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QUICK REVIEW ON TYPE-1 HYPERSENSITIVITY: ETIOLOGY, DIAGNOSIS, AND ITS MANAGEMENT

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ABSTRACT

Hypersensitivity reactions represent exaggerated or inappropriate immune responses that can result in significant tissue injury and systemic manifestations. Among the four classical types described in the Gell and Coombs classification, Type I hypersensitivity—also known as immediate hypersensitivity—is mediated predominantly by immunoglobulin E (IgE) and is responsible for a wide spectrum of allergic disorders, ranging from mild atopic reactions to severe, life-threatening anaphylaxis. This review focuses on the immunological basis, etiology, epidemiology, and pathophysiology of Type I hypersensitivity reactions. Sensitization to environmental, food, or drug antigens leads to IgE production and its binding to high-affinity Fcε receptors on mast cells and basophils. Subsequent re-exposure to the antigen triggers rapid mast cell degranulation and the release of preformed mediators, lipid-derived mediators, cytokines, and chemokines, resulting in acute and late-phase allergic inflammation. Key mechanistic concepts, including the hapten hypothesis, pro-hapten hypothesis, and pharmacological interaction (p-i) concept, are discussed to explain drug-induced immediate hypersensitivity. The review also highlights epidemiological trends, common triggers such as foods and medications, and emerging evidence of alternative IgG-mediated pathways in anaphylaxis. A comprehensive understanding of these mechanisms is essential for accurate diagnosis, effective management, and prevention of immediate hypersensitivity reactions and their long-term complications.

KEYWORDS: Type I hypersensitivity, IgE-mediated reactions, anaphylaxis, mast cell activation, immediate allergic response.

1. INTRODUCTION

The term "hypersensitivity" refers to a wide immune response that might be harmful or excessive to either self-antigens or foreign antigens. But the same system can also cause heightened inflammatory and immunological responses, which can have negative effects known as hypersensitive reactions. Type I, Type II, Type IlI, and Type IV Hypersensitive reactions are the four categories used by the original Gell and Coomb's classification system.[1] *Type I Hypersensitivity* is known by the name "immediate reaction". It is characterized by the production of antibodies against the soluble antigen through the action of immunoglobulin E (IgE). Histamine and other inflammatory mediators are released as a result, along with the degranulation of the mast cell.[2] *Type 11 Hypersensitivity* is referred to as cytotoxic reactions; type Il hypersensitivity activates IgG and IgM antibodies, which activate the complement system and causes cell lysis or damage.[2] *Type III Hypersensitivity* is associated with IgG, IgM, and occasionally IgA antibodies are involved, commonly referred to as immune complex reactions. Complement system activation from the accumulation of these immune complexes causes polymorphonuclear leukocytes (PMNs) to chemo tact and ultimately inflict tissue damage.[2] *Type IV Hypersensitivity* also referred to as delayed-type hypersensitivity, type IV hypersensitivity is caused by T-cell-mediated responses.

The production of cytokines activates T-cells or macrophages, which results in tissue destruction. *Sell et al* have proposed a more modern classification scheme that divides the reactions into seven categories and takes into consideration various immune system components. This paper, however, will concentrate on the traditional Type I hypersensitivity reactions.[2]

2. Etilogy

The exposure to an antigen results in type I hypersensitivity. There are two phases to the antigen response: the sensitization stage and the effector stage. The host comes into contact with the antigen asymptomatically during the sensitization phase. The pre-sensitized host is then reintroduced to the antigen during the "effect" phase, which subsequently triggers a type I anaphylactic or atopic immunological response.[2] Cats, dust mites, German cockroaches, grass, rats, fungi, plants, and medications are a few of these. They increase the synthesis of IgE. Anaphylaxis can be caused by a variety of substances, such as shellfish and anaesthetics, bee and wasp venoms, tree nuts (such as almond, hazelnut, walnut, and cashew), eggs, milk, latex, antibiotics (such as cephalosporins), heterologous antisera, hormones (such as insulin), and others.[3]

3. Epidemiology

Type I hypersensitivity is unpredictable since there are differences in the way the type of reaction is classified. Some patients, for example, record their anaphylactic reaction status after experiencing milder symptoms, while others report a full-blown anaphylactic presentation. Anaphylaxis is estimated to occur in people 1% to 2% of the time worldwide, with a higher incidence in younger people, according to a study.[2] According to data from Europe, 0.3% of people will experience anaphylaxis at some point in their lives. Furthermore, each year in the United States, 1 in 3000 inpatients has a serious allergic reaction. In contrast, 1.5% of Koreans had bronchial asthma. According to a study by Fernandez Soto et al(2018), fungal infections may account for as much as 50% of cases in inner cities and are a risk factor for allergic bronchial asthma development.[3]

4. Pathophysiology of Immediate Type Hypersensitivity

Immediate type hypersensitivity drug reactions are dynamic in nature, ranging in intensity from minor to fatal, and they can progress quickly under supervision. Almost all kinds of therapeutic reagents, including antibiotics, anticonvulsants, anaesthetics, neuromuscular blocking drugs (NMBD), chemotherapeutic medications, and non-steroidal anti-inflammatory drugs (NSAIDs), have been linked to immediate onset hypersensitivity, including anaphylaxis. Anaphylaxis is a severe, potentially fatal hypersensitivity reaction that develops quickly after exposure and is broad (systemic).[4] Observation for at least 1 hour is necessary to prevent a moderate reaction from escalating. About 20% of instances may involve no skin characteristics at all and without any noticeable skin features, abrupt cardiovascular collapse or even cardiac arrest can happen. Therefore, if there is immediate, life- threatening bronchospasm or hypotension in the appropriate setting—that is, if there is no alternative diagnosis that could account for the hypotension—a provisional diagnosis and treatment as anaphylaxis are required.[5] The majority of immune-mediated immediate-type reactions to medications that are clinically significant are believed to be T-cell or IgE-mediated. The pathophysiology of type 1 hypersensitivity has been so far associated with 3 mechanisms:

