An anaphylactic reaction is an emergency that can be life-threatening if not recognized immediately. Signs and symptoms that appear vary from mild to severe. After knowing that it is an anaphylactic reaction, it needs immediate action and special attention, especially from general practitioners who work in the emergency unit.

Case presentation: In this scientific publication, three cases will be presented, all of which were found in the emergency room at Cikarang Medika Hospital, Bekasi. These cases of anaphylaxis vary in the onset of signs and symptoms, clinical manifestation, allergen, degree of severity, and therapeutic response. However, in these three cases, the initial management, which was an emergency, was the same for each patient, and all cases occurred at home; thus, education on anaphylaxis in the general community is vital, especially for the patients and their families.

Conclusion: As a physician who works in the emergency room is essential to know how to quickly recognize the signs and symptoms of an anaphylactic reaction and carry out treatment as soon as possible so that patients can be helped. The first line treatment is Epinephrine and other treatment may follow after the first line has been given. It is essential that the public needs to know about the occurrence, the cause or trigger, and first aid (what they should do in the event of an anaphylactic reaction).

INTRODUCTION

Anaphylaxis is an allergic reaction that has a rapid immune response to an allergen. It has various clinical manifestations. Anaphylaxis represents the most severe end of the spectrum of allergic reactions. Recent publications show a global incidence of anaphylaxis between 50 and 112 episodes per 100,000 person-years while the estimated lifetime prevalence is 0.3–5.1%, variations depending on the definitions used, study methodology, and geographical areas. Most common clinical manifestations of anaphylactic reaction are involving of skin and mucosal symptoms, followed by respiratory and cardiovascular system.

Sources of allergens that induce anaphylactic reactions are food, drug, and Hymenoptera venom. The prevalence of anaphylactic reaction cases depends on age and geographical region. Data in Europe found that anaphylactic reactions in children are mostly induced by food like peanut, hazelnut, milk, and egg; while in adults can be caused by wheat, celery, and shellfish. Some drugs like beta-lactam antibiotics and non-steroid anti-inflammatory are common induced anaphylactic reactions. Fruits such as peach are also typical causes of food-induced anaphylaxis in adults in some European countries such as Spain and Italy. Indonesia does not have data on the prevalence of food-induced anaphylactic reactions since allergy does not belong to our country’s priority at this time. Drug-induced anaphylaxis is typically caused by antibiotics and non-steroidal anti-inflammatory drugs. Among antibiotics, beta-lactam antibiotics are the leading eliciting allergens. Venom-induced anaphylaxis is typically caused by wasp and bee venom.

The most common cause of anaphylactic reaction in Dr. Soetomo General Hospital was drugs, namely antibiotics, from groups of penicillin and cephalosporin. The most clinical manifestation was skin-related. Most anaphylactic reactions patients showed improvement after getting treatment from the doctor. In response to anaphylactic reaction cases, we will discuss three different cases of anaphylactic reaction that we found in the emergency room and get a lesson from these cases.

CASE ILLUSTRATION

Case 1

A male, 18 years old, came to the emergency room with difficulty breathing 1 hour after eating two servings of shrimp. Initially, he felt itching all over the body and redness. After 5 minutes, he experienced shortness of breath. The patient reported vomiting once and was finally taken to the hospital.

Keywords: anaphylaxis, anaphylactic reaction, allergen, epinephrine.
He was healthy and had a history of shrimp allergy since childhood and drug allergy was denied.

Physical examination revealed that the patient was still fully aware. Respiratory rate was 28x/min, heartbeat 112x/min, blood pressure of 80/65 mmHg, on thorax auscultation wheezing was found from both sides of lungs, no wet Ronchi, no gallop, unpalpable liver nor spleen, cold extremities. In the emergency room, the patient was put in a Trendelenburg position. He was given 4 L/min oxygen, an epinephrine shot of 0.5 ml IM in the lateral femur, simultaneously loading 1 L of ringer lactate intravenous (IV), dexamethasone 5 mg, ranitidine 50 mg, and ondansetron 4 mg.

For the next ten minutes, the vital sign showed blood pressure was at 86/55 mmHg, heartbeat 101 x/min, and respiratory rate 24 x/min. He was given a second shot of 0.5 ml epinephrine intramuscular (IM) and 1 ml diphenhydramine. Following ten minutes, the blood pressure was measured at 106/62 mmHg, heartbeat 72 x/min, and respiratory rate 24 x/min. The patient was sent to the ward after his blood pressure was normal and he was still fully aware. The next day, the patient was sent home with a blood pressure of 110/75 mmHg, a heartbeat of 76 x/min, full consciousness, and regular activity. He was prescribed cetirizine 10 mg/day and methylprednisolone 12 mg/day for three days and was advised to have follow-up care at the polyclinic.

Case 2
A 69 years old man was transferred to the emergency room unconscious after taking one capsule of super tetra 2 hours before due to diarrhea, which he bought at the drug store. After about five minutes, he complained that all of his body was itchy and reddish; he felt nauseated, was sweating, and finally unconscious. He was immediately brought to the nearest hospital. According to his family, he never had asthma or an allergy to certain drugs. After about five minutes, he had a history of knee pain and body aches. According to the patient’s family, he had a history of shortness of breath a few years ago.

