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

ATHLETES & PRESCRIBING PHYSICIANS PLEASE READ

For treatment in response to anaphylaxis and/or allergic reactions, **please consider your health first** – all the decisions about your medical care are between you and your physician. During a medical emergency, you are not required to notify USADA prior to receiving treatment.

PLEASE DO NOT WAIT FOR AN APPROVAL BEFORE RECEIVING TREATMENT IN AN EMERGENCY.

USADA will not approve TUEs for epinephrine or systemic glucocorticoids in advance of an allergic reaction/acute medical emergency. Due to the uncertainty of the need for these medications, USADA will consider TUE Applications for these medications during or after the occurrence of the acute medical emergency.

If you are prescribed a short course of systemic glucocorticoids to treat an allergic reaction or exacerbation (i.e. poison ivy), please begin and complete the course of medication prescribed by your physician. Waiting for an approval suggests the medical condition was not severe enough to warrant the requested treatment.

TUE APPLICATION CHECKLIST – ANAPHYLAXIS/ALLERGIC REACTION

- ☐ Complete and legible TUE Application form
- ☐ Copies of all relevant examinations and clinical notes from the acute medical emergency
- ☐ Copies of all laboratory results/reports related to the medical emergency
- ☐ A statement from the physician explaining why the Prohibited Substance is needed (specifically for systemic glucocorticoids)
    - o Please explain why permitted alternative treatments were not effective or not appropriate/indicated for treatment
- ☐ For short course systemic glucocorticoids, please specify when the medication was started and when it is intended to finish

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Anaphylaxis

Medical Condition

Anaphylaxis is a serious, life-threatening generalized, systemic hypersensitivity reaction that is rapid in onset. It commonly occurs in community settings and has a lifetime prevalence of 0.05-2%. The rate of occurrence is increasing (although there are geographic variations), especially in young people, as reflected in increasing emergency department visits, hospitalizations, and critical care unit admissions; however, the fatality rate in hospitalized patients is low.

Anaphylaxis usually involves an IgE-dependent mechanism. Common triggers include foods, (e.g. peanuts, tree nuts, shellfish), stinging insect venoms, natural rubber latex, radio-contrast media and drugs (e.g. beta-lactam antibiotics or non-steroidal anti-inflammatory medications). It can also be mediated through direct (non-immune) activation of mast cells through triggers such as exercise, cold, heat, sunlight/UV radiation, ethanol and some drugs (e.g. opioids). Idiopathic anaphylaxis is a diagnosis of exclusion that is made when no trigger can be identified.

2. Diagnosis

A. Medical History

The clinical diagnosis of anaphylaxis is based on a detailed history of the episode and on recognition of the sudden onset of characteristic symptoms and signs, usually within minutes but can be up to a few hours of exposure to the trigger. The progression of anaphylaxis symptoms and signs may be extremely rapid and death can occur within minutes of symptom onset.

B. Diagnostic Criteria

Anaphylaxis is highly likely when one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. hives, pruritus, flushing, swollen lips/tongue) and at least one of the following:

a. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia);
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (hypotonia, collapse, incontinence).

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2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to hours):

   a. Involvement of the skin-mucosal tissue
   b. Respiratory compromise
   c. Reduced blood pressure (BP)
   d. Gastrointestinal symptoms (crampy, abdominal pain, vomiting)

3. Reduced BP after exposure to a known allergen for that patient (minutes hours);inadults:systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

C. Differential Diagnoses

Can include: acute generalized hives, acute asthma, syncope (faint), panic attack or acute anxiety attack, aspiration of a foreign body, cardiovascular event, neurologic event, food poisoning, non-organic disease, e.g. vocal cord dysfunction.

D. Investigations

Laboratory tests to confirm the clinical diagnosis of anaphylaxis are not universally available, and are not available on an emergency basis as the assays take at least 3-4 hours to perform.

The most common test used worldwide is measurement of a serum tryptase level for which the blood sample is optimally obtained from 15 minutes to 3 hours after symptom onset. Although an elevated tryptase level can sometimes be used to confirm the clinical diagnosis of anaphylaxis, the test is not specific for anaphylaxis, as it is elevated in some patients with myocardial infarction. A tryptase level within normal limits cannot be used to rule out anaphylaxis. Tryptase levels are seldom elevated in anaphylaxis triggered by food; however, they are frequently elevated in anaphylaxis triggered by insect stings.

In summary, anaphylaxis is a clinical diagnosis not requiring laboratory diagnostic confirmation.

3. Prohibited treatments

A. Epinephrine (Adrenaline). (S6 Stimulant. Prohibited in–competition period only). Epinephrine is given during an acute anaphylactic attack as a first-line treatment.

Route: Intramuscular injection in the mid- lateral thigh.

Dose: i) Epinephrine auto-injector (0.3mg for adults i.e.>30kg or 0.15mg for 15-30kg child) or

ii) Adrenaline ampule 1:1000 (1mg/1ml) solution: 0.01mg/kg to maximum of 0.5 mg for adolescents >12years and adults).

Frequency: This injection may be repeated in 5-15 minutes, if needed.

Recommended duration: Most patients respond to 1-2 doses.

(*Note: in severe cases not responding to IM epinephrine, an IV adrenaline infusion may be required. 1ml of 1:1000 adrenaline in 1000ml normal saline. This should only be done by, or in liaison with, emergency/critical care specialists. IV boluses of adrenaline carry a risk of cardiac arrhythmia and should be used with extreme caution.)*

TUE requirements: For the first episode of anaphylaxis, a retroactive, emergency TUE for epinephrine (or adrenaline) is required, *if given during an in-competition period.* Athletes who need to carry an epinephrine (adrenaline) auto-injector with them at all times are advised to apply for a prospective (*in advance) TUE*, as the World Anti-Doping Code prohibits athletes from carrying a prohibited substance without a valid TUE.

