CHAPTER 1

DRUG HYPERSENSİTİVİTY

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INTRODUCTION

Separate articles provide a thorough explanation of the etiology of drug hypersensitivity as well as a method for diagnosing and treating these diseases. Drug hypersensitivity reactions (DHR), which are brought on by heightened immune or inflammatory responses, include allergic, exaggerated pharmacologic, and pseudoallergic reactions to drugs.

CATEGORIES OF ADVERSE DRUG REACTIONS

Any unfavorable response to a medication is referred to as an adverse drug reaction in general. Type A and Type B adverse medication reactions (table 1.) can be used as a general classification system.

Type A reactions: 85 to 90 percent of all negative medication reactions are type A reactions. Given an adequate dose and exposure, they can have an impact on anyone, and they can be anticipated based on a drug's recognized pharmacologic qualities. Type A reactions include, for instance, nephrotoxicity from aminoglycosides and diarrhea brought on by antibiotics. Type A reactions also include gastritis brought on by long-term use of NSAIDs.

Type B reactions: Reactions of a hypersensitive nature are Type B reactions. They account for 10 to 15 percent of unfavorable medication reactions, happen in a vulnerable subset of patients, and feature signs and symptoms that are unrelated to the drug's pharmacologic effects. Inflammatory and/or immunologic mechanisms mediate the vast majority of hypersensitivity reactions. Exaggerated sensitivity reactions and idiosyncratic drug reactions are two further types of reactions that manifest with symptoms unrelated to the immune system or inflammatory cells.

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Table 1. Type A and Type B reactions
Type A drug reactions are seen in the majority of healthy patients with the appropriate dosage and length of therapy: Typical and foreseeable • Overdose (acetaminofen related hepatic failure, aspirin related metabolic acidosis etc.) • Side effects at subtherapeutic doses (nephrotoxicity with aminoglycosides, methylxanthines related nausea and headache, vaginal candidiasis or oral thrush with glucocorticoids) • Secondary/ indirect effects (diarrhea due to antibiotics, doxycyclin and thiazide diuretics related phototoxicity) • Drug interactions
Type B drug hypersensitivity reactions, which only affect a small portion of the general population: Rare and frequently erratic • Intolerance • Idiosyncrasy due to pharmacogenetics that drug effect not attributable to known pharmacologic properties of drug and not immune-mediated. (G6PD deficiency-hemolytic anemia after dapsone*, TPMT deficiency- toxicity with azathioprine*, Pseudoallergic reaction with NSAIDs) • Immunologic drug reactions (Anaphylaxis due to beta-lactam antibiotics, photoallergy with quinidine,vasculitis with phenitoin, steven Johnson syndrome due to trimethoprim-sulfamethoxazole,immune-mediatedthrombocytopenia with heparin, drug induced hypersensitivity syndrıme wit allopurinol in HLA-B*58:01 individuals*)

*Predictable Type B reactions
G6PD: glucose-6-phosphate dehydrogenase; TPMT: thiopurine methyltransferase; NSAIDs: nonsteroidal anti-inflammatory drugs.

Drug hypersensitivity reactions (DHR) are brought on by the medicine stimulating immunological or inflammatory cells. They represent 6–10% of all unfavorable medication reactions, but up to 10% of fatal reactions (1).

Idiosyncratic drug reactions and exaggerated sensitivity – Idiosyncratic drug reactions are qualitatively different from the medicine›s recognized pharmacologic toxicities. Azithromycin toxicity can develop in patients with thiopurine methyltransferase (TPMT) deficiency, while primaquine can cause nonimmune hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency or glucose-6-phosphate dehydrogenase insufficiency (2-4). At modest and occasionally subtherapeutic doses, other patients have a heightened sensitivity. An illustration might be someone who experiences tinnitus after taking a single aspirin dose. This may indicate changed medication metabolism or elevated end-organ sensitivity.

Definition of drug hypersensitivity reactions — DHRs are reactions that happen when a medicine unintentionally and unwantedly stimulates immunological or inflammatory cells.

