1. Medical Condition

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. It commonly occurs in community settings. The lifetime prevalence is 0.05-2%. The rate of occurrence is increasing, 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 or 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 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. Patients with this diagnosis should be checked for mast cell activation syndromes, including mastocytosis.

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 to 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 1 of the following 3 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).

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); in adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

C. Co-factors that may contribute to the severity of anaphylaxis

1. Age related factors:
   Adolescence (risk-taking), pregnancy, old age.

2. Concomitant diseases:
   Asthma and other respiratory diseases, hypertension and other cardiovascular diseases, mastocytosis and other mast cell activation syndromes, allergic rhinitis, eczema, psychiatric illness

3. Concurrent medications or chemicals:
   Beta-adrenergic blockers, ACE inhibitors, sedatives, hypnotics, antidepressants, recreational drugs.

4. Co-factors that potentially amplify anaphylaxis:
   Exercise, acute infection (e.g. a cold or fever), alcohol (ethanol), emotional stress, premenstrual status, disruption of routine (travel)

D. Differential Diagnosis

Acute generalized hives
Acute asthma
Syncope (faint)
Panic attack or acute anxiety attack
Aspiration of a foreign body
Cardiovascular event
Neurologic event
Postprandial syndromes, e.g. scombroidosis, anisakiasis, food poisoning
Non-organic disease, e.g. vocal cord dysfunction

E. Laboratory Investigations

Laboratory tests to confirm the clinical diagnosis of anaphylaxis are not universally available, and are not available on an emergency basis anywhere because 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 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. Name of Prohibited Substance:

S6. Specified Stimulant. Epinephrine (Adrenaline). In–competition period only.

- This is given during an acute anaphylactic attack as a first line treatment.
- Route: Intramuscular injection in the mid- lateral thigh
- Dose: 0.01mg/kg of a 1:1000 (1mg/1ml) solution (maximum of 0.5 mg for adolescents or adults).
- Frequency: This injection may be repeated in 5-15 minutes if needed.
- Recommended duration: Most patients respond to 1-2 doses.
- TUE requirements: A retrospective/emergency TUE for epinephrine (adrenaline) during in-competition period only is required.

B. Name of Prohibited Substance:

S.9 Systemic Glucocorticoids (GC). In-competition period only.
(e.g. methylprednisolone or prednisone)

**Please note that GC should be second line treatment in anaphylaxis. Dosing is extrapolated from their use in acute asthma. Onset of action takes several hours or more, therefore, GC are not recommended as initial treatment or the only treatment. Although their efficacy in the treatment of anaphylaxis has not been proven, they may have some role in prevention of biphasic anaphylaxis.

Route:
Intravenous or oral routes are the recommended routes of administration.
Intramuscular injection is utilized in some regions of the world

Dose:
Methylprednisolone 50-100 mg or prednisone 40-50 mg

Frequency:
Usually only one dose during period of stabilization is sufficient. A short course of up to a few days is not the latest recommended treatment, but is still given in some instances.

Recommended duration:
Short finite period of time during period of emergency stabilization

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

4. Non-Prohibited alternative treatments

As anaphylaxis is a medical emergency, it is important to have an anaphylaxis protocol which is rehearsed on a regular basis

***Emergency Protocol for the Initial Treatment of Anaphylaxis*:**

- Eliminate exposure to the suspected relevant trigger or amplifying co-factor if possible; e.g. discontinue an intravenous medication, remove exposure to latex, or stop exercise.

- Assess patient's circulation, airway, breathing, mental status, skin, and body weight.

- Promptly and simultaneously:
  - Call for emergency medical services or a resuscitation team
  - Immediate intra-muscular injection of epinephrine (adrenaline) (see #3 above)
  - Position patient on the back with lower extremities elevated; place dyspneic or vomiting patients in a position of comfort.