4.1 Hapten Hypothesis

A hapten is an agent that lacks its own antigenicity but can combine with a particular antibody. When injected intraperitoneally into animals, numerous tiny compounds (less than 1000 atoms), including hormones, medicines, and poisons, are incapable of triggering an immune response. Thus, they are referred to as haptens, and by themselves they are not immunogenic. To become immunogenic, these small-molecular-weight molecules must be attached to a larger molecule, such as a protein, before being injected into an animal. Haptens can be conjugated to protein molecules by means of their reactive carboxylic or amino groups. As an alternative, a hapten may have a reactive group like carboxylic acid added to it for this reason. The carrier proteins' histidine, tyrosine, or lysine residues can be utilized for linking.[6] According to the hapten idea, a drug (metabolite) binds covalently to protein, and drug(metabolite)-modified peptides produced from the conjugation interact with antigen-presenting cell MHC proteins before stimulating T-cells. Antigen-presenting cells' enzymatic machinery is responsible for the production of drug-(metabolite)-modified peptides. Following their migration to the cell surface, the MHC proteins present peptides to the extracellular environment. When a T-cell recognizes the hapten-modified peptide as a "foreign entity," TCR interaction and a subsequent T-cell response including the release of many soluble mediators are triggered.[7]

4.2 Pro-Hapten Hypothesis

According to the pro-hapten hypothesis, binding covalently to autologous proteins requires some kind of metabolism, usually through cytochrome P450 (CYP450) enzymes in the skin or liver. In some circumstances, the metabolite is so reactive that it reacts spontaneously with the CYP450 enzyme responsible for its synthesis. Sulfamethoxazole is the most studied drug in this regard, but it has mostly been investigated in the context of T-cell mediated hypersensitivity reactions.[8]

4.3 p-i Concept

According to the PI concept, drugs or metabolites that bind directly (non-covalently) to MHC proteins or peptides that are already lodged in the MHC peptide binding cleft can activate T-cells. Since peptides are spontaneously displayed by surface MHC molecules,

antigen processing within antigen-presenting cells to create peptide sequences is not required in this instance for T-cell activation. The PI concept states that T-cells are activated via their T-cell receptor after obtaining signals from MHC-bound peptide and drugs like carbamazepine.[7]

4.4 Chemical Mediators of Immediate-Type Hypersensitivity

Activated mast cells release a variety of lipid mediators within five to thirty minutes of the initiation of type I hypersensitivity. The ability to analyse lipid mediators simultaneously has been made possible by recent advancements in detection techniques. They found that six types of lipid mediators, namely 5-HETE[9,10,11], LTC4[12,13,14], LTB4[15,16,17], PGD2[18,19,20], Thromboxane A2 (TXA2)[21], 12-heptadecatrienoic acid (HHT)[22] accounted for 73% of the total lipid mediators. Recently, Shimanaka et al. discovered that EPA/CYP metabolites 17,18-epoxyeicosatetraenoic acid and DHA/CYP metabolites, 19,20-epoxydocosapentaenoic acid were released by activated mast cells. These metabolites increase mast cell activation and anaphylaxis.[23] IgE causes a patient to become "sensitized" by attaching itself to high-affinity Fce receptors on the surface of various cells, especially mast cells and basophils. Mast cell surface-bound IgE antibody is cross-linked upon subsequent allergen exposure, which raises intracellular calcium levels and releases preformed mediators (like histamine and proteases) as well as freshly synthesized lipid-derived mediators (like leukotrienes and prostaglandins). Changes in physiology and anatomy brought on by mediators may then result in allergic reactions.[24]

Following the resolution of the acute symptoms of immediate hypersensitivity, a variety of chemokines (RANTES, eotaxin, MIP1α) and cytokines (IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL- 25, IL-33, TNFα, GM-CSF) are produced by IgE-stimulated mast cells, which coordinate the influx and activation of allergy-related cell types.[25] Eotaxin and RANTES attract T cells, which are powerful makers of mast cell growth factors, and eosinophils, which proliferate in the presence of IL- 5.[26] IL-4 stimulates the vascular endothelium's very late antigen-4 (VLA-4), which attracts T cells, basophils, eosinophils, and monocytes that express vascular cell adhesion molecule-1 (VCAM-1). In addition, IL-4 stimulates B cells to generate additional IgE, which restores the IgE depleted during the degranulation process.[27] All of these processes work together to create the conditions for the induction of a T cell and eosinophil-dominant allergic tissue inflammation, which is the root cause of long-term allergic diseases like atopic dermatitis, allergic rhinitis, and asthma. They also serve to enhance the pathways that lead to future acute hypersensitivity reactions that occur when an allergen is encountered repeatedly.[28]

Additional research conducted by other researchers revealed that IgG1 may mediate anaphylaxis in mice and that anaphylaxis may happen even when mast cells or FcεR1 are absent.[29] It eventually became evident that this pathway was completely independent of mast cells and that platelet-activating factor (PAF) instead of histamine was responsible for increasing vascular permeability and bronchoconstriction through IgG binding to FcγRIII on macrophages.[29,30]

