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Allergen Immunotherapy: Tactic in manipulating food allergen induced anaphylaxis

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Abstract

The pervasiveness of food allergy and associated anaphylactic reactions are proliferating consecutively and the absence of a proper treatment adds to it. Food, both animal as well as plant derived, are presented as the major risk factors. There are several pathways deduced in favour of the food-induced anaphylaxis, ultimately leading to the activation of T-cells. One of the efficient way to solve this issue is allergen immunotherapy that involves the administration of small doses of modified allergen content and increasing the dose geometrically until tolerant level is achieved. The present treatment includes the symptomatic treatment just though a perpetual fix can be accomplished through the immunotherapy. It focus on the development of innate and adaptive immunity and further acts as a shield to prevent recurrent episodes of anaphylaxis. Specific allergen induced immunotherapy can induce a response that can benefit up to a period of 3 years even after discontinuation of the therapy. Persistent advancement of immunology and bioengineering improves understanding diagnostics. Oral and subcutaneous routes are mostly exploited for the allergen immunotherapy. There is also a need to shed more light on the availability of a standardized allergen extract for the specific treatment of food allergy. Additional research on possible pathogenesis/ pathways and newer route of administration can lead to more safe and efficient treatment methodology.

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BACKGROUND

The worldwide prevalence of food-induced anaphylaxis is increasing at an alarming rate. Various food and food additives such as milk, egg, peanuts, and shellfishes, etc., recognized as allergenic substances may present as a potential threat to various individuals. The symptomatic treatment leading to acute relief in patients seems to be insufficient. Therefore a personalized therapy leading to the development of innate immunity is required.

INTRODUCTION

Food induced anaphylaxis is a sudden allergic response occurring due to the induction of immune cells that is triggered by any food substances ingested into the body and may even lead to death. The exact allergenic substance causing anaphylaxis may vary for each food substances but in a majority of the cases, it is the protein present that is involved in the triggering process.

An overview directed by the World Allergy Orga-

nization, half of them had no information on food allergy predominance, while a quarter had information dependent on patient/parent report, and just 10% had nourishment sensitivity commonness information dependent on oral nourishment challenges (OFCs). At present, most of the accessible information depends on self-detailing, which by and large overestimates nourishment sensitivity commonness by a factor of three to four (Woods *et al.*, 2002). One surrogate proportion of food allergy which has been recommended to give more noteworthy exactness in deciding nourishment sensitivity predominance is the nearness of a clinical history of response to the nourishment in the mix with a positive allergen-explicit immunoglobulin E (sIgE) or skin prick test. In any case, it is imperative to take note that most sharpened people can endure the nourishment without response, so this methodology may, in any case, overestimate the genuine pervasiveness if the historical backdrop of response depends on self-report (Osborne *et al.*, 2011). In the United States and other Western nations, the commonness of food allergy has been on the ascent, and appraisals recommend that up to 8% of youngsters might be influenced. Roughly 1.5% to 3% of youngsters experience the ill effects of shelled nut sensitivity (Gupta *et al.*, 2011; Dyer *et al.*, 2015). The refinement of a specific food allergen can contrast with people. In 2013, the assessed generally monetary weight of food allergy was evaluated to be $24.8 billion every year because of direct costs, for example, crisis room visits, hospitalizations, prescriptions, and backhanded costs. The expense of food allergy has been significantly featured by discussion over the increasing expense of epinephrine auto-injectors. Families should likewise pay for isolated nourishments for kids with food allergy (Chen *et al.*, 2018).

Accepting the general budgetary just as the individual weight of food allergy, noteworthy research has been committed to the counteractive action of food allergy. The present treatment includes the symptomatic treatment just though a perpetual fix can be accomplished through the immunotherapy. This review exemplifies the ongoing advances in our comprehension of food allergy avoidance by stressing on allergen immunotherapy.

Major causes and the associated allergens

The causes of food induced anaphylaxis may vary from person to person as it depends on the particular immune response to the food substance. Some of the common food substances along with the chemical components present in it that have shown allergenic properties are listed in the Tables 1 and 2, (Cianferoni and Muraro, 2012; Hugh and Sampson, 2000).