Vital sign examination found blood pressure 90/60 mmHg, pulse 108 x/min, respiratory rate 26 x/min. The face looked swollen; wet cracksle and wheezing in both lung fields and the extremities were cold. Immediately the patient is positioned supine. The patient was given oxygen of 4-5 liters per minute by nasal cannula. Subcutaneous epinephrine 0.5 ml was given, along with an IV flush of ringer lactate. After ten minutes, blood pressure was 120/80 mmHg, pulse was 77 x/min, and respiratory rate 25 x/min. The patient still has shortness of breath. Wheezing and wet Ronchi are still available. She was given an injection of dexamethasone 5 mg, diphenhydramine 10 mg and ranitidine 50 mg, and it was decided to provide nebulization with one respule of Combivent and Pulmicort. After one hour of evaluation in the emergency room, the shortness of breath decreased and the respiratory rate was 22-24 x/min. The patient was sent to the ward after her condition was stable.

The next day, the patient was discharged in good condition and she was given cetirizine 10 mg/day and methylprednisolone 12 mg/day for three days and was advised to have follow-up care at the polyclinic.

DISCUSSION
Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.1 Anaphylaxis is an IgE-mediated hypersensitivity (type 1).2 Allergen activates IgE caused it binds to the receptor, FceRI, on the surface of mast cells and basophils. This cross-link causes degranulation and releases chemical mediators including histamine, tryptase, carboxypeptidase A, and proteoglycan. Histamine is a major mediator of anaphylaxis.1–3 There are four histamine receptors named H1R, H2R, H3R, and H4R. Histamine increases vascular permeability and vasodilation, leading to hypoperfusion of tissues. In response to these changes, the body will increase heart rate and cardiac contraction. Prostaglandin D functions as a bronchoconstrictor. It also potentiates peripheral vasodilation, thus contributing to the hypo-perfusion of vital organs. Leukotrienes add to bronchoconstriction and vascular permeability as well as induce airway remodeling.9–11

According to World Allergy Organization (WAO), anaphylaxis is highly likely when any one of the following two criteria are fulfilled: (1) acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula) and at least one of the
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following: (a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia), (b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence), (c) Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens; (2) Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.1–3

The three patients described here presented with anaphylaxis signs and symptoms. The most common triggers of anaphylactic reaction were food and drugs. Other triggers have been reported in the literature, such as insect bites, exercise, and latex, up to unknown causes or idiopathic. Focus on the presented case series regarding allergic reactions to food and drugs, because this is most often found in daily practice.

Case 1 had an anaphylactic reaction with shock. There are several triggers of anaphylaxis. The specific triggers can vary with age.12,13 Case 1 is a young man who had a history of food allergy. Although sensitivity to most food allergens such as milk, wheat, and eggs tends to remit in late childhood, the persistence of certain food allergies such as peanut, tree nut, and seafood most commonly continues throughout one’s lifetime. Peanuts and seafood, especially shrimp, have been reported as the trigger of anaphylaxis and are the most frequent cause of food allergy.14

The most frequent mechanism of anaphylaxis is mediated by IgE. In this type, anaphylaxis is triggered by an allergen (usually a protein) interacting with the allergen-specific IgE/high-affinity receptor (FcεRI) complex expressed on effector cells, predominantly mast cells and basophils.15 The four most frequent food-induced anaphylaxis in children are hen’s egg (in infants and pre-school children), cow’s milk, wheat, and peanut. In Adults, food-induced anaphylaxis varies depending on the region and local food exposure. Peanut and tree nuts are dominating causes of food-induced anaphylaxis in adults in North America and Australia, whereas shellfish is a frequent elicitor of food-induced anaphylaxis in Asia.16,17

Severe anaphylactic reaction can cause death by obstruction of the upper and lower respiratory tract, while it is due to anaphylaxis shock in drugs.1,2 In this case, the patient experienced shortness of breathing because of bronchospasm, known by the presence of wheezing. The patient immediately got treatment as soon as possible by receiving a prompt epinephrine injection and being placed in the Trendelenburg position. According to literature, the prompt administering of epinephrine intramuscularly in the anterolateral thigh is the initial treatment for acute anaphylaxis immediately after the diagnosis is made.1,2,18,19

There are no absolute contraindications to this treatment; the treatment should be provided even if the diagnosis is uncertain. Epinephrine acts on alpha and beta-agonist receptors, resulting in peripheral vasoconstriction, increasing the rate and force of cardiac contractions and bronchodilatation, also reducing the release of inflammatory mediators.20,21

The patient was also placed in the Trendelenburg position to prevent distributive shock and empty vena cava/empty ventricle syndrome.5