5. Common Triggers of Immediate Hypersensitivity (Diagnosis and Management)

5.11 Food Allergy: Food allergies include both immunoglobulin E (IgE) mediated and non-IgE mediated reactions to food, since they are defined as unpleasant reactions to food in which "immunologic mechanisms have been demonstrated'(Table 1). There is a significant risk of illness like fatal anaphylaxis and even death from food allergies.[31,32] According to recent studies, food allergies are a major public health concern, affecting 10% of adults and 8% of children in developed nations,[33] which leads to anxiety and food restriction for many patients and families.[34] Food allergies are thought to be more common in regions further from the equator because they receive less sunlight there, which results in lower vitamin D levels. Eg ; Australia[34] The most prevalent food allergies in infancy are Cow milk allergy (CMA) and egg allergy, with estimated prevalences of 2.5% and 1.3%, respectively, for milk and egg allergy at 1 year of age in developed nations.[34] Primary beef allergy primarily affects young, atopic children, while it can very rarely affect adults. The major allergen Bos d 6 and Bos d 7 found in milk and muscle therefore the children who has primary beef allergy may also be allergic to milk and vice versa. The symptoms of alpha-gal syndrome usually appear 2–24 hours later[35-36], and allergic reactions to meat from mammals usually happen at night, a few hours after meat consumption. Allergies are brought on by alpha-gal, a carbohydrate that is present in animals but missing in humans and primates. Tick bites that cause skin contact can sensitize an individual to IgE by introducing algal chemicals into their bloodstream. The most common food-related cause of deadly anaphylaxis is peanuts.[37] A peanut allergy impacts approximately 1%– 4.5%[37 and 0.05%–4.9%[38] of people in the western world suffer from tree nut allergies.[34] Infants with a family history of allergies or atopic disorders, but no maternal asthma, allergic rhinitis, atopic eczema, or hepatitis (HE) sensitization, are at increased risk of developing HE clinical allergy. Food allergies, including HE, cow's milk allergy, and peanut allergy, are frequently linked to atopic dermatitis. Children with eczema are 5-8 times more likely than healthy children to have a HE allergy, and they are also 6-18 times more likely to become sensitized to particular foods.[39]

Table 1: Food associated immunologic mechanisms with clinical features and prognosis. Adopted from Muraro A et al (2014).[40]

Immunopathology	Disorder	Clinical features	Typical age group	Prognosis
IgE mediated	Pollen food allergy syndrome	Pruritus, mild oedema confined to oral cavity	Onset after pollen allergy established (adult > young child)	May be persistent and may vary by season
	Urticaria/angioedema	Triggered by ingestion or direct contact	Children > adults	Depends on food
	Rhino conjunctivitis/asthma	Accompanies food- induced allergic reaction but rarely isolated symptoms may be triggered by the inhalation of aerosolized food protein	Infant/child > adult, except for occupational disease	Depends on food
	Gastrointestinal symptoms	Symptoms such as nausea, emesis, abdominal pain, and diarrhoea triggered by food ingestion	Any age	Depends on food
	Anaphylaxis	Rapid progressive, multisystem reaction	Any age	Depends on food
Mixed IgE and cell mediated	Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	Onset in late childhood/adulthood	Presumed persistent
	Atopic eczema/ dermatitis	Associated with food in 30–40% of children with moderate/severe eczema	Infant > child > adult	Usually resolves
	Eosinophilic gastrointestinal disorders	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Any age	
Cell mediated	Dietary protein-induced proctitis/ proctocolitis	Mucus-laden, bloody stools in infants	Infancy	
	Food protein-induced enterocolitis syndrome	Chronic exposure: emesis, diarrhoea, poor growth, lethargy. Re-exposure after restriction: emesis, diarrhoea, hypotension a couple of hour after ingestion	Infancy	

5.12 Diagnosis

Food allergies can show clinically with a wide range of symptoms, including gastrointestinal (vomiting, colic, abdominal discomfort, diarrhoea, constipation), respiratory (rhinorrhoea, sneezing, coughing, dyspnoea), and skin (urticaria, angioedema, atopic eczema/dermatitis), to the circulation.[41,42,43] A patient is categorized as sensitive only if they have IgE-ab but no symptoms. People without a clinical allergy (i.e., tolerance) frequently have sensitization.[34] It is important to remember that food consumption, inhalation, and skin contact might cause responses. A thorough food history is essential for the diagnosis of a food allergy. Ex: One example is wheat-dependent exercise-induced anaphylaxis due to omega-5-gliadin sensitization.[44]

5.13 Management of Food Allergy

Clinical treatment for food allergies entails both short-term medicines to manage acute reactions and long-term planning to lower the likelihood of relapses. Carbohydrates have recently been connected to serious reactions [alpha-gal 15]. Effective management of patients with food allergies requires the ability to recognize the possibility of severe reactions. People who have previously suffered from severe asthma attacks or anaphylaxis are more susceptible than others. Early signs of anaphylactic shock can be hidden by using preventive antihistamines.[45]

5.14 Long term management

Dietary restrictions should be tailored to the specific nutritional needs and allergy requirements of each individual, as well as to remove the aggravating food allergen or allergens. Extended and comprehensive abstinence requires careful monitoring since it may result in dietary deficits and reduced quality of life. This is particularly important for infants and young children.[46,47] There is proof that introducing food sooner rather than later has benefits and reduces the likelihood of food allergies.[34] For example, infants and young children who are allergic to cow's milk can take formula based on soy or amino acids in place of the milk. Probiotics are an additional option for treating individuals with food allergies.

5.15 Patient Education

Understanding risk factors, how to read food labels, and how to avoid certain food allergies both inside and outside the home are crucial skills for patients, their families, close friends, and caregivers to possess. They should also be informed about potential substitute products for the majority of food sensitivities. Interpretation of warning signals, patient-specific avoidance strategies at home and in the community, and when and how to control reactions should all be included in training.

