# BRIEF OVERVIEW OF ANAPHYLAXIS AS AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) AND PRACTICAL GUIDANCE ON ITS IDENTIFICATION, CASE MANAGEMENT AND RESPONSE IN A PRIMARY CARE SETTING

World Health Organization

Brief overview of anaphylaxis as an adverse event following immunization (AEFI) and practical guidance on its identification, case management and response in a primary care setting

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## 1. What is anaphylaxis?

Anaphylaxis is an acute allergic reaction with multisystem involvement that can present as, or rapidly progress to, a life-threatening reaction. It may occur following exposure to a variety of allergen triggers including food, insect venom, drugs and vaccines.[1]

## 2. What causes anaphylaxis?

Anaphylaxis results when mast cells and basophils degranulate (break open) and release multiple preformed mediators such as histamine and tryptase into the circulation. These mediators cause widespread capillary dilatation and increase in permeability which then result in the symptoms and signs of anaphylaxis that involve the skin, respiratory, cardiovascular and gastrointestinal systems.

When an individual is sensitized to the allergen, immunoglobulins (called IgE) in the body bind to mast cells. When the same individual is subsequently exposed, the allergen binds to the IgE on mast cells, causing them to degranulate and resulting in anaphylaxis. However, this process can also occur without IgE being involved when the trigger directly stimulates degranulation of mast cells.

## 3. What are the anaphylaxis rates after vaccination?

Anaphylaxis following immunization is very rare – estimates are in the range of 1–10 episodes per 1 million doses, depending on the vaccine.[2] Accurate estimates are hampered by limited data and inconsistent use of standard case definitions. Most publications on anaphylaxis following immunization are case reports or case series and do not consistently use standardized case definitions. Some studies have had to extrapolate their estimates from small absolute case numbers.

## 4. What are the symptoms and signs of anaphylaxis?

Anaphylaxis[3] is a multisystem condition that effects any combination of the skin, respiratory, mucosa (eyes and nose), cardiovascular and gastrointestinal symptoms. Anaphylaxis is defined by the involvement of the respiratory and/or cardiovascular systems together with one or more systems – usually the skin. Some 90% of presentations are multisystem, but uncommonly cardiovascular collapse may occur without other organ involvement.

**Skin:** Symptoms include generalized skin itch, redness of the skin and/or hives/urticaria (rash, which is red, raised and itchy) and/or swelling of the face/body/limbs (angioedema).

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1 Rich RR, Fleisher TA, Shearer WT, Kotzin WT, editors. Clinical immunology. Principles and practice. Toronto: Mosby; 2001: 46.1–11.

2 WHO vaccine reaction rates information sheets. Geneva: World Health Organization (https://www.who.int/initiatives/the-global-vaccine-safety-initiative/tools-and-methods/reaction-rates-information-sheets, accessed 8 April 2021).

3 Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675–84. doi:10.1016/j.vaccine.2007.02.064.

**Mucosa:** Symptoms include red and watery eyes and/or runny and blocked nose.

**Respiratory:** Symptoms include persistent cough, tightness in the throat, hoarse voice, noisy breathing (inspiratory stridor/expiratory wheeze) and/or increased work of breathing (fast breathing/recession/grunting).

**Cardiovascular:** An early symptom of low blood pressure is dizziness which can progress to loss of consciousness. If severe, anaphylaxis can lead to hypoxia (manifesting as cyanosis) and hypovolaemic shock (low blood pressure, tachycardia, reduced peripheral perfusion and loss of consciousness). Urgent management is required to avoid a cardiorespiratory arrest.

**Gastrointestinal:** Symptoms include abdominal pain, nausea, vomiting and diarrhoea.

A small number of patients may have a biphasic reaction. This is a recurrence of anaphylaxis after appropriate treatment has been administered and can occur even with no additional exposure to the allergen. In such cases, the late phase begins between 1 and 72 hours after the initial phase, usually with similar clinical manifestations.

Table 1 describes the progression of signs and symptoms from a mild allergic reaction to a severe reaction (anaphylaxis).

**Table 1:** Recognition of the signs and symptoms of an acute allergic reaction

| Clinical progression | Signs and symptoms of an acute allergic reaction |
|---|---|
| Mild early-warning signs<br>  <br>Severe symptoms of anaphylaxis | — Generalized skin itch, rash which can be urticarial (red, raised lumps) or flushing (redness)<br>— Swelling of the face or other body parts<br>— Blocked and runny nose, sneezing, red and itchy eyes<br>— Nausea, vomiting, abdominal pain<br><br>Noisy breathing (wheeze or stridor), hoarse voice, difficulty swallowing or talking, difficulty breathing (fast breathing, recession), collapse, low blood pressure, weak pulse, capillary filling time > 3 seconds |

## 5. *How soon after immunization can an acute allergic reaction occur?*

The symptoms and signs of an acute allergic reaction will generally occur between 5 and 60 minutes after vaccination and usually within 15 minutes.

If a person collapses within 5 minutes of vaccination, this could be an acute stress response (vasovagal syncope) rather than anaphylaxis (see Table 2 below). If there is any doubt about the cause of immediate collapse, this should be treated as anaphylaxis and treatment should include administration of adrenaline.