DRUG HYPERSENSITIVITY CLASSIFICATION

Based on the timing of the onset of symptoms, the medication's mode of action on immune/inflammatory cells, or the immunologic mechanism, drug hypersensitivity can be further differentiated. A drug hypersensitivity reaction (DHR) is frequently identified in practice using a multifaceted approach that takes into account the timing of the reaction's onset, any potential mechanisms of action (such as immunological activation), and its pathophysiology (5).

Because the mechanisms of action and subsequent adverse responses differ significantly between DHRs caused by small compounds used as drugs and DHRs induced by big proteins used as medications (such as monoclonal antibodies), it is crucial to distinguish between the two (6).

Based on when symptoms first appeared: Based on the timing of the onset of symptoms, the World Allergy Organization (WAO) suggests categorizing immunologic drug reactions into immediate reactions (i.e., onset within one hour of exposure) and delayed reactions (i.e., beginning beyond one hour) (7).

Immediate: IgE-mediated, type I reactions are supposed to be distinguished from other types of reactions using the WAO distinction between immediate and delayed drug reactions. Typically, Type I reactions start happening within an hour of the initial dose being given. But some IgE-mediated reactions take up to an hour to manifest, especially if the medication was taken orally with food, which inhibits absorption. However, the bulk of IgE-mediated reactions, which offer a risk of anaphylaxis if the patient is exposed again, are detected within this hour-long window.

Delayed: Although the majority of delayed reactions start after six hours and generally after days of therapy, reactions that manifest within one hour are categorized as delayed. As an illustration, delayed effects to amoxicillin typically appear on days 7 to 10 of therapy and occasionally even one to three days after therapy ends. These reactions are not IgE mediated, although they could be brought on by a number of other pathways. Immunologic reactions of types II, III, and IV are all regarded as delayed reactions.

After several weeks of ongoing treatment, certain delayed reactions start. Drug rash with eosinophilia and systemic symptoms (DRESS), a systemic drug reaction that starts one to twelve weeks into continuous treatment, is one such condition (8). Eosinophilia and lymphocytosis may or may not be connected to this reaction, also known as "drug-induced hypersensitivity syndrome" (DiHS), which is characterized by fever, rash, and multiorgan involvement. Hypersensitive myo-

carditis and hepatitis are two possible effects. Even when the medicine is stopped, these effects may continue for several weeks to months.

According to the mode of action: Often less than 1000 Daltons in size, drugs can interact with the immune and inflammatory systems in a variety of ways.

Drug allergy/immune reactions: Most medications are made of tiny molecules that cannot trigger immunological reactions. However, some medications can attach to proteins covalently and change a self-protein into a new antigen (hapten protein or hapten-peptide complex). These hapten-protein complexes behave like traditional antigens and trigger immunological responses against the hapten-modified protein/peptide, which can be carried out by lymphocytes, IgE, or IgG. These reactions can lead to a variety of clinical presentations of drug allergies, such as contact dermatitis to 1-chloro-2,4-dinitrobenzene (DNCB) and IgE-mediated anaphylaxis to penicillin. Below is a description of the many immunologic medication reactions.

Interaction of drugs and immunological receptors (p-i reactions): Due to a drug's "off-target" effect on immune receptor proteins such T cell receptors and HLA proteins, a significant proportion of immunological-mediated DHR is caused by these proteins (TCR). P-i responses, also known as "pharmacologic interactions with immunological receptors," are what these interactions known. The drug's role as a novel antigen does not cause P-i-mediated immune stimulations. Instead, the medication immediately creates a potent, non-covalent interaction with the immunological receptor on T cells (TCR) or antigen-presenting cells (HLA), stimulating the T cell (9). When a drug binds to the HLA-protein and triggers a T cell response against the drug-modified HLA-protein-peptide complex, the stimulation can either be direct (if it binds to the TCR) or indirect (if it binds to the HLA-protein). Thus, T cell activation and the impact of that activation on the implicated cells are the causes of the clinical symptoms in all p-i responses. Clinical manifestations include hepatitis, maculopapular eruption, SJS/TEN, DRESS, and more. P-i responses have some dose dependence because they are normal pharmacologic drug-receptor interactions.

