



Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

ATHLETES & PRESCRIBING PHYSICIANS PLEASE READ

USADA can grant a Therapeutic Use Exemption (TUE) in compliance with the World Anti-Doping Agency International Standard for TUEs. The TUE application process is thorough and designed to balance the need to provide athletes access to critical medication while protecting the rights of clean athletes to compete on a level playing field.

Included in this document is a checklist of items necessary for a complete TUE Application and the WADA Guidelines used to evaluate TUE Applications for your specific condition. (Please be aware that the TUE Committee may ask for additional information while evaluating TUE Applications). It is important that the TUE Application include all the documentation outlined in the checklist below. Please reference the included guidelines for details related to types of diagnoses, specific laboratory tests, and more.

TUE APPLICATION CHECKLIST – ADRENAL INSUFFICIENCY

- Complete and legible TUE Application form
- Copies of all relevant examinations and clinical notes from the original diagnosis through present
- Copies of all laboratory results/reports related to the diagnosis (please see the guidelines for specific results to include)
- A statement from the physician explaining why the Prohibited Substance is needed
 - Please explain why permitted alternative treatments were not effective or not appropriate/indicated for treatment

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ADRENAL INSUFFICIENCY

1. Medical Condition

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. 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 incidence 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, but the focus is on conditions likely to be encountered in athletes at different activity levels.

1) Chronic Adrenal Insufficiency

a) Chronic primary adrenal insufficiency:

This is due to a dysfunction of the adrenal glands from congenital or acquired causes. In primary adrenal insufficiency, there is an anatomical loss or severe structural damage to the three adrenal cortical zones.

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 non-classic form (manifested only in late childhood to early adulthood).

The most common type of acquired primary adrenal insufficiency is idiopathic adrenal insufficiency due to autoimmune destruction of the adrenal cortex (Addison's disease). 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.

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 intact but functionally inhibited by reductions in adrenocorticotrophic hormone (ACTH) secretion from the pituitary.

Secondary adrenal insufficiency is most commonly iatrogenic, caused by suppression of the hypothalamic-pituitary-adrenal axis due to exogenous glucocorticoid use. This cause is particularly relevant in an athletic population due to the frequent use of glucocorticoids and their unpredictable uptake into the circulation. Local treatment of musculoskeletal disease with glucocorticoids may inhibit the axis and daily oral use may lead to suppression of the axis within as little as two weeks. Another important consideration in athletes is the fact that adrenal insufficiency may occur months or even years after traumatic brain injury due to pituitary insult. Other reasons for central adrenal insufficiency include hypopituitarism from other forms of hypothalamic-pituitary disease most notably pituitary tumours and their treatment.

Furthermore, a number of medications (e.g., azole antifungals such as ketoconazole, miconazole, fluconazole, itraconazole) may inhibit adrenal steroidogenesis and precipitate adrenal insufficiency.

2) Acute Adrenal Insufficiency (adrenal crisis)

In a previously undiagnosed patient, acute adrenal insufficiency may be the initial presentation. Acute adrenal insufficiency is usually a presentation of complete primary adrenal failure and may be a life-threatening emergency. Acute crisis or exacerbation in secondary adrenal insufficiency is rare. However, it may be seen with acute cortisol deficiency due to pituitary infarction, or if there is abrupt withdrawal of glucocorticoid use. Although efforts should be made to ascertain the cause of the adrenal crisis, treatment should not be delayed.

2. Diagnosis

The diagnostic and therapeutic work-up in adrenal insufficiency of whatever cause differs, depending on the presentation, either as an acute crisis or from slowly evolving chronic disease. It is important to establish whether the adrenal insufficiency is primary or secondary.

A. Medical history

History taking must confirm the signs and symptoms and time of onset, i.e. acute onset/crisis or chronic disease.

Acute adrenal insufficiency (adrenal crisis)

In an acute crisis, history is of particular importance and together with findings on examination represents the main pillar of a presumptive diagnosis necessitating immediate treatment after securing blood samples. Any delay in diagnosis by more extensive laboratory investigations may result in poor outcome. Although there may be a number of non-specific symptoms, shock is the predominant feature of adrenal crisis. The patient is severely ill, may become dehydrated, hypotensive, hypoglycemic and of altered mental status.

