



ASTHMA

I. Medical Condition

Introduction

Asthma is a syndrome of the respiratory airways typified by recurrent episodic symptoms associated with variable airway obstruction that is reversible either spontaneously or with treatment, the presence of airway hyperresponsiveness and chronic airway inflammation. There is a high prevalence of these features in active competitive athletes, often in the form of exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB). Exercise induced asthma (EIA) may be defined as a transient airway narrowing induced by exercise in an individual with asthma while exercise induced bronchoconstriction (EIB) represents reduction in lung function only after exercise, even in the absence of a previous asthma diagnosis (reference 5).

As of January 01, 2010, salbutamol and salmeterol, when taken by inhalation and in therapeutic doses, were removed from the Prohibited List. Hence, a TUE is not required. As of January 01, 2012, inhaled formoterol up to a maximum dose of 36 micrograms over 24 hours is no longer prohibited. If a delivered dosage in excess of 36 mcg/day is legitimately required by the athlete, then a TUE must be requested (see Annex 1 for more information on formoterol).

Much of the following information and testing requirements only pertain now to alternate beta-2 agonists, e.g. terbutaline, procaterol and for inhaled dosages of formoterol in excess of 36 micrograms. Despite the fact that some beta-2 agonists have been removed from the Prohibited List, it is recognized that asthma is not always well diagnosed or treated and therefore it is recommended that all athletes who are considering taking any asthma medications seek a clear diagnosis from a respiratory specialist and undergo the appropriate tests.

The requirement for a Declaration of Use was removed on January 01, 2011 and therefore it is not required to send in a Declaration of Use to any Anti-Doping Organization. However, the athlete should still write all the medications and substances taken in the last seven days on the Doping Control Form, at the time of testing.

II. Diagnosis

Diagnostic criteria

- The diagnosis of asthma demands the synthesis of medical history with respiratory symptoms, physical examination and appropriate laboratory or field tests.
- Airway hyper-responsiveness is a continuum and the minimum criteria for the diagnosis of asthma are not known. However, recurrent symptoms of

bronchial obstruction such as chest tightness, wheeze and cough provoked by hyperventilation, exercise or other stimuli, are a diagnostic prerequisite for asthma or EIA in athletes. Laboratory tests alone are not sufficient for the diagnosis.

- The symptoms of asthma should be verified by the evidence of the reversibility of airflow obstruction and interpretation of the test results by a respiratory physician may be required in difficult cases.

Medical history

- A history of asthma may include a family history of allergies, hay fever or eczema. Individuals may also describe a personal history of childhood respiratory problems, rhinitis, allergic conjunctivitis or dermatitis. In these cases, the development of asthma may be part of an atopic predisposition. However asthma might also develop in otherwise healthy individuals at any age.
- There may also be a history of persistent cough following a respiratory tract infection, frequent "colds" without fever, or specific seasonal influences and intermittent nocturnal symptoms. Alternatively, symptoms may be entirely activity-induced.
- In sport, examples of potential provocation include variations in ambient temperature, endurance training and exposure to pollution such as from combustion engines or swimming pool chemicals.
- Other factors important to the history are the age of onset of asthma, the past history of prescribed medication including detailed use of beta-2 agonists and inhaled corticosteroids, a history of acute asthma exacerbations including hospital admissions or emergency department attendance and previous treatment with oral corticosteroids.
- If a diary of symptoms and peak flow recordings has been kept, this would provide additional helpful information. Previous investigations should also be recorded including relevant skin tests (RAST), IgE, total eosinophil count in peripheral blood and sputum eosinophils, spirometry reports and any previous bronchial provocation tests at any age.
- Consider co-morbidities or conditions that mimic asthma such as hyperventilation syndrome, vocal cord dysfunction, exercise induced laryngomalacia, non-reversible airflow obstruction disease, heart failure or psychological problems.

