WORLD ANTI-DOPING AGENCY
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The World Anti-Doping Program

MEDICAL INFORMATION TO SUPPORT THE DECISIONS OF THERAPEUTIC USE EXEMPTION COMMITTEES (TUECs)

Version 1.0

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Introduction and Scope

This Medical Information to Support the Decisions of Therapeutic Use Exemption Committees (TUEC) has been developed as part of the World Anti-Doping Program. It is based on the World Anti-Doping Code (Code, or WADC) and on the International Standard for TUE set out in the Code.

This document should, in particular, be read in conjunction with the principles set out in the International Standard for TUE regarding the granting criteria for TUE (Article 4.2 to 4.5). It was drafted in order to guide and assist TUECs in decision making for TUE applications. This Medical Information must be considered as the most widely accepted medical best practice at present. This Medical Information is not mandatory and has no legal value.

This Medical Information is a living document. It will be updated as necessary based on the evolution of medical best practice. Pathologies covered at this stage are the most current ones encountered in the TUE field. Other pathologies will be covered as needed.

The experience and knoweldge sharing in decision making in the TUE field will help to enrich this document over time. It should help to answer with more precision the questions TUECs may encounter in their decision making process.

1. Medical Condition

ARTERIAL HYPERTENSION

2. Diagnosis

A. Medical history

Hypertension may be either primary or secondary. Primary or essential hypertension is of unknown aetiology and constitutes the predominant group. However evidence of a history of sustained elevated blood pressure is mandatory for the consideration of therapeutic use exemption to use listed drugs.

B. Diagnostic criteria

- The diagnosis of hypertension must be accompanied by an appropriate history of documented elevated recordings of systolic and/or diastolic blood pressure.

- Elevated BP readings should conform to current diagnostic criteria (see references below).

C. Relevant medical information

- It is necessary to provide the history of sustained elevated blood pressure recorded by the medical practitioner with appropriate specialist endorsement when indicated (see below).

- Evidence of a sustained trial of non-prohibited agents must be included in the medical information.

3. Medical best practice treatment

A. Name of prohibited substances

Combination therapy may be required including the use of:
1) Beta-Blockers
2) Diuretics

B. Route

All agents may be administered orally

C. Frequency

Daily doses of medication may include a single therapy protocol or combinations of diuretics and beta-blockers.

D. Recommended duration of treatment

The treatment of arterial hypertension is usually life-long. In the case of an active competitive athlete it is recommended that there be an annual review by the treating medical practioner or another specialist.

4. Other non-prohibited alternative treatments?

Combination therapy may modify the course of this condition including weight reduction, dietary advice, exercise prescription, smoking cessation and the use of a number of possible non-prohibited drug choices. These may include calcium channel blocking agents, ACE inhibiters, Angiotensin II receptor blocking agents and alpha-Adrenergic blockers.

5. Consequences to health if treatment is withheld

Untreated hypertension is unequivocally linked to an increased risk in particular of left ventricular failure, myocardial infarction, a cerebrovascular accident or renal failure. There is international agreement that the treatment of hypertension is mandatory.

6. Treatment monitoring

Routine monitoring of blood pressure may be at the discretion of a medical practitioner with reference to a specialist as appropriate.

7. TUE validity and recommended review process

Lifetime therapy in accordance with clinical status and an annual review is acceptable. Any changes to the therapeutic regime should be well documented, endorsed by a specialist physician and form the basis of a revised TUE.

8. Any appropriate cautionary matters

At the time of doping control there is a specific necessity for an adequate urinary concentration. A specific gravity of 1.005 by refractometer or 1.010 by dipstick should be obtained.
A TUE will only be granted in sports where there is no potential for performance enhancement. The current WADA Prohibited List and International Standard should be consulted for a list of these sports.

9. References

1. New Guidelines for treatment of hypertension
   The Merck Manual 17th Ed, Sec 16, Ch 199 Arterial Hypertension

2. KDOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 39:S1-S266, 2002 (suppl 2)

3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC report. JAMA 289:2560-2572, 2003

4. 2003 European Society of Hypertension- European Society of CardiologyNew Guidelines for treatment of Hypertension J Hypertens. 2003 Jun;21(6):1011-53

1. Medical Condition

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND YOUNG ADULTS

Introduction

ADHD is the most common neurobehavioral disorder of childhood and amongst the most prevalent chronic health conditions affecting school-aged children. The core symptoms of ADHD include inattention, hyperactivity, and impulsivity. Children with ADHD may experience significant functional problems that may continue as they enter adolescence and adult life. Recent literature also suggests that ADHD may present for the first time in young adulthood.

2. Diagnosis

- A. Medical history

The diagnosis of ADHD is essentially a clinical diagnosis, frequently initiated by parents, teachers or other significant adults such as coaches and trainers who deal regularly with young people.
However these early anecdotal suspicions must be established and confirmed by experienced clinicians. In most parts of the world these include paediatricians, child psychiatrists or clinical psychologists. Obviously a record of the onset of symptoms is required and the DSM-IV or ICD-10 criteria outlined in the following section must be met.