5.2 Insect Venom Allergy: Several significant allergens, usually glycoproteins with a molecular weight of 10–50 kDa, have been found in venoms of bees, vespids, and ants(Table 2). Immunologic (IgE mediated or not) or non-immunological pathways may be involved in venom hypersensitivity. Risk factors that can impact the result of an anaphylactic reaction include the frequency and duration of stings, the severity of the previous reaction, age, medication use and cardiovascular conditions, kind of bug, increased blood tryptase, as well as mastocytosis, Social Aculeatae, specifically Vespidae (vespids), Apididae (bees), and Formicidae (ants), are significant in relation to allergic sting reactions.[48] Zone, weather, temperature, insect behaviour, and certain jobs or hobbies will all affect the likelihood of getting stung. It is necessary to consider beehives or vespid nests that are close to homes, workplaces, and outdoor recreation areas as risk factors.

Table 2: Insect venom allergy associated immunologic mechanisms. Adopted from Bilo BM et al (2005).[49]

Venom	Allergen	Common name	Molecular weight	Major/Minor
Apis mellifera	Api m 1	Phospholipase A2	16	Major
	Api m 2	Hyaluronidase	43	Major
	Api m 3	Acid phosphatase	49	Major?
	Api m 4	Melittine	2.9	Minor
	Api m 6		7.9	Minor
		Protease	39	Major?
Bombus pennsylvanicus	Bom p 1	Phospholipase A2		Major
	Bom p 4	Serine protease		Major?
Vespula vulgaris (accordingly in *V. germanica*, *maculifrons*, etc.)	Ves v 1	Phospholipase A1	35	Major
	Ves v 2	Hyaluronidase	45	Major
	Ves v 5	Antigen 5	25	Major
Dolichovespula maculata (accordingly in *D. arenaria*, *D. media*, etc.)	Dol m 1	Phospholipase A1	35	Major
	Dol m 2	Hyaluronidase	45	Major
	Dol m 5	Antigen 5	25	Major

5.21 Diagnosis: Data on the following should be gathered: the quantity and timing of sting reactions; the type and intensity of symptoms; the time interval between the stung and the beginning of symptoms; and the risk factors for subsequent stings.[32] Blisters are rare but may occasionally be present in a large local reaction, which is defined as a swelling larger than 10 cm in diameter that lasts longer than 24 hours. Test results for certain patients suggest either cell-mediated or IgE-mediated pathways, or occasionally both.

5.3 Pollen_allergy: Pollen allergies occur when grass, weeds, and tree pollen gets inside our bodies and our immune system interprets it as a threat, which can lead to allergic reactions like hay fever. Some pollen allergens as follows:[50]

1. Grass: In many regions of the world, grass pollen is the primary cause of pollinosis.[51]
2. Trees: In this group of trees that are allergic, birch has the highest allergenic potency, followed by alder, hazel, olive and cypress.[52]
3. Weeds: The two species primarily implicated in pollenosis are mugwort (Artemisia) and ragweed (Ambrosia).[53]
4. Ornamental Plants: New sources of aeroallergens were created by the growing usage of ornamental plants in homes, workplaces, parks, and gardens. According to recent research, sap is the allergen's source.

5.31 Pathology of pollen allergy: Recent research has shown that when pollen grains are exposed to physiological circumstances, they release bioactive lipids and allergens that activate human neutrophils and eosinophils in vitro.[54] Furthermore, undamaged pollen grains can activate and mature dendritic cells, indicating that they serve as an adjuvant during the induction phase of the allergic immune response in addition to acting as a transporter of allergens.[55] Pollen grains are the primary allergens but can also carry secondary allergens like starch grains, pollen fragments, non- pollen plant parts, and non-plant particulate matter.[56,57] Changes in the climate can have an impact on pollen generation and distribution by affecting the duration and beginning of the season. When thunderstorms occur, a cooler air outflow gathers particles of pollen and deposits them at the surface. Thunderstorm asthma has been linked to a possible rise in fungal spores during a thunderstorm.[58]

5.32 Diagnostic Tests

1. The initial diagnostics for determining IgE sensitization are in vivo SPT and sIgE for dietary allergens.
2. Oral food challenges and elimination diets for diagnostic purposes are still necessary to determine the clinical significance of the preliminary studies, both IgE- and non-IgE-mediated food allergies were considered.
3. Specific IgE: in vitro and skin tests.[59]
4. Atopy patch test.[60,61]
5. Elimination diet.
6. Oral food challenges.

6. Drug induced hypersensitivity reaction

One of the most popular groups of important antibiotics, penicillin provides a first-line treatment against a variety of bacteria, including the often-encountered Staphylococcus aureus and Streptococcus pneumoniae. Penicillin, which includes amoxicillin (AX) and flucloxacillin (Flux), belongs to the class of antibiotics known as beta-lactams (β-lactam).[63] The actual incidence, prevalence, and death rates of drug-induced anaphylaxis are not known, though.[64]

The age group of 20 to 49 years old is considered to be the most vulnerable to severe allergic reactions when it comes to penicillin.[65] Penicillin-specific IgE antibodies are not always present in those who experience hypersensitive reactions, although prior exposure is necessary for anaphylactic reactions to penicillin. Sensitization can also result from environmental exposures to things like milk, meat, frozen dinners, and soft beverages. While it is illegal to sell meat or milk from cows given penicillin treatments, new research indicates that tainted food items may cause sensitivity and responses in some people.[65] Penicillin can also result in drug-induced liver injury (DILI), a general term for drug-induced hepatotoxicity or toxic hepatitis.[66]

6.1 Diagnosis and Management: A reliable diagnosis of a drug-induced reaction necessitates a thorough history that includes information about the drug's composition, dosage, and time course evaluation. and the reaction's clinical pattern.

