



Anaphylaxis: Life-Threatening Allergic Reaction

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Received: 18-02-2021; Revised: 25-03-2021; Accepted: 03-04-2021; Published on: 20-04-2021.

ABSTRACT

Anaphylaxis is an extreme allergic response that occurs quickly and even sometimes ends up killing. The episodes of anaphylaxis range from moderate ones and resolve spontaneously to fatal ones within minutes. The actual worldwide magnitude of anaphylaxis is unknown as multiple episodes do not exist in the population and several regions have not yet evolved reliable systems to track extreme allergic events. Global rates of all anaphylaxis attributable primarily to drugs and food-based anaphylaxis can be convincingly improved. Idiopathic anaphylaxis applies to unexplained anaphylaxis, which entails a death possibility, whether by shock or from upper or lower airway blockages. It is increasingly important to consider causes, stimuli, and patient-specific risk factors for serious or lethal anaphylaxis. Professionals in the health industry must be able to detect anaphylactic symptoms, handle the incident quickly and properly, and make decisions on prevention. The awareness of gaps in our knowledge and diagnosis of anaphylaxis will aid in the detection of promising objectives for potential care and prevention. Anaphylactic patients and their families and caregivers' knowledge help avoid and rapidly recognize and manage anaphylactic episodes. The emphasis of this paper is on signs and symptoms, disease pathogenesis, causes of risk, medication, management, education of anaphylaxis, and, also focuses on the Idiopathic anaphylaxis.

Keywords: Allergy, Lethal, Idiopathic anaphylaxis, Anaphylaxis, Prevention, Education of anaphylaxis.

QUICK RESPONSE CODE →

DOI:

10.47583/ijpsrr.2021.v67i02.019



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2021.v67i02.019>

INTRODUCTION

The global prevalence of allergic diseases, which are partially due to an increased sensitivity to allergens and toxins to the atmosphere, continues to grow.¹ In the last two decades, there is a high rise in anaphylaxis. Earlier there was no universal statement for anaphylaxis and the consequence of that is misdiagnosis, miscoding, underreporting approaching epidemiological research on this condition.² Anaphylaxis is a rapid onset and may cause death.³ From the current data, it is figured out that new cases of Anaphylaxis arise at a rate of 21 per 100000 patients per year.⁴

Anaphylaxis is regarded as a severe systemic allergic reaction that can be proved fatal and requires prompt recognition and immediate management.⁵ Anaphylaxis is regarded as a catastrophic allergic reaction that creates an imbalance between the threats and benefits of an immune response.⁶ The most serious end of allergic reactions is those caused by anaphylaxis, most of which are caused by medications, foodstuffs, or insect stings. Measurement and evaluation of epidemiological evidence on anaphylaxis events is an important way of recognizing patterns, disease

prevalence, and risk factors.⁷ We cannot assume the accurate definition of anaphylaxis because it comprises of a group of features that is multiple signs and affects the skin, cardiovascular system (CVS), gastrointestinal tract (GIT), and respiratory tract (RT) symptoms but according to Canadian Pediatric Surveillance Program, the definition of anaphylaxis is a severe allergic reaction to any stimulus, having sudden onset and generally lasting less than 24 hours involving one or more body systems' and producing symptoms like flushing, itching, wheezing, shortness of breath, vomiting, diarrhea, or shock.^{8,9} Anaphylaxis is also caused by specific antigens in sensitive individuals. Anaphylaxis causes a hypersensitive reaction.⁸

In young people, food is the most common trigger; in middle-aged and older adults, medications and insect stings are relatively common triggers. Regardless of the mechanism or trigger, mast cells (MC) and basophils initiate and amplify anaphylaxis, leading to a cascade of mediators, including tryptase and histamine. Target organs in anaphylaxis include the skin, RT, GIT, CVS, and central nervous system (CNS).¹⁰ Tryptase is an enzyme that is released along with histamine MCs and basophils and enters the bloodstream and plays role in inflammation. Serum tryptase concentration is increased in anaphylaxis and anaphylactoid reaction.¹¹ Another aspect is Vitamin-D, it also plays role in allergic diseases, food allergies, and anaphylaxis in particular. Vitamin-D is a recent aspect that plays a pathogenic role in anaphylaxis. As anaphylaxis is rising in public and personal health conditions over the past decade in developed countries which in turn increases the demand for specialized medical services, the proper



economic cost of care.¹² The true rate of occurrence of anaphylaxis from all triggers is unknown, but it appears to be increasing. Another factor that plays a vital role in anaphylaxis is IgE and the high-affinity IgE receptor on MCs or basophils.¹³ The reaction develops gradually, starting with itching of gums, palms, soles; developing to a multiple organ reaction. Current therapies are restricted for the treatment of allergic reactions which are caused by Histamine and Leukotrienes, these are few mediators which basophils and MCs activate. Even anti-histamines are not capable of preventing anaphylaxis reactions because besides histamine other mediators are also involved in this major reaction which includes hypertension and shock.¹⁴