- B. Diagnostic criteria

These are in accordance with the DSM-IV criteria (see reference). The Connor scale has also shown utility in correlating the psychopathology in children with ADHD. (ref Journal of the American Academy of Child & Adolescent Psychiatry. 42(2):193-200, February 2003.)
Some recent research indicates that objective diagnosis by PET (Positron Emission Tomography) or SPECT (Single-photon Emission

Computed Tomography) may be of possible diagnostic assistance in the near future.
When ADHD first appears at a young adult age, diagnostic confirmation demands a second expert opinion.

- C. Relevant medical information

See above.

3. Medical best practice treatment

- A. Name of prohibited substance

Stimulants form the basis of the treatment of ADHD and these may include short, intermediate and long acting methylphenidate, or dextroamphetamine.

- B. Route

Oral

- C. Frequency

Short-acting: 5-20 mg BID to TID
Intermediate acting: 20-40 mg QD
Extended release: 18-72 mg QD

- D. Recommended duration of treatment

It must be made clear that the treatment of ADHD is a long term treatment (possibly over years), but regular intermediate assessments every 3 to 4 months are useful. It is a mandatory requirement for any athlete on continued therapy with methylphenidate or dextroamphetamine to provide evidence of an annual review by a specialist in the management of ADHD (see above). Any change in therapy must constitute a renewed application for TUE.

4. Other non-prohibited alternative treatments?

Atomoxetine has been identified as a non-prohibited alternate treatment for some patients with ADHD. However this medication is not available in all countries. Where it is available there should be evidence that it has been tried as a therapeutic alternative. Otherwise, apart from some behaviour-modifying techniques, treatments with non-prohibited substances have not been shown to be effective.

5. Consequences to health if treatment is withheld

Untreated, true ADHD is widely recognized as having detrimental effects on the quality of life and psycho-social development of the patient. Psychiatric degradation is not excluded.

6. Treatment monitoring

Measures of treatment compliance together with target outcomes should be undertaken every 3 to 4 months by an experienced clinician.

7. TUE validity and recommended review process

The treatment will last as long as necessary, indicated by the instruments of clinical monitoring and specialist opinion mentioned above. Continued therapy with prohibited drugs must be justified by a full report.
A TUE in a case of ADHD will not be granted for longer than 1 (one) year without adherence to strict review by a specialist in the field.

8. Any appropriate cautionary matters

Specialist opinion in the field of ADHD confirms that youngsters on prescribed medication frequently require their drugs more for behavioral control at school and in the home rather than for sports. It may be possible for the intake of a prohibited substance to be reduced or even stopped on the day of competition without disadvantaging an athlete and affecting the overall treatment.

9. References

1. B.Corrigan Attention Deficit Hyperactivity Disorder in Sport: a review In Int.J.Sports Med 2003; 24: 535 – 540

2. G.Hicky, P.Fricker Attention Deficit Hyperactivity Disorder, CNS Stimulants and Sport, In Sports Med 1999, Jan 27(1): 11-21

3. Treatment of the School-Aged Child With Attention-Deficit/Hyperactivity Disorder by the Committee of Quality Improvement, Subcommittee on ADHD of the American Academy of Pediatrics in Pediatrics Vol.108 No.4 October 2001, 1033-1044

4. Treatment of the School-Aged Child With Attention-Deficit/Hyperactivity Disorder by the Committee of Quality Improvement, Subcommittee on ADHD of the American Academy of Pediatrics in Pediatrics Vol.108 No.4 October 2001, 1033-1044

5. Journal of the American Academy of Child & Adolescent Psychiatry. 42(2):193-200, February 2003. Connor, Daniel F. M.D.; Edwards, Gwenyth PH.D.; Fletcher, Kenneth E. PH.D.; Baird, Janette M.A.; Barkley, Russell A. PH.D.; Steingard, Ronald J. M.D.

1. Medical Condition

CHRONIC INFLAMMATORY BOWEL DISEASE

Introduction

This classification specifically includes Crohn's disease and ulcerative colitis but also embraces chronic colitis of indeterminate cause. It is well known that these conditions may have a familial tendency and commonly affect younger patients within their first three decades. Consequently it is not uncommon for active young athletes to seek exemption to use prohibited substances including glucocorticosteroids for the long-term management of their bowel disease.

2. Diagnosis

A. Medical history

Inflammatory bowel disease (IBD) carries a characteristic medical history that may include altered bowel habit, fever, abdominal pain, anorexia and weight loss. In the very young there may be a history of growth retardation. Toxic complications in ulcerative colitis are a common and serious complication. A family history is an important historical correlate.

B. Diagnostic criteria

Given a suspicious history and family history, the definitive diagnosis of IBD demands specific investigations carried out under the supervision of a specialist-gastroenterologist. Apart from routine laboratory screening to confirm the presence of inflammation and anaemia, endoscopic examination and Barium enema X-ray is required to demonstrate the specific pathological features of Crohn's disease. Computerised Tomography (CT) or virtual colonoscopy may also be employed. Ulcerative colitis on the other hand requires stool examination, sigmoidoscopy to demonstrate typical mucosal changes and biopsy evidence of chronic inflammation and altered mucosal vascularity.

- C. Relevant medical information

A relevant medical history of functional bowel disturbance and associated weight loss, anorexia and inappropriate fatigue is frequently obtained by the primary care/family physician. Where the patient is also an elite athlete there is added urgency to seek specialist opinion and diagnostic confirmation. Clearly during periods of acute exacerbation of IBD it is unlikely that an athlete would be fit for training or competition.