B. Systemic Glucocorticoids (GC) (S9 Glucocorticoids, Prohibited in-competition period only) e.g. IV hydrocortisone or methylprednisolone/prednisone.

The benefit of glucocorticoids in anaphylaxis remains unproven and as such should only be used as a second line treatment. Onset of action takes several hours or more, therefore, GC are not generally recommended as an initial treatment or the only treatment but may be useful in the 5% of those with anaphylaxis who experience bi-phasic reactions or those with persistent wheeze. It is quite common practice to prescribe a 2-3 day course of oral GC to hopefully reduce the risk of symptom recurrence after a severe reaction. Dosing is extrapolated from their use in acute asthma.

In some cases a severe skin allergy/reaction, that is not responsive to topical glucocorticoids and oral antihistamines, may be treated appropriately with oral glucocorticoids. If this is required during or close to competition, a TUE request will need to be made. These skin allergies/reactions will usually have no systemic component and should not be confused with anaphylaxis.

Route:
Oral or intravenous routes are the recommended routes of administration depending on the clinical indications mentioned above.

Dose:
Oral prednisolone 1 mg/kg (usually up to a maximum of 50 mg) or intravenous hydrocortisone 5mg/kg (usually up to 200-250mg).

Frequency:
Usually only one dose during the initial period of stabilization is sufficient. A short course of an oral GC for a few days following a severe attack may be prescribed.

Recommended duration:
Short, finite period of time during period of emergency stabilization and in the days afterwards.

TUE requirements:
A retroactive TUE is required for the use of intravenous or oral GC during an in-competition period only.

C. Inhaled B2 agonists (S3 Beta-2 Agonists, Prohibited at all times) e.g. salbutamol.

A beta-2 adrenergic agonist, such as salbutamol, may be used if there is persistent wheeze despite the use of IM epinephrine.

Route: Inhaler (+/- spacer) or nebulizer.

Dose: Inhaler: starting dose of 2-4 inhalations, with additional doses as required.
Nebuliser: 2.5mg/3ml or 5mg/3ml via nebulizer and mask.

Duration: At the time of the acute event and in the subsequent 2-3 days.

TUE requirements: Although salbutamol is not prohibited by inhalation at ordinary therapeutic dosages, if higher doses* are used, a retroactive/emergency TUE is required.

**The salbutamol dose that would require a TUE is one that exceeds the maximum permitted dose defined in the WADA Prohibited List.*

In general, the administration of nebulized salbutamol would exceed this threshold and should be confined to the treatment of acute, severe bronchoconstriction associated with the anaphylactic event; and therefore it would also require a retroactive TUE (see TUE Physician Guidelines, Medical Information to Support The Decisions of TUE Committees, Asthma).

4. Non-Prohibited alternative treatments

There are no non-prohibited first line treatments for anaphylaxis. Second-line medications are not life-saving because they do not relieve upper airway obstruction, hypotension, or shock.

Antihistamines:

- Antihistamines have no role in treating or preventing respiratory or cardiovascular symptoms of anaphylaxis.
- Do not use oral sedating antihistamines as side effects (drowsiness or lethargy) may mimic some signs of anaphylaxis.
- Injectable promethazine should not be used in anaphylaxis as it can worsen and cause muscle necrosis.

Intravenous Saline:

May be required for resuscitation of hypovolemic shock. Saline is not prohibited but delivery of fluid/saline via an intravenous route greater than 100ml in 12 hours is a prohibited method. Should IV saline be required, it is likely that it will be administered in a hospital setting and therefore **not** require a TUE. Should this treatment be required outside a hospital setting then a retroactive emergency TUE should be sought. (See TPG for IV fluids for more information).

5. Consequences to health if not treated

Death or permanent disability due to hypoxic-ischemic encephalopathy.

6. Treatment monitoring

Ideally, the patient should be monitored in an Emergency Room.

At the time of discharge, the patient should be equipped with epinephrine (adrenaline) for self-administration for use in the event of anaphylaxis recurrence. Patients at risk for recurrence should have one or more epinephrine (adrenaline) auto-injectors available at all times. Patients should also have a written personalized anaphylaxis emergency action plan and should wear medical identification.

A follow-up visit with a specialist physician for an allergy/immunology evaluation is recommended to confirm the anaphylaxis trigger.

7. TUE duration and recommended review process

An athlete's application for a TUE for epinephrine (adrenaline) after their first presentation and treatment for anaphylaxis will be retrospective in nature.

Athletes who are at risk of future anaphylaxis and are required to carry an epinephrine (adrenaline) auto-injector with them at all times should request an ongoing TUE to allow them to carry the auto-injector and administer it if required. This is because World Anti-Doping Code prohibits athletes from carrying a prohibited substance without a valid

TUE. Such applications should be approved for 5 years and include the provision that the athlete should notify their Anti-Doping Organization whenever the epinephrine (adrenaline) injection has been administered.

Intravenous therapy during the course of hospital admissions is not prohibited and does not require a TUE. (Note: IV therapy outside a hospital setting does require a TUE).

An emergency, retroactive TUE may be required for administration of systemic GCs, if administered during or very close to competition.

An emergency retroactive TUE is required for inhaled (if the dose exceeds the threshold specified on the WADA Prohibited List) or nebulized salbutamol.

8. Any Appropriate Cautionary Matters

Long-term approval for the use of oral or IM glucocorticoids (GCs) in case of emergency anaphylaxis should not be approved. If there is a need for their use as a concomitant treatment for anaphylaxis around the time of competition an emergency retroactive TUE can be sought.

9. References

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