Algorithm for the management of a suspected adverse drug reaction shown in Figure 1.[67]

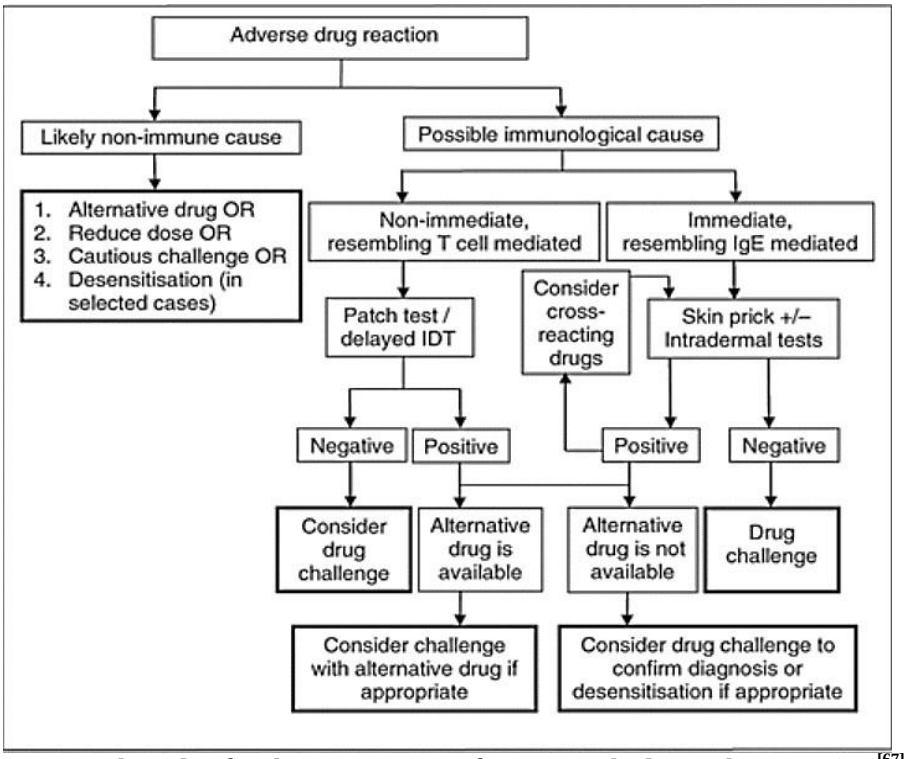

Figure 1: Algorithm for the management of a suspected adverse drug reaction.[67]

The cornerstones of emergency care for a severe response are stopping the causing medication, requesting help, positioning the patient in a supine position, giving airway assistance, and administering intramuscular adrenaline. Because drug allergy diagnostic tests are not flawless, clinical assessment is the first step in the decision-making process.[68] Although oral provocation is frequently regarded as the gold standard diagnostic test, it is not advised for patients with severe T-cell-mediated disorders like TEN and DRESS since it may pose a risk to the patient.[68,69] The penicillin skin test that is now available is only useful for diagnosing IgE-mediated or immediate-type hypersensitivity reactions; it is not useful for diagnosing non-IgE-mediated reactions.[70] The primary determinant, benzoyl penicilloyl, is no longer marketed.[70] For individuals who need penicillin therapy and have a positive skin test, penicillin desensitization should be taken into consideration.

Additional measures for reactions involving hypotension may be required, such as vigorous fluid resuscitation with up to 5 litres of normal saline in the first 30 minutes[70,71], adrenaline intravenous infusion, and other strong vasoconstrictors like metaraminol or vasopressin if the adrenaline response is insufficient. An additional method for diagnosing IgE-mediated penicillin allergy is the use of in vitro tests (radioallergosorbent or enzyme-linked immunosorbent) for IgE antibodies.[70] In addition, some doctors refuse to perform penicillin skin tests on patients who have previously experienced anaphylaxis due to the negligible chance of anaphylaxis from the test. Antihistamines inhibit the skin test response, hence patients taking tricyclic antidepressants and antihistamines (because to their antihistamine characteristics) should avoid doing penicillin skin tests.[70] Vancomycin, clindamycin, and fluoroquinolones are common substitutes for penicillin that are unquestionably linked to the development of resistant pathogens, including Enterococcus bacteria resistant to vancomycin and higher prevalence of Clostridium difficile.[72]

Penicillin skin testing comprises both intradermal and prick skin tests using the major and minor penicillin determinants. The primary factor utilized in penicillin skin testing is polylysine- penicilloyl. For testing purposes, benzylpenicillin (penicillin G) and minor determinant mixtures such as benzylpenicilloate, benzylpenilloate, or benzylpenicilloyl-n-propylamin have been employed as minor determinants of penicillin. During testing, saline should be used as the negative control and histamine as the positive control. There is little chance that a patient will experience an allergic reaction of the acute kind to penicillin if the skin test results are negative.[72]

7. Sulphonamide Allergies

HIV positive is consistently the most important known risk factor for sulphonamide allergies, especially in AIDS patients. There isn't a trustworthy skin test to confirm or rule out sulfa allergies.

Approach to prescribing sulfa nonantibiotics for patients with sulfa allergy[73] – Figure 2.