3. Medical best practice treatment

A. Name of prohibited substance

Glucocorticosteroids are a critical adjunct in the treatment of IBD in conjunction with other permitted agents including immunomodulating drugs, 5-aminosalicylates, analgesics and antibiotics.

B. Route

Oral, rectal

C. Frequency

Large doses of oral prednisone (40-60mg per day) may be necessary in the acute management of IBD tapering over a period of weeks to months. Acute ulcerative colitis may also require high dose systemic corticosteroids. Doses are individualized and demand specialist oversight in combination with other appropriate therapeutic agents. A small proportion of patients with IBD become corticosteroid-dependant and requires long-term maintenance.

D. Recommended duration of treatment

Given the chronic nature of IBD, the duration of treatment for athletes is likely to be lifetime or at least for the life of their exposure to high performance sport.

4. Other non-prohibited alternative treatments?

No other permitted alternative drugs exist that provide the same effect as glucocorticosteroids.

5. Consequences to health if treatment is withheld

If untreated, IBD may run an undulating, unremitting course with a fatal outcome.

6. Treatment monitoring

During periods of remission from chronic inflammatory bowel disease the athlete may be totally asymptomatic. Treatment is routinely monitored by the family physician with recommended review by the specialist-gastroenterologist at least annually or as clinically indicated.

Indices exist for scoring the activity of IBD and these may be applied to the initial assessment of acute exacerbations of the disease.

7. TUE validity and recommended review process

Athletes competing at the elite level of sport will usually have a good understanding of their condition and respond quickly to acute crises. Their altered requirement for glucocorticosteroids should be reflected in at least an annual specialist review and renewed application for therapeutic use exemption.

8. Any appropriate cautionary matters

The sustained use of systemic glucocorticosteroids carries well-documented long-term risks.

9. References

1. Best WR, et al., "Development of a Crohn's disease activity index." Gastroenterology; 70:439-444, 1976.

2. Carter MJ, A J Lobo, Travis SPL, “Guidelines for the management of inflammatory bowel disease in adults.” Gut;53: v1 - v16, 2004.

3. Walmsley RS, Ayres RCS, Pounder RE, Allan RN, “A simple clinical colitis activity index.” Gut; 43:29-32, 1998.

4. Inflammatory Bowel Diseases. Merck Manual 17th Ed. Section 3: 302-312

1. Medical Condition

DIABETES MELLITUS (INSULIN-DEPENDENT)

Introduction

This condition, also known as Type-1 Diabetes Mellitus (type-1 DM), characteristically occurs in childhood or adolescence and may therefore implicate athletes. Cases of elite athletes with type-1 DM are not uncommon and it behooves all physicians to enable these individuals to meet their full potential in sport.

The pathophysiology invokes a well-documented genetic susceptibility to the destruction of most insulin-secreting pancreatic islet cells resulting in hyperglycaemia and the risk of ketoacidosis. Aside from the genetic, immune-mediated causes of type-1 DM, environmental influences including exposure to certain viruses, cow's milk albumin and even the geographic location of populations have been implicated.

Early diagnosis in athletes, in accordance with accepted methods of investigation enables timely recognition and application for Therapeutic Use Exemption. Most type-1 DM patients are diagnosed before the age of 30 years.

2. Diagnosis

- A. Medical history

Type-1 DM characteristically presents with a history of symptomatic hyperglycaemia. Polyuria, polydipsia and unexplained weight loss are common clinical associates. However a spectrum of vague symptoms including inappropriate lethargy, nausea, blurred vision and recalcitrant fungal or bacterial infections may be the first early clues. Astute clinicians will include undiagnosed, type-1 DM on their list of differential diagnoses in such young patients.

- B. Diagnostic criteria

Agencies such as the National Diabetes Data Working Group (Australia) and the American Diabetes Association have well-established diagnostic criteria that must be met before a patient is declared diabetic and in this instance, be labeled as insulin-dependant. These criteria identify specific fasting plasma glucose levels and should be referenced. The traditional oral glucose tolerance test may assist in identifying previously undeclared diabetics but this test may be influenced by aging and concurrent drug use. Specialist input is mandatory in most major medical communities where diabetic clinics investigate, monitor and educate affected patients.

- C. Relevant medical information

A relevant medical history as described previously, together with suggestions of a familial link should always alert the consulting physician. Where the patient happens to be an active adolescent involved in high performance sport, the diagnosis of type 1 DM should always be considered, appropriately investigated and referred for specialist opinion as necessary.

3. Medical best practice treatment

- A. Name of prohibited substance

Insulin in a variety of preparations ranging from rapid to long-acting forms is the standard treatment for type-1 DM. The dose of insulin is determined in accordance with such factors as food intake and energy expenditure and the goal of all insulin regimes is to control postprandial plasma glucose surges. Such regimes are individualized in accordance with monitored plasma glucose levels from fingertip blood samples.

- B. Route

Subcutaneous

- C. Frequency

The dosage and frequency of insulin administration is entirely dependent upon individual requirements. Plasma glucose levels provide an immediate indication of insulin need, whilst the determination of glycosylated haemoglobin provides an indication of plasma glucose control over the preceding 1 to 3 months.
Many active type-1 diabetics, including some high level athletes, may employ small indwelling pumps to achieve a continuous subcutaneous infusion of insulin. These enable a predetermined basal rate of insulin infusion to be augmented manually before meals. Continuous infusion is a costly option and has been associated with the potential for hypoglycaemia particularly where athletes are adapting to metabolic control.