Chronic adrenal insufficiency

The physical findings in chronic adrenal insufficiency are often subtle.

Chronic primary adrenal insufficiency may manifest as chronic fatigue, weakness, tiredness, hyperpigmentation, anorexia, weight loss, nausea, abdominal pain, diarrhea or constipation with orthostatic hypotension, dizziness or even syncopal episodes. Episodes of salt-craving are typical for primary adrenal insufficiency.

In chronic secondary adrenal insufficiency due to exogenous glucocorticoids, hyperpigmentation is not seen due to chronic glucocorticoid suppression of corticotropin-releasing hormone (CRH) and ACTH. Dehydration and hyperkalemia are also not present. Gastrointestinal symptoms and hypotension may be seen, but are usually not prominent. Patients may feel cold, have difficulties in concentrating, bone and muscle pain or headache. In athletes, poor performance might be observed but may be caused by overtraining.

In congenital disease, females with classic 21-OH deficiency (a primary adrenal insufficiency) 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 mineralocorticoid deficiency. Males without salt loss may present with precocious puberty (pubic hair, accelerated growth at 2-4 years of age), however many remain asymptomatic (other than being of short stature) and may not present themselves to a physician at all, or be incidentally diagnosed in adult life (e.g., during fertility investigations). Females with a non-classic form of CAH show signs of hyperandrogenism from late puberty onwards whereas males are usually asymptomatic.

Distinguishing between primary and secondary adrenal insufficiency

The clinical distinction between primary and secondary insufficiency is important because secretion of the adrenal androgen precursor dehydroepiandrosterone (DHEA) is affected in a similar manner to that of mineralocorticoid secretion. With structural damage (loss or severe damage) to all three adrenocortical zones in primary adrenal insufficiency, neither DHEA nor mineralocorticoids are produced. By contrast, in secondary adrenal failure (as in ageing as well), mineralocorticoid

and DHEA secretion and blood DHEA concentrations may be reduced, but both are still produced.

However, reductions in serum DHEA are often difficult to interpret as prolonged exogenous glucocorticoid treatment will suppress residual adrenal DHEA secretion. There is some evidence, although controversial and not conclusive, that women with primary adrenal insufficiency and pituitary insufficiency may suffer from quality of life symptoms such as sexual dysfunction, which may be alleviated by DHEA treatment.

A TUE for DHEA should only be considered in women with primary adrenal insufficiency who have significantly impaired mood or sense of well-being despite optimal glucocorticoid replacement.

B. Diagnostic criteria (see annex)

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

Laboratory measurements¹

- Electrolytes: hyponatremia with or without hyperkalemia is commonly found in primary adrenal insufficiency, occasionally in secondary
- Fasting blood glucose: hypoglycemia particularly 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 (83 nmol/L). Values below 18 µg/dL (500 nmol/L) in the presence of a markedly elevated ACTH and plasma renin concentrations are very suggestive of primary adrenal insufficiency and may require further investigation by provocative testing (cosyntropin, CRH, insulin). Values above 18 µg/dL generally rule out adrenal insufficiency.
- Plasma ACTH concentration: When serum cortisol is low, ACTH can be decreased or inappropriately normal (secondary adrenal insufficiency) or increased (primary adrenal insufficiency).
- Plasma renin and aldosterone concentration: considered in conjunction with concurrent evaluation of blood pressure (including postural), ECF volume (hydration status) and electrolytes. High plasma renin with low aldosterone

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 and exercise may need to be considered. Threshold values provide some guidance in the case of athletes.

and ECF volume depletion is characteristic of untreated primary adrenal insufficiency.

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. The appropriate test chosen as well as the test results need to be interpreted in the specific clinical context.

Cosyntropin testing

Adrenal insufficiency is likely if serum cortisol level is less than 18 µg/dL (500 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 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 superior to cosyntropin testing in individuals with short-term (less than 3 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 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.

Antibody tests

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

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 skull CT or MRI may show destruction or mass lesion of the pituitary.

² This information mentions limit values for testing though these are not all scientifically proven and will be difficult to apply in a clinical setting where the effect of the hormones and exercise may need to be considered. However, threshold values provide some guidance in the case of athletes.