Classification of food induced anaphylatic reactions

Although the pathogenesis does not solely depend on one type of pathway, anaphylactic reactions due to food substances in majority of the cases, is mediated through IgE-mediated pathway followed by the release of preformed chemical mediators like histamine, tryptase, chymase etc. as well as newly synthesized mediators like bradykinins, cytokinins and leukotriene (Cianferoni and Muraro, 2012).

Based on the type of mediators involved in the induction of anaphylaxis (Hugh and Sampson, 2000), it can be broadly classified into Immune-mediated reactions and Non-immune mediated reactions.

Immune-mediated reactions

When the allergic substance enters the body by oral ingestion, the proteins which act as the allergens triggers the immune system of the body, causing a cascade of reactions to occur as a result numerous chemical moieties are produced, which in turn lead to severe anaphylactic reactions such as inflammation, skin rashes, respiratory issues etc. These reactions occurring as a result of the activation of the immune system is called the immune-mediated reactions (Uetrecht, 2009). From Figure 1.

In the majority of the cases, the IgE mediated responses occur primarily because of its quick onset of action when compared to the Non-IgE mediated response having a slow onset of action. The presence of food substances like peanut, tree nut and seafood causes fatal anaphylaxis due to the induction of IgE mediated immune cells (Anvari *et al.*, 2019).

Non-immune mediated reactions

Anaphylactoid reactions or the non-immune mediated reactions are described as the responses which present similar symptoms related to the anaphylaxis but are not IgE mediated. The initiation of the complement and/or bradykinin cascade and the direct stimulation of mast cells and/or basophils are the main steps in the activation of Anaphylactoid reactions, which may even lead to cardiovascular failure and death (Lagopoulos and E, 2011). From Figure 2.

The most common sources of foods for non-IgE-mediated food allergies are cow's milk and soy proteins in infants and wheat in older children. Non-IgE food allergies are occasionally life-threatening because they do not result in anaphylaxis. Abdominal discomfort, vomiting, and diarrhoea are com-

Table 1: Allergenic chemical constituent present in various food substances

SI.No	Food Substance	Allergenic Chemical Constituent Present
1	Peanut (Arachis hypogea)	1. Seed storage proteins such as Ara h1, Ara h2, Ara h3, Ara h4, Ara h6, Ara h7 2. Oleosin plant lipid storage bodies such as Ara h10 and Ara h11 3. Profilin (Bet v 2 like) i.e. Ara h5 4. Bet v 1 family (PR-1 O, Bet v 1 like) i.e. Ara h8 5. LTP- Ara h9
2	Hen's egg (Gallus domesticus)	1. Gal d 1 (Ovomucoid) 2. Gal d 2 (Ovalbumin) 3. Gal d 3 (Ovotransferrin/conalbumin) 4. Gal d 4 (Lysozyme) 5. Gal d 5 (alpha-Livetin)
3	Cow's milk	1. Bos d 8 (α-,α.2-n, β-, γ1, γ2 γs K-casein) 2. Bos d 4 (α-Lactalbumin) 3. Bos d 5 (β-Lactoglobulin) 4. Bos d 7 (Immunoglobulin) 5. Bos d 6 (BSA)
4	Soybean (Glycine max)	1. Gly m 1 (LTP) 2. Gly m 2 (Defensin) 3. Gly m 3 (Profilin) 4. Gly m 4 [Bet v 1 family (PR-1 O, Bet v 1 like)] 5. Gly m 5 (Vicilin) 6. Gly m 6 (Legumin)
5	Pea (Pisum sativum)	1. Pis s 1 (Vicilin) 2. Pis s 2 (Convicilin)
6	Green bean (Phaseolus vulgaris)	1. Pha v 3 (nsLTP type 1)
7	Hazelnut (Corylus avellana)	1. Cor a 1 [PR-10 (Bet v 1 homologous)] 2. Cor a 2 [Profilin] 3. Cor a 8 [PR-14 (LPT) 9] 4. Cor a 9 [Globulin (11S)] 5. Cor a 11 [Vicilin (7S)]

(Hefle *et al.*, 1996)

Table 2: Allergenic chemical constituent present in various food substances (*Continue from Table 1*)