World Health Organisation (WHO) and International Classification (ICD) of disease also found limited accurate records of anaphylaxis.¹⁵ Anaphylaxis involves several organ systems, therefore; it is regarded as a multi-system disorder. The most specific combination is skin changes and CVD-RT signs with mucosa. The presence of these signs is the key to differentiating anaphylaxis from similar clinical syndromes of different symptoms such as myocardial infarction, septic shock, and many more. Hence, skin involvement is regarded as major evidence for the presence of Anaphylaxis. But in the case of some patients,

the symptoms might be incomplete. This may include the most acute and several clinical cases which may result in death.³ Anaphylaxis can be treatable if caught in an early stage.¹⁶ The treatment of anaphylaxis also recommends an injection of epinephrine which is designated by WHO as essential medication for anaphylaxis.¹⁷ Further, the World Allergy Organization (WAO) proposed the nomenclature in October 2003 that anaphylactic reactions will be classified as allergic and non-allergic reactions.¹⁸ Nonetheless, it is essential to be vigilant for those at risk of anaphylaxis and to establish appropriate measures to reduce the risk of death from anaphylaxis even further.

Signs and Symptoms

As anaphylaxis is a prevalent systemic reaction, numerous clinical and skin, GI, RT, and CV symptoms can be seen (see Table 1). Anaphylaxis is the most frequent systemic reaction. Cutaneous signs, such as urticaria and angioedema, erythema (flushing), and pruritus (itching), are the most frequent clinical manifestations.¹⁹ RT and Dermatological effects are most frequent in 70% and 90% of the cases, respectively. Clinical and medication delays can cause death by airway blockage or vascular breakdown.²⁰ The signs and symptoms of anaphylaxis are uncertain and can differ from person - to - person and from the reaction - to - reaction.

Table 1: Sign and Symptoms of Anaphylaxis.¹⁹

Skin	Respiratory	Cardiovascular	Gastrointestinal	Neurologic	Others
<ul style="list-style-type: none"> • Urticaria • Angioedema • Erythema • Pruritus • Eczema 	<ul style="list-style-type: none"> • Nasal congestion • Sneezing • Cough • Bronchospasm • Wheezing • Chest tightness 	<ul style="list-style-type: none"> • Hypotension • Dizziness • Syncope • Tachycardia 	<ul style="list-style-type: none"> • Nausea • Vomiting • Abdominal pain • Diarrhoea 	<ul style="list-style-type: none"> • Light headedness • Dizziness • Confusion 	<ul style="list-style-type: none"> • Sense of impending doom • Anxiety • Tingling • Pruritus