C. Relevant medical 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 may confirm the diagnosis.

3. Medical best practice treatment

The mainstay of treatment for primary adrenal insufficiency is substitution with glucocorticoids. Patients with additional mineralocorticoid deficiency might require fludrocortisone acetate.

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. The duration of treatment will depend on the duration of initial glucocorticoid therapy.

A. Name of prohibited substances

Glucocorticoids

- Hydrocortisone: drug of choice in emergency treatment; effective in controlling androgen production (in higher than physiological doses); easy to titrate, mineralocorticoid activity.
- Prednisone: agent is inactive and needs to be metabolized to active prednisolone; conversion might be impaired in liver disease.
- Prednisolone, methylprednisolone.
- Dexamethasone: alternative to hydrocortisone to avoid interference with testing, but its lack of mineralocorticoid activity makes it less safe to be used alone.

Mineralocorticoids

Fludrocortisone is not generally needed unless a glucocorticoid with low mineralocorticoid activity is used (e.g., dexamethasone).

DHEA

While the scientific data remain inconclusive and contentious, DHEA may have a role in some females with primary adrenal insufficiency only.

Androgens

Testosterone has no role in the treatment of female athletes with either form of adrenal insufficiency.

B. Route of administration

Glucocorticoids:

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

DHEA: Oral

C. Frequency

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

After emergency treatment, intravenous doses of glucocorticoids need to be tapered and may be discontinued 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 a surgical intervention, patients require stress doses (triple the normal dosage) of glucocorticoids and additional doses should be continued throughout the procedure.

Where symptomatic DHEA deficiency affecting the quality of life is established unequivocally in females with primary adrenal insufficiency, and the patient is on optimal glucocorticoid therapy, DHEA up to a maximum of 25mg may be administered daily. Dose titration based on mass spectrometry-based assays (not immunoassays) for serum testosterone and DHEA may be required.

D. Recommended duration of treatment

In primary adrenal insufficiency treatment is lifetime with regular clinical and laboratory evaluation. Careful balancing of glucocorticoid therapy 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 glucocorticoids.

In secondary adrenal insufficiency with hypopituitarism due to posttraumatic permanent damage or hypothalamic-pituitary disease including pituitary tumours treatment is also lifetime. Secondary adrenal insufficiency due to oral (or local) glucocorticoid therapy may last for weeks to months and even years, depending on the dose and duration of initial exposure. 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.

4. Other non-prohibited alternative treatments

In the case of confirmed primary adrenal insufficiency, there is 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 at least monthly assessment. This may apply to athletes with secondary adrenal insufficiency due to glucocorticoid use.

Furthermore, in female athletes with proven primary adrenal insufficiency who are granted supplementation with DHEA, a baseline steroid profile should be performed prior to therapy using validated mass-spectrometry-based methods³ and documented in ADAMS. Profiling should be repeated at regular intervals to be defined by the granting ADO to ensure levels of serum testosterone and DHEA remain within the individual athlete's normal range during supplementation. Reference should be made to the laboratory criteria used to monitor the serum testosterone and DHEA levels of athletes who have been granted supplementation for proven DHEA deficiency.

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 10 years. 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.

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.

In treatment of adrenal insufficiency due to glucocorticoid withdrawal, TUEs may be granted for 4-12 weeks, depending on a review of the values of serial basal or stimulated cortisol concentrations. A new TUE will only be issued after clinical and biological verification of a further need due to persisting adrenal insufficiency.

Reference is made to article 4.1 of the International Standard for 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.

Requirements for the monitoring of DHEA supplementation are described under Section 6.

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

³ The direct (unextracted) testosterone immunoassays currently used by most laboratories are too inaccurate for monitoring serum testosterone during physiological DHEA replacement therapy.

suspicion of adrenal insufficiency from any cause, the initiation of treatment with glucocorticoids should always take precedence over further investigations.

- With adequate replacement therapy, no restriction in physical activity is required in an otherwise healthy person.

- In the small group of female athletes who present with established primary adrenal insufficiency, and where the supplemental use of DHEA is considered, 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.

9. References

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Medical Information to Support the Decisions of TUECs
Adrenal insufficiency

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