## 6. What are the differential diagnoses of anaphylaxis?

Differential diagnoses of anaphylaxis include acute stress responses (general anxiety and/or a vasovagal reaction), myocardial dysfunction, pulmonary embolism, foreign body aspiration, poisoning, hypoglycaemia, convulsive disorders, urticaria and angioedema, hereditary angioedema and asthma. Table 2 outlines the difference between anaphylaxis and an acute stress response (general and vasovagal reaction with syncope).

**Table 2:** Differentiation of anaphylaxis from an acute stress response of general and vasovagal reaction with syncope

| Manifestation | Anaphylaxis | Acute stress response | |
|---|---|---|---|
| | | General | Vasovagal reaction with syncope |
| Onset | Usually 5 minutes after immunization but may be delayed up to 60 minutes | Sudden, occurs before, during or shortly after (< 5 minutes) immunization | Sudden, occurs before, during or shortly after (< 5 minutes) immunization. May present after 5 minutes if the individual stands suddenly |
| Clustering of cases | Rare | Can occur | Can occur |
| ***System*** | | | |
| Skin | Generalized urticaria (hives) or generalized erythema, localized or generalized angioedema, generalized pruritus with or without skin rash, red and itchy eyes | Pale, sweaty, cold, clammy | Pale, sweaty, cold, clammy |
| Respiratory | Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest | Hyperventilation (rapid, deep breathing) | Normal-to-deep breaths |
| Cardiovascular | ↑ heart rate, ↓ blood pressure, circulatory arrest | ↑ heart rate, normal or ↑ systolic blood pressure | ↓ heart rate with or without *transient* ↓ in blood pressure |
| Gastrointestinal | Nausea, vomiting, abdominal cramps | Nausea | Nausea, vomiting |
| Neurological and other symptoms | Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat | Fearfulness, light-headedness, dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet | Transient loss of consciousness, good response once supine or lying flat, with or without tonic-clonic seizure |

## 7. What is the initial management of anaphylaxis following vaccination?

Every health facility providing vaccinations should have health staff trained in the practical steps for recognition and treatment of anaphylaxis. They should have immediate access to an emergency kit (Table 3) containing adrenaline. Once anaphylaxis is suspected, consider the vaccine recipient as having a potentially life-threatening condition, begin treatment immediately and follow the treatment protocol (Figure 1) below.

1. First aid response, including:

   - Stop administering any further vaccine.
   - Call for help and never leave the vaccine recipient alone.
   - Place the vaccine recipient in the supine position (lying flat on the back with head lower than the legs if the patient is hypotensive). If the vaccine recipient has difficulty breathing, place him/her in a semi-supine (lying flat on the back but with bent knees/elevated legs) position. Do not stand the vaccine recipient up or allow the vaccine recipient to walk. If already unconscious, place the vaccine recipient in the recovery position (on the left side) and ensure that the airway is clear.
   - Assess airway, breathing and circulation (ABC). If appropriate, begin cardiopulmonary resuscitation (CPR).

2. Diagnose anaphylaxis by doing an RAPD assessment (see Table 5) by examining for symptoms and signs involving the following body systems:

   - **R**ash and mucosa.
   - **A**irway and respiratory.
   - **P**ulse and cardiovascular.
   - **D**iarrhoea and gastrointestinal.

3. Administer initial treatment – the first dose of adrenaline:

   - Draw up the correct dose of adrenaline 1:1000, according to age and/or weight (Table 4).
   - Generally, the dose for individuals weighing more than 50 kg is 0.5 mL.
   - Using the appropriate needle size (length and gauge), administer adrenaline by deep intramuscular injection into the opposite limb to that in which the vaccine was given. For children, administer in the upper lateral thigh, and in adults in the upper arm (deltoid) or into the muscle of the upper lateral thigh.
   - Give oxygen by face mask (oral-nasal mask), if available.

4. Assess the response and treat if there are ongoing respiratory and/or cardiovascular symptoms or signs:

   - If needed, repeat the same dose of adrenaline IM every 5–10 minutes up to TWO additional doses; give high-flow oxygen if available.

5. Documentation and patient transfer:

- Call an ambulance (or arrange other means of transport) after the first injection of adrenaline, or sooner if there are sufficient people available to help you.
- Record (or get someone to record) vital signs (pulse rate, respiratory rate and blood pressure) and all other symptoms and signs, as well as time and exact dose of any medication given. Make sure the details accompany the vaccine recipient when s/he is transferred to the appropriate care centre.