When a medicine binds preferentially to an HLA protein (such as abacavir to HLA-B*57:01), adverse responses may affect people with these alleles more severely or exclusively (10). This explains the HLA-linkage of some DHRs and establishes the predictability of some p-i-mediated types of DHR. Abacavir, carbamazepine, allopurinol, dapsone, and flucloxacillin hypersensitivity reactions are a few well-studied instances of p-i reactions. Before giving patients abacavir and carbamazepine in communities where the genotype is very prevalent, it is advised

that they undergo an HLA test. There are different discussions that go into further detail about specific screening suggestions.

Pseudoallergy — Medication intolerance or pseudoallergy is another diverse type of adverse drug reaction (11,12). Although pseudoallergic reactions resemble immunologic drug reactions, there is no proof that the immune system is specifically involved (drug-specific IgE, IgG, or specifically activated T cells) (table 2.) Uncertainty exists regarding the pathomechanism of these reactions (13). Most pseudoallergic reactions have the same signs and symptoms as IgE-mediated (immediate) allergic reactions. Each can entail urticaria, angioedema, or anaphylaxis due to mast cell degranulation, and both manifest quickly (within minutes). There is both mast cell activation and eosinophilic inflammation in pseudoallergy brought on by NSAIDs. Separate reviews are given to pseudoallergic responses to NSAIDs.

Table 2. Pseudoallergic drug reactions

Drug	Mechanism	Possible clinical exacerbations
Radiocontrast media	Unknown mechanism	Anaphylaxis, shock (may be result from Type 1 reaction)
Aspirin and other NSAIDs	Inhibited prostaglandin production and enhanced leukotriene production	Exacerbations of rhinitis, asthma (in patients with aspirin-exacerbated respiratory disease) Urticaria/angioedema (may be result from Type 1 reaction)
Vancomycin	Direct stimulation of mast cells through MRGPRX2, causing release of mediators	Flushing during infusion
Opiates	Direct stimulation of mast cells and/or basophils causing release of mediators	Pruritus, urticaria
Local anesthetics	Vasovagal reflex	Syncope
Ciprofloxacin	Direct stimulation of mast cells through MRGPRX2, causing release of mediators	Urticaria
Choline	Unknown mechanism	Pruritus, urticaria
Isoniazid	Unknown mechanism	Hepatitis
Protamine	Unknown mechanism	Hypotension, pulmonary hypertension

NSAIDs: nonsteroidal anti-inflammatory drugs: IgE: immunoglobulin E; MRGPRX2: Mas related protein coupled receptor member X2.

According to the immunologic mechanism — Historically, the Gell and Coombs method has classified immunologic reactions into four groups (I to IV), depending on whether they were brought on by medications, infections, or autoimmune mechanisms (table 3.)

- Type I- Immediate in onset, mediated by mast cells, basophils, and/or IgE.
- Type II – Antibody-mediated cell death that has a delayed onset and is typically IgG-mediated.
- Type III – IgG:drug immune complex deposition and complement activation are the causes of this delayed-onset condition.
- Type IV – T cell-mediated with a delayed onset. It's important to note that this classification was made before it was physically feasible to do a thorough investigation of T cell subsets and functions. Type IV reactions were further separated into types IVa, IVb, IVc, and IVd as new immunologic instruments were created (14).

Table 3. Immunologic drug reactions: Gell and Coombs classification

Type of reaction	Mechanism	Clinical features
I Immediate reaction (within one hour) IgE-mediated, immediate-type hypersensitivity	Mast cells and basophils are activated by IgE after exposure to an antigen, and vasoactive molecules like histamine, prostaglandins, and leukotrienes are released.	Anaphylaxis Bronchospasm Angioedema Hypotension Urticaria
II Antibody-dependent cytotoxicity	When an antibody attaches to an antigen or hapten that is closely linked to a cell, cell or tissue damage results.	Thrombocytopenia Hemolytic anemia Neutropenia
III Immune complex disease	Antigen-antibody complexes that form or are deposited in tissues or blood vessels cause damage. By interacting with Fc IgG receptors, immunological complexes that have been deposited trigger complement activation and/or neutrophil recruitment.	Serum sickness Arthus reaction
IV Cell-mediated or delayed hypersensitivity	Antigen exposure stimulates T lymphocytes, which then mediate tissue damage. Different subtypes can be distinguished based on the type of T cell activation and the other effector cells recruited (ie, types IVa to IVd).	Severe exfoliative dermatoses (eg, SJS/TEN) Contact dermatitis Some morbilliform reactions DRESS/DiHS AGEP Drug-induced hepatitis Interstitial nephritis Other presentations

IgE: immunoglobulin E; Fc IgG: Fc portion of immunoglobulin G; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS/DiHS: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

Medications cause types I and IV reactions far more commonly than types II and III, which usually follow prolonged, higher dose therapy. Most medications cause just one type, although certain drugs, such as penicillin, can induce all four types.

