



# Anaphylaxis in the paediatric intensive care patients

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## Abstract

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is a sudden IgE-mediated allergic reaction when a susceptible person is exposed to a specific, sensitised allergen. It is characterised by rapidly developing airway, breathing or circulatory problems, which usually associated with skin or mucosal changes. Food allergy is the leading cause for admissions of severe systemic allergic reactions or anaphylaxis in Hong Kong. There are two potential scenarios where anaphylaxis could be encountered in the paediatric intensive care unit (PICU): 1) a child who is admitted for intensive care after anaphylaxis; 2) a patient who develops anaphylaxis to therapy while in the PICU. Two recent cases suffered from anaphylaxis were managed in PICU in Prince of Wales Hospital: 1) 5-month-old girl had injection of Amikacin for sepsis; 2) 33-month-old boy, suffers from mucopolysaccharidosis, was given thymoglobuline during the conditioning of stem cell transplantation. The keys to management anaphylaxis are 1) removal exposure to the anaphylaxis trigger if possible; 2) maintain airway, breathing and circulation; 3) use of adrenaline. Intramuscular route is generally recommended in PICU setting.

Keywords: Adrenaline, Anaphylaxis, IgE mediated

## Introduction

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is a sudden allergic reaction due to IgE-mediated release of vasoactive substances such as histamine from mast cells and basophils, which occurs when a susceptible person is exposed to a specific, sensitised allergen. It is characterised by rapidly developing airway, breathing or circulatory problems, which usually associated with skin or mucosal changes. In the western countries, it has been estimated that 1-2% of the population is at risk for anaphylaxis and 5% of the children is at risk of food allergy. Food allergy is the leading cause for admissions of severe systemic allergic reactions or anaphylaxis in Hong Kong. About 10% of these patients have severe cardiovascular compromise, and more than one third has significant respiratory symptoms.

The definitions of anaphylaxis are summarized in Table 1. The symptoms and signs are summarized in Table 2.<sup>1</sup>

Although anaphylaxis accounts for 0.5/100000 of Hospital Authority paediatric admissions, all staff must be prepared and regularly rehearsed anaphylaxis assessment using a written emergency protocol. There are two potential scenarios where anaphylaxis could be encountered in the paediatric intensive care unit (PICU): 1) a child who is admitted for intensive care after anaphylaxis; 2) a patient who develops anaphylaxis to therapy while in the PICU.

## Case 1: Amikacin allergy

A 5-month-old full term girl with normal birth weight, suffered from laryngomalacia and arytenoids prolapse. She had biliary atresia with Kasai operation done June 2015. She had recurrent episodes of cholangitis. There were 2 episodes in next two months and she were treated with IV Tazocin. The third episode was happened in the third month after the operation. It was refractory to IV tazocin, vancomycin and meropenem. Amikacin was later added. However, anaphylaxis happened two hours after the third dose of amikacin. Patient had angioedema, generalised urticaria, desaturation and respiratory distress. One dose IM adrenaline 0.05 mg and IV hydrocortisone 20 mg was given immediately. Regular hydrocortisone was given. The allergic response was fluctuating and paediatric intensive care unit admission for close monitoring was required.

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## Case 2: Thymoglobuline allergy

A 33-month-old boy, with history of peanut allergy with angioedema, suffers from mucopolysaccharidosis 1 (Hurler syndrome). He has cord blood transplant in the children cancer center. Thymoglobuline was used in the pre-transplantation conditioning. After infusion 8 ml of thymoglobuline, patient had desaturation with oxygen

**Table 1. Definitions of anaphylaxis**

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

1. Acute onset of an illness (minutes to several hours) with involvement of skin, mucosal tissue, or both (e.g. generalised hives, itch, flushing, swollen lips-tongue-uvula) and  $\geq$  one of the following:
  - a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia)
  - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotension\* [collapse], syncope, incontinence)
2.  $\geq$  Two of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - a. Involvement of skin or mucosal tissue (e.g. generalised hives, itch, flushing swelling)
  - b. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia)
  - c. Cardiovascular compromise (e.g. hypotension\*, collapse)
  - d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Hypotension\* after exposure to known allergen for that patient (minutes to several hours)

\* Hypotension for children is defined as systolic blood pressure  $<70$  mmHg (1 month-1 year),  $<(70 \text{ mmHg} + [2 \times \text{age}])$  (1-10 years), and  $<90$  mmHg (11-17 years).