Physical examination

Although the physical examination in EIA may be normal in the office it should be performed in order to:

- Verify present or recent upper or lower respiratory tract infections;
- Assess the severity of airflow obstruction at rest, if present;

- Identify co-morbidities that may complicate management, (e.g. rhinosinusitis, gastroesophageal reflux, heart failure).

Laboratory Testing

Spirometry

The most objective indicator of asthma severity is the measurement of airflow obstruction by spirometry. Spirometry is a more sensitive measure of airflow than peak flow meters (PEF) and consequently is the best reference method. PEF measures are nevertheless useful, particularly for the patient, in order to follow treatment responses.

Specific cut-off points for spirometry are recommended in the accompanying references. Many elite athletes have levels of lung function above normal predicted values and therefore normal lung function may still represent a sign of airway obstruction. A carefully kept peak flow diary should be established to allow the clinician to chart a patient over time.

Spirometry in an asthmatic patient will demonstrate a typical pattern of obstructive airway disease (reduced FEV₁/FVC ratio) with a diminished expiratory flow that improves with bronchodilator therapy. However, the absence of a bronchodilator response does not exclude a diagnosis of asthma. A 12% or higher increase in FEV₁ following the use of an inhaled beta-2 agonist is considered to be the standard diagnostic test for the reversibility of bronchospasm.

Bronchial Provocation Tests

A number of bronchial provocation tests are currently available to evaluate airway responsiveness in patients with asthma or atypical chest symptoms of indeterminate etiology.

Bronchial provocation may be performed by the use of physiological (exercise or eucapnic voluntary hyperventilation tests) or pharmacological (metacholine, mannitol, hypertonic saline, histamine) challenge tests or hyperventilation. A test-specific decrease in FEV₁ following the administration of a provocative agent is considered to be diagnostic and comparable to the stimulus of exercise.

These tests may provoke significant respiratory symptoms and should only take place in a supervised setting with appropriate medical support. To accurately evaluate these tests, patients should stop all bronchodilator or anti-inflammatory therapy prior to the provocation test. For short acting beta-2 agonists this will be for 8 hours and for long acting beta-2 agonists and inhaled glucocorticosteroids (GCS) for 24-48 hours prior to testing. Further reference should be made to the European Respiratory Society (ERS) and American Thoracic Society (ATS) standards.

It is not within the scope of this document to provide the full details of each bronchial provocation test. These should be undertaken in collaboration with a respiratory physician in an established respiratory laboratory. You may also refer to the IOC Asthma Consensus Document. Provocation may be by inhalation of cold, dry air, inhalation of aerosols or exercise. Common provocation tests, in no specific order, include the following:

- The Eucapnic Voluntary Hyperpnea (EVH) test ($\geq 10\%$ fall of FEV_1)
- Methacholine Aerosol Challenge ($\geq 20\%$ fall of FEV_1 - $PC20 < 4\text{mg/mL}$, [steroid naïve]) or if taking inhaled GCS > 1 month, then $PD20$ should be less or equal to 1600 mcg or $PC20$ less or equal to 16.0 mg/mL
- Mannitol Inhalation $\geq 15\%$ fall in FEV_1 after challenge
- Hypertonic Saline Aerosol challenge (15% fall of FEV_1)
- Exercise Challenge Tests (field or laboratory) ($\geq 10\%$ fall of FEV_1)
- Histamine Challenge ($\geq 20\%$ fall of FEV_1 at a histamine concentration of 8mg/mL or less during a graded test of 2 minutes)

A positive response to any one of the above provocation tests is required to confirm airway hyperresponsiveness. If not, a review of the medical file will be required. The medical file should be updated and relevant test results should not be older than four years at the time of application.

III. Relevant medical information

In accordance with the International TUE Standard and consistent with current best medical practice, the medical file required to support an application for a TUE in the case of an athlete with asthma or any of its clinical variants must include the following details:

- a) a complete medical history as described;
- b) a comprehensive report of the clinical examination with specific focus on the respiratory system;
- c) a spirometry report;
- d) if airway obstruction is present, the spirometry will be repeated after inhalation of a short acting beta-2 agonist to demonstrate the reversibility of bronchoconstriction;
- e) in the absence of reversible airway obstruction, a bronchial provocation test is required to establish the presence of airway hyperresponsiveness. Test results should not be older than four years at the time of application;
- f) exact name, speciality and contact details of examining physician.

Note that since there are now permitted substitutes salbutamol/salmeterol and formoterol, an explanation must be included as to why an alternate Beta-2 agonist is being prescribed. The intent is not to deny the use of these alternate

beta-2 agonists particularly where a treatment regimen has already been established.

IV. Medical best practice treatment

The mainstay of treatment for asthma is inhaled glucocorticosteroids with the use of beta-2 agonists for emergency or breakthrough symptoms.

It should be emphasized that the overuse of short and long acting bronchodilators (beta-2 agonists) lead to tolerance and may have significant detrimental effects to health.

1. Name of prohibited substances

a) Beta-2 agonists

i) All beta-2 agonists (e.g. terbutaline, procaterol) not mentioned as exceptions below are prohibited and require a TUE.

ii) Salbutamol

Inhaled salbutamol is no longer prohibited. However, the presence of salbutamol in the urine in excess of 1000 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an adverse analytical finding. The athlete would then need to document the details of his/her, medical condition and medication use. The athlete may then be required to prove, by a controlled pharmacokinetic study (see annex 2) that the abnormal test result was the consequence of the use of a therapeutic dose (maximum 1600 micrograms over 24 hours) of inhaled salbutamol.

iii) Salmeterol

Inhaled salmeterol is no longer prohibited.

iv) Formoterol

Inhaled formoterol to a maximum dose of 36 micrograms over 24 hours is no longer prohibited. (This is the equivalent of a 48 mcg/24 hours of a metered dose – see annex 1). The presence in urine of formoterol in excess of 30 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of the no greater than 36 micrograms over 24 hours. If a dosage in excess of 36 mcg/day is legitimately required by the athlete, then a TUE must be requested.

b) Glucocorticosteroids

The systemic use (e.g. oral or intravenous administration) of GCS is prohibited and requires a TUE. When systemic GCS are used for the treatment of an exacerbation of asthma, a retroactive/emergency TUE should be submitted as soon as possible to the appropriate anti-doping organization.

V. Route

- a) Only certain inhaled beta-2 agonists are permitted and only when used **by inhalation** at therapeutic dosages.
- b) The systemic use (oral, intravenous or rectal) of GCS are prohibited and requires a TUE.

VI. Frequency

- a) The athlete should always be treated at the lowest medication level necessary to control symptoms. Tolerance may develop for beta-2 agonists. A prescription for a beta-2 agonist that simply states "as needed" is rarely appropriate and should be clarified by the prescribing physician with dosage and frequency described. Nevertheless, the athlete's health should never be jeopardized by restricting medication when necessary (see point # 9 Special Circumstances).
- b) Inhaled GCS should be considered as a mainstay of treatment and used on a regular and ongoing basis rather than in response to immediate symptoms.

VII. Recommended duration of treatment

Asthma may be a life-long condition. In the case of EIB, the duration will be symptom dependent.

VIII. Other non-prohibited alternative treatments

- Leukotriene receptor antagonists
- Anticholinergics
- Cromones
- Theophyllines (Xanthines)
- Anti-IgE agents

IX. Consequences to health if treatment is withheld

- Chronic ill health
- Acute exacerbations of asthma
- Sudden death from "status asthmaticus"
- Inability to participate fully in physical activity and competitive sport

X. Treatment monitoring

Due to the nature of “variable airways obstruction”, ongoing monitoring should involve a diary with daily symptoms and a peak flow chart to assess the effect of treatment and the influence of exercise. In the same way, the correct inhaler technique should be learned and monitored.

The treatment should be modified or stopped if the diagnosis is revisited. Monitoring the use of acute emergency services and the need for courses of systemic corticosteroid therapy would also be helpful indicators of therapeutic control.