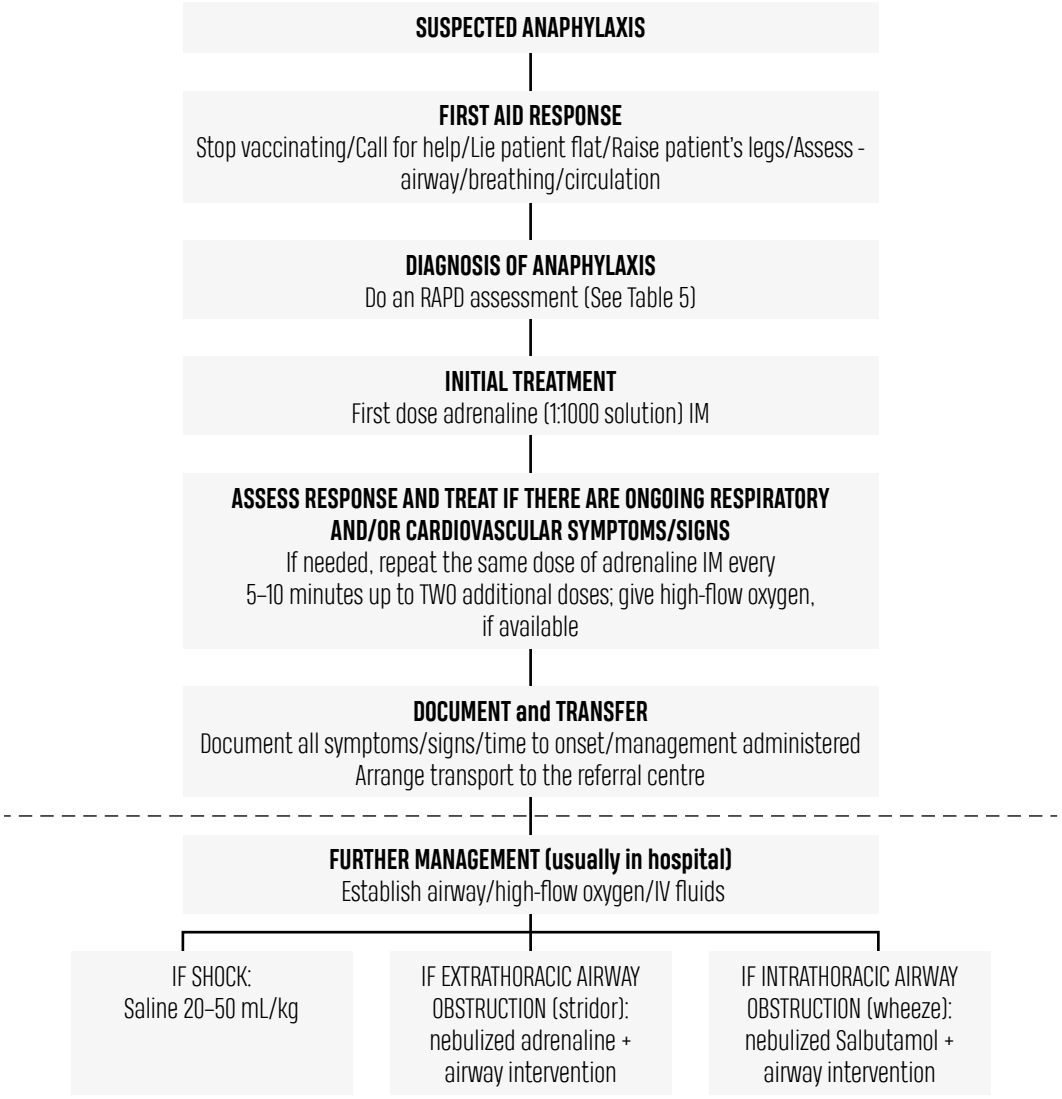
6. Further management is usually provided in a medical centre or hospital:

- If there is shock (hypotension) – IV saline.
- If there is extrathoracic airway obstruction (stridor) – nebulized adrenaline/ airway intervention.
- If there is intrathoracic airway obstruction (wheeze) – nebulized salbutamol and airway intervention.

**Table 3:** AEFI treatment kit

| Contents of an AEFI treatment kit | |
|---|---|
| — Injection adrenaline (1:1000) solution – 2 ampoules<br>— Disposable syringe (insulin type) having 0.1 mL graduations and IM needle (gauges and length adjusted to targeted recipients) – 2 sets<br>— Scalp vein set – 2 sets with medium-bore needles (gauges and length to be adjusted to targeted recipients)<br>— IV canula (various sizes, adjusted to targeted recipients)<br>— Paracetamol (500 mg) – 10 tabs<br>— IV fluids (Ringer's lactate or normal saline) – 1 unit in plastic bottle | — IV fluid therapy – 1 unit in plastic bottle<br>— IV drip set – 1 set<br>— Cotton wool + adhesive tape – 1 each<br>— AEFI reporting forms<br>— Label showing: date of inspection, expiry date of injectable adrenaline and shortest expiry date of any of the components<br>— Drug dosage tables for injecting adrenaline<br>— At hospital, oxygen support and airway intubation facility should be available. |

**Fig 1:** Sample treatment protocol for anaphylaxis




## 8. *What precautions need to be taken when giving adrenaline?*

Adrenaline (epinephrine) is the only medication indicated for the initial treatment of anaphylaxis. Adrenaline stimulates the heart and reverses the spasm and swelling in the lung passages, reduces the loss of fluid from blood vessels, raises blood pressure and stops