**Table 2. Symptoms and signs of anaphylaxis**

Symptoms and signs	Frequency (%)
Cutaneous	90
Urticaria and angioedema	85-90
Flushing	45-55
Respiratory	40-60
Breathlessness, wheeze	45-50
Angioedema of upper airway	50-60
Rhinitis	15-20
Cardiovascular	
Dizziness, syncope, hypotension	30-35
Abdominal	
Nausea, vomiting, diarrhoea, pain	25-30
Miscellaneous	
Headache	5-8
Chest pain	4-6
Seizure	1-2

saturation down to 50%. Oxygen supplement was given via non-rebreathing mask and the infusion was stopped immediately. He had cyanosis and had severe insucking of chest with minimal air entry. He was managed as anaphylactic reaction to thymoglobulin with bronchospasm. The following regimen was given: one dose of hydrocortisone 60 mg IV, 1 dose Adrenaline 1:10,000 1 ml diluted in 5 ml NS slow IV and ventolin inhaler 10 puffs. There was only transient improvement in the saturation and patient developed desaturation again, which required face mask bagging for 5 minutes. Hence second dose IV adrenaline was given. There was no documented hypotension. He was transferred to paediatrics intensive care unit for close monitoring for respiratory distress (with anticipated difficult airway) and arterial line monitoring of possible anaphylactic shock.

## Common allergens or triggers in children

The most common allergens or triggers in children are listed in the table below:

Items	Examples
Food	Peanut, tree nuts, cow milk, eggs, soy, shell-fish, fish and wheat
Insects bites/stings	Bee, wasp, jumper ants
Medications	Antibiotics (beta-lactams), muscle relaxants, anaesthetics
Others	Exercise induced anaphylaxis, idiopathic anaphylaxis, and latex anaphylaxis, food additives etc.
Blood products transfusion*	

\*with similar presentation but different pathophysiology as others

## Anaphylactoid reaction

Anaphylactoid reaction is clinically indistinguishable from anaphylaxis. It is caused by the release of histamine and other mediators from mast cells which are triggered by non-IgE mechanisms. As prior sensitisation is not required, which means the reactions can occur upon the first exposure to a substance, e.g. reaction to the contrast agent during radiological imaging.

## Anaphylaxis is a clinical diagnosis

Anaphylaxis is a clinical diagnosis. Laboratory test only for under the research setting and doubtful cases. The



detection of mast cell degranulation products can provide supportive evidence for anaphylaxis. Serum histamine and tryptase are the available biomarkers, however they are not specific and normal level does not exclude the clinical diagnosis of anaphylaxis.

Blood samples for the biomarkers should be collected within 1-3 hours respectively after symptom onset (short half-life). Serial measurement of tryptase levels are needed. Serum tryptase can be checked in the clinical Immunology Unit of Queen Mary Hospital. The test of serum histamine level is not available in Hong Kong.

### Allergic and anaphylactic transfusion reaction

The pathophysiology of allergic and anaphylactic transfusion reaction is still unknown. The following mechanisms have been implicated in anaphylactic reactions.

- 1) Type I hypersensitivity reaction –IgE
  - Transfusing an allergen to a sensitised patient (for example, penicillin or nuts consumed by a donor)
- 2) Anti-IgA
  - Patients with congenital IgA deficiency may develop anti-IgA antibodies; exposure to IgA can lead to anaphylactic reaction
  - 1:500 blood donors are IgA deficient, and 1:1200 blood donors have anti-IgA antibodies, but most are not at risk of an anaphylactic transfusion reaction
- 3) Antibodies to other normal plasma proteins
  - Patients with antibodies to other plasma proteins, such as haptoglobin, C3/C4, alpha-1-antitrypsin)
- 4) Rarely the transfusion of IgE antibodies from a donor to an allergen present in the recipient.