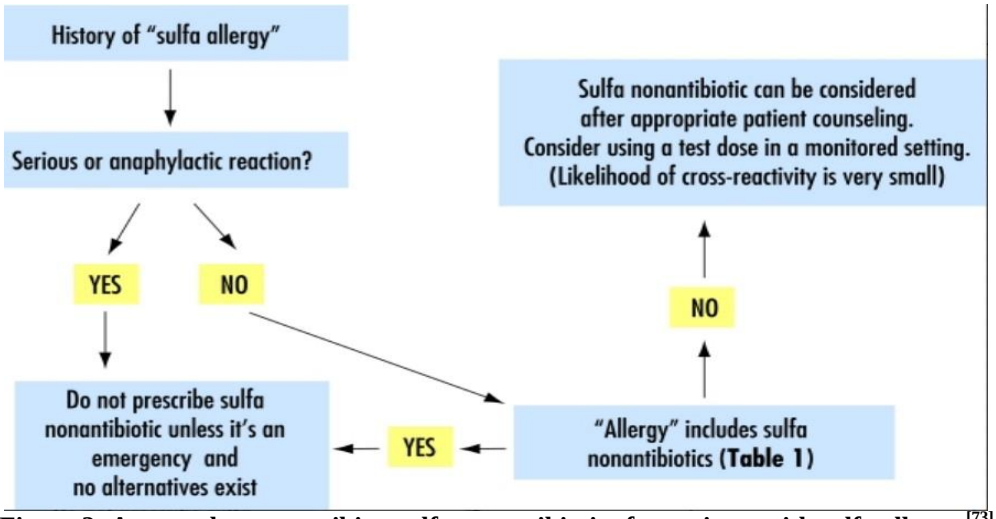

Figure 2: Approach to prescribing sulfa nonantibiotics for patients with sulfa allergy.[73]

7.1 Diagnostic Test: Solid-phase immunoassays such as the RAST have been developed to detect IgE antibodies directed against the penicilloyl determinant.

- SPT/IDT is the preferred diagnostic test for penicillin allergy.[68]
- The intradermal test is carried out if the prick test yields negative results.[70]
- Skin prick test.

8. Clinical Manifestations of Immediate Hypersensitivity

8.1 Anaphylaxis: A "severe, life-threatening systemic hypersensitivity reaction" is what is known as anaphylaxis.[72] It is usually distinguished by its quick onset and possibly fatal respiratory, circulatory, or airway complications, not always associated with alterations in the skin and mucosa.[74]

8.11 Triggers: Food, medications, and stinging insects are important triggers, with age-related variations. The most common cause of anaphylaxis in children is food. Anaphylaxis caused by venom from Hymenoptera and drugs is more common in adults.[4]

8.12 Risk Factors: They include Physical exertion**,** Alcohol**,** Drugs**,** NSAID**,** ACE inhibitors**,** β- blockers**,** Patient-speciXic factors, adolescence, advanced age and sex**,** Infections**,** Hormonal status**,** Psychogenic stress**,** Pre-existing conditions**,** Asthma and other IgE-dependent diseases**,** Cardiovascular disease**,** Mastocytosis and /or increased basal tryptase.[75]

An increased risk of severe or fatal anaphylaxis is also linked to co-occurring cardiovascular illnesses, mast cell disorders, and asthma.[5] Individuals who have allergies to peanuts, tree nuts, or insect venom are also more vulnerable. Cofactors, which include physical activity,

fever, acute infections, premenstrual syndrome, and mental stress, raise the chance of an allergic reaction happening or the intensity of the reaction. Alcohol and NSAIDs appear to exacerbate certain food allergies as well.

8.13 Diagnosis: The organ systems involved determine how anaphylaxis presents clinically. Anaphylaxis symptoms and signs often appear two hours after being exposed to allergen[76], thirty minutes for food allergies, and much faster with parenteral medicine or stings from insects. The median time from symptoms to arrest in a large case series of fatal anaphylaxis has been recorded as 15, 30, and 5 minutes for food, insect venom, and parenteral medicine, respectively.[77]

The majority of anaphylaxis cases[4] had cutaneous signs, which are followed by cardiovascular symptoms (72%) and respiratory symptoms (68%). Up to 20% of reactions have been documented to develop biphasic anaphylactic reactions. These reactions often manifest 4–12 hours after the onset of symptoms or signs, but they can also manifest more severely. The diagnosis may also be aided by skin prick evidence of IgE sensitization or in vitro testing.

8.14 Management

1. Stay with the patient,
2. Look for signs of anaphylaxis,
3. Administer adrenaline if signs of anaphylaxis,
4. Repeat adrenaline as necessary,
5. Other treatments as indicated (e.g., oxygen, beta-2 agonist, Xluids, antihistamine, corticosteroid),
6. Look for trigger (e.g., food, drug, venom),
7. Adrenaline is effective for all symptoms.[75]

Anaphylaxis patients need to be assessed right away utilizing the Airway, Breathing, Circulation, Disability, and Exposure methods. Issues ought to be resolved as soon as they arise, and an emergency services call should be placed. Emergency care needs to concentrate on symptoms related to upper airway, lower respiratory, and/or cardiovascular compromise since these conditions can lead to death. In the event of a cardiorespiratory arrest, resuscitation should start right away. Once the triggering allergens have been identiXied, patients who have suffered anaphylaxis can begin long-term therapy. Allergen immunotherapy and allergen avoidance[78] are preventive measures to prevent recurrence.

