adrenal crisis, the underlying problem precipitating the crisis also requires treatment.

Athletes with secondary adrenal insufficiency due to withdrawal from previous glucocorticoid therapy may require tapering doses of glucocorticoids over weeks or months to, in rare cases, years until symptom-free.

a. Name of prohibited substances

Treatment of primary adrenal insufficiency involves oral replacement of cortisol and aldosterone with steroids. Generally one of hydrocortisone, cortisone acetate, prednisolone, prednisone, or, rarely, dexamethasone to replace cortisol (hydrocortisone) is administered in a dose and schedule compatible with the steroids pharmacokinetics. Aldosterone is replaced with oral daily fludrocortisone.

Glucocorticoids^{1,6,8}

Oral and any injectable routes of administration of glucocorticoids are prohibited in-competition only. However, the levels of an in-competition urine sample may be above the established laboratory reporting levels of glucocorticoids even though the administration took place out-of-competition. In accordance with the Code, the resulting positive doping test, known as an adverse analytical finding (AAF), could render the athlete liable to a sanction under the concept of Strict Liability. However, if the athlete and attending physician provide appropriate clinical justification for systemic (e.g. oral, injectable) glucocorticoid use, a retroactive application for a TUE may be granted. See ISTUE Article 4.1e where the

athlete can apply retroactively for a TUE if one tests positive for a substance that was taken out of competition but only prohibited in competition.

Athletes with organic causes of permanent primary and secondary adrenal insufficiency require daily treatment with glucocorticoids and will in general require a TUE to compete. In athletes where adrenal insufficiency manifests with an acute crisis, a retroactive TUE application would be need to be submitted under ISTUE Article 4.1a.

- Hydrocortisone: intravenous drug of choice in emergency treatment; effective in controlling androgen production (in higher than physiological doses) in CAH; easy to titrate, some mineralocorticoid activity.
- Cortisone acetate is an alternative glucocorticoid used for daily oral replacement therapy in all but emergency situations.
- Prednisone: pro-drug that needs to be metabolized to active prednisolone; conversion is variable and might be impaired in liver disease.
- Prednisolone, methylprednisolone (parenteral).
- Dexamethasone: alternative to hydrocortisone to avoid interference with testing, but its lack of mineralocorticoid activity and high potency makes it less appropriate to be used alone for ongoing oral replacement therapy in primary adrenal insufficiency. Accurate dose titration is difficult.

Mineralocorticoids^{1,4,6,12}

Fludrocortisone acetate is needed for primary but not for secondary adrenal insufficiency.

DHEA¹³

In all forms of adrenal insufficiency, the production of dehydroepiandrosterone (DHEA) and its biologically inactive sulfate metabolite (DHEAS) are impaired. However, reductions in serum DHEA are often difficult to interpret as prolonged exogenous glucocorticoid treatment will suppress residual adrenal DHEA secretion. There is some controversial and inconclusive evidence from small studies that women with primary adrenal insufficiency and pituitary insufficiency may suffer from quality of life symptoms, primarily sexual dysfunction, which may be alleviated by DHEA treatment, but a meta-analysis showed only minimal, probably unimportant clinical benefits of DHEA administration.¹⁴ Consequently, DHEA treatment is not recommended.¹⁵ Furthermore, it has to be considered that DHEA treatment is generally not available in prescription form and that its long term safety is not established.

Androgens

Testosterone has no role in the treatment of female athletes with either form of adrenal insufficiency.¹² Serum androstenedione and testosterone may actually be elevated in individuals with CAH from 21-hydroxylase deficiency.

b. Route of administration

Glucocorticoids:

- Intravenous in an emergency situation or during hospitalization and surgeries;
- Oral for ongoing glucocorticoid treatment once the patient is stable and for chronic replacement therapy;
- Intramuscular, e.g., in emergency treatment prior to admission in adrenal crisis or prior to surgical intervention.