### Management

Remove exposure to the anaphylaxis trigger (e.g. IV drug or contrast) if possible. Assess and maintain airway, breathing and circulation. In general, patients should be placed on the back and with lower limbs elevate, and recumbent position if patient is vomiting. If the major problem is airway or breathing problem, patient is advised to sit upward. For hypotension as the major concern, patient should lie supine. High-flow oxygen should be given to children with respiratory symptoms or hypotension.

### Adrenaline

Adrenaline is the first-line treatment. It can stabilise mast cells. It works better if given early. Adrenaline is the most important drug for anaphylaxis. It *must not be withheld* for any patient labelled as "anaphylaxis" because of concomitant therapies such as H<sub>1</sub>-antihistamine and corticosteroid.

Intramuscular (IM) route is generally recommended. It is faster than subcutaneous route but not as risky as intravenous route in case of inappropriate diagnosis. Subcutaneous (SC) route is accepted as a possible route for pre-hospital use. IM is more rapid onset and the absorption is more reliable when compared with SC. Although IV route is mentioned in some guides, it is 'restricted' to highly experienced specialists in intensively monitored setting. Intravenous (IV) route is an alternative especially in patients with cardiac arrest and/or severe refractory hypotension. Second dose of adrenaline is recommended 5-10 minutes after the first dose.

#### Dosage of adrenaline

- ◆ Preferably given via IM injection into anterolateral thigh (vastus lateralis muscle)
- ◆ The dosage IM
  - 0.01 mg/kg (i.e. 0.01 mL/kg of 1:1000 adrenaline)
  - Max. single dose is 0.3 mg in children, 0.5 mg for adult-sized adolescents
  - Can be repeated every 5-10 minutes, more frequent dosing can be given if deemed appropriate by the clinician
- ◆ The dose IV
  - 0.1 µg/kg/min
  - Continuous blood pressure and cardiac monitoring should be available due to the possibility of hypertensive crisis and ventricular arrhythmia
- ◆ There is no good evidence to recommend a dosage for infants <1 year of age
- ◆ **Never give 1:1000 adrenaline intravenously due to high risk of toxicity**
- ◆ If a third dose of adrenaline is required – consider IV adrenaline infusion
- ◆ An adrenaline infusion (0.05-1 mcg/kg/min) should be considered if repeated doses of IM adrenaline are required
- ◆ Nebulised adrenaline is not recommended as first-line therapy, but may be a useful adjunct to IM adrenaline if upper airway obstruction is present. If airway oedema is not responding to parenteral and nebulised adrenaline, early intubation is indicated.



## Corticosteroids

Corticosteroids should not be used as a first-line treatment for anaphylaxis because they usually have delayed effect. The use and dosing of corticosteroids in anaphylaxis are extrapolated from acute asthma treatment. It may be useful in patients with history of asthma to prevent protracted or biphasic anaphylaxis. However, a Cochrane review commented that there was no high-quality clinical trial to support corticosteroid use in anaphylaxis management.

### Dosages for corticosteroids:

- ◆ Hydrocortisone (IM or slow IV) 2-4 mg/kg/dose (max: 200 mg for >12 years old and 100 mg for ≤12 years old)
- ◆ Methylprednisolone (IV) 1-2 mg/kg/day (max: 100 mg for >12 years old and 50 mg for ≤12 years old)

## H<sub>1</sub>-antihistamines (anti-H<sub>1</sub>)

H<sub>1</sub>-antihistamines should not be used as monotherapy for anaphylaxis. There was also no randomised control trial with sufficient quality to demonstrate its efficacy in anaphylaxis management according to the recent Cochrane review. Despite this, fast-acting oral anti-H<sub>1</sub> should be given at the start of allergic reaction regardless of its severity. Anti-H<sub>1</sub> is viewed as a second line treatment. Most guidelines include anti-H<sub>1</sub> in the discharge 'package', which consists of 2-3 days medications with steroid.