- D. Recommended duration of treatment

The continuing need for insulin is self-evident in those with true type-1 DM. Given their review by diabetic specialist clinics it is prudent for those athletes requiring continued Therapeutic Use Exemption to reapply annually for this exemption.

4. Other non-prohibited alternative treatments?

Whilst the treatment of type-1 DM includes dietary control and patient education, insulin, for which there is no non-prohibited alternative, is the mainstay of therapeutic control. Oral antidiabetic agents have no place in the treatment of type-1 DM.

5. Consequences to health if no treatment

If untreated, type-1 DM is unequivocally linked to a number of co-morbidities including retinopathy, nephropathy, various neuropathies, an increased risk of ischaemic heart disease and diabetic ketoacidosis with a potential fatal outcome.

6. Treatment monitoring

The monitoring of patients with type-1 DM rests with the various agencies currently available to manage this condition. The primary care physician, diabetic nurse educator and diabetesphysician may all play a part.

7. TUE validity and recommended review process

As described, treatment is for life and demands review by appropriate specialist clinicians. Athletes competing at the elite level will be well-educated in the control of their diabetes and experienced in coping with acute crises. Their requirement for insulin is individualized and should be under automatic review by the agencies mentioned above. A commonsense approach to the annual review of TUE is recommended in these cases.

The dosage and frequency of insulin administration is entirely dependent upon individual requirements. Plasma glucose levels provide an immediate indication of insulin need, whilst the determination of glycosylated haemoglobin provides an indication of plasma glucose control over the preceding 1 to 3 months.

8. Any appropriate cautionary matters

Prolonged periods of poor plasma glucose control carries well-documented clinical consequences and these have been discussed elsewhere.

9. References

1. THE MERCK MANUAL (17th Edition) Chapter 13, Disorders of Carbohydrate Metabolism

2. National Diabetes Data Working Group
www.aihw.gov.au/committees/nddwg/index.cfm

3. American Diabetes Association. Clinical Practice Guidelines (2006) care.diabetesjournals.org/content/vol29/suppl_1

4. Silverstein J, Klingensmith, Copeland GK, et al Care of Children and Adolescents With Type 1 Diabetes: A statement of the American Diabetes Association. Diabetes Care 2005 28: 186-212.

1. Medical Condition

GROWTH HORMONE DEFICIENCY (ADULT)

2. Diagnosis

A. Medical history

Pure GH deficiency in adults may not be clinically obvious. It may however be part of a disorder affecting hyposecretion of all the anterior pituitary hormones and involve a wide constellation of signs and symptoms. Where the patient is an athlete, the diagnosis of such deficiency must be clearly defined within an appropriate clinical context and with the support of an experienced endocrinologist. The particular issue of relative adult GHD must be managed by an experienced specialist and meet strict diagnostic criteria before treatment commences.

B. Diagnostic criteria

- The diagnosis of adult GH deficiency is biochemical. An evaluation for GH deficiency should be considered only in patients with evidence of hypothalamic-pituitary disease, childhood onset of GH deficiency or after cranial irradiation (therapeutic or accidental).

- Because of the fast half life of GH in blood (around 19 min), serum GH levels are frequently very low or even undetectable. For this reason the diagnosis of GH deficiency is established by provocative testing of GH secretion. The insulin tolerance test is the diagnostic test of choice. It should be performed in an endocrine unit where the test is performed frequently. After insulin-induced hypoglycemia most normal subjects respond with a peak of GH in serum **above 5 mcg/L**. A peak of GH to **less than 3 mcg/L** constitutes a severe GH deficiency. In patients with contraindications to the insulin tolerance test, the arginine test combined with GHR can be used as an alternative. One provocative test is sufficient for the diagnosis of GH deficiency in adults with hypothalamic-pituitary disease. To

diagnose isolated GH deficiency it is recommended that a second biochemical test of GH status be abnormal. The **cut-off point of 5 mcg/L** is used for provocative tests as the current reference, regardless the stimulation test or the GH assay used (see references at the end of the document). It does not vary with age.

C. Relevant medical information

- A serum IGF-1 concentration below the normal range is suggestive but not conclusive proof of GH deficiency. It is recommended that the diagnosis be confirmed by a provocative test of GH release.

- GH and IGF-1 results should be expressed in mass units.

- Currently, the benefits of the treatment of partial GH deficiency remain debatable. Consequently, only patients with documented, severe GH deficiency should be eligible for an exemption to use growth hormone therapeutically.

3. Medical best practice treatment

A. Name of prohibited substance

Recombinant growth hormone

B. Route

Due to the short half-life of GH, daily subcutaneous injections in the evening are recommended. Where practically possible it is recommended that GH administration is carried out and logged daily by an appropriate health professional. However where this is impractical it is strongly recommended that the quantity of GH delivered to the patient be strictly controlled by the physician in charge.

C. Frequency

The current consensus states that the therapy should start with a low dose (0.15-0.30 mg/day; 0.45-0.90 IU/day) and should be increased gradually based on the clinical and biochemical responses at monthly intervals. The normal maintenance dose may vary until 1.0 mg/day (3 IU/day) is achieved, but should never be reached by increments more than 0.1 or 0.2 mg/day each month.