8.15 Patient Education: Education on managing signiXicant concurrent conditions and how to self-treat anaphylaxis recurrence in the community should be given. A dietician who specializes in allergies can assist in identifying trigger foods and offering avoidance guidance. Patients need to be properly informed about conditions that pose a unique risk, such as dining out, hidden allergies, and cross-reactions to other allergens.[79]

8.2 Allergic Rhinitis

Clinically speaking, nasal discharge, itching, sneezing, and nasal congestion or obstruction are the signs of rhinitis. The name rhinosinusitis is more appropriate because it also typically affects the sinus linings. It can be divided into allergic, non-allergic, and infectious. Atopy sufferers, individuals with a history of rhinitis in the family, Xirst-born children, and immigrants are especially at risk.[80]

Sneezing, rhinorrhoea, itching, and nasal obstruction are the quick reactions that follow IgE- mediated mast cell degranulation and mediator release in AR. Eosinophilic inXiltrates cause inXlammation during the late-phase response.[81]

8.21 Diagnosis

1. Patient history - family history, social history.[82]
2. Signs and symptoms - sneezing, itchy nose and itchy palate, rhinorrhoea, nasal obstruction and congestion, eye and other symptoms.
3. Examination and investigations - anterior rhinoscopy, acoustic rhinometry, rhinomanometry, nasal endoscopy, skin prick test, routine laboratory test, olfactory etc.[83]

8.22 Patient Education

1. The nature of the illness, the mechanisms and causes of rhinitis, the symptoms, and the potential therapies should be explained to the patient or the parents of minors.
2. It is important to provide information about pharmacological therapy, allergen avoidance strategies, safety precautions, and possible adverse effects.
3. Appropriate training is essential as using nasal sprays and drops incorrectly can lead to treatment failure.
4. By counselling the patient on allergens to stay away from, such as pollen in cases of seasonal allergic rhinitis, house dust mites, cat allergens, occupational allergens, and irritants.

8.3 Urticaria: Urticaria is characterized by the rapid appearance of wheals which may be accompanied by angioedema. The classical Xleeting wheal demonstrates edema with an upregulation of endothelial adhesion molecules, a mixed inXlammatory perivascular inXiltrate of variable intensity consisting of neutrophils and/or eosinophils, macrophages and T-helper lymphocytes.[84] The spectrum of clinical manifestations of different urticaria subtypes is very wide. Additionally, in one patient two or more different subtypes of urticaria can coexist. The following presents a classiXication for clinical use (Table 3).

Due to the heterogeneity of the disease with its many subtypes, guidelines for diagnosis cover a routine programme only Standardized diagnostic tests for a number of urticaria subtypes are summarized in Table-3

below. Currently, the only generally available test to screen for autoantibodies against the IgE receptor is the autologous serum skin test. This needs to be performed with utmost care as infections could be transmitted particularly if by mistake patients are not injected with their own serum.[85]

Table 3: Types of Urticaria and its diagnostic tests.

a. Spontaneous urticaria	Frequency And Duration	Routine diagnostic tests
Acute urticaria	<weeks 6, Spontaneous wheals appearing most days	No routine diagnostic tests (unless strongly suggested by patient history)
Chronic urticaria	>weeks 6, Spontaneous appearance of wheals	Differential blood count; ESR, omission of suspected drugs, e.g. NSAID Possibly, autologous serum skin test test for *Helicobacter*, gastroscopy, ANA, stool for worm eggs/parasites, skin tests, specific IgE, thyroid hormones and autoantibodies, pseudo allergen-free diet for 3 weeks.
1. Chronic continuous urticaria	Daily or on most days of the week	
2. Chronic recurrent urticaria	Symptom free intervals ranging from days to weeks	
b. Physical urticaria	Eliciting Factor	
1. Dermographic urticaria	Mechanical shearing forces (wheals arising after 1–5 min)	Elicit dermographism Differential blood count and ESR (as indication of severe systemic disease)
2. Delayed pressure urticaria	Vertical pressure (wheals arising with a 3–8h latency)	Pressure test (0.2–0.4 kg/cm^2 for 10 and 20 min)
3. Cold contact urticaria	Cold air/water/wind	Cold provocation test (ice cube, cold water); use different temperatures to identify threshold possibly: exposure to cold wind (ventilator) differential, ESR, cryoglobulins
4. Heat contact urticaria	Localized heat	Warm arm bath (42°C; vary temperature to detect threshold)
5. Solar urticaria	UV and/or visible light	UV and visible light of different wave lengths
6. Vibratory urticaria/angioedema	Vibratory forces, e.g. pneumatic hammer	UV and visible light of different wave lengths
c. Special types of urticaria		
1. Cholinergic urticaria	2. Adrenergic urticaria	Exercise or hot bath according to patient history
3. Contact urticaria (allergic or pseudoallergic)	4. Aquagenic urticaria	
d. Different diseases related to urticaria for historical reasons		
1. Urticaria pigmentosa (mastocytosis)	2. Urticarial vasculitis	Biopsy, differential blood count, ESR, ANA
3. Familial cold urticaria (avasculitis)		

8.31 Management: Although the subtypes of urticaria are elicited by a great variety of factors, its treatment mainly follows some basic principles. These are: Avoidance or elimination of the eliciting stimulus like drugs, physical stimuli, dietary management, removal of FCERI autoantibodies. Inhibition of mast cell mediator release, Therapy of target tissues of mast cell mediators.