TYPES OF IMMUNOLOGIC DRUG REACTIONS

Type I Reactions

Drug-specific IgE is necessary for type I responses. When exposed to a medication, a tiny percentage of patients develop drug-specific IgE, while the majority do not, not even with continuous treatment.

Clinical features: Mast cells and basophils release vasoactive mediators, which are directly responsible for the signs and symptoms of type I reactions. Urticarial rash, pruritus, flushing, angioedema of the face, extremities, or larynx (resulting in throat tightness with stridor, or rarely asphyxiation), wheezing, gastrointestinal problems, and/or hypotension are the most typical signs and symptoms.

The most serious form of an IgE-mediated drug reaction is anaphylaxis. In the initial few hours following anaphylaxis, mast cell tryptase and histamine levels might rise in the blood, and the discovery of these mediators links mast cells and basophils to the reaction, validating the anaphylactic diagnosis.

Because the typical wheal and flare are defining features of mast cell degranulation, the presence of urticaria helps determine IgE-mediated responses. It might be challenging to determine whether a rash was urticarial based solely on history because various skin manifestations associated with medication reactions can mimic urticaria. A pruritic exanthem or rash that causes diffuse skin swelling is a common component of delayed responses, and patients who experience them often complain of elevated, itchy skin patches. These edematous exanthems with delayed onset, though, are NOT urticarial rashes. Additionally, as long as the skin does not blister or slough and there are no indications of organ irritation, they are typically not harmful. The next section discusses reactions that cause organ inflammation and rashes.

The absence of urticaria in such patients should not be interpreted as a sign of anaphylaxis, on the other hand, urticarial rashes may be altered in appearance or repressed by continued antihistamine therapy.

IgE-mediated responses do not result in fever or increases in blood C-reactive protein. IgE-mediated reactions can be distinguished from other unwanted medication reactions by the absence of these characteristics.

Timing: Type I reactions start quickly, but the timing varies depending on the clinical situation and presentation. IgE-mediated reactions take place soon after the last delivered dose, which is why the World Allergy Organization classifies them as immediate (WAO). The manner of administration affects how quickly symptoms appear; intravenously administered drugs may do so in seconds to minutes, but orally administered versions of the same medication may do so in 3 to 30 minutes when taken on an empty stomach and in 10 to 60 minutes when taken with meals.

- If the patient has been continuously exposed to the medicine, IgE-mediated anaphylaxis responses should NOT start several days into a course of therapy. A few missed doses, though, can cause symptoms when the medication is restarted.
- In "pseudoallergic" reactions, urticaria can also develop minutes to hours after medication consumption.
- Late in the course of continuous therapy, isolated urticarial skin eruptions can develop:
- When taking medications known to cause allergies, such as beta-lactam antibiotics, urticarial rashes may take longer to manifest (similar to late-occurring serum sickness reactions).
- Serum sickness is indicated by urticaria that appears one to two weeks after therapy and is followed by arthralgias, fever, and other symptoms.
- Urticarial eruptions occasionally have maculopapular features and frequently start to show up days after the initiation of medication. These urticarial rashes often result from the use of medications (such as macrolide antibiotics) that rarely induce acute allergy and are not likely to be IgE mediated. Although the etiology is unknown, T cells might potentially be implicated.