D. Recommended duration of treatment

The duration of therapy is decided by the consulting specialist in accordance with the current model of best practice. A continuous evaluation of the results of treatment on appropriate serum levels (see below) and clinical benefits must be undertaken.

4. Other non-prohibited alternative treatments?

No alternative for growth hormone substitution in proven cases.

5. Consequences to health if treatment is withheld.

Debatable if only a partial deficiency exists.

6. Treatment monitoring

The best biochemical marker of GH action is serum IGF-1. Values should imperatively be kept in the age-related normal range, in order to avoid any over replacement.

7. TUE validity and recommended review process

Three years as a maximum, with continuous evaluation of results of treatment on serum levels and clinical benefits. Based on the results of monitoring a review should be achieved annually.

8. Any appropriate cautionary matters

Given the potential for the inappropriate use of GH, this is a controversial area that demands strict adherence to diagnostic criteria confirmed by an endocrinologist.
The personal administration of GH is not recommended but in many circumstances is the only practical option. In such cases it is recommended that a log book of administration be maintained by the patient and that this may be subject to review at any time.
Quantities of GH delivered to the patient must be strictly controlled and limited by prescription.

9. References

1. The Merck Manual, sec 2, Ch. 6, sec 19 Ch 269 Endocrine and metabolic disorders.

2. Journal of Clinical Endocrinology and Metabolism Vol.83, No 2, *Consensus Guidelines for the Diagnosis and treatment of Adults with GH Deficiency.*

3. American Association of Clinical Endocrinologists. *Medical Guidelines for clinical practice for growth hormone use in adults and children.* 2003 update.

1. Medical Condition

GROWTH HORMONE DEFICIENCY (CHILDHOOD AND ADOLESCENT)

2. Diagnosis

A. Medical history

The history of GHD in childhood is clearly linked to short stature and a failure to meet accepted growth milestones. These features are most frequently identified by concerned parents who may initially consult their family physician. Clinical practice suggests that such parental concerns are enhanced when the child is engaged in sport and peer comparisons are frequently made.

B. Diagnostic criteria

The diagnosis of GHD in childhood requires a comprehensive clinical assessment combined with biochemical tests of the GH-IGF axis and radiological evaluation.

1. **To authorize GHD investigation in children** of **short stature** one of the following criteria should be present:
   - severe short stature, defined as a height more than 3 SD below the mean.
   - height more than 1.5 SD below the mid parental height
   - height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a decrease in height SD of more than 0.5 over 1 year
   - (other minor criteria as mentioned in the 2000 Consensus paper)

2. In a child with a history and clinical suggestions of GHD, testing for IGF-1/IGFBP-3 levels and GH provocation tests are required. In suspected isolated GH deficiency, two GH provocation tests are required. If there is defined central nervous system pathology, irradiation, MPHD, or a genetic defect, one GH test is sufficient.

3. The evaluation of spontaneous GH secretion over 12 or 24 hours can be applied in accordance with a standardized protocol when GH and IGF-1 data are in conflict (normal GH and low IGF1).It is not necessary when IGF1 is normal and GH low.

4. However there are some patients who have IGF-1/ IGFBP-3 levels below the normal range on repeated tests but GH responses in provocation tests above the cut-off level. These children have an abnormality of the GH axis and could be considered for GH treatment, despite not being classically GH deficient. In this case the response to GH treatment must be carefully reviewed by a specialist in pediatric endocrinology.

- C. Relevant medical information

- Biological markers other than the GH-IGF axis (bone density, body composition, and bone markers) are presently not considered specific enough to diagnose GHD.

- Bone age estimated from an X ray of the left wrist and hand should be undertaken as part of the routine evaluation in children. It should be read by an experienced person.

- An MRI (or CT scan) of the brain with particular attention to the hypothalamic-pituitary region may be carried out in any child diagnosed as having GHD.

- To report assay data, a clear statement of methodology is required. An assay that measures 22-kDa hGH, using monoclonal antibodies, is recommended.

- For GH provocation tests a limited number of provocative agents should be used in a well standardized protocol (arginine, clonidine, glucagons, insulin and L-Dopa, Betablockers, coupled tests) and monitored carefully by an experienced team. As an indication in a child with clinical criteria of GHD, a peak GH concentration **below 10 microg/L** is traditionally used to support the diagnosis. The criteria values should be based on the updated consensus guidelines for the diagnosis of GHD in a child (see references at the end of the document).

3. Medical best practice treatment

A. Name of prohibited substance

Recombinant hGH

B. Route

Subcutaneous injection

C. Frequency

The current dosage of GH is in the range of 25-50 mcg/kg per day with six subcutaneous injections in a week or sometimes daily.

D. Recommended duration of treatment

The treatment should be discontinued on the recommendation of the relevant specialist in charge of the case.

4. Other non-prohibited alternative treatments?

No other treatment

5. Consequences to health if treatment is withheld

Significant growth-related consequences.

6. Treatment monitoring

A routine follow up should be performed by a pediatric endocrinologist in partnership with the pediatrician or family physician on a 3-6 monthly basis. The single most important parameter in the monitoring is the growth response with height measurement and height velocity (expressed in SD for comparison). For safety and assurance of compliance, monitoring of serum IGF-1 and IGFBP-3 is useful. Values should imperatively be kept in the age-related normal range, in order to avoid any over replacement (with evaluation of bone age).