1. Case Studies

a. In Cardiff (Wales), 10% of pollinosis patients experienced symptoms in the presence of 10 grass-pollen grains/m3, and again in London a concentration of more than 50 grains/m3 induced symptoms in all pollinosis patients.[86] In Bilbao (Spain), 100% of pollinosis patients experienced symptoms when the pollen count was above 37 grass-pollen grains/m3.[87] In Turku (Finland), a count of less than 30 grass- pollen grains/m3 was significantly correlated with nasal symptoms at the start of the grass-pollen season.In a population of 59 subjects with persistent rhinitis and exposed to indoor decorative plants in the domestic environment 78% were sensitized to at least one ornamental plant (weeping fig, yucca, ivy, palm tree and geranium).[88]

b. In a case study Approximately 58% of 60 patients who received at least 2 g of penicillin daily for ten days or longer developed penicilloyl-specific IgG antibodies, 18% produced penicilloyl-specific IgE antibodies, and 38% produced neither.[80] There is little to no danger of allergic reactions in patients who do not quickly develop a penicillin-specific immune responses to penicillin. It is unknown if penicillin-responsiveness of the immune system is genetically based.[68]

c. If the egg allergic patient is exposed to the stove

where the eggs are boiled, he may get symptoms because during heating cooking egg proteins is released in air. There was a case study which said that mother stated that first time at the age of 9 months after eating a whole egg and breastfeeding 45 minutes later, the child suffers sever restlessness hives and wheezing and vomiting for 20mins. After the performance of SPT the results where clear which made it a mystery case. 2 months later the child again suffered anaphylaxis in the arm of his older sister who has eaten eggs 10mins before hugging Jim. With all the findings it was proved that egg aerosols cause anaphylaxis.[89]

d. In this case which was done on 50 patients which included male: female ratio 1.7: 1 with different conditions resulted that significant number of children with CMPA who presented with delayed type allergic reaction may be at risk of developing immediate reaction upon reintroduction. Therefore, evaluation of these children for possible IgE mediated Reactions may be advisable for cow milk protein Introduction. It was found that Early Introduction of cow's milk protein may prevent CMPA.[90]

2. Ongoing Studies and Researche

a. The Prevalence of Immediate Hypersensitivity Reactions to the BNT162b2 mRNA Vaccine against SARS-CoV-2: The first vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) (the virus responsible for COVID-19) used on a large scale was BNT162b2, which has been reported to be associated with common adverse effects including pain, swelling and redness at the injection site, fatigue, headache, muscle pain, chills, joint pain, fever, nausea, malaise, and lymphadenopathy.[91] The vaccine component that has been hypothesized to be involved as the potential eliciting allergen in patients with BNT162b2-induced hypersensitivity reactions is the excipient polyethylene glycol (PEG), a hydrophilic polymer that is frequently used as an excipient in everyday products including medicines, cosmetics, and foods.[92] As for hypersensitivity reactions to BNT162b2, although rare, there are some reported cases of both allergic reactions and anaphylaxis.[93]

b. Risk Factors of Challenge-Proven Beta-Lactam Allergy in Children with Immediate and Non-Immediate Mild Cutaneous Reactions: Two hundred fourteen (119 male and 95 female) patients with a median age of 4.9 years were evaluated. BL allergy was confirmed in 10.7% (23) of the patients, according to the OCT results. Most of the proven allergic reactions were of the immediate type (73.9%), and urticaria was the most common presenting complaint (60.8%) in proven BL-allergic patients.[94]

c. Practical Approach to Hypersensitivity to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Children: Hypersensitivity to NSAIDs is a difficult diagnostic problem in paediatric allergy. Thirty- one (55.4%) reactions were immediate, and 25 (44.6%) were delayed or late. The most common manifestation of hypersensitivity to ibuprofen in children is acute urticaria and angioedema. Two important problems in the differential diagnosis are cofactors such as vitamin D levels and viral infections, which require further research.[95]

d. Biologics to treat anaphylaxis: Biologic management of anaphylaxis involves the use of large- molecule drugs such as monoclonal antibodies. Omalizumab, an IgG1 monoclonal antibody targeting unbound IgE, is the most prevalent and widely studied biologic in the prevention of anaphylaxis. Other monoclonal antibodies in development or approved for other indications, such as ligelizumab, quilizumab, MEDI4212, and dupilumab, may also have potential for preventing anaphylaxis through various mechanisms.[96]

CONCLUSION

Type I hypersensitivity is brought on by exposure to an antigen and is brought on by the sensitization and effect phases. Anaphylaxis or an atopic immunological response is caused by substances, medicines, and animals that increase the synthesis of IgE. The three mechanisms linked to type 1 hypersensitivity are the p-i concept, pro-hapten hypothesis, and hapten hypothesis. Type 1 hypersensitivity is primarily T-cell or IgE-mediated. Agents known as haptens are not immunogenic, but they can bind to antibodies to produce an immune response. The p-i concept asserts that drugs or their metabolites bind directly to MHC proteins or peptides, activating T-cells via their T-cell receptor, while the pro-hapten hypothesis requires metabolism through CYP450 enzymes. 10% of adults and 8% of children in developed countries suffer from food allergies, which is a serious public health issue. Allergies to cow's milk and eggs, primary beef allergies, alpha-gal syndrome, peanut allergies, and atopic dermatitis are common triggers. Hepatitis clinical allergies are more likely to develop in infants with a family history of allergies or atopic disorders. Important allergens are produced by bees, vespids, and ants in their venoms. Frequency, severity, age, use of medications, and environmental factors are risk factors. Reactions can also be influenced by beehives and nest locations. Penicillin, a popular antibiotic, can cause drug-induced hypersensitivity reactions in the 20-49 age group. Sensitization can result from environmental exposures, tainted food items, and drug-induced liver injury, which is illegal in some countries. Clinical manifestations of immediate hypersensitivity include, Anaphylaxis, allergic rhinitis, urticaria. Research on the BNT162b2 mRNA vaccine against SARS-CoV-2 has found common adverse effects, including pain, swelling, and fever. The vaccine component, polyethylene glycol, may elicit allergens. Challenge-proven beta- lactam allergy in children was confirmed in 10.7% of patients. Hypersensitivity to

NSAIDs is a difficult diagnostic problem, with urticaria and angioedema being common manifestations. Biologics like Omalizumab may prevent anaphylaxis.

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