Sl.No	Food Substance	Allergenic Chemical Constituent Present
8	Chestnut (Castanea sativa)	1. Cas s 5 [Chitinase Ib]] 2. Cas s 8 [PR-14 (LPT)]
9	Brazil nut	1. Ber e 1 [Albumin (2S)] 2. Ber e 2 [Legumin (11S)]
10	Sesame	1. Ses i 1, Ses i 2 (S albumin) 2. Ses i 3 (7S globulin) 3. Ses i 4, Ses i 5 (Oleosin) 4. Ses i 6, Ses i 7 (Basic subunit of 11S globulins)
11	Lupine (Lupinus angustifolius)	1. Lup an 1 [β-Conglutin (vicilin)]
12	Lentil (Lens culinaris)	1. Len c 1 (γ-Vicilin subunit)) 2. en c 2 (Seed specific) 3. Len c 3 (nsLTP type 1)
13	Cashew (Anacardium occidentale)	1. Ana o 1 [Vicilin (7S)] 2. Ana o 2 [Legumin (11S)]
14	Walnut (Juglans regia)	1. Jug r 1 [Albumin (2S)] 2. Jug r 2 [Vicilin (7S)] 3. Jug r 3 [PR-14 (LTP)] 4. Jug r 4 [Legumin (11S)]
15	Shellfish	1. Met e 1, Pen a 1, Pen m 1, Pen i 1, Cha f 1, Hom a 1, Pan s 1, Tod p 1, Hel as 1, Hal m 1 (Tropomyosin)

(Hefle *et al.*, 1996)

mon symptoms associated with non-IgE mediated reactions (Connors *et al.*, 2018).

Pathogenesis of food-induced anaphylaxis

The immune system consists of two broad cellular responses: Innate immunity and Adaptive immunity. The innate immune response is your first line of defense against pathogens. It provides a quick response to pathogens by many mechanisms, including cytokine production and complement activation. The adaptive immune response uses antigen-specific receptors to detect foreign antigens. This is a slow occurrence that results from efforts of T Cells, B cells, and natural killer T Cells. Humoral immunity uses antibodies for detection, whereas cell-mediated immunity uses T Cells to destroy the affected cells. The regulation of immune cells occurs through a number of key signalling pathways. Each pathway is comprised of a complex network of proteins that interact with one another to induce a specific cellular response to stimuli. From Figure 3.

When the antigen is encountered for the first time, lymphocytes exert the primary immune response. The same cells can "learn" from their experience, so that a subsequent encounter with the same antigen will result in a quicker, secondary immune response.

The cell types involved in the innate immune response are phagocytic cells: neutrophils, macrophages, natural killer cells, basophils, and others (Warrington *et al.*, 2011).

The food-induced anaphylaxis may occur by immune-mediated as well as non-immune mediated with respect to the food substance as well as the tolerance of the patient towards that particular allergen. Since the exact mechanism behind the non-IgE mediated reactions is not known, the pathogenesis of IgE-mediated anaphylaxis can be studied in detail (Lemon-Mulé *et al.*, 2008).

IgE-mediated food allergies occur as a result of lost integrity in the key insusceptible components that maintain a state of tolerance and prevent positive food antigens from being seen as pathogens. Even more explicitly, oral tolerance to foods is characterized as the intersection of food antigen over the mucosal limit, taking care of by dendritic cells in a non-activated state, and the induction of suppressive cytokines, for instance, interleukin 10, by those antigen-presenting cells. This, thus, results in the differentiation of simple T-cells into T regulatory cells and concealment of food antigen-explicit Th2 cells, just as extended IgA and IgG4 production and a reduction in IgE by B cells. Finally, there is sheltered concealment of eosinophils, basophils, and mast cells, effector cells that reason symptoms (Berin and Sicherer, 2011).

T-Cell signalling

T Cells play a critical role in cell-mediated immunity and arise from lymphoid progenitor cells that originally developed from hematopoietic stem cells in the bone marrow.

T Cells are identified by the expression of CD3 and develop into their various subtypes in the thymus (hence the name T cell). Each subtype is defined by the specific receptors expressed on the cell surface, making these cells highly selective to non-self pathogens. Mature T Cells are released into the bloodstream where they can be induced to become one of several classes of T cells including,

1. Helper T Cell - CD4+ T Cells suited to recognize peptide antigens bound to class II MHC proteins and release a variety of cytokines.
2. Cytotoxic T Cell - CD8+ cells that recognize virus-infected cells or tumour cells.
3. Regulatory T cell - The main job of regulatory T Cells (Treg) is to maintain tolerance to self-antigens, as well as limit T-effector cell function and proliferation.
4. Natural Killer T Cell - NK cells release small granules containing granzymes and perforin, which form pores and break down intracellular proteins in order to induce apoptosis in virally-infected or tumour cells.