7. TUE validity and recommended review process

One year for the first approval combined with continuous clinical and biochemical monitoring of results. After one year an approval for 3 years is acceptable if recommended by specialists in charge of the patient. In this case a simplified review of the file will be required annually.

8. Any appropriate cautionary matters

Provided all the criteria for the diagnosis of GHD in childhood have been met and standards of treatment monitoring are in place there are no other significant cautionary matters. The primary objective of therapy with recombinant hGH is the normalization of growth during childhood in order to reach a normal adult height.

9. References

1. The Merck Manual, sec 2, Ch. 6, sec 19 Ch 269 Endocrine and metabolic disorders

2. Journal of Clinical Endocrinology and Metabolism Vol. 85, No 11, *Consensus Guidelines for the diagnosis and Treatment of GH Deficiency in Childhood and Adolescence*

3. American Association of Clinical Endocrinologists. *Medical Guidelines for clinical practice for growth hormone use in adults and children.* 2003 update.

1. Medical Condition

MALE HYPOGONADISM

2. Diagnosis

A. Medical history

The etiology of hypogonadism must be clearly identified:

- **Primary hypogonadism** (e.g. Klinefelter syndrome, bilateral anorchia, cryptorchidism, Leydig cell aplasia, male Turner syndrome, Noonan's syndrome, congenital adrenal hyperplasia)

- **Or secondary hypogonadism** (e.g. panhypopituitarism, idiopathic hypogonadotropic hypogonadism, Kallmann's syndrome, constitutional delay of puberty, LH deficiency, Prader Willi syndrome)

B. Diagnostic criteria

- Clinical history with **biological assays** of testosterone, LH and FSH, confirming the diagnosis must be presented. The obtained values must be interpreted by an endocrinologist or specialist in internal medicine.

- Appropriate **stimulation of the gonadal axis** by hCG and results should be provided.

C. Relevant medical information

In cases of traumatic hypogonadism (bilateral anorchia) surgical evidence or imaging should be provided when possible.

3. Medical best practice treatment

A. Name of prohibited substance

Enanthate testosterone or cypionate testosterone

B. Route

1. Testosterone will be preferably administered by regular intramuscular injection. The treatment must be recorded by a health professional and kept available for control at any time. The use of transdermal testosterone skin patches could be an alternative to consider based on specialist advice. For medical reasons (hepatocellular risks) oral androgens should not be used.

2. The administration of testosterone will be conducted **by IM injection every two to four weeks** to replace endogenous secretion.

C. Frequency

1. The dosage must be decided by at least one endocrinologist or internal medicine experienced physician and confirmed by appropriated serum measures in relation to injection times. The age-related normal range for testosterone serum levels must always be respected. Permanent high levels (levels should normalise in the two days following injection) and over replacement should never been accepted.
2. The reference dosage is from 50 to 250 mg cypionate testosterone by IM every two weeks or enanthate testosterone every three to four weeks to replace endogenous secretion.

D. Recommended duration of treatment

The treatment may be for life but an annual review including evidence of well-controlled therapy must be provided.

4. Other non-prohibited alternative treatments?

If the diagnosis is confirmed there is no non-prohibited alternative treatment.

5. Consequences to health if treatment is withheld

Serious impairment.
- Under developed genitals (if before puberty)
- Muscle weakness
- Serious osteoporosis
- Diminished libido
- Erectile dysfunction /impotence
- Male infertility
- Depression

6. Treatment monitoring

Frequent and unannounced serum testosterone measures should be imposed and related to the injection period or patch application.

7. TUE validity and recommended review process

The duration of approval will be limited in all cases to 3 years at a maximum. In all cases an annual review process with a control of well adapted dose should occur each year. Another independent specialist may be consulted as necessary.

8. Any appropriate cautionary matters

- Oral androgens should not be used for medical reasons.
- In the particular case of a young athlete with delayed puberty the opinions of a pediatrician and an endocrinologist must confirm the diagnosis and a need for testosterone supplementation. This should be accompanied by the report of a relevant clinical examination. The approval must always be for a period of no more than one year.
- Given the potential controversy associated with the approval of a TUE for testosterone the opinion of an independent expert is strongly recommended.

9 References

1. The Merck Manual, sec 19, Ch. 269, Endocrine and metabolic disorders

2. The American Association of Clinical Endocrinologists "2002 update guidelines for evaluation and treatment of hypogonadism in adult male patients"

3. Rhoden El, Morgentaler A. Risks of testosterone replacement therapy and recommendations for monitoring. *New Eng J Med* 2004; 350:482-92

4. Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in male. *Horm Res.* 1995; 43:25-28

1. Medical Condition

MUSCULOSKELETAL CONDITIONS

Introduction

Common health problems related to the musculoskeletal system include acute and overuse injuries. There are essentially two classes of prohibited substances frequently linked to the management of these conditions. They are the narcotics (S7) and the glucocorticosteroids (S9) both prohibited only in-competition, making their use in other circumstances quite permissible provided the route of administration and duration of activity are recognised and fully understood, for example the parenteral, slow released forms of corticosteroids.

With respect to narcotic analgesics, there would seem to be few, if any circumstances in competitive sport where their use is indicated.