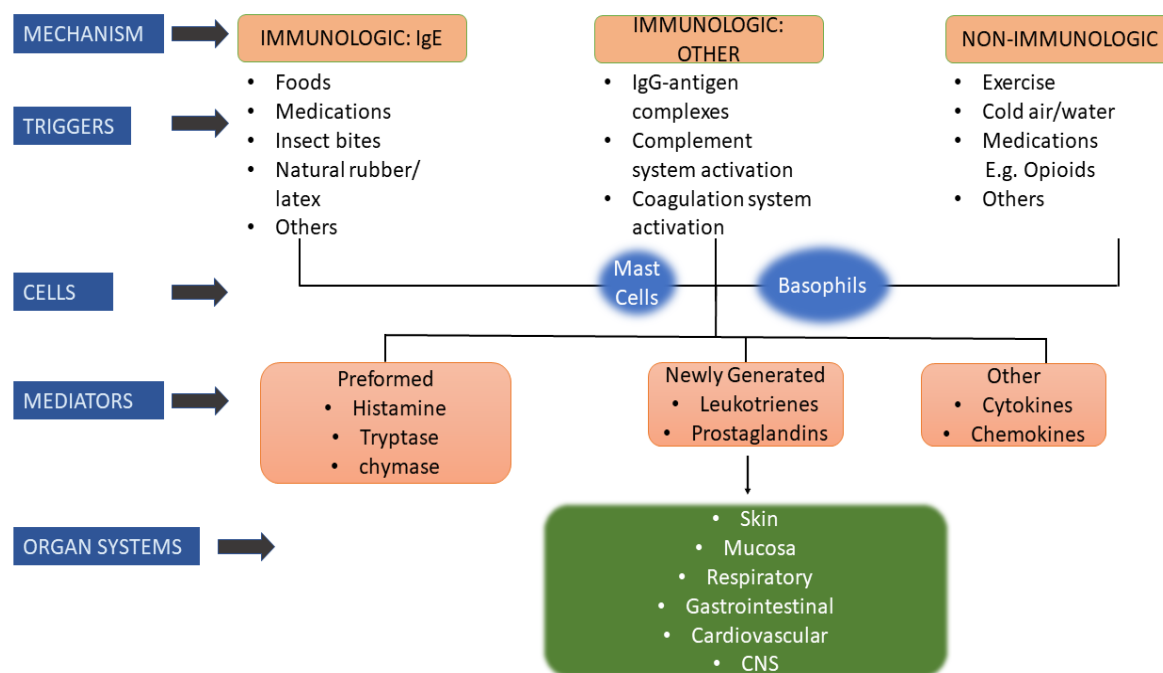


Figure 1: Demonstrating the Mechanism, Triggers, Cells, Mediators, and, Organ Systems involved in Anaphylaxis.

Pathogenesis

While IgE is the majority of cases of anaphylaxis, it includes other pathways and clinical presentations. There are also no possible differences between IgE-mediated and anaphylactoid reactions (NO-IgE) since this leads to a dangerous belief that anaphylactoid reactions are often less severe than those of other anaphylactoid agents.²¹ The pathogenesis of anaphylaxis involves IgE and high-affinity IgE receptor. MCs and basophils initiate anaphylaxis and also amplifies it which leads to a cascade of mediators that involve histamine and tryptase.¹⁷ Vasodilatation, Smooth muscle contraction, increased mucosal secretions, fluid extravasations are caused by anaphylactic mediators. These are some of the characteristic features considered to recognize an anaphylactic reaction and to avoid initial misdiagnosis.¹¹ There is no evidence found in confirmation that tryptase play role in anaphylaxis but it contributes to the pathology of anaphylaxis as it spread the signal of degranulation from MC to MC. It is seen in theory that blood-borne tryptase can spread the sign throughout the body but not seen actively participating in catalytic events. It inactivates pro-coagulant proteins and promotes lysis of fibrin clot and promotes bronchoconstriction which play role in tissue swelling, rashes, and many more symptom.²² Another is that blood-borne allergens activate IgE sensitized MCs indirectly. In addition to this, it is also noted that peri-vascular enhances inflammatory and immune responses by discharging antigen-bearing micro-vesicles around the immune cells.⁶ Mediators in anaphylactic induce vasodilation, fluid extravasation, smooth friction, and elevated mucus secretions. Hypoxaemia and/or shock may lead to death.²³ Figure 1 demonstrates the different mechanisms, triggers, cells, mediators, and, organ systems involved in anaphylaxis.

Risk Factors

The anaphylaxis risk factors differ and can be considered when seeing the patients affected. Peanut allergy is a risk factor for adverse reactions in younger patients. Even minute concentrations can cause extreme or fatal reactions in patients with significant hypersensitivity. Just a couple of micrograms of peanut protein are sufficient.²⁴ Another major anaphylaxis risk factor is age. We show that, with growing age, the relative risk of extreme CVD symptoms rises significantly using evidence from the anaphylactic registry.²⁵ Worldwide, all of the patients' causes raising the likelihood of moderate or fatal anaphylactic episodes are common. They are age-related causes, accompanying conditions such as asthma and other chronic respiratory illnesses as well as CVDs, mastocytosis or clonal MC diseases, and extreme atopic conditions such as rhinitis allergy. Any concurrent drugs, such as beta-adrenergic blockers and Angiotensin Converting Enzyme (ACE) inhibitors, can also increase the probability.²⁶ Anaphylaxis is generally triggered by various means like food for example-nuts, milk, wheat, some fruits, fish, etc.⁵ Other triggers can be insect stings – particularly wasp and bee stings and general anesthetics also.²⁷ In the case of serious or lethal

anaphylactic episodes, a deficit may also result in high tryptase, histamine, bradykinin (because of low serum ACE production), and platelet-activating factor (PAF) in median degradation pathways (because of low serum PAF production of acetyl hydrolases).²⁸⁻³²

