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Review Article

Anaphylaxis – A must know for all

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ABSTRACT

Anaphylaxis is a severe, acute, and potentially fatal multi-organ reaction caused by exposure to an allergen. The most involved organ systems are skin, pulmonary, cardiovascular, and gastrointestinal systems, with cutaneous system involvement witnessed in up to 90% of cases. Three commonest reported triggers are food, medicine, and insect venom. It is characterized clinically by wheals and/or angioedema in association with dyspnea, tachypnea, wheezing, tachycardia, vomiting, abdominal pain, diarrhea, clammy skin, confusion, and anxiety. According to the available data, the likelihood of experiencing an episode of anaphylaxis during a lifetime can be expected in up to 2% of population. The incidence of anaphylaxis has been increasing because of the globalization, which has resulted in increased migration of inherent population to distant areas of the world, wider distribution of food and medicines. Furthermore, because of the climate change brought about by industrialization and automation, there has been a noticeable change in the local insect species. People manifesting with any of the three clinical presentations of atopic diathesis (namely, asthma, eczema, and allergic rhinitis) generally have higher chances of experiencing anaphylaxis, and the three most common incriminating triggers include food item, latex rubber, and radio contrast agents. Depending on the patho-physiological mechanism involved, anaphylaxis can be either immunologic, non-immunologic, or idiopathic. The diagnosis of anaphylaxis can largely be made based purely on the presenting sign and symptoms. However, in some rare cases, when it is not possible to make the diagnosis clinically, laboratory investigations are used to supplement or to exclude a specific entity. The standard protocol for managing a case of anaphylaxis includes removal of the trigger, initiation of epinephrine therapy at an earliest, appropriate positioning of the patient to maintain free airway, and hemodynamic balance and call for help for multidisciplinary approach. It is often misdiagnosed owning to the markedly varying clinical presentations, and absence of specific diagnostic laboratory test. Thus, in the present review we have given a comprehensive update to freshen up the knowledge of the physician, to enable them to easily diagnose and manage a suspected case of anaphylaxis, to avoid potential complications and fatalities, and even prevent repeated attacks in some of the cases.

Keywords: Anaphylaxis, Epinephrine, Insect venom, Idiopathic, Food, Medicines

INTRODUCTION

Anaphylaxis is a severe, acute, potentially fatal multi-organ system reaction caused by exposure to an allergen. It characteristically involves an immune mediated reaction on re-exposure to a previously sensitized allergen. It basically results from the body's natural defense mechanism (immune system) overreacting to a trigger. The clinical manifestations of the reactions are caused by the effects brought about by the numerous inflammatory mediators released from mast cells and basophils. The most involved organ systems are skin, pulmonary, cardiovascular, and gastrointestinal systems, with cutaneous system involvement witnessed in up to 90% of cases. Three commonest reported triggers are food, medicine, and insect venom. Its onset is sudden and worsens very quickly, and symptoms may vary from feeling lightheaded to losing consciousness. Other commonly noted clinical features are dyspnea, tachypnea, wheezing; tachycardia; clammy skin; confusion; and anxiety; skin findings include hives and swelling on skin and/or mucosa. Other less commonly reported symptoms are abdominal pain and diarrhea. It is a potentially fatal condition requiring urgent management. Mortalities can be due to respiratory failure resulting from mucosal edema leading to asphyxia and severe bronchoconstriction, hypotensive shock, and cardiac arrest.

Common triggers include

- Foods – including nuts, milk, fish, shellfish, eggs, and some fruits
- Medicines – including some antibiotics and non-steroidal anti-inflammatory drugs like aspirin, biologic agents, and vaccines particularly mRNA COVID vaccines and non-replicating viral vector vaccines
- Insect stings – particularly wasp and bee stings
- General anesthesia

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- Contrast agents – dyes used in some medical tests to help certain areas of your body show up better on scans, rarely hair dyes, and mehndi
- Latex – a type of rubber found in some rubber gloves and condoms

In some cases, where the trigger cannot be identified, the term "Idiopathic anaphylaxis" is used.

DEFINITION

Turner *et al*.[1] have recently proposed a revised definition: "Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present."