2. Diagnosis

- A. Medical history

Obviously, a clear medical history is a mandatory requirement.

- B. Diagnostic criteria

The main diagnostic criterion for musculoskeletal conditions is the clinical examination by an experienced sports physician. From case to case, imaging procedure (X-rays, Sonography, CT-Scan or MRI) or other appropriate special investigations can be useful.

- C. Relevant medical information

The request should always include evidence that permitted therapeutic alternatives have been tried.

3. Medical best practice treatment

- A. Name of prohibited substance

Corticosteroids or narcotics (see preliminary remarks).

Concerning corticosteroids, they are all prohibited when administered by oral, rectal, intravenous or intramuscular routes. If used systemically, a standard TUE is required. Topical preparations to treat dermatological, auricular, nasal, buccal and ophthalmologic diseases do not require authorisation. Intraarticular, periarticular and less frequently intrathecal corticosteroid use requires an abbreviated TUE.

- B. Route

Oral, intramuscular, intravenous, topical, intrathecal, spinal.

- C. Frequency

Dependent on the diagnosis.

- D. Recommended duration of treatment

Also dependent on the diagnosis, but ideally as short as possible

4. Other non-prohibited alternative treatments?

Non-Steroidal Anti-inflammatory Drugs;
Muscle relaxants;
Minor permitted analgesics;
Physiotherapy modalities;
Ice, compression, elevation and rest;
Alternative Training methods.

5. Consequences to health if treatment is withheld

In most cases, the consequences are minor however persisting pain that affects daily activities or disturbs sleep, may be considered as a significant clinical indication for more aggressive intervention.

6. Treatment monitoring

Generally not regarded as a priority but with respect for the potentially addictive qualities for the prolonged use of narcotic analgesics.

7. TUE validity and recommended review process

Extremely dependent on diagnosis, but mostly short, and measured in days or weeks.

8. Any appropriate cautionary matters

The use of oral corticosteroids to treat chronic inflammatory conditions of the musculoskeletal system (e.g. rheumatologic arthralgias or chronic degenerative spinal diseases) is not normally compatible with high level sport participation. Any application for such a treatment will obviously require thorough documentation and clear evidence that permitted therapeutic alternatives have been ineffective.

1. Medical Condition

NARCOLEPSY – CATAPLEXY

Introduction

The most common cause of excessive daytime somnolence is sleep respiratory disturbance, best treated with nasal continuous positive airway pressure ventilation. However, in younger, non-snoring, non obese subjects, narcolepsy is not an uncommon disease (prevalence ca. 0.03-0.06%) which may warrant treatment by modafinil.

Its clinical picture is well delineated, with two major symptoms (irresistible sleepiness and cataplexy), and two minor symptoms (sleep paralysis and hypnagogic/hypnopompic hallucinations). Diagnostic criteria are outlined in the following section and require input from a physician experienced in sleep medicine, often this may be a neurologist or a psychiatrist.

2. Diagnosis

- A. Medical history

A familial history of narcolepsy is only found in a small subset of patients (5-10%). A documented history suggestive of excessive daytime somnolence deserves investigation.

- B. Diagnostic criteria

Adapted from the ASDA criteria (American Academy of Sleep Medicine)

1. Complaint of excessive daytime sleepiness occurring daily for at least 3 months; typically, patients sleep for a short time and feel refreshed afterwards.
2. Definite history of cataplexy, i.e. sudden loss of muscle tone triggered by strong emotions (fear, surprise, or, most reliably, positive items, such as joking or laughing); this is transient (less than 2 minutes, usually much briefer); symptoms may involve the entire body, or only the knees, neck, or face.

3. Normal neurological and psychiatric examination. Negative drug screen. Brain imaging is not mandatory.
4. Exclusion of respiratory or other causes of sleep disturbance by night time polysomnography in an accredited Sleep-Wake Disorders Center.
5. Demonstration of at least 2 sleep onsets in REM (SOREMs) during a Multiple Sleep Latency Test (MSLT), with a mean sleep latency of less than 8 minutes (typically less than 5 minutes) for the 5 sessions of the test.
6. HLA genotyping is almost constantly DQB1*0602 across all ethnic groups in sporadic cases. Its absence strongly argues against the diagnosis, unless cataplexy is ascertained, and SOREMs are repeatedly demonstrated. Conversely, DQB1*0602 presence in itself is clearly insufficient.
7. Hypocretin-1 level in CSF should be obtained in dubious cases (disputable cataplexy, unclear MSLT results). Levels below 110 pg/ml, or a third of reference value, confirm the hypocretinergic alteration, pathognomonic of the disease.

Clinical variant: Narcolepsy without cataplexy
This diagnosis, in the context of a TUE application, may only be accepted with the greatest caution, if the following items are present:

1. Excessive daytime sleepiness with refreshing naps, and no clear cataplexy (which may however appear several years after the onset of sleepiness).
2. Absence of respiratory disturbance on night time polysomnography; in the case of repeated awakenings, upper airway resistance syndrome (i.e. multiple respiratory events related arousals) must be ruled out through esophageal pressure monitoring, and periodic limb movements through tibialis anterior EMG recording.
3. Demonstration of at least 2 SOREMs during the MSLT, with a mean sleep latency of less than 8 minutes. The preceding night time sleep duration should be more than 6 hours, in order to rule out “sleep rebound.” Recent use of antidepressants should be eliminated by drug screening, since there may be a rebound of REM-sleep in the days following cessation of these compounds.
4. CSF hypocretin-1 measurement is advisable: it is normal in 90% of cases, but if the level is significantly low, the diagnosis will be firmly established.