Frequently-implicated drugs: The following medicines are frequently linked to type I reactions:

- Beta-lactam drugs (penicillins and cephalosporins).
- Neuromuscular blocking agents.
- Quinolones – Quinolone antibiotics have been linked to hypersensitivity reactions frequently in Europe but less frequently in the US, suggesting that there may be significant regional differences that will become clearer over time (15). IgE is only a small part of these reactions (16,17).
- Chemotherapeutic drugs like carboplatin and oxaliplatin that include platinum.
- Proteins from outside the body, such as chimeric antibodies like cetuximab and rituximab. The likelihood that these substances will result in anaphylaxis can also change depending on where you live.

Usage of the suspicious substance in the past: Usually, prior exposure to the substance in question is necessary for IgE-mediated responses. Even though the patient showed no symptoms of sensitivity to the sensitizing chemical, sensitization may have happened from exposure to a cross-reactive substance, therefore the absence of a known prior exposure does not rule out an IgE-mediated reaction.

The following instances highlight this occurrence:

- Numerous cosmetics, personal care items, and over-the-counter cough medications (such pholcodine in Norway) that contain tertiary and quaternary ammonium groups are thought to have previously predisposed patients to anaphylaxis when they were first exposed to neuromuscular blocking drugs (18–20). All of these drugs share the immunoreactive ammonium groups, which might cause IgE antibodies to cross-react.
- When exposed to cetuximab, some patients experience anaphylaxis and show signs of prior oligosaccharide sensitization (21). The proteins of several non-primate mammalian species, including beef, hog, and lamb, contain the same oligosaccharides. Though bites from specific tick species have been linked, the cause of the initial sensitization is still unknown.

Type II Reactions

Type II reactions are rare and entail cell apoptosis caused by antibodies. When medications bind to the surfaces of particular cell types and function as antigens, type II reactions may occur. When antibodies subsequently bind to the cell surface, macrophages target the cells for destruction. Complement activation may occur during type II reactions, but this is unpredictable.

Clinical signs necessitate the existence of large titers of preformed drug-specific IgG (or very infrequently, IgM) antibodies, which are only produced by a small proportion of people and typically in the context of high-dose, prolonged, or repeated drug exposure. The causes of people developing these antibodies are not entirely understood.

Clinical characteristics and timing: Due to the most frequent cell types impacted by type II medication responses, hemolytic anemia, thrombocytopenia, or neutropenia are typically the symptoms that manifest.

Patients may present asymptomatically or with a fulminant disease, and the severity of the clinical presentation can vary greatly. The first signs of the condition typically show up five to eight days after exposure, though they can start much later. If the offending medication is withdrawn and then restarted, symptoms may appear within hours.

Specific presentations: Depending on the cell type involved, certain symptoms can occur:

- **Drug-induced hemolytic anemia** – In addition to dyspnea, different levels of weariness, pallor, jaundice, dark urine, splenomegaly, and signs and symptoms of the hyperdynamic condition such bounding pulses, palpitations, and «roaring in the ears,» hemolytic anemia can also manifest as dyspnea.

Cephalosporins, penicillins, nonsteroidal anti-inflammatory medications (NSAIDs), and quinine-quinidine are the pharmaceuticals most frequently linked to hemolytic anemia. Drug-induced hemolytic anemia examination and diagnosis are covered in more detail separately.

- **Drug-induced thrombocytopenia** – When a patient is taking one or more drugs, isolated thrombocytopenia that is frequently severe (i.e., 20,000/microL) and petechial bleeding in the skin and oral mucosa are the typical symptoms of thrombocytopenia. Due to platelet sequestration in these organs, there may be splenomegaly and hepatomegaly.

Heparin, abciximab, quinine and quinidine, sulfonamides, vancomycin, gold compounds, beta-lactam antibiotics, carbamazepine, NSAIDs, and other medications have been linked to thrombocytopenia. It is covered elsewhere how this disease was evaluated and diagnosed.

- **Drug-induced neutropenia or agranulocytosis** – Days to weeks after taking the prescription, severe neutropenia or agranulocytosis brought on by type II drug responses commonly accompany acute and clinically obvious signs of infection, such as fever, sore throat, pharyngitis, pneumonia, or sepsis. Even with low doses, rechallenge or unintentional repeat ingestion is linked to an immediate recurrence.

The culprit medications include propylthiouracil (PTU), amodiaquine, and mono-desethyl amodiaquine, one of the drug's main metabolites. This disorder's assessment and diagnosis are presented individually.

