Anaphylaxis

Prohibited Substances: Epinephrine, glucocorticoids and inhaled beta-2 agonists

1. Introduction

Anaphylaxis is a serious, life-threatening generalized, systemic allergic reaction that is rapid in onset. Anaphylaxis occurs after exposure to an allergen, most commonly a food, medication, or insect sting or bite, that a person is allergic to. 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. There are a number of factors that can influence the severity of reactions including exercise, heat, alcohol, and the amount of allergen exposure.

2. Diagnosis

a. Medical history

The clinical diagnosis of anaphylaxis is based on a detailed history of the episode and on recognition of the rapid 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.

Identification of the trigger for anaphylaxis is important and can often be elucidated by careful history pertaining to the circumstances preceding the episode and identification of potential triggers. The history will also help exclude conditions that may be confused with anaphylaxis (see differential diagnosis below).

b. Diagnostic criteria

Anaphylaxis is highly likely when any one of the following three scenarios is present:

1. No Known Allergen Exposure - 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 involvement (dyspnea, wheeze-bronchospasm, stridor, hypoxemia);
    b. Cardiovascular involvement (reduced blood pressure or associated symptoms of end-organ dysfunction, such as hypotonia, collapse, incontinence).

2. Likely or Known Allergen Exposure - Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to hours):
    a. Skin-mucosal tissue involvement;
    b. Respiratory involvement;
    c. Cardiovascular involvement;
    d. Severe gastrointestinal involvement.

3. Known Allergen Exposure – Sudden onset of either:
    a. Respiratory involvement after exposure to a non-inhaled allergen;
    b. Cardiovascular involvement.

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. They 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.

Once a potential trigger has been identified, testing for sensitization to this trigger may be undertaken via specific IgE testing, either by skin prick testing or serum specific IgE testing. In some cases, particularly in children, oral challenge testing may be undertaken to confirm the allergy. In children this is the gold standard for diagnosis of food allergy.

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

3. Treatment

a. Name of prohibited substances

A. Epinephrine (Adrenaline) (S6 Stimulant, prohibited in–competition only)

Epinephrine is administered during an acute anaphylactic attack as a first-line treatment.

Route: Intramuscular injection in the mid-lateral thigh.

Dose:

i. Epinephrine auto-injector (0.5 mg for individuals >50kg, 0.3mg for adults i.e. >30kg or 0.15mg for 15-30kg child) or,
ii. Adrenaline ampoule 1:1000 (1mg/1ml) solution: 0.01mg/kg to maximum of 0.5 mg for adolescents >12 years 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: A retroactive (i.e., after the emergency has been managed) TUE for epinephrine (or adrenaline) is required, i**f given during an in-competition period.** If given out-of- competition, then no TUE is required, but in the relatively unlikely event that a pre-competition use results in an AAF, the athlete would be allowed to apply retroactively. Thus, the athlete should gather medical documents related to the incident should a TUE be required in the future.

Note: Changes to the WADA Code 2021 now specifically allows athletes to carry an EpiPen without worrying about being charged for possession of a prohibited substance. However, the athlete should be able to produce the medical evidence of a history of allergies or anaphylaxis should they be requested to do so by a relevant Anti-Doping Organization (ADO).

WADA Code 2021 [Comment to Articles 2.6.1 and 2.6.2: *Acceptable justification may include, for example, (a) an Athlete or a team doctor carrying Prohibited Substances or Prohibited Methods for dealing with acute and emergency situations (e.g., an epinephrine autoinjector), or (b) an Athlete Possessing a Prohibited Substance or Prohibited Method for therapeutic reasons shortly prior to applying for and receiving a determination on a 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, glucocorticoids 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, however, quite common practice to prescribe a 2–3 day course of oral glucocorticoids 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 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 5 mg/kg (usually up to 200-250mg).

Frequency: Usually, a single dose during the initial period of stabilization is sufficient. A short course of oral glucocorticoids for a few days following a severe attack may be prescribed.

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

TUE requirements: As of the 2022 Prohibited List, oral, rectal or any injectable routes of administration of glucocorticoids (GCs) are prohibited in-competition only, and their use during competition will require a TUE (usually a retroactive application using ISTUE retroactive *Article 4.1a*.“urgent medical treatment”). However, an in-competition urine sample may show GC levels above the established laboratory reporting levels even though administration occurred out-of-competition. In accordance with the Code, a resulting positive doping test, known as an adverse analytical finding (AAF), could render the athlete liable to a sanction under the concept of Strict Liability. As per ISTUE Article 4.1e, the athlete is permitted to apply retroactively for a TUE if there is an in-competition AAF from out-of-competition use. Thus, the athlete should gather medical documents related to the incident should a TUE be required in the future.

C. Inhaled beta-2 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.
- Nebulizer: 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 usual therapeutic dosages, if higher doses* are used, a retroactive TUE is required. Salbutamol (above the maximal levels) or by oral route is prohibited at all times. Thus, the athlete should gather medical documents related to the incident should a TUE be required in the future

*If the athlete needs to inhale more than the permitted dose of salbutamol, 1600 micrograms/24 hours (not to exceed 600 micrograms/8 hours they would require a TUE).

*The use of salbutamol with a nebulizer would likely lead to urinary levels exceeding the urinary threshold of 1,000 ng/ml and would also require a TUE (for further details on dosage limits see TUE Physician Guidelines - Asthma).

D. Intravenous saline

Intravenous saline may be required for resuscitation of hypovolemic shock associated with the anaphylactic episode. Saline is not prohibited but delivery of fluid/saline via an intravenous route when 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 Intravenous infusion for more information).

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:

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

5. Consequences to health if treatment is withheld

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 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

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 have a medical file containing the details of their medical condition should they be required to use their EpiPen during competition or asked to explain their reason for carrying an EpiPen by a relevant ADO.

A retroactive TUE may be required for administration of glucocorticoids by prohibited routes, if administered during competition or very close to competition and detected in a doping control urinary sample.

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

Long-term approval for the use of oral or IM glucocorticoids 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.

8. Summary table

Table 1

Substance	Route of admin	TUE required if used in comp? (will be retroactive)	TUE required if used out of comp? Will be retroactive	Retroactive criteria
Epinephrine/adrenaline	IM/IV	yes	no	4.1(a)
Glucocorticoids	Oral/injection	yes	no**	4.1(a) (**if detected in an in-competition test, use 4.1.e)
B2 agonist (salbutamol) i. >1600mcg/24hrs (not to exceed 600mcg/8hrs) ii. nebulized	Inhaled or nebulized	yes	yes	4.1(a)
Saline >100ml in 12 hours outside a hospital setting	IV	yes	yes	4.1(a)

ISTUE Article 4.1(a) - Emergency or urgent treatment of a medical condition was necessary

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