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*Graduation reserch*

# *Review In Desensitization Of Hypersensitivity To Drugs*

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{" وَيَسْأَلُونَكَ عَنِ الرُّوح
قُلِ الرُّوحُ مِنْ أَمْرِ رَبِّي
وَمَا أُوتِيتُم مِنَ الْعِلْمِ إِلَّا قَلِيلًا "}

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# Introduction :

Hypersensitivity reactions to drugs pose a significant challenge in medical practice, often limiting treatment options for patients with critical conditions. Allergic reactions to medications can range from mild skin rashes to severe anaphylaxis, a life-threatening response. These hypersensitivity reactions occur when the immune system recognizes a drug as a threat and launches an immune response against it.

In recent years, drug desensitization research has emerged as a promising approach to manage drug allergies and sensitivities. Desensitization involves a carefully controlled and gradual reintroduction of the offending drug to desensitize the immune system, enabling patients to safely receive necessary medications that were previously deemed intolerable.

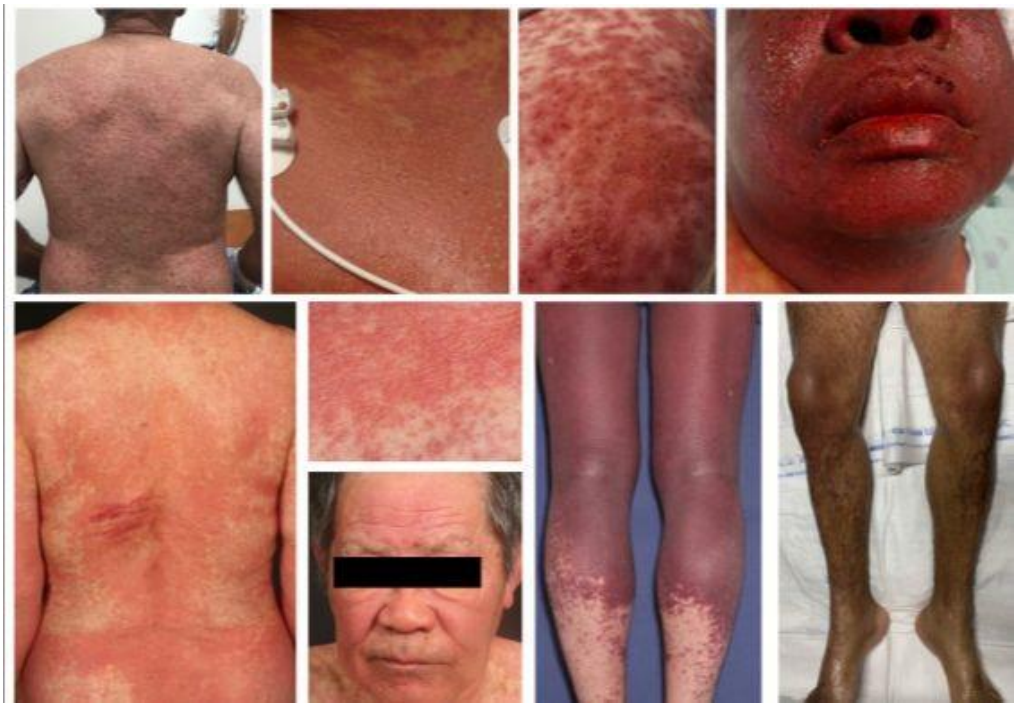
Desensitization protocols have shown success in various drug classes, such as antibiotics, chemotherapy drugs, and biologic agents, offering hope to patients who once faced limited treatment options. By progressively exposing patients to increasing doses of the allergenic drug, under close medical supervision, desensitization aims to reprogram the immune system's response and promote tolerance.[1]

Successful drug desensitization not only expands treatment possibilities for patients with drug allergies but also enhances our understanding of the immune system's intricate workings. By unraveling the mechanisms underlying hypersensitivity reactions and the processes involved in desensitization, researchers are making significant strides in refining desensitization protocols and identifying potential targets for intervention.