HISTORICAL PERSPECTIVE

In 1902, Portier and Richet were the first to recognize and name "anaphylaxis" (derived from the Greek, meaning "against protection") for the "property that has a poison to lower immunity rather than reinforce it." While working with dogs sensitized to *Physalia physalis* antigens.[2] They noticed that when the dogs that had been previously exposed to *P. physalis,* were injected with a nonlethal dose, died suddenly of multi organ system failure involving pulmonary, cardiovascular and gastrointestinal systems. Ishizaka *et al*.[3] in 1966 discovered immunoglobulin E (IgE), and later on the demonstration of antigen/IgE cross linking of IgE receptors on human basophils and mast cells, that produced the vasoactive mediators capable of inducing vasodilatation, bronchoconstriction, and increased GI motility explained the possible mechanism involved in pathogenesis of anaphylaxis. On the other hand, contrary to our conventional knowledge, recently IgE-associated Th2 immune response has been found to increase the host resistance against hymenopteran, neurotoxins, and snake venoms.[4,5]

EPIDEMIOLOGY

Although, the true burden of anaphylaxis may not be known, because the available data are essentially based on the hospital admission database. And, not so infrequently, anaphylaxis happens in the communities, with only minority of these cases needing hospitalization are accounted for. Thus, the data probably underestimates the true rate. According to one report, 4–100/100,000 persons/year, experience an anaphylactic attack.[6] Furthermore, up to 2% of the population is likely to get anaphylactic attack at some point in life.[7] Anaphylaxis accounts for up to 0.26% of total hospitalizations, and this rate is on the increasing trend globally.[8] Taiwan is the only exception, which has not reported increase in hospitalization rate of anaphylaxis, in spite of increase in overall number of hospital referrals for the same.[9] The available data from South Korea[10] and New Zealand, shows 1.7 fold increase in the rate, remarkably the children have been more affected. Also, New Zealand has witnessed a 2.8 fold rise in anaphylaxis hospitalizations caused by food related substances.[11] In spite of global increase in the hospitalization rates, the fatalities related to anaphylaxis have been gradually declining,[12,13] with the exception of Australia, which showed 6.2% increase per annum from 1997 to 2013.[14] However, on analyzing the data on fatalities related to trigger specific anaphylaxis, mortalities related to drug induced anaphylaxis have risen in Australia and USA.[13] In addition, Australia has also shown rise in death rate related to food induced anaphylaxis.[14]

RISK FACTORS

People manifesting with any of the three clinical presentations of atopic diathesis (namely, asthma, eczema, and allergic rhinitis) generally have higher chances of experiencing anaphylaxis due to food item, latex rubber, and radio contrast agents, but not from injectable medications or stings.[15] Furthermore, a positive family history of anaphylaxis puts a person at higher risk. Similarly, past history of anaphylactic attack increases the risk of anaphylaxis. Antihypertensive medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics increase the risk for severe reactions because of their BP lowering and bronchoconstriction causing properties. Furthermore, teenagers are at high risk of more severe and even fatal anaphylaxis reaction.[16]

TRIGGERS

Globalization has led to the recent increase in potential triggers, especially with the worldwide circulation of food products, newer drug molecules, and climate change causing change in insect flora of the regions.[17,18] The most commonly described triggering agents in adults are medications (35%), foods (32%), insect venom(19%), and idiopathic (14%). Whereas, in children the majority (85%) are related to foods, idiopathic (11%), and insect venom (4%).[19-21]

PATHOPHYSIOLOGICAL TYPES

Depending on the pathophysiological mechanism involved, anaphylaxis can be either immunologic, non-immunologic, or idiopathic. Immunologic can be IgE or non-IgE mediated. Examples of IgE mediated anaphylaxis include those caused by foods, insect venom, and beta lactam antibiotics. IgE binds to the FceR1 receptor located on the surface of basophils and mast cells. Moreover, on exposure to a bi or multivalent allergen, cross linking of Fcer1-bound IgE results in activation of the basophils and tissue mast cells.[22] This not only induces immediate release of various preformed inflammatory mediators including histamine and proteases. But also leads to *de novo* synthesis of many more mediators such as prostaglandins, cytokines, and leukotrienes. Thus, the

formation of antigen specific IgE antibodies plays a key role in the development of anaphylaxis in a sensitized individual. However, only IgE levels alone cannot explain individual's risk of developing anaphylaxis. Because, even in patients with nearly undetectable levels of specific IgE can also develop near fatal anaphylaxis. Conversely, some patients do not manifest allergy even in presence of high level of allergen specific antibodies, when exposed to the allergen. Therefore, there has to be another IgE nondependent pathway of anaphylaxis.