Current management & treatment available to the patients Management

Avoiding the consumption of allergic food is the prime approach to avoid food allergy. Checking the ingredient given in the food product labels and learning the auxiliary names of allergic substances can also benefit in the management of food allergy.

It has been made mandatory in the United States, to present in simple and clear language about the presence of any of the eight most common food allergens such as egg, milk, peanut, wheat, soy, tree nut, fish and crustacean shellfish in the respective products by The Food Allergy Labelling and Consumer Protection Act of 2004 (FALCPA), even if the allergen is only an incidental ingredient, as in an additive or flavoring. Allergies to milk, eggs, wheat, and soy may withdraw after a certain age, while allergies to peanuts, tree nuts, fish and shellfish tend to be eternal (Keet, 2011).

The British Society for Allergy and Clinical Immunology (BSACI), in conjunction with the Royal College of Paediatrics and Child Health, has recently updated its Allergy Management Plans for children, highlighting the potential for skin symptoms to be absent in anaphylaxis (Nair *et al.*, 2014). From Figure 4.

Treatment

Acute treatment

Since the anaphylactic attack can occur unexpectedly, individuals susceptible to the food-induced anaphylaxis should be equipped with epinephrine auto-injector as a first line treatment. If no improvement is observed, intramuscular adrenaline injection is given every 5 minute interval under the supervision of an expert (Nair *et al.*, 2014). Along with epinephrine, oral antihistamine such as diphenhydramine or chlorpheniramine may be administered. Additional treatment such as oxygen, inhaled albuterol, systemic corticosteroids and antihistamines may be given upon reaching a medical facility (Tsoumani *et al.*, 2015).

Chronic treatment

Effective treatments targeting immunomodulation such as oral immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy, and epicutaneous immunotherapy are under development with allergen immunotherapy with promising results (Muraro *et al.*, 2014).