A Swedish study found 11 of 37, fatal asthma cases at ages 1–34 was triggered by the ingestion of a food allergen, raising the possibility to cause anaphylaxis.³³ All food-related reactions caused difficulty in breathing, the paramedics commonly had difficulty deciding whether to use the protocol for anaphylaxis or asthma.³⁴ Other paramedic triggers are medicines including some antibiotics, non-steroidal, and, anti-inflammatory drugs like aspirin.⁸ Studies in the United States have found that bee stings are the second leading culprit for anaphylaxis and constitute 18.5% of anaphylactic cases, backed up by pharmaceutical products (13.7%), principally β -lactams, but more recently biological modifications including infliximab, omalizumab, and cetuximab are impacted. In other research, however, the leading cause of anaphylaxis is stated to be insect sting or narcotics. Latex, immunotherapy, washing agents, and chemical allergens are other less popular causes.³⁵

Treatment

The first treatment recommended for patients of Anaphylaxis is Adrenaline (epinephrine).³⁶ Epinephrine is helpful for the reduction of the body's allergic response.²⁴ Epinephrine could be proved as life-saving and play role in delaying the progression of life-threatening reactions to provide medical attention. In children, the dose of epinephrine is recommended as 0.01 mg/kg of a 1:1000 (1 mg/ml) solution in mid-anterolateral thigh via intramuscular (IM) injection.⁹ There is no solid evidence to prove that adrenaline can be the first-line treatment of anaphylactic reaction but this is successful management.¹⁵ In children consuming IM epinephrine in the leg with an auto-injector, absorption is complete and faster. IM thigh injection in adults is even safer than IM or subcutaneous (SC) arms injection.³⁷ According to the existing recommendations on the management of anaphylaxis IM administration, although data remains low due to lack of controlled trials, the first-line treatment is for those with extreme allergic reactions that have RT and/or CV symptoms is epinephrine.³⁸

In the case of insect venom anaphylaxis, Specific Immunotherapy (SIT) are available. The vaccine for anaphylaxis caused by honeybee, wasp stings is commercially available in the market. Military servicemen with insect venom anaphylaxis, who may not be otherwise fit to continue military duties, may benefit from SIT. However, the benefits of SIT have to be balanced with the inconvenience posed to servicemen in active duty, which is a major reason for non-compliance in a previous study of SIT in military servicemen.¹⁸ Venom immunotherapy is seen as preventive in case of insect sting anaphylaxis and it also improves the quality of life in comparison with injectable adrenaline.³⁹



The second treatment recommended for anaphylaxis is anti-histamines, beta-agonists, and glucocorticoids. These are the agents that are subjected or administrated to the patient in a hospital-based setting along with activated charcoal, vasopressors, and glucagon.⁹ Prompt treatment of anaphylaxis is critical with intravenous fluids, epinephrine, and IM or SC remaining the mainstay of management. Measures include steroids, β -agonists, antihistamines, airways protection. Antihistamines and cortisone are helpful for the reduction of inflammation in air passages and also improves breathings. Patients take β -blockers also for the treatment of anaphylaxis to relieve RT symptoms.¹¹

The treatment of anaphylaxis depends upon the large part of the ability of the patient to describe the situation but as the patient may be unconscious or not properly conscious, he might not be able to explain the symptoms. Therefore, skin indications may be hidden by surgical drapes. Another is CV might be considered as an indication of anaphylaxis or it may confuse it with CV collapse. But tachycardia develops in case of anaphylaxis and bradycardia in case of CV collapse. The common cause of anaphylaxis during anesthesia is neuromuscular blocking agents or muscle relaxants. Sometimes muscle relaxants cause the release of MC histamine without the requirement for a specific antibody.³⁴

Management

Anaphylaxis is a life-threatening condition whose clinical diagnosis is a must, so it difficult to manage. The guidelines for the management of anaphylaxis are given by many organizations such as EAACI and WAO and many more. But the therapeutic agents for anaphylaxis is epinephrine and oxygen.³⁴ Specialist follows up is a must to determine the particular trigger of anaphylaxis. WAO has provided us the guidelines to approach the management of Anaphylaxis. These guidelines are provided by the National Institute of Allergy and Infectious Diseases (NIAID).⁹ The emergency treatment of Anaphylaxis involves breathing, systemic airways, circulation approach and the patient should receive adrenaline.¹⁵ There are four ways to manage Anaphylaxis effectively and that is:⁴⁰

- 1) timely diagnosis,
- 2) early administration of a dose of adrenaline,
- 3) aggressive administration of intravenous fluids,
- 4) amplification of therapy.