Suggested dosage for anti-H<sub>1</sub>: chlorpheniramine by IM or slow IV routes

- ◆ >12 years old: 10 mg
- ◆ 6-12 years old: 5 mg
- ◆ ≤5 years old: 0.1 mg/kg, up to maximum 2.5 mg
- ◆ *Caution – antihistamine use in infants younger than 6 months old requires close observation*

## Fluid

Intravenous fluid should be given in patients with tachycardia and hypotension due to severe anaphylactic reaction. Either crystalloids or colloids can be used at 20 mL/kg to be given over 10-20 minutes, which can be repeated according to patient's clinical status. If more than 40 mL/kg of IV fluid is needed, inotropic support with dopamine or adrenaline should be considered.

## Others medications

### Bronchodilators

- ◆ Salbutamol (Ventolin) and ipratropium (Atrovent) are often mentioned as "other treatments" suggesting they are to be used for bronchoconstriction but most guidelines do not list out the choice for drug.

Glucagon (for refractory anaphylaxis in patients receiving β-blockers)

- ◆ 20-30 µg/kg/dose, maximum 1 mg IV over 5 minutes
- ◆ Continuous infusion 5-15 µg/min, titrate according to clinical response

Magnesium sulphate (for refractory bronchospasm during anaphylaxis)

- ◆ Mentioned in some guidelines as one of the medications for treatment of bronchoconstriction but warned the possibility of hypotension with its use

### Anti-H<sub>2</sub>

- ◆ Most consider there is no solid evidence to recommend its routine use
- ◆ Ranitidine 1 mg/kg IV over 5 minutes
- ◆ No dosage recommendation for cimetidine

### After stabilisation:

- ◆ Record the allergic history in CMS
- ◆ Provide allergy alert card to patient
- ◆ +/- further workup for transfusion reaction
- ◆ Consider referral to paediatric allergy specialist
- ◆ EpiPen/EpiPen Jnr<sup>®</sup>, current dose recommendations are: <20 kg = EpiPen Jnr<sup>®</sup> (150 µg) and >20 kg = EpiPen<sup>®</sup> (300 µg)

## Reference

1. Management guideline for childhood anaphylaxis. HA COC Paediatrics and COC Accident and Emergency Medicine, June 2015.

## Further readings

1. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: An updated practice parameter. *J Allergy Clin Immunol* 2005;115:S483-523.
2. Simons FE, Arduzzo LR, Bilò B, El-Gamal YM, Ledford DK,



- Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-93. e1-22.
3. Leung TF, Yung E, Wong YS, Lam CW, Wong GW. Parent-reported adverse food reactions in Hong Kong Chinese preschoolers: epidemiology, clinical spectrum and risk factors. *Pediatr Allergy Immunol* 2009;20:339-46.
  4. Severe allergic reactions (anaphylaxis). [http://www.transfusion.com.au/adverse\\_transfusion\\_reactions/severe\\_allergic\\_reaction](http://www.transfusion.com.au/adverse_transfusion_reactions/severe_allergic_reaction)
  5. Cystic Fibrosis Medicine. <http://www.cysticfibrosismedicine.com>
  6. Sánchez-Borges M, Thong B, Blanca M, Ensina LF, Gonzalez-Diaz S, Greenberger PA, et al. Hypersensitivity reactions to non beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy. *World Allergy Organ J* 2013;6(1):18.
  7. Etherington C, Whitehead A, Conway SP, et al. Incidence of antibiotic related allergies in an adult CF unit and the success rate of a desensitisation regimen. *Pediatr Pulmonol* 1998; Suppl 17: A427.