Non-IgE immunologic anaphylaxis is mediated by complement derived anaphylatoxins (C3a, C5a, Bradykinin), as seen with radiographic contrast material and contaminated heparin induced anaphylaxis. These anaphylatoxins are strong inflammatory mediators and activate basophils and mast cells.[23]

Non-immunologic anaphylaxis involves direct degranulation of mast cells, and reportedly occurs after exercise, exposure to cold, due to drugs such as opioids or vancomycin. Idiopathic anaphylaxis also involves activation of mast cell as evidenced by sudden spike in urinary histamine or elevated serum tryptase levels, and activated lymphocytes.[24]

DIAGNOSIS

The diagnosis of anaphylaxis is considered to be "highly likely" in presence of one of the following two criteria: [1]

1. Sudden appearance of generalized wheals or mucosal swelling, associated with one of the following: respiratory features (dyspnea, wheezing, and stridor); or low blood pressure (BP) (including signs of end organ damage); or persistent gastrointestinal symptoms (Vomiting and abdominal cramps).
2. Sudden drop in BP following exposure to an associated trigger factor (systolic BP <90 mm hg or >30% drop from base line BP); or, respiratory compromise (dyspnea, wheezing, and stridor) due to bronchospasm and or laryngeal involvement after exposure to an allergen.

CLINICAL PRESENTATIONS

The characteristic presenting features of anaphylaxis may not be the same in all the patients, and can differ depending upon the nature of the triggering agent, time of presentation, age of the patient, presence of co-morbid conditions, and concurrent drug therapy. They are primarily related to 5 main organ systems:

- **Skin (80–90%)** - Urticaria, angioedema, maculopapular rash, conjunctival congestion, lip, tongue and/or lid swelling, erythema, and itching
- **Respiratory system (70%)** - Nasal itching, rhinorrhea, stridor, cough, sneezing, throat tightness, dyspnea, tachypnea, wheezing, and respiratory arrest
- **Cardiovascular system (45%)** - Chest pain/tightness, palpitations, arrhythmias, hypotension, shock, cardiac arrest, urinary, or fecal incontinence
- **Gastrointestinal system (45%)** - Pain in abdomen, nausea, vomiting, diarrhea, and difficulty swallowing
- **Central Nervous system (15%)** - Altered mental status, headache, dizziness, confusion, and tubular vision.

Making a correct diagnosis in infants can be challenging, because some of the characteristic signs of anaphylaxis such as flushing, dysphonia after crying, spitting up after feeds, and loss of urinary/bowel control are normally seen at this age.

LABORATORY INVESTIGATIONS

Although, the diagnosis of anaphylaxis is usually made clinically. However, laboratory investigations can sometimes be used to supplement or to exclude a specific entity.[25] In cases of IgE mediated immunological anaphylaxis, the confirmation of diagnosis can only be made on demonstration specific IgE antibodies. Besides, it can sometimes help in predicting a severe attack, and can also be useful in the identification of cross-reacting food substances in cases where food is the known trigger factor. Identification of high serum basal tryptase levels indicates increased risk of severe anaphylaxis, and initiating prompt therapy in these cases can possibly avoid further acute episodes.[26] Normally, either an increase of serum basal tryptase level over 11.4 ng/mL, or an increase of baselineX1.2+ 2 ng, indicates mediator release from activated mast cell/basophil.[27] The estimation of histamine and prostaglandins in urine, or on skin testing in a patient with suspected anaphylactic reaction in recent past can be useful in making the diagnosis retrospectively.

TREATMENT

Current guidelines published by different associations, concur for the need of standardized uniform protocol for the management of anaphylaxis, to reduce the mortality rate. Almost, all of them include following basic steps: Removal of the trigger, initiation of epinephrine therapy at an earliest, appropriate positioning of the patient to maintain free airway and hemodynamic balance, and call for help for multidisciplinary approach.[28] The standard protocol for managing a case of anaphylaxis includes removal of the trigger, initiation of epinephrine therapy at an earliest, appropriate positioning of the patient to maintain free airway and hemodynamic balance, and call for help for multidisciplinary approach [Figure 1]. It can be summarized in an easy to memorize mnemonic "ABCM" (airway patency, breathing, circulation, and mental status assessment). Among the available medications, epinephrine is the only recommended drug, and it can affectively reverse hypotension, bronchoconstriction, and mast cell degranulation, characteristically seen during anaphylaxis attack. Other drugs like, β2-agonists and glucagon are used as the second-line treatment, meanwhile systemic steroids

Figure 1: Flow diagram showing the management of anaphylactic reaction.

and H1 antihistaminic drugs are reserved as the third-line treatment. And they should never be administered before adrenaline injection. Newer data suggests that the steroids have limited role and can even be potentially harmful. Biologicals, as monotherapy or as combination therapy with food or venom immunotherapy, possess a preventive role, and can effectively reduce the most severe of anaphylactic reactions.

EPINEPHRINE

The α1 receptor agonist action leads to vasoconstriction, which helps both to prevent and relieve laryngeal edema, hypotension, and as well as shock. Whereas its β1-receptor agonist action produces positive inotropic and chronotropic effects on heart muscles, as wells as causes bronchodilatation and reduced release of inflammatory markers. It is the most effective treatment for anaphylaxis and should be given right away (usually in the thigh), preferably intramuscularly in a pre-filled, auto-injectable device. To avoid the unnecessary delay in loading the injection in conventional syringe, and it also minimizes the chance of errors in administration. In case of established shock, local vasoconstriction can reduce the systemic absorption of the drug. Thus, the subcutaneous administration route should generally be avoided. The dose used is 0.01 mL/kg of aqueous adrenaline 1:1000 (1 mg/mL), to a maximum of 0.3 mg in a child and 0.5 mg in case of adults. If required, it can be repeated after 5–15 min.[29] Usually, one fourth of the patients would need a repeat injection.[30] If someone has had an anaphylaxis reaction before, that person should always carry at least two doses of epinephrine.[31]

SECOND LINE TREATMENT

Several other drugs (Beta agonist and Glucagon) are used in anaphylaxis as an additional treatment. However, they must all be used as second line, after administering epinephrine. The treatment with beta agonists agents like salbutamol, are initialed in cases having bronchospasm not relieved by epinephrine. They can be administered either by nebulization or with spacers.

Another agent commonly used as a second line drug is Glucagon. It is a peptide hormone produced by α-cells in the Islet of Langerhans of the pancreas. It is associated

with positive inotropic and chronotropic action, which is independent of the β2-adrenergic receptors. Thus, it is primarily used in patients being treated with beta blockers, in whom the action of epinephrine on beta adrenergic receptors is blocked.[32] However, its rapid administration can induce vomiting. Thus, it should be used with caution in patients not in fully conscious state, while maintaining a clear airway.

THIRD LINE AGENTS

Although, there is no definite supporting evidence available in the literature favoring the role of H1 blocker drugs in the management of anaphylactic reaction.[33] They are effectively used to manage urticarial wheals, angioedema, and to relieve symptoms such as itching and flushing. The disadvantages with these classes of drugs are that their onset of action is slow require at least 30 min to act. Furthermore, parental preparations are available for only first generation antihistaminic, which are known to cause somnolence and confusion, and less frequently can even have severe adverse effects such as hypotension and cardio toxicity.[34] Combining these, with H2-antihistmines can increase their efficacy in urticaria.

Parental corticosteroids are very commonly used, even though the recent literature shows no evidence of them being effective in the management of anaphylaxis.[35]

Methylene blue is another agent used in cases of refractory hypotension. It acts by inhibiting the NO pathway.

In cases of pre-operative anaphylaxis induced by neuromuscular blocker such as rocuronium and sugammadex is given to inactivate the implicated agent, and thus has been used in these specific circumstances.[36]

NEWER INSIGHTS

It is now being recommended to screen all the patients presenting with anaphylactic reaction with Tryptase levels, it can effectively rule out other conditions like hereditary alpha tryptasemia syndrome, which can mimic clinically with anaphylactic reaction. Furthermore, now the consensus is developing for the long-term treatment with biologic agents that can alter IgE and mast cell responses, like anti-IgE, anti-IL–4/13, and others agents. Omalizumab has been found useful in idiopathic anaphylaxis as a preventive medication.

Newer devices using needle free injection technology have become commercially available recently and play a significant role in cases of Injection phobia. Such devices (Bioject® from Inovio Pharmaceuticals, Zeneo® from Crossject), which can consistently deliver intramuscular liquid preparations.[37] Furthermore, sublingual tablets of adrenaline are under animal testing for their role in anaphylaxis, because they are easy to carry and needle phobia can also be avoided.

To prevent specific food induced anaphylaxis, immunotherapies using modified proteins targeting specific immunoglobulin pathways are becoming increasingly available.

Finally, during COVID times, CDC is currently recommending post COVID vaccination extended observation periods for those with history of anaphylaxis or other immediate allergic reaction of less severity, to those persons who do not otherwise possess any contraindications to receive mRNA COVID-19 vaccine.[38] The guidelines regarding post-COVID vaccination observation duration are as follows:

- **30 min:** Anyone with a past history of an immediate allergic reaction to a vaccine or any injectable drug or history of anaphylaxis due to any cause
- **15 min:** All other persons.

CONCLUSION

Anaphylaxis is an acute and potentially fatal condition, which requires a quick clinical diagnosis and initiation of therapy by the attending physician in order to save the patient's life. Thus, if every medical specialist (including a dermatologist) is equipped with the basic up to date knowledge about the clinical features and management of this entity, it may prove to be handy in the hour of need. Epinephrine(preloaded), still remains the drug of first choice and must be readily available in every clinic, to tackle any such urgent situation effectively. On the other hand, steroids do not have any significant role to play, and should be better avoided. Lastly, newer biological agents seem to have a role in the prevention of severe attack of anaphylactic reaction in an appropriate case.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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