In this context, ongoing research in drug desensitization plays a vital role in advancing medical practice, improving patient outcomes, and expanding the horizon of treatment options. As researchers delve deeper into the intricacies of immunological processes, we can anticipate further advancements in desensitization techniques, fostering a brighter future for individuals affected by drug allergies and sensitivities.[2]

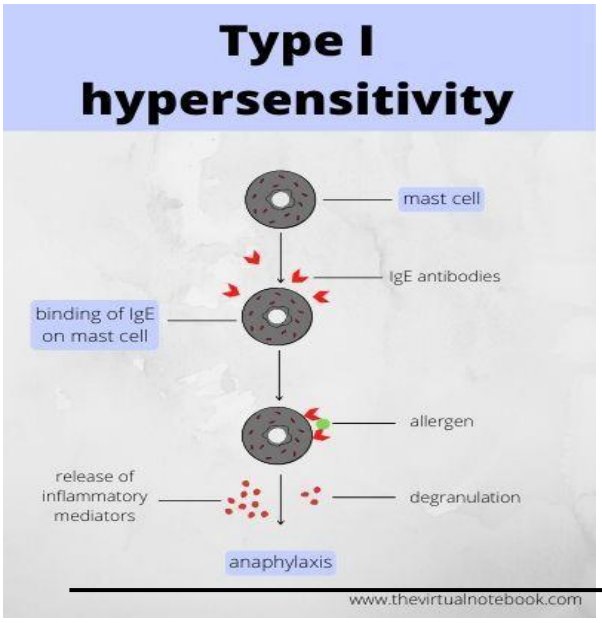
# Hypersensitivity :

Drug hypersensitivity reactions (DHRs) are unexpected adverse effects of medications that clinically resemble allergies and are not related to their pharmacological actions. The clinical manifestations of DHR vary from mild skin reactions to potentially fatal systemic reactions, such as anaphylaxis. These phenotypes are classified as immediate or delayed re actions based on their onset and the occurrence of typical symptoms. Both allergic and non-allergic mechanisms can contribute to the development of DHR; allergic reactions are defined as either drug-specific antibody-mediated or cell mediated immunological responses.[3]