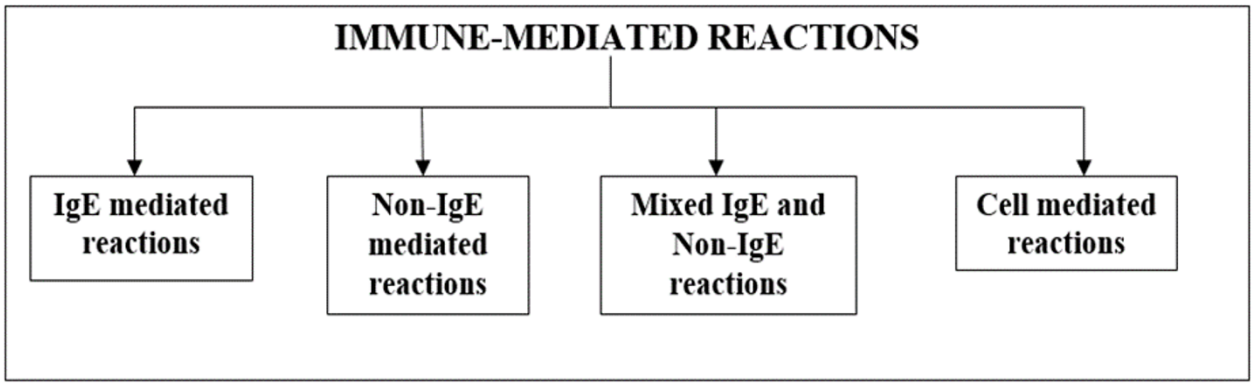


Figure 1: Types of immune-mediated reactions

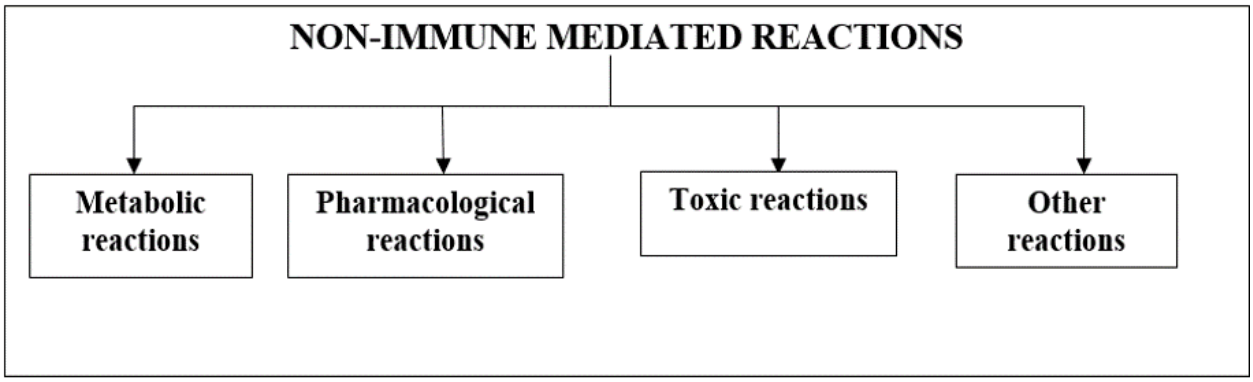


Figure 2: Types of non-immune mediated reactions

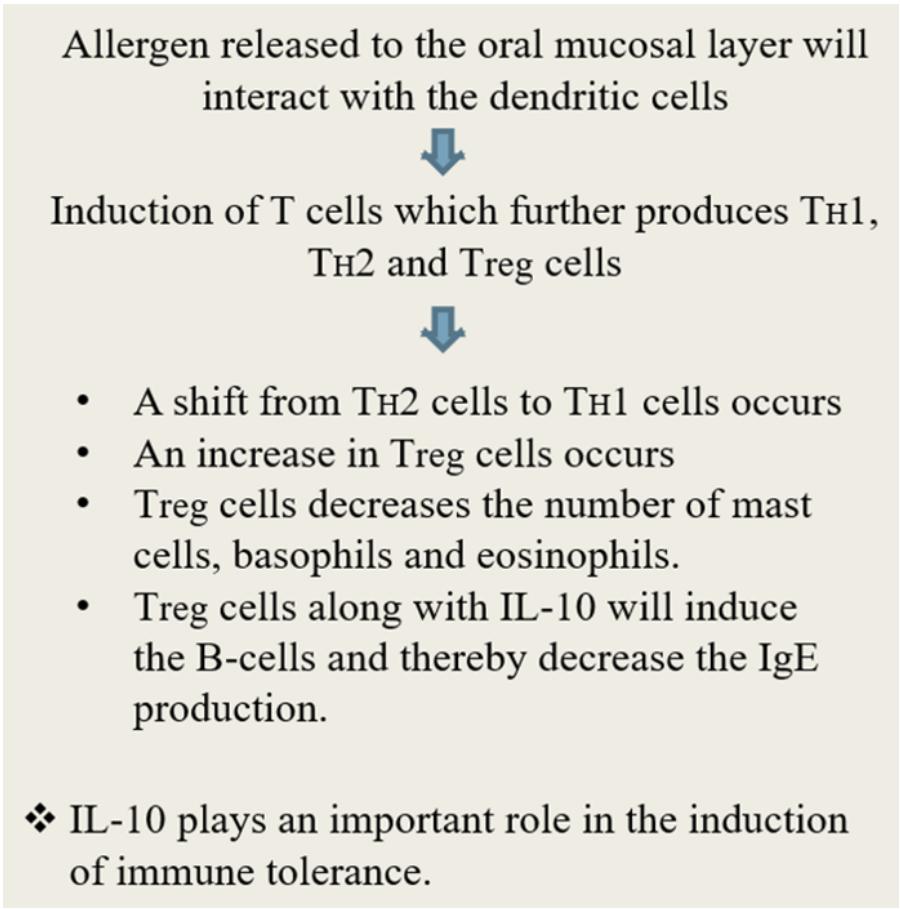
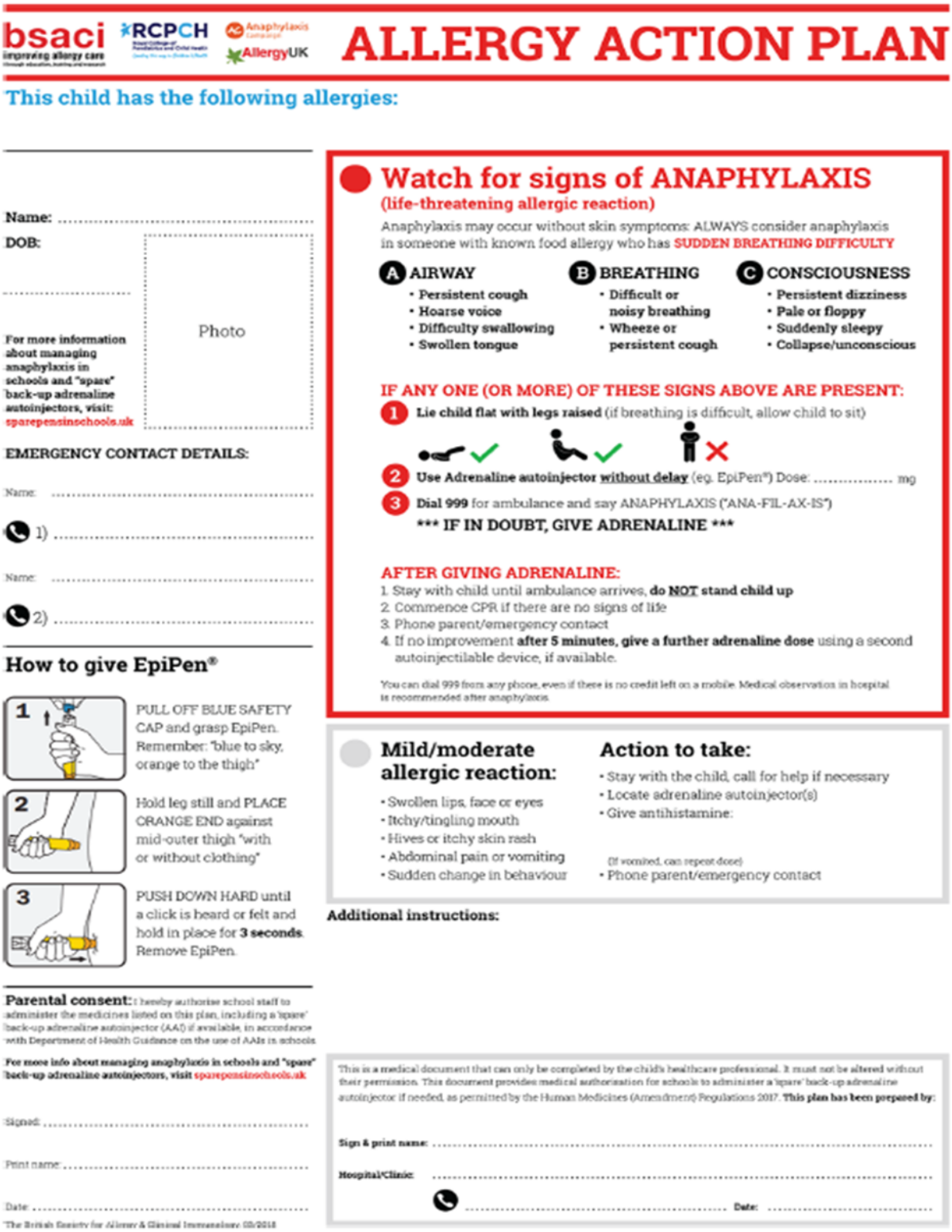


Figure 3: Pathogenesis of food-induced anaphylaxis



bsaci improving allergy care · RCPCH · Anaphylaxis Campaign · AllergyUK

ALLERGY ACTION PLAN

This child has the following allergies:

Name: .....

DOB: .....

Photo

For more information about managing anaphylaxis in schools and "spare" back-up adrenaline autoinjectors, visit: sparepensinschools.uk

EMERGENCY CONTACT DETAILS:

Name: .....

1) .....

Name: .....

2) .....

How to give EpiPen®

1. PULL OFF BLUE SAFETY CAP and grasp EpiPen. Remember: "blue to sky, orange to the thigh"
2. Hold leg still and PLACE ORANGE END against mid-outer thigh "with or without clothing"
3. PUSH DOWN HARD until a click is heard or felt and hold in place for **3 seconds**. Remove EpiPen.