Type III Reactions

Antigen-antibody complexes mediate type III reactions, which typically manifest as serum sickness, vasculitis, or drug fever. Similar to type II responses, these reactions are rare and typically occur when a high dose of medicine is administered over a lengthy period of time.

The medicine (including biologicals) is thought to function as a soluble antigen in a type III response. In this function, the medication binds drug-specific IgG, resulting in the formation of tiny immune complexes that can activate com-

plement and precipitate in a variety of tissues, including blood arteries, joints, and renal glomeruli. An inflammatory response results when these immune complexes link to the Fc-IgG receptors on inflammatory cells or activate complement. A quicker and more severe recurrence can be brought on by re-exposure to the same substance at similar or greater levels.

Timing: Symptoms and signs following drug exposure because considerable amounts of antibodies are required to produce symptoms linked to antigen-antibody complexes, which might take one or more weeks to manifest.

Clinical presentation: There are various types of Type III reactions:

Serum sickness: Fever, an urticarial or purpuric rash, arthralgias, and/or severe glomerulonephritis are symptoms of classic serum sickness. Alternatively, only one or two of these characteristics might be noticeable. Lymphadenopathy, low complement levels in the serum, and a high erythrocyte sedimentation rate are further findings. A side effect of various antitoxins, such as those for rabies, botulism, and venoms, is serum sickness.

Vasculitis: Hypersensitivity brought on by drugs Most commonly, lymphadenopathy, visible purpura and/or petechiae, fever, urticaria, arthralgias, high erythrocyte sedimentation rate, and low complement levels are the symptoms of vasculitis. Lower extremities are frequently affected by purpuric lesions. Rarely, are other organs including the kidneys or gastrointestinal system are affected. Penicillins, cephalosporins, sulfonamides (including most loop and thiazide-type diuretics), phenytoin, and allopurinol are the most typical offenders.

Arthus reaction: When antibody-antigen complexes that fix complement are deposited in the walls of tiny blood arteries, it results in an Arthus reaction, a localized type III hypersensitivity reaction that causes acute inflammation, neutrophil infiltration, and regional skin necrosis. Laboratory animals that had been hyperimmunized were used to first report arthus responses. It has not been definitively proven that strong local reactions to booster doses of current immunizations are real Arthus reactions. Such responses typically manifest at the locations of booster injections of a vaccine as excruciating local swelling and erythema that start within a few hours and typically peak within 24 hours. Tetanus, diphtheria, and hepatitis B vaccines have all been associated with this kind of reaction (22–24).

Type IV Reactions

In contrast to the other three types of responses mentioned above, type IV reactions are not mediated by antibodies. Delayed-type hypersensitivity is the desig-

nation given to medication reactions of type IV that require time (often many hours or days after antigen exposure) for T cell activation and expansion (DTH). Other cell types, such as neutrophils, eosinophils, or macrophages, may also be implicated in some circumstances. Type IV reactions can manifest in a variety of ways and range in severity from inconvenient to life-threatening.

Timing of type IV reactions: Type IV reactions often take at least 48 to 72 hours, and perhaps even days or weeks, to manifest after exposure to the offending substance. Within 24 hours after a new challenge, symptoms may return. The quantity of T cells that the drug activates determines in part how long symptoms take to appear in reactions. If the medication stimulates numerous distinct T cell clones, these responses are polyclonal, and symptoms manifest quickly. On the other hand, a medication that only stimulates a small number of clones could not show clinical symptoms until these T cells have multiplied for a few weeks.

The most dangerous delayed drug hypersensitivity reactions, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Figure 1) and drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DiHS), frequently manifest after weeks of straightforward therapy, at which point patients abruptly exhibit signs and symptoms of a fulminant immune reaction. This presentation is due to the drug's massively stimulating oligoclonal T cells, which are similar to those triggered by superantigens (25).

Subcategories of type IV: Depending on the cytokines released and the other types of cells involved, T cells can orchestrate various forms of inflammation, giving rise to the subcategories of types IVa to IVd. (14). Each of these subcategories is covered in depth independently.

Clinical presentations: Because the skin is a major storehouse for T lymphocytes, reactions involving them frequently manifest as skