



## I. Medical Condition

# ASTHMA

### Introduction

Asthma is a syndrome of the respiratory airways typified by recurrent episodic symptoms. These may include variable airflow obstruction that is reversible (either spontaneously or with treatment), the presence of airway hyper-reactivity and chronic airway inflammation. These features represent increasing problems for the active competitive athlete in whom exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB) may present. A broad comprehensive definition of these conditions is currently favored. Exercise induced asthma (EIA) infers symptoms provoked directly by exercise, whereas exercise induced bronchoconstriction (EIB) represents reduced lung function after provocation by an exercise test or occurring during self-induced exercise even in the absence of a previous asthma diagnosis (reference 5). It should also be noted that hyperventilation alone may induce bronchospasm.

Note that as of January 01, 2010, salbutamol and salmeterol, when taken by **inhalation** and in **therapeutic doses**, have been removed from the Prohibited List. Hence, a TUE is not required. The requirement for a Declaration of Use is removed as of January 01, 2011 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

Much of the following information and testing requirements only pertain now to the alternate Beta-2 agonists, (e.g. terbutaline, formoterol). Nevertheless, a clear diagnosis with appropriate tests are recommended for all athletes taking medications.

## II. Diagnosis

### 1. 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.

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- In sport, examples of potential provocation include variations in ambient temperature, endurance training and exposure to pollution including 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 crises 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.

### 2. 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.

**A physical examination** is important to:

- a. Confirm a diagnosis and exclude mimics such as hyperventilation syndrome, vocal cord adduction, exercise induced laryngomalacia, non-reversible airflow obstructive disease or heart failure;
- b. Assess the severity of airflow obstruction at rest;
- c. Identify factors that might place a patient at risk of poor outcome;
- d. Identify co-morbidities that may complicate management, (e.g. sinusitis, gastroesophageal reflux).

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### **Laboratory Testing**

The most objective indicator of asthma severity is the measurement of airflow obstruction by spirometry. The PEF and the FEV<sub>1</sub> yield comparable results although FEV<sub>1</sub> is clearly a more sensitive measure of airflow. Consequently, the latter is the best reference.

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 FEV<sub>1</sub>/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 FEV<sub>1</sub> following beta-2 agonist use is considered to be the standard diagnostic test for the reversibility of bronchospasm.

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 of hyperventilation. A test-specific decrease in FEV<sub>1</sub> 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 hours prior to testing. Further reference should be made to the European Respiratory Society (ERS) and American Thoracic Society (ATS) standards.

### **Bronchial Provocation Tests**

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 IOC Asthma Consensus Document.

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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<sub>1</sub>)
- Methacholine Aerosol Challenge  $\geq 20\%$  fall of FEV<sub>1</sub> - PC20 < 4mg/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 FEV1 after challenge
- Hypertonic Saline Aerosol challenge (15% fall of FEV<sub>1</sub>)
- Exercise Challenge Tests (field or laboratory) ( $\geq 10\%$  fall of FEV<sub>1</sub>)
- Histamine Challenge  $\geq 20\%$  fall of FEV<sub>1</sub> 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 bronchial 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.

### 3. Relevant medical information

Additional helpful information includes the response to alternative medical treatment.

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
- e) inhalation of a short acting Beta-2 agonist to demonstrate the reversibility of bronchoconstriction;
- f) in the absence of reversible airway obstruction, a bronchial provocation test is required to establish the presence of airway hyperresponsiveness;
- g) exact name, speciality and contact details of examining physician.

Note that since there is now a permitted substitute (salbutamol/salmeterol), 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. For

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athletes with newly diagnosed asthma, permitted Beta-2 agonists should be considered as the primary treatment unless otherwise justified.

### III. Medical best practice treatment

The mainstay of treatment for asthma is inhaled GCS 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

From 1 January 2010, all beta-2 agonists (including both optical isomers where relevant) are prohibited except **inhaled** salbutamol and **inhaled** salmeterol. 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.

##### b) Glucocorticosteroids

Inhaled glucocorticosteroids (GCS) are permitted. The systemic use of GCS is prohibited and requires a TUE.

#### 2. Route

- a) Only inhaled Beta-2 agonists are permitted. The use of salbutamol and salmeterol at therapeutic dosages by inhalation, does not need a TUE. Other inhaled Beta-2 agonists require a TUE.
- b) In severe cases, when oral or intravenous GCS are used, a TUE is required.

#### 3. 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 Beta-2 agonist "as needed" is rarely appropriate and should be clarified by the prescribing physician. Nevertheless, the athlete's health should never be jeopardized by restricting medication when necessary (see 9. Special Circumstances).

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- b) GCS should be considered as a mainstay of treatment and used on a regular and ongoing basis rather than in response to immediate symptoms.

### 4. Recommended duration of treatment

Lifetime, but with annual review by an appropriately qualified physician for asthma. In the case of EIB, the duration will be symptom dependent.

## IV. Other non-prohibited alternative treatments

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

## V. 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

## VI. 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.

## VII. TUE validity and recommended review process

The validity of a TUE for an asthmatic athlete is 4 years with at least annual confirmation of the treatment regime by a respiratory physician or a physician experienced in treating asthma in athletes. After 4 years, repeated pulmonary function tests must meet the agreed diagnostic criteria.

## VIII. Any appropriate cautionary matters

Remember that all Beta-2 agonists and Glucocorticosteroids by systemic routes require a TUE. 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.

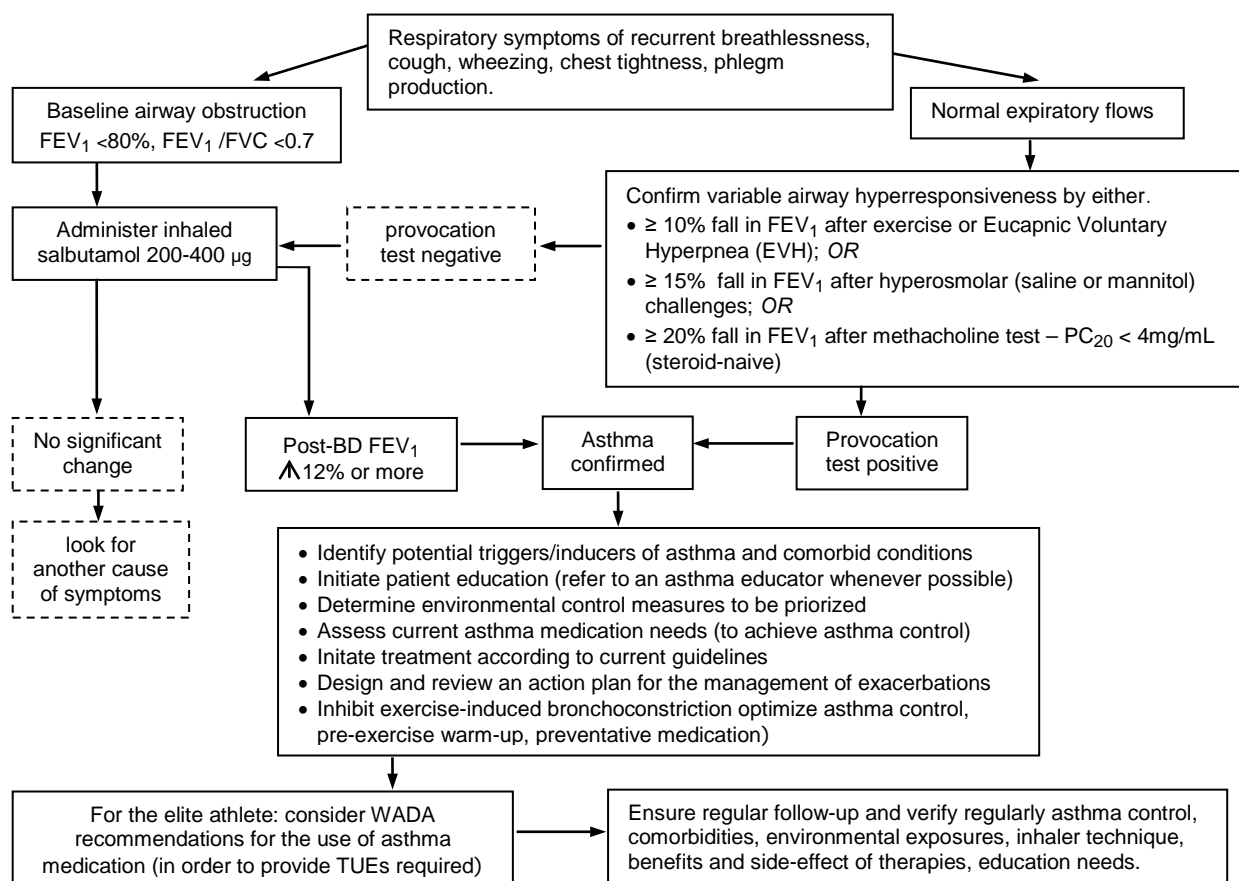
## IX. Special circumstances

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 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.

Figure: 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.

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### X. References

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## ANNEX 1: (previously part of ISTUE)

### **Summary of requirements for the medical file to be used for the TUE process in the case of asthma and its clinical variants**

The file must reflect current best medical practice to include:

1. A complete medical history
2. A comprehensive report of the clinical examination with specific focus on the respiratory system
3. A report of spirometry with the measure of the Forced Expiratory Volume in 1 second (FEV1)
4. If airway obstruction is present, the spirometry will be repeated after inhalation of a short acting Beta2 agonist to demonstrate the reversibility of bronchoconstriction
5. In the absence of reversible airway obstruction, a bronchial provocation test is required to establish the presence of airway hyper-responsiveness
6. Exact name, speciality, address (including telephone, e-mail, fax) of examining physician



## 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.