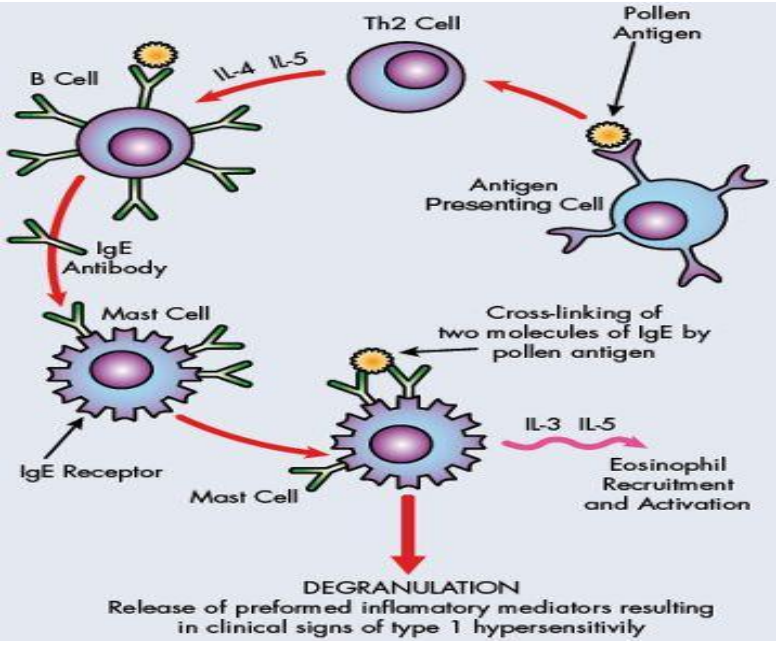


# Type of Hypersensitivity :

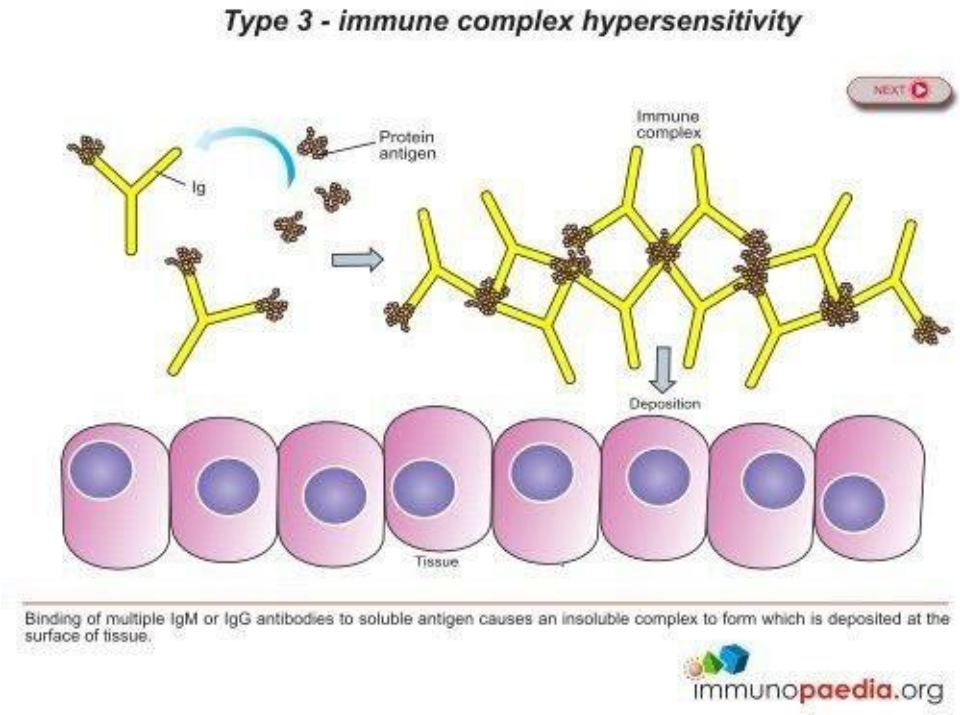
Type I or immediate hypersensitivity is mediated by IgE specific for allergens. An overview of allergens is provided in this issue.[4] Sensitization to allergens occurs when T-helper (Th) type 2 cells and their mediators drive isotype switching in B cells to produce IgE antibodies. A large portion of IgE remains bound to the high-affinity IgE receptor FcRI on the surface of mast cells and basophils. On re exposure, allergen crosslinks specific IgE on these cells, which causes release of mediators in two main phases. The early phase occurs within minutes and is caused by histamine, proteases (tryptase and chymase), lysosomal enzymes, and other preformed mediators released immediately on mast cell and basophil degranulation. In addition, mast cells produce lipid mediators, including prostaglandin D2 and leukotriene C4 from arachidonic acid and release them into circulation within 15 minutes of IgE crosslinking. The late phase occurs 4 to 8 hours after allergen exposure and is caused by cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)- **α**, IL-4, IL-5, IL-13, and granulocyte monocyte colony-stimulating factor (GM-CSF) produced de novo by mast cells. The route and location of allergen exposure determine the ensuing symptoms. Inhaled allergens may exacerbate allergic rhinitis or asthma by causing nasal congestion, rhinorrhea, sneezing, and bronchospasm. Topical contact with allergens can cause urticaria. Also, exposure to allergen via the oral or intravenous route typically produces systemic symptoms. Anaphylaxis is a potentially life-threatening type I systemic allergic response to allergens, such as foods, medications, or stinging insect venoms, and is characterized by urticaria, angioedema, bronchospasm, nausea, vomiting, diarrhea, hypotension, and, rarely, shock.[5]