Note: HLA genotyping has only limited value in narcolepsy without cataplexy, the DQB1*0602 association being much lower than in full-blown narcolepsy.

- C. Relevant medical information

None

3. Medical best practice treatment

- A. Name of prohibited substances

Modafinil (Provigil®, Modiodal®)

- B. Route

Oral

- C. Frequency

The mean dosage is 300 mg in one or two doses (morning & noon; not later than 4 pm to avoid sleep onset insomnia, the half-life being 10-12 hours).

- D. Recommended duration of treatment

Indefinite but an annual review by a sleep specialist is considered to be the accepted practice to regulate medication and observe clinical progress.

4. Other non-prohibited alternative treatments

Scheduled or *ad libitum* naps
Caffeine
SSRI, SNRI or tricyclic antidepressants in small dosages are often necessary for controlling cataplexy.

5. Consequences to health if treatment is withheld

Impairment of daytime functioning through sleepiness could be minor or significant, depending on the professional or leisure activity.

6. Treatment monitoring

Although there is no commonly available drug monitoring, its implementation is feasible in selected laboratories. It may be used to verify compliance with the recommended dosage.

7. TUE validity and recommended review process

Patients must always be referred to a sleep specialist on a yearly basis, in order to monitor the clinical efficacy of the therapeutic regime. A new TUE request must be submitted.

If the response to modafinil is not satisfactory, methylphenidate (or dexamphetamine) is usually tried. In such case, a new TUE application must be initiated. If the above medications are not successful, sodium oxybate (gammahydroxybutyrate) at bedtime is another alternative. These compounds are obviously not compatible with competitive sport.
Treatment with stimulants may be tapered or stopped after retirement from sport, or where a vocational change demands less vigilance.

8. Any appropriate cautionary matters

Treatment is only symptomatic and is not mandatory every day, many patients preferring to take it only on working days, or before a given task (e.g. long trip). In the particular case of a TUE, one should question the absolute necessity of alleviating sleepiness, which may vary according to the type of sport activity.

9. References

1. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed.: Diagnostic and coding manual. Westchester, Illinois: American academy of Sleep Medicine, 2005).

1. Medical Condition

RENAL TRANSPLANTATION (SECONDARY TO END-STAGE RENAL DISEASE)

2. Diagnosis

A. Medical history

The aetiology of the end-stage renal disease necessitating transplantation must be well-documented with confirmation by the attending surgeon and renal physician. Although uncommon in elite athletes recent cases of renal transplantation in high-profiled athletes have been reported.

B. Diagnostic criteria

- The diagnosis of end-stage renal disease must be accompanied by an appropriate history of documented decline in renal function confirmed by a renal physician.

- A report from the treating surgeon including surgical procedures must also be provided.

C. Relevant medical information

It is necessary to provide the history of declining renal function and associated evidence that the criteria for renal transplantation have been met. This may be provided by the family physician with appropriate specialist endorsement.

3. Medical best practice treatment

A. Name of prohibited substances

- In the management of post-transplant patients it is possible that combination therapy may be required including the use of:

1. Glucocorticoids
2. Beta-Blockers
3. Diuretics
4. Erythropoietin (EPO)

B. Route

All agents should be administered orally with the exception of erythropoietin which is by either intravenous or subcutaneous injection.

C. Frequency

Daily doses of glucocorticoids (5-10mg daily for maintenance), beta-blockers, diuretics and EPO in accordance with current guidelines (see references). For EPO the current guidelines recommend a haemoglobin of 120g/L.

D. Recommended duration of treatment

The treatment is life-long with recommended annual review by a renal physician.

4. Other non-prohibited alternative treatments?

Following renal transplantation there is no other appropriate, non-prohibited treatment available.

5. Consequences to health if treatment is withheld

Most renal transplant recipients will present a history of hypertension secondary to chronic renal disease. Untreated, hypertension appears to be linked to reduced long-term graft survival. In cases where moderate graft impairment is confirmed, patients may require EPO supplementation. Given that the criteria for renal transplantation have been met the consequences of withholding treatment from these individuals will impact significantly upon the function of the transplanted kidney and ultimately have fatal consequences.

6. Treatment monitoring

Routine assessment of renal function including monitoring of blood pressure will be at the discretion of the renal physician.

7. TUE validity and recommended review process

Lifetime therapy in accordance with clinical status and an annual review is acceptable. Any changes to the therapeutic regime involving prohibited agents should be well documented endorsed by a renal physician and form the basis of a revised TUE.

At annual review, athletes on EPO should have blood tests including Hb, Hematocrit, RBC count, Reticulocyte count.

A further TUE may be issued annually after review of the appropriate parameters.

8. Any appropriate cautionary matters

Renal transplantation in elite athletes is not a common occurrence. However there are documented contemporary cases and the consistent application of best practice guidelines is essential.

9. References

1. 2003 European Society of Hypertension- European Society of CardiologyNew Guidelines for treatment of Hypertension J Hypertens. 2003 Jun; 21(6):1011-53

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3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 289:2560-2572, 2003