A study of fatal food-induced anaphylaxis in the United Kingdom showed that the median respiratory or cardiac arrest time was 30 minutes. The recommended dosage of epinephrine in a setting where an exact dose can be drawn up is 0.01 mg/kg (maximum dose, 0.5 mg), administered intramuscularly every 5 to 15 minutes as necessary to control symptoms.22–24 There is a circulatory collapse in this patient and there should be rehydrated up to 1000 mL to maintain blood pressure in the early stages of anaphylaxis. Based on some literature, patients who experience circulatory collapse from anaphylaxis need to be administered aggressively large volumes of IV or IO normal saline through large-bore catheters. Aggressive fluid resuscitation helps to counteract the significant plasma leak associated with anaphylaxis and complements parenteral epinephrine therapy.23,25

Children might require successive IV fluid boluses of 20 mL/kg; adults might require successive IV boluses of 1000 mL to maintain blood pressure in the early stages of anaphylaxis. Fluids administered through IO catheters should be infused under pressure using an infusion pump, pressure bag, or manual pressure is crucial to overcome venous resistance. Fluid resuscitation depends on the patient’s blood pressure and condition, such as the patient with heart failure. This consideration is aimed at avoiding volume overload.25 The patient was discharged in stable condition or restored health after two days of treatment.

The second and third cases had anaphylactic reactions associated with drugs allergy. Case 2 is an example of a very severe case of anaphylaxis on this case report, involving several vital organs or organ systems such as the brain (somnolent condition), heart (tachycardia), lungs (wet Ronchi), gastrointestinal tract (nausea), and the skin (pruritus, erythema, and edema). Even though the drug was administered orally, the symptoms appeared very fast (5 minutes), which is a sign of severe anaphylaxis. According to the World Allergy Organization for anaphylaxis guidance in 2020, drug-induced anaphylaxis is most frequently triggered by antibiotics and nonsteroid anti-inflammatory story drugs (NSAIDs).26

Among drug-induced anaphylaxis, new elicitors have been identified; these include biologic containing alpha-gal (cetuximab), small molecules, or novel chemotherapeutics like Olaparib.26 Campbell et al. reported cases the most common cause of drug-induced anaphylaxis is beta-lactam antibiotics.25 In this case, the patient got an anaphylaxis reaction from tetracycline. Most of the primary literature on tetracycline reactions is described in case reports and case series studies. The most common reported reaction due to tetracycline administration is a fixed drug reaction.27

Overall, IgE-mediated immediate-type anaphylactic hypersensitivity reactions due to tetracycline use are rare, typically nonfatal when an adequate intervention is performed. When reported, most anaphylactic reactions noted by case
reports have occurred within 10-45 minutes following oral or intravenous administration of tetracycline, while one case of anaphylaxis following intramuscular administration occurred rapidly in less than 20 seconds. In contrast to case 3, even though the case was similar, the cause of anaphylaxis reaction is Chinese herbal medicine. The patient had a history of knee pain and body aches, so she took herbal medicine pills. In recent years, traditional Chinese medicine (TCM) has been widely used in the clinic for the treatment of varied mild conditions. China’s National Center for Adverse Drug Reaction lists the top ten TCM injections that caused serious side effects.28,29

The abovementioned data and examples showed that doctors should pay more attention to the drug that frequently causes anaphylaxis reactions. The first reason that anaphylaxis reaction occurs is that components are complex. They are composed of organic compounds, such as pigment, tannin, starch, protein, and other ingredients in colloidal form, which can stimulate the body’s immune system and produce antibody-sensitized T lymphocytes to induce hypersensitivity. The same as in the second case, the first-line treatment was epinephrine. However, in the third case, the route of administration was subcutaneous, so it should note that some studies of the subcutaneous route of administration were slower in achieving the concentration and desired effect than the intramuscular route. Thus, it is preferable to take it intramuscularly.

Three patients got anti-histamine and corticosteroid, the third patient got nebulization to relieve bronchospasm. All of these medications should not be used as an initial treatment for an anaphylactic shock because they are not prevent nor treat airway obstruction and circulatory collapse.9,30

CONCLUSION
It is important to know that it must be fast and precise in making the diagnosis and treatment of anaphylactic reactions. It begins with how a physician can quickly recognize the signs and symptoms of an anaphylactic reaction and carry out treatment as quickly as possible so that patients can be helped. Epinephrine remains the first line in the treatment of anaphylaxis by far. Early diagnosis and early administration of epinephrine as the first line in the treatment will give a better outcome to patients with anaphylactic shock. There is no absolute contraindication in the administration of epinephrine.

Other treatments such as fluid administration and other drugs such as (corticosteroids and antihistamines) can be given after the first line has been given. After the patient recovers, the most important thing is that it is necessary to be educated about avoiding the trigger because it is very risky or fatal if you have had an anaphylactic reaction before. The public needs to know about the occurrence, the cause or trigger, and first aid (what they should do in the event of an anaphylactic reaction). In the three cases above, there are still many corrections and things that need to be improved in handling anaphylactic reactions, especially in the emergency department. Hopefully, it can be a lesson in the future and is getting updated every time.

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