Mineralocorticoids

Fludrocortison acetate: oral

c. Dosage and frequency

Daily oral glucocorticoid medication is timed with the first and largest dose administered in the morning and subsequent smaller dose(s) in the afternoon to approximate diurnal physiological secretion.^{3,6,17}

After emergency treatment, intravenous doses of glucocorticoids need to be tapered and may be discontinued, usually by switching to oral maintenance, once symptoms resolve, depending on the cause of the crisis. Maintenance glucocorticoid and mineralocorticoid (only in primary adrenal insufficiency) replacement therapy is with oral medication. The athlete should be treated with the lowest possible glucocorticoid dose to avoid symptoms of adrenal insufficiency in order to avoid adverse effects of excessive glucocorticoids.

Immediately prior to major surgical intervention, patients require stress doses of glucocorticoids (25–100 mg hydrocortisone intravenously at induction), and additional doses should be continued throughout the procedure and postoperatively (up to 200 mg/24 hours intravenously until the patient can take double their usual dose orally). Doses in keeping with the extent of the surgery are recommended.

<https://www.addisonsdisease.org.uk/Handlers/Download.ashx?IDMF=b1278634-5c59-4252-a0e1-8b93e4647a75>).

4. Non-prohibited alternative treatments

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

5. Consequences to health if treatment is withheld

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

Other consequences of chronic adrenal insufficiency are chronic ill health with underperformance in physical activity and competitive sport.

6. Treatment monitoring

It is absolutely essential that a specialist endocrinologist is involved in the management of any athlete with proven adrenal insufficiency of any cause. Due to the delicate balance between administering the lowest possible dose to achieve sufficient substitution on the one hand or overdosing on the other, specialist monitoring should be undertaken at least annually in case of stable disease. Where there is instability of control or in acute cases, monitoring must be more frequent with more frequent, even monthly assessments. This may apply to athletes with secondary adrenal insufficiency due to prior glucocorticoid use.

7. TUE duration

In primary adrenal insufficiency, **treatment is lifetime** with regular clinical and laboratory evaluation.^{16,17} Careful balancing of glucocorticoid therapy is vital and requires continuous surveillance. In secondary adrenal insufficiency with hypopituitarism due to structural permanent posttraumatic hypothalamo-pituitary damage or hypothalamic-pituitary disease, including pituitary tumours, treatment is also lifelong.

The recommended validity of a TUE for an athlete suffering from primary adrenal insufficiency or in case of pituitary disease or surgery, therefore, is **10 years**, the maximum available under WADA's data protection and privacy rules. Under the supervision of a specialist endocrinologist, there should be 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.

Athletes need to be educated to increase cortisol dosage in times of physical stress (e.g., operations, infections, but also major endurance competitions). Normal exercise including regular training does not require stress doses of glucocorticoids.^{5,18}

In cases of anticipated increased physical stress, such as infections, trauma, or surgery, any dosage variation of glucocorticoids, as advised by the treating endocrinologist, **should be covered by the original TUE without the need for a new application**. The athlete should be advised to report such intermittent increase in dose on the doping control form at the time of testing in case of doping control in the following months.

Secondary adrenal insufficiency due to glucocorticoid therapy may last for weeks to months and even years, depending on the dose and duration of initial exposure.⁷ Recovery of the

hypothalamic-pituitary-adrenal axis in these patients requires regular monitoring of serum cortisol levels over time. Results should be interpreted by an experienced endocrinologist who will assess the need for further treatment.

In the treatment of adrenal insufficiency due to glucocorticoid withdrawal after out-of-competition treatment or an in-competition course of treatment for which a TUE had been granted previously, further TUEs may be granted for 4–12 weeks, depending on a review of the values of serial basal or stimulated cortisol concentrations. These new TUEs will only be issued after clinical and biological verification of a further need due to persisting adrenal insufficiency.

8. Appropriate cautionary matters

- Adrenal insufficiency is potentially life-threatening. Therefore, any delay in treating an acute exacerbation is unjustifiable. In cases where there is clinical suspicion of adrenal insufficiency from any cause, the initiation of treatment with glucocorticoids should always take precedence over further investigations. Athletes' health should never be jeopardized while waiting for prospective TUE approval.
- If female athletes who present with established primary adrenal insufficiency wish to apply for the supplemental use of DHEA, the opinion of an independent, expert endocrinologist must guide and ultimately inform the TUE application. Without such specialist input, the application will be considered incomplete by any TUEC.

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