Medications such as corticosteroids and anti-histamine tend to treat mild-cutaneous allergy. Hypotensive Anaphylaxis can be treated with a large dose of Adrenaline. Therefore, people living in remote areas may need additional supplies but it should always be in an account that medical emergency must be taken without delay. These people must have access so that at the time of emergency they could have medical care.¹¹ Some anaphylactic reaction is so severe that the treatment is not proved successful and results in the death of the suspected

patient. It is figured out that the patient must be educated enough to suspect the triggers of anaphylaxis.³⁷ Patients can experience temporary symptoms after administration of epinephrine, including pallor, anxiety, palpitations, dizziness, and headache. After a 5-minute cycle, the epinephrine dose may be repeated. For each patient, a cautious, thorough evaluation of the risks and advantages of administering an auto-injector system is necessary.⁴¹

NSAIDs which are non-steroidal anti-inflammatory drugs that include cyclo-oxygenase-2 specific inhibitors have been seen to contribute to causing anaphylaxis reaction. One of the most common causes of severe anaphylaxis reaction is NSAIDs.³⁷ The quantifying of serum MC tryptase (MCT) is also used as an anaphylaxis marker. The patients with hypersensitive anaphylaxis have an increased level of MCT. The analyst is never the less motivated to determine MCT level in suspected anaphylaxis cases.²⁷ Whereas the management for second-line treatment of anaphylaxis is considered limited. It should be considered as an only adjunct therapy to epinephrine. It is concluded that the successful key for the management of anaphylaxis involves the recognition of people at risk for example food allergy in children and the rapid diagnosis and treatment.⁹ Hospital institutions should have a routine anaphylactic action plan and facilities for the treatment of anaphylaxis. The professional experience for anaphylaxis treatment should be retained by physicians and office personnel. Telephone numbers for paramedical rescue units and emergency services can also be helpful.⁴² An integrated management strategy including families, allergic children, schools, camps, and other youth groups is important to adequately care for people at risk of anaphylaxis. The risk prevention includes triggering clarification, discussion of allergy avoidance, the writing of the individualized response plan for emergency anaphylaxis, and adult monitoring instruction on anaphylaxis detection and care.²⁶ The self-management of anaphylaxis is described in figure 2.

Steps involved in the management of anaphylaxis.²⁶

Step 1: Have a written emergency protocol for recognition and treatment of anaphylaxis and rehearse it regularly.

Step 2: Remove exposure to trigger if possible, e.g., Discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

Step 3: Assess the patients' circulation, breathing, mental status, skin, and, body mass.

Note: Promptly and simultaneously perform steps 4, 5, and 6.

Step 4: Call for help: resuscitation team or hospital or emergency medical services if available.

Step 5: Inject epinephrine (adrenaline) IM in the mid-antrolateral aspect of the thigh, 0.01mg/kg of 1:1,000 (1 mg/ml) solution, maximum of 0.5 mg or 0.3mg (child); record the time of dose and repeat it in 5-15 minutes, if needed.



Step 6: Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if patients stand or sit suddenly.

Step 7: When indicated, give high-flow supplemental oxygen (5-8L/minute), by face mask or oropharyngeal airway.

Step 8: Establish intravenous access using needles or catheters with wide-bore cannulae. When indicated, give 1-2 liters of 0.9 % saline rapidly (e.g., 5-10ml/kg in the first 5-10 minutes to an adult; 10ml/kg to a child).

Step 9: When indicated at any time, perform cardiopulmonary resuscitation with continuous chest compressions.

Step 10: Besides, at frequent, regular intervals, monitor patients' blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).

stimulus to anaphylaxis. It becomes an exclusions diagnosis after consideration of other factors such as diet, drugs, exercise, food and drink, pinions or bites of insects, mastocytosis, and the deficiency/dysfunction of Clesterase inhibitor.⁴⁵ Table 3 shows the hypothesis for the episodes of IA.