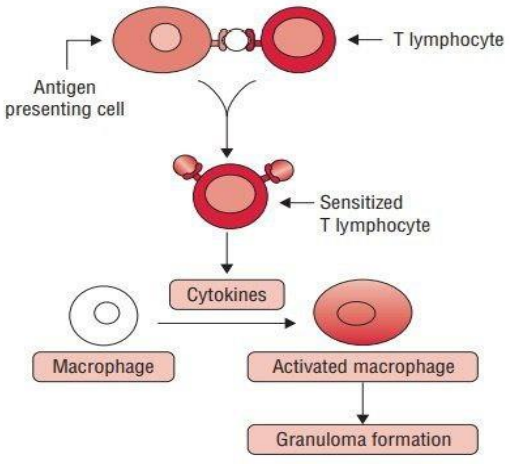
Type II IgG and IgM antibodies are key components of host defense, which bind to microbes and aid in their direct killing via multiple mechanisms. Unfortunately, when these antibodies bind to self antigens, they can direct the cytotoxic response against the host itself and cause potentially extensive damage. This is the basis of type II reactions, termed cytotoxic reactions, which are characterized by IgG and/or IgM antibodies against cellsurface antigens. These antigens are typically found on circulating blood cells, such as red blood cells, platelets, neutrophils, or on epithelial cells in mucosal surfaces and basement membranes. Type II reactions are further divided into two subtypes: type IIa and type IIb. Type IIa refers to reactions characterized by cytolytic destruction of targeted cells. IgG/IgM binding to cell-surface components causes cytotoxicity via three main mechanisms. The first is complement-dependent cytotoxicity, which is the primary etiology in autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura. Antigen-antibody complexes on the surface of cells activate the classic complement pathway, creating the membrane attack complex (C5-C9), which causes lysis of the target cell. Second, IgG antibodies can induce damage via antibody-dependent cell-mediated cytotoxicity. IgG on target cells binds to Fc gamma receptor IIb (FcγRIIb) on natural killer cells and macrophages, which causes them to release granules that contain perforin and granzyme to directly kill cells. Finally, both IgG and IgM can bind to Fc receptors on phagocytes to activate them and initiate phagocytosis. Type IIb reactions involve autoantibodies stimulating cells directly to create pathogenic states. For example, in Graves disease, antibodies to thyrotropin receptors stimulate the thyroid gland to produce excessive amounts of thyroid hormone. Chronic idiopathic (spontaneous) urticaria may be categorized as a type IIb disorder (at least in some patients), due to IgG antibodies directly binding to and stimulating FcεRI receptors on mast cells, which causes mast cell degranulation in the skin and, subsequently, the development of urticaria. In this subset of patients, these autoantibodies are necessary but not sufficient for mast cell activation.[6]



Type III In type III responses, IgG and IgM antibodies bind to antigens to form immune complexes. These complexes deposit in tissues and activate complement, which then causes organ damage. Common sites of complex deposition include small arteries, renal glomeruli, and synovial capsules of joints, thereby causing vasculitis, glomerulonephritis, and arthritis, respectively. Thus, the symptoms associated with type III reactions are determined by the site of immune complex deposition and not by the source of the antigen. Antigens involved in type III responses can either be self, such as in autoimmune diseases including lupus, or foreign, as is the case in serum-sickness reactions caused by various medications, including proteins (such as thymoglobulin) or small molecules (such as penicillin or procainamide).[6]