- Additional important steps when indicated include:
  - Administer supplemental oxygen at 8-10 litres per minute by face mask
  - Maintain the airway

- Establish an intravenous access
- Administer fluid resuscitation (infuse 1-2 litres of normal saline in the first 5-10 minutes) for severe hypotension/shock
- Initiate cardiopulmonary resuscitation
- Monitor blood pressure, cardiac rate, respiratory status, and oxygenation continuously if possible for at least 4 hours, longer if the anaphylactic episode involves severe respiratory symptoms, hypotension, or shock. Biphasic reactions occur in about 5% of patients.

Second-line medications are not life-saving because they do not relieve upper airway obstruction, hypotension, or shock. These medications include:

- A beta-2 adrenergic agonist such as salbutamol 2.5mg/3ml or 5mg/3ml given by nebulizer and face mask, or 2-8 puffs of salbutamol given by metered-dose inhaler. Note that although salbutamol is not prohibited by inhalation at ordinary therapeutic dosages, e.g. 2 puffs from a salbutamol MDI; higher doses may be needed, at which point one should request a retroactive/emergency TUE for this substance.

- A non-impairing, non-sedating H_1-antihistamine such as desloratadine 5 mg or levocetirizine 5 mg given orally, or a potentially impairing and sedating first-generation H_1-antihistamine such as chlorpheniramine 10 mg or diphenhydramine 25-50 mg given intravenously. Modern non-impairing, non-sedating H_1-antihistamines such as desloratadine or levocetirizine are not available in intravenous formulations.

- Systemic GC such as methylprednisolone 50-100 mg (adult) for intravenous infusion or prednisone 40-50 mg orally (see #3 above).

At 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 containing a 0.3 mg dose available at all times. Use of the auto-injector during the competition period requires a retroactive/emergency TUE to be submitted as soon as possible to the appropriate anti-doping organization. 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.

Prevention of recurrences depends on strict avoidance of the confirmed relevant allergen(s) or other trigger. Patients with anaphylaxis induced by insect stings should receive immunotherapy with the relevant standardized insect venom.

For prevention of exercise-induced anaphylaxis, exercise itself should not be avoided; however, relevant food co-triggers should be strictly avoided and athletes should be aware that co-factors such as NSAIDs, ethanol, and ambient conditions of extreme humidity, cold, or heat, or high pollen counts are relevant.

Athletes with exercise-induced anaphylaxis should never exercise alone, should discontinue exertion immediately when the first symptoms of anaphylaxis occur, and always have an epinephrine auto-injector immediately available. In sports such as cross-country skiing or running, carrying a mobile phone is mandatory.

5. Consequences to health if not treated

Potential fatality or permanent disability due to hypoxic-ischemic encephalopathy.

6. Treatment monitoring

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

Follow-up with a specialist is recommended for confirmation of the specific trigger of the anaphylactic episode and if indicated, immunotherapy to prevent recurrences of stinging insect venom anaphylaxis.

7. TUE duration and recommended review process

The TUE for anaphylaxis is retrospective in nature. Therapy should be continued until symptoms dissipate. Treatment is usually of short term as is the TUE duration.

Consideration may be given to granting a TUE to enable an athlete to carry medications such as: Epinephrine (Adrenaline) I.M. (e.g. Epi-Pen®) for emergency purposes. Provisions to ensure notification of the Anti-Doping Organization should the Epinephrine be utilized can be included as a condition of the TUE.

Intravenous therapy during the course of hospital admissions is not prohibited (M2) and does not require a TUE although a TUE may be required for administered prohibited substances (e.g. GC).

8. Any Appropriate Cautionary Matters

Delay in injecting epinephrine (adrenaline) has been associated with fatality or hypoxic-ischemic encephalopathy.

Some patients do not respond to the prompt basic initial anaphylaxis treatment with epinephrine by intramuscular injection, supplemental oxygen and intravenous fluid resuscitation as outlined in section #4.

Such patients should be transferred promptly to the care of a specialist team in emergency medicine or critical care medicine for skilled management of the airway and optimal shock management with intravenous vasopressors given through an infusion pump with dose titration based on continuous non-invasive monitoring of heart rate, blood pressure and oxygenation.

9. Reference

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