Parental consent: I hereby authorise school staff to administer the medicines listed on this plan, including a 'spare' back-up adrenaline autoinjector (AAI) if available, in accordance with Department of Health Guidance on the use of AAIs in schools.

For more info about managing anaphylaxis in schools and "spare" back-up adrenaline autoinjectors, visit sparepensinschools.uk

Signed: .....

Print name: .....

Date: .....

'The British Society for Allergy & Clinical Immunology 05/2018

Watch for signs of ANAPHYLAXIS

(life-threatening allergic reaction)

Anaphylaxis may occur without skin symptoms: ALWAYS consider anaphylaxis in someone with known food allergy who has **SUDDEN BREATHING DIFFICULTY**

A AIRWAY	B BREATHING	C CONSCIOUSNESS
• Persistent cough	• Difficult or noisy breathing	• Persistent dizziness
• Hoarse voice	• Wheeze or persistent cough	• Pale or floppy
• Difficulty swallowing		• Suddenly sleepy
• Swollen tongue		• Collapse/unconscious

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:

1. **Lie child flat with legs raised** (if breathing is difficult, allow child to sit)
2. **Use Adrenaline autoinjector without delay** (eg. EpiPen®) Dose: ..... mg
3. **Dial 999** for ambulance and say ANAPHYLAXIS ("ANA-FIL-AX-IS")

***** IF IN DOUBT, GIVE ADRENALINE *****

AFTER GIVING ADRENALINE:

1. Stay with child until ambulance arrives, **do NOT stand child up**
2. Commence CPR if there are no signs of life
3. Phone parent/emergency contact
4. If no improvement **after 5 minutes, give a further adrenaline dose** using a second autoinjectilable device, if available.

You can dial 999 from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Mild/moderate allergic reaction:

- Swollen lips, face or eyes
- Itchy/tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting
- Sudden change in behaviour

Action to take:

- Stay with the child, call for help if necessary
- Locate adrenaline autoinjector(s)
- Give antihistamine:

(If vomited, can repeat dose)

- Phone parent/emergency contact

Additional instructions:

This is a medical document that can only be completed by the child's healthcare professional. It must not be altered without their permission. This document provides medical authorisation for schools to administer a 'spare' back-up adrenaline autoinjector if needed, as permitted by the Human Medicines (Amendment) Regulations 2017. **This plan has been prepared by:**

Sign & print name: .....

Hospital/Clinic: .....

..... **Date:** .....

Figure 4: Allergy action plan as per The British Society for Allergy and Clinical Immunology (BSACI), in conjunction with the Royal College of Paediatrics and Child Health

Other immunomodulatory approaches explored are the effect of coadministration of probiotics with immunotherapy, addition or separate treatment with antibodies and the role of distinct kinases in particular food allergies.

Allergen immunotherapy

The European Academy of Allergy and Clinical Immunology (EAACI) Task power on Allergen Immunotherapy for IgE-interceded Food hypersensitivity arranged a rule which expects to give proof based suggestions to the dynamic treatment of IgE-intervened nourishment sensitivity with nourishment allergen immunotherapy (Husain and Schwartz, 2012). Allergen immunotherapy, otherwise called desensitization or hypo-refinement, is the rehashed organization of high dosages of causative allergen by subcutaneous or sublingual course, to initiate a condition of perpetual resilience after stopping.

The essential targets of allergen-explicit immunotherapy are,

1. To decline the manifestations activated by allergens
2. To anticipate a repeat of the ailment in the long haul

As of now, it is the main distinguished sickness adjusting mediation that prompts the natural invulnerability in patients with hypersensitive malady (Nair *et al.*, 2015).

Potential mechanisms of immunotherapy

Several probable processes have been proposed to identify the underlying reactions occurring during the immunotherapy (Pajno *et al.*, 2018).

Reduction in the particular IgE levels

During the early stages of immunotherapy itself, there are elevated allergen-explicit IgE levels causing early desensitization of mast cells and basophils happens, which lead to the effective concealment of mast cells, basophils, eosinophils, and ILC2. The high-affinity receptor for IgE (FcεRI)- dependent activation of these cells results in the degranulation and arrival of their preformed and anew synthesized mediators and type-2 cytokines, (for example, IL-4, IL-13) that indorse unfavourably susceptible inflammation and IgE production (Moote and Kim, 2011).