Type IV Type IV hypersensitivity responses are collectively termed delayed reactions and involve T cells as the major effector cells. Sensitized T cells can cause damage directly, as in the case of cytotoxic T cells, or helper T cells may activate other leukocytes, such as macrophages, neutrophils, and eosinophils, which may impart tissue injury through the production and release of reactive oxygen species, lysosomal enzymes, and inflammatory cytokines. Relatively recent enumeration of T-cell subsets has allowed for further categorization, and type IV reactions are now divided into four subtypes according to the immune mechanisms and pathogenesis of each: types IVa, b, c, and d. The classic type IV reaction as first described by Gell and Coombs [7] is now termed types IVa and is mediated by Th1 cells, which activate macrophages to secrete cytokines such as interferon γ and TNF-**α**. A prototypical example of this type is contact dermatitis, which can occur to various substances, including poison ivy, oak, and sumac (members of the Toxicodendron genus). Type IVb reactions involve the production of IL-4, IL-5, and IL-13 by Th2 cells to induce eosinophilic inflammation and IgE production from B cells. For example, in patients with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) drug-sensitized Th2 cells promote eosinophilic survival, activation, and tissue migration to cause multiorgan injury. In addition, type IVb reactions may be involved in the latephase inflammation of atopic disorders, such as asthma or allergic rhinitis. Type IVc is primarily mediated by cytotoxic CD8 + T cells, which directly kill targeted cells by using a number of mediators, including perforin, granulysin, and granzyme B. Type IVc reactions seem to be the underlying mechanism of tissue damage in Stevens-Johnson syndrome and toxic epidermal necrolysis, in which activated CD8 + T cells induce apoptosis and/or necrosis of keratinocytes. Type IVd responses cause tissue damage when Tcell–derived CXCL-8 (also known as IL-8) recruits neutrophils into tissues to create sterile neutrophilic inflammation, as is the case with acute generalized exanthematous pustulosis.[8]




A schematic diagram showing type IV hypersensitivity

| Modern classification of hypersensitivity reactions* | | |
|---|---|---|
| Classification Type | Immunologic Mechanisms | Clinical Examples |
| I | Mast cell-mediated reactions IgE-dependent (anaphylactic) | Anaphylaxis, angioedema, urticaria, asthma, allergic rhinitis |
| | IgE-independent (nonimmunologic or anaphylactoid) | Reactions to iodinated contrast reagents and some biologics |
| IIa | Antibody-mediated cytotoxic reactions (IgG/IgM antibodies); complement often involved | Immune cytopenias |
| IIb | Antibody-mediated cell-stimulating reactions | Graves disease, chronic idiopathic (spontaneous) urticaria |
| III | Immune complex-mediated complement activation | Serum sickness, drug-induced lupus, vasculitis |
| IVa | Th1 cell–mediated macrophage activation | Type 1 diabetes, contact dermatitis (with type IVc), tuberculin test reactions |
| IVb | Th2 cell–mediated eosinophilic inflammation | Maculopapular exanthems, DRESS syndrome, persistent asthma, allergic rhinitis |
| IVc | Cytotoxic T cell–mediated reactions | SJS and/or TEN, bullous exanthems |
| IVd | T cell–mediated neutrophilic inflammation | AGEP, Behçet's disease |
| IgE Immunoglobulin E; Th T-helper cell; DRESS Drug Reaction with Eosinophilia and Systemic Symptoms; SJS Stevens-Johnson syndrome; TEN toxic epidermal necrolysis; AGEP acute generalized exanthematous pustulosis. *Adapted from Ref. [9] | | |

There are many drugs that cause hypersensitivity reactions include:

1_ Antibiotics(amoxicillin,ampicillin,penicillin,tetracycline,cephalosporins).

2_NSAIDs(ibuprofen,aspirin,naproxen).

3_Chemotherapy drugs(L-asparaginase, paclitaxel, docetaxel, teniposide, procarbazine, and cytarabine).

4_HIV drugs (abacavir,nevirapine).

# Desensitization :

Drug desensitization is the temporary induction of tolerance to a sensitized drug by administering slow increments of the drug, starting from a very small amount to a full therapeutic dose. It can be used as a therapeutic strategy for patients with drug hypersensitivity when no comparable alternatives are available.[10]
The treatment of many disorders including cancer and autoimmune diseases can be complicated by hypersensitivity reactions (HRs). Clinical manifestations vary considerably, ranging from mild to severe and life-threatening reactions leading to drug discontinuation, which in turn can decrease patients' quality of life and/or life expectancy. Phenotypes in drug allergy focus on symptoms and timing, classifying the reactions as immediate or delayed, depending on the time between treatment administration and the onset of symptoms. The most frequently involved culprit drugs are represented by antibiotics, aspirin, chemotherapeutics and biological agents.[11]
Management of HRs, beyond an allergological work-up aimed to define the pathogenic mechanism of the reaction, may include drug desensitization (DD) when there is no alternative therapy available. The culprit drug is usually avoided in order to prevent future reactions and DD was developed as a treatment option to maintain patients on first line therapy. The activation of mast cells (MC) plays a critical role in HRs, not only limited to the immediate release of an array of preformed inflammatory mediators including histamine, tryptase, serotonin, chymases, cytokines, and growth factors, but also de novo synthesis of lipid mediators such as leukotrienes. In addition to the classical IgE-mediated MC activation, other mechanisms may be involved. [12]
Management of HRs in patients without treatment alternatives is based on the DD procedure, able to induce a temporary hyporesponsive state by incremental escalation of sub-optimal doses of the offending drug, until reaching required dosage. Drug desensitization was developed due to the pressing need to reintroduce drugs in a safe fashion in patients who had developed both IgE-and/or non IgE-mediated HRs to critical drugs. Because DD is able to induce a temporary tolerance to the culprit drug, and considering that some medications (chemotherapy, biologic agents) have prolonged dosing intervals, subsequent administrations must be preceded by a DD procedure in order to overcome the loss of tolerance. Desensitization is conceptually dedicated to patients in which an IgE-mediated mechanism is demonstrated by positive skin testing or serum IgE for culprit drug, however, patients who suffered immediate reactions to taxanes and other chemotherapies in which the IgE mechanisms cannot be demonstrated have also been successfully desensitized. Two types of DD protocols are available: rapid drug desensitization which addresses type I reactions with mast cells/basophils/IgE involvement, and slow drug desensitization which addresses delayed type IV reactions with T-cell involvement.[13]

# Method of Desensitization :

## 1/ rapid drug desensitization

Rapid drug desensitization (RDD) is a therapeutic technique that modifies the immune response of allergic patients to those drugs they are allergic to. The RDD induces a temporary tolerance that can only be maintained while drug serum levels are maintained, and the temporary tolerance is lost as soon as the drug is eliminated.2 Based on in vivo and in vitro evidence, RDD protocols follow specific methodology, namely, starting at very low doses that are subthreshold for anaphylaxis, with doses doubling every 15 to 30 minutes at each increment until the target dose is attained.[14] The Brigham and Women's Desensitization Program generated a flexible 12- to 20-step protocol, which rendered mast cells unresponsive by delivering x2 to x2.5 doses of drug antigens at fixed time intervals starting at 1/1000 to 1/100 dilutions of the final concentration . The most commonly used protocol is based on 3 bags and 12 steps, with 3 x 10-fold diluted solutions at escalating rates . Patients with severe HSRs and anaphylactic reactions are desensitized with 16 steps (4 bags) or 20 steps (5 bags). Other protocols have been successfully used by other groups, and shorter protocols with only 2 bags have been proposed for patients with a mild-to moderate risk . These new protocols are empiric and not based on in vitro or animal data, and their success may depend on the target patient population. They should be used with extreme caution in highly sensitized patients, since in vitro data suggest that the small doses of antigen delivered during the early phase of the desensitization provide the platform for further doses and enable the target dose to be reached .[15]

Table 1. An example of aspirin desensitization protocol proposed by Silberman et al. and the EAACI guidelines (target dose: 100 and 325 mg)

| Dose of aspirin, mg | | | | |
|---|---|---|---|---|
| Cardiovascular or musculoskeletal diseases | | Aspirin-exacerbated respiratory disease or chronic sinusitis with or without nasal polyps | | |
| Dosing interval, min | Day 1 | Dosing interval, hr | Day 1 | Day 2 |
| | 1 mg | | 20–40 mg | 100–160 mg |
| 30 | 2 mg | | | |
| 30 | 4 mg | | | |
| 30 | 8 mg | 2 | 40–60 mg | 160–325 mg |
| 30 | 16 mg | | | |
| 30 | 32 mg | | | |
| 30 | 64 mg | 2 | 60–100 mg | 325 mg |
| 30 | 100 mg | | | |

## 2/slow drug desensitization

Slow desensitization, also known as allergen immunotherapy or allergy shots, is a method used to prevent or reduce the severity of allergies. It involves exposing the individual to small and gradually increasing doses of the allergen to which they are allergic. The purpose of this approach is to retrain the immune system and decrease its hypersensitivity to the allergen.