XI. TUE validity and recommended review process

The recommended validity of a TUE for an asthmatic athlete is 4 years with an annual review by a physician experienced in treating athletes. In some cases, an ADO may impose conditions such as a review by a specialist within a certain time frame.

XII. Any appropriate cautionary matters

Remember that all beta-2 agonists and glucocorticosteroids by systemic routes are prohibited.

The athlete should not be exposed to any tests of bronchial provocation at the time of, or immediately prior to, a major sporting event, when their health may be significantly affected. The athlete should plan accordingly. The necessity for tests and options available would have to be evaluated on a case by case basis.

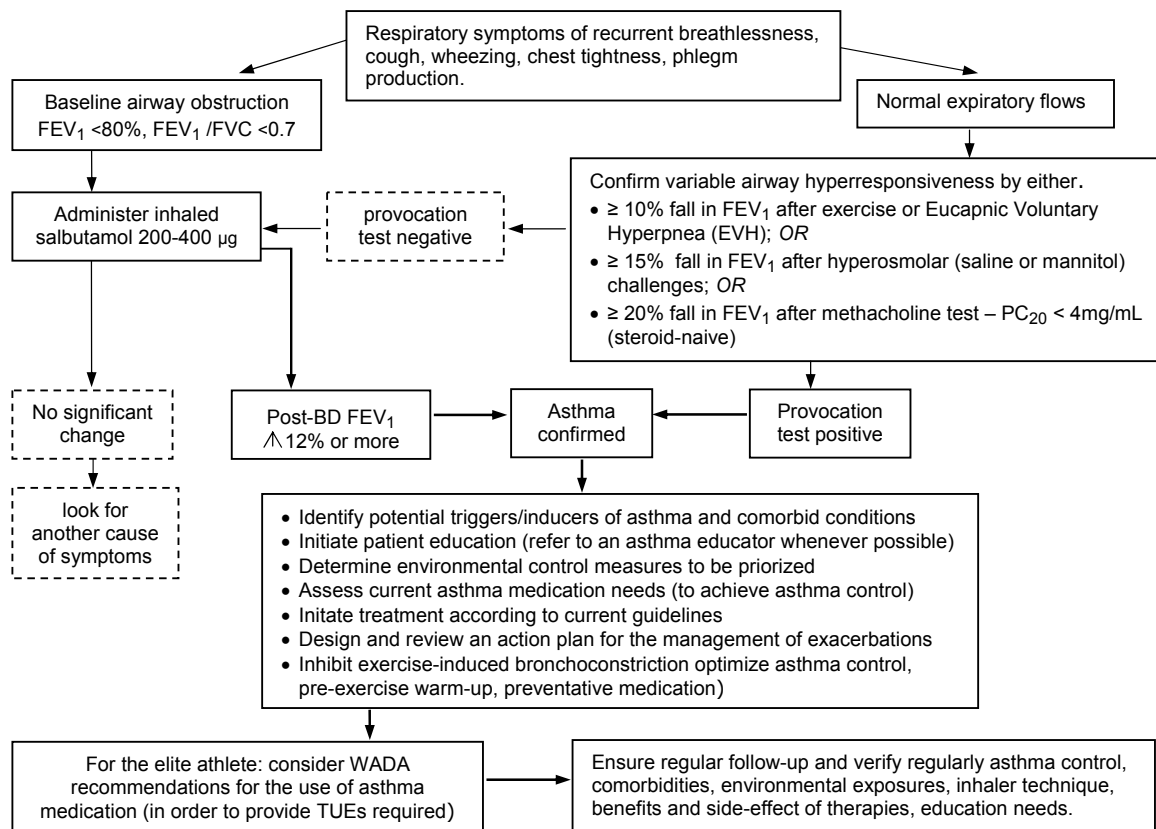
XIII. Special circumstances

Where circumstances are deemed to be exceptional and treatment must be initiated before a TUE could be approved, reference should be made to WADA ISTUE article 4.3 concerning retroactive/emergency TUEs. Full and clear documentation of the medical incident is required and the TUE application process must be initiated at the first opportunity.