Anaphylaxis Education

Awareness of people about anaphylaxis, their family and caregivers tend to banish distress and apprehension and instills trust in their capacity to cope, not just by anaphylactic episodes but even by identification and timely treatment. The Anaphylaxis curriculum has to be revised annually by all healthcare providers, including all medical staff, nurses, emergency medical services, and first responders. Ideally, the advanced guidance on the support of heart life should include the principles of recruiting self-injecting epinephrine in people treated with anaphylaxis arising in the population.⁴⁷ Appropriate diagnosis and management, guidance, and preparation for this specific population are important. Every adolescent should be taught how and when to use an epinephrine autoinjector and the signs and effects of anaphylaxis. Several reasons resolve increased risk-taking, dating, and transitional treatment between adults and patients. Management techniques must also be taken in public areas that are frequently put together by young people.⁴⁸ Security in kindergarten, nursery, or the camp of children at risk of anaphylaxis requires a collective initiative. A list of common roles surrounding food allergies of education, infant, teenage, and parent use has been established by several organizations. The practitioner should collaborate with school officials, students, nurses, and others to ensure a correct diagnosis is achieved and an adequate emergency anaphylaxis response plan is prescribed.⁴⁴

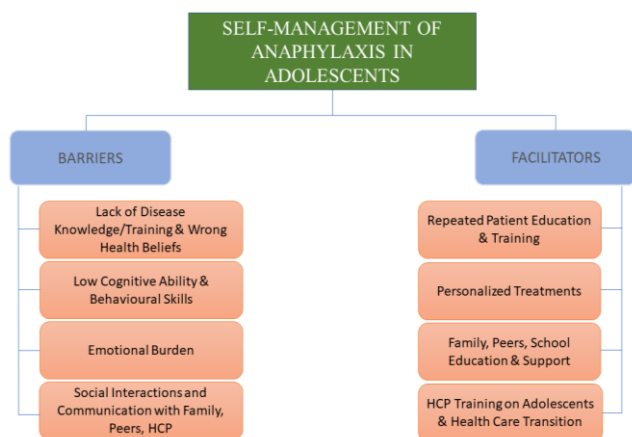


Figure 2: Self-Management of Anaphylaxis.

Idiopathic Anaphylaxis

Table 3: Episodes of IA were given hypotheses ⁴⁶

Allergens Concealed
Cytokine abnormality lowers the mast cell degranulation threshold
Mast cells and/or basophils have a female hormone effect
Changes in the population of T-cells
Histamine exposure at the target organ site has improved
Serum histamine release factor involvement
IgE autoantibodies involvement

Experts show that allergic diseases — in specific allergic diseases regulated with IgE — are growing worldwide. The most serious allergic condition is anaphylaxis.⁴³ The cause is uncertain and unreliable for idiopathic anaphylaxis (IA), but the symptoms are completely the same as those found in anaphylaxis. As low aerobic workouts can induce anaphylaxis, it is important to draw a very careful background to differentiate between the anaphylactic groups.⁴⁴ IA is not a confirmed or presumptive cause or

CONCLUSION

Anaphylaxis is a rare condition, can be deadly. For physicians who treat allergic conditions, it is a particular problem. To recognize causes, patients must be identified and properly briefed about the illness how to treat it with emergency drugs. Medical and laboratory allergists appear to be met with idiopathic anaphylaxis. Further research on pathophysiology and the mechanistic significance of co-factors to cause an anaphylactic reaction is required. Anaphylaxis is a unique opportunity for doctors, other health practitioners, researchers, politicians, patients, carers, and the world's population. Additional study is important to help identify self-management facilitators for teenagers at anaphylaxis danger. In this respect, there is a need for self-evaluation methods for anaphylaxis, which will help to assess the preparation for the change of young people and for intervention trials to examine the possible benefits of friends and social reinforcement. It is also critical for medical practitioners to provide detailed guidance on how to help the treatment of young people with anaphylaxis and how to ensure a better and effective transition from pediatric to adult care. A referral to a registered nutritionist may be useful in situations where the



food allergies are reported and have some dietary limitations.

Acknowledgement: The author acknowledges the cooperation of Iqbaljit Kaur of Lovely Professional University and all those who have contributed in one sense or another in this review.

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Source of Support: None declared.

Conflict of Interest: None declared.

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