Here's how the slow desensitization process typically works:

Diagnosis: First, an allergist identifies the specific allergen or allergens that trigger an individual's allergic reactions through a series of tests, such as skin prick tests or blood tests. Customized Allergen Extract: Once the allergens are identified, a customized allergen extract is prepared. This extract contains small amounts of the allergen(s) to which the person is allergic. Initiation Phase: The treatment begins with an initial phase where the person receives injections of the allergen extract once or twice a week. The concentration of the allergen is low at the beginning to minimize the risk of a severe allergic reaction.

Build-Up Phase: Over time, the concentration of the allergen in the injections is gradually increased. This helps the immune system adapt and become less reactive to the allergen. The build-up phase can last several months.

Maintenance Phase: Once the desired maintenance dose is reached, the frequency of the injections is typically reduced to every two to four weeks. This phase may continue for three to five years or even longer.

The slow desensitization process aims to desensitize the immune system by exposing it to the allergen in controlled doses. The mechanism behind this therapy is not fully understood, but it is believed to involve various immunological changes. These changes include a shift from an allergic response (Th2) to a more tolerant response (Th1), a decrease in allergen-specific IgE antibodies, and an increase in allergen-specific IgG antibodies.

By gradually exposing the immune system to increasing amounts of the allergen, slow desensitization can help reduce the frequency and severity of allergic symptoms over time. The goal is to modify the immune response, leading to improved tolerance and decreased allergic reactions.

It's important to note that slow desensitization should only be carried out under the supervision of a qualified allergist or immunologist. Allergy shots can be an effective treatment for certain allergies, such as allergic rhinitis, allergic asthma, and insect venom allergies. However, they may not be suitable for everyone, and the decision to pursue this treatment should be based on a thorough evaluation of the individual's specific allergy profile and medical history.[16]

# Contraindication and criteria :

Desensitization is contraindicated in patients whose reaction suggests a history of severe cutaneous reactions, such as Stevens-Johnsons syndrome, toxic epidermal necrolysis, drug induced hypersensitivity syndrome, drug reaction (rash) with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis. Desensitization is also not considered appropriate for reactions ofserum sickness or haemolytic anemia. Omalizumab is a humanized IgG1 monoclonal antibody, initially approved for the treatment of severe allergic asthma and more recently, for the treatment ofchronic idiopathic urticaria. In several case reports it has been applied to control the reactions occurring during DD, for aspirin, insulin, elosulfasi α, carboplatin, and oxaliplatin. [17]

## criteria

- Drug therapy is essential
- Drug is irreplaceable, more effective than alternatives, or it has a unique mechanism
- Unavailability of a non-cross-reacting drug
- Previous reaction is well documented and not severe, for example maculopapular exanthem or fixed drug eruption; preferably, the mechanism is known after allergologic workup
- Potential benefits outweigh the potential risks

# Conclusion :

Here, we discussed the mechanism of desensitization and its actual implementation for many drugs . The development of hypersensitivity following repetitive administration of drugs is a major impediment to treatment. Desensitization induces temporary tolerance to the drug by gradually incrementing the dose to reach the therapeutic dose. Drug desensitization should be considered when the benefits of the culprit drug outweigh the risk. However, it should be applied carefully in patients with significant risk factors such as those with a history of severe hypersensitivity reactions. In the desensitization procedure, various BTRs ranging from mild to severe can occur, but most resolve if desensitization is stopped immediately. the Success rates in the reports described (mostly IgE-mediated allergy) range from 50% to 100% . However, due to the low number of cases reported and lack of comparative prospective studies, success rate may be either lower or higher in reality. Larger case series in adult patients report a success rate of more than 90% in both allergy to antibiotics and to cytostatics.

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