Induction of IgG (blocking) antibodies

For allergen binding IgE is competed with Allergen-specific IgG. Orengo et al demonstrated the significance of the IgG/IgE proportion and revealed that expanding the IgG/IgE proportion through the immediate organization of recombinant allergen-explicit IgG antibodies is a well-endured and powerful way to deal with decrease the side effects of allergy (Frew, 2010).

Altered T-cell cytokine balance (Shift to TH1 from TH2)

Two subsets of T cells, T_H1 and T_H2, invoke different responses to allergens. T_H1 directs a non-allergic response whereas T_H2 directs an allergic response, ranging from the release of histamines to anaphylactic shock. The presence of a cytokine called IL-2 alters the T cell balance and a shift from T_H2 to T_H1 occurs (Scadding *et al.*, 2017).

T-cell anergy

T-cell anergy is a tolerance system wherein the lymphocyte is intrinsically functionally inactivated following an antigen encounter but stays alive for an extended timeframe in a hyporesponsive state. This mainly affects CD4(+) and CD8(+) cells, known as clonal anergy and adaptive tolerance or in vivo anergy respectively (Orengo *et al.*, 2018).

Stimulation of regulatory T-cells

The regulatory T cell (T_{reg}) has the ability to recognize harmful "self" antigens. The primary function of the Treg cells is to limit T-effector cell function and proliferation by tolerating the self-antigens. The stimulation of Treg cells by the transcription factor Foxp3 during their thymic development prompts invulnerable concealment (Johnston *et al.*, 2014).

Types of immunotherapy

Based on the route of administration, immunotherapy can be of various types such as oral, subcutaneous, sublingual, epicutaneous, etc. By taking the drug into consideration, immunotherapy can be achieved by administering Anti-IgE drugs, new protein molecules, modified or biotechnological molecules like modified- recombinant DNA molecules, etc. Recently the most exploited routes are the oral and subcutaneous, in which the allergens are made into pills or injections and delivered via their corresponding routes.

Oral immunotherapy

The ingestion of small amounts of allergen orally in an increasing manner to achieve a level of tolerance and lead to the desensitization towards the specific allergen is termed as oral immunotherapy or OIT. It is not a complete remedial therapy and patients are advised to carry epinephrine auto-injectors as a matter of precaution. Abdominal pain, vomiting, cramping, oral itching, rash, hives, swelling are some of the side effects associated with OIT. At present

there is no OIT treatment available for food allergy, which shows the necessity of more research in the area (Schwartz, 2003).

Subcutaneous immunotherapy

AIT is given mainly by subcutaneous injections whose frequency depends on the type of allergy and the individual scheme proposed to the patient. The conventional schedule for SCIT using allergen extracts consists of a dose build-up by injection once weekly, followed by maintenance dose injections at 4-8 week intervals (Kanamori *et al.*, 2016). In a study conducted to find the long-term efficacy of grass pollen immunotherapy, it was found that continued therapy up to four years induced a persistent change in immunologic reactivity (Durham *et al.*, 1999).

Sublingual immunotherapy

Over the last 2 decades, there has been increasing use of SLIT. In SLIT, the build-up period is short or not needed. Evidence support a better response to daily SLIT administration. Sublingual AIT is safe and effective even in children as young as 3 years of age (Wilson *et al.*, 2005).

CONCLUSION AND FUTURE OUTLOOK TO CONTROL THE FOOD-INDUCED ANAPHYLAXIS

The significant issue includes the role of AIT in refinement or allergy anticipation. Such systems are as of now under assessment and an institutionalized reference for specific allergen isn't accessible. In any case, approval of the utilization of explicit instruments, particularly biomarkers, which will give assistance to distinguish subjects who can conceivably profit by such modalities is as yet deficient.

Persistent advancement of immunology and bioengineering improves understanding diagnostics just as the quality and organization of novel mixes. New courses of an organization to treat explicit food-allergen induced anaphylaxis, for example, sublingual courses additionally gives a promising option in contrast to current treatment. Anyway, new guidelines request the conductance of an enormous number of over the top expensive clinical preliminaries, particularly in youngsters. This is constraining the advancement of novel moieties which doesn't keep pace with the fast innovative improvement vivified by progress in immunology and biotechnology.

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