An athlete’s health should never be jeopardized by withholding medication in an emergency.

Asthma management for the athlete

BD: Bronchodilator; FVC: forced vital capacity.



Source: Fitch K et al. "Asthma and the elite athlete: Summary of the IOC Consensus Conference, Lausanne Switzerland, January 22-24, 2008, Journal Allergy & Clinical Immunology Volume 122, Number 2, August 2008, p. 257.

XIV. References

1. Report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI): *Recognizing and diagnosing exercise related asthma, respiratory and allergic disorders in Sports. Diagnosis, treatment and the relationship to Doping*. Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, Del Giacco S, Delgado L, Drobnic F, Haahtela T, Larsson K, Palange P, Popov T, van Cauwenberge P.
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ANNEX 1

FORMOTEROL

From 2012, inhaled formoterol to a maximum delivered dose of 36 micrograms (mcg) in 24 hours is permitted in sport. When inhaled formoterol as the fumarate salt, either singly or in combination with budesonide (commonly marketed worldwide as Symbicort) is delivered as a powder by a turbuhaler, 75% of the administered dose is released and thus delivered. Hence, a preparation containing 12mcg of formoterol delivers to the patient ~9mcg per inhalation. If two inhalations twice a day (i.e. 48mcg) are administered, the delivered dose to the patient is 36mcg. If formoterol is delivered via an aerolizer, the amount inhaled is variable but even at 48 mcg/day in divided doses, this should not result in the athlete exceeding the urinary threshold of 30ng/mL.

The WADA Prohibited List refers to the inhaled (delivered) dose and not the dose released from the metered dose inhaler.

The standard dose of formoterol is 24 mcg/day with a maximum of 36 mcg/day. In some countries the maximum dosage may be 54 or even 72 mcg/day, however this is usually only for short term treatment of asthma during exacerbations. Whenever a dosage of greater than 36 micrograms (inhaled) over 24 hours is prescribed, the athlete will be required to apply for a Therapeutic Use Exemption with appropriate pulmonary function tests and respiratory specialist notes. If this is due to an asthma exacerbation, then an emergency/retroactive TUE should be submitted at the earliest convenience as per the International Standard on TUE.

Unless a TUE was granted, the presence in urine of formoterol in excess of 30 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of inhaled formoterol at no greater than 36 micrograms over 24 hours.



ANNEX 2

Key guiding principles for a controlled excretion study

Key guiding principles for a controlled pharmacokinetic study as referred to in the Prohibited List:

1. The study shall be conducted in a controlled setting allowing a strict and independent supervision of the drug administration (route, dose, frequency, etc) and sample collection (matrix, volume, frequency) protocol.
2. A wash-out period should be established in order to collect baseline urine or blood samples just prior to the administration of the drug, i.e. the athlete should not be taking the medication before the test. Necessity of the drug for health reasons as well as the known pharmacokinetics of the product will need to be taken into account, if necessary.
3. Collection of urine samples shall occur whenever that athlete wishes to deliver samples but no less than every two hours during the monitoring period. Sampling periods should be adjusted to the known pharmacokinetic of the product (e.g. every 30 min. or night collections might be considered, if justified).
4. The athlete shall take the drug in accordance with the treatment course (dose, frequency, route of administration) declared in the doping control form or, alternatively, following the therapeutic regime indicated on a granted TUE, if any. The administered dose shall never exceed the maximal dose/frequency recommended by the drug manufacturer or a safe level prescribed by the athlete's physician.
5. The samples shall be analyzed in a WADA accredited laboratory with the validated relevant anti-doping method. Correction for specific gravity shall be applied in accordance with the provisions of the ISL and related Technical Documents.
6. The WADA accredited laboratory will issue a comprehensive report indicating the results of the analyses and interpretation, if needed. If deemed necessary, review of the results by an independent expert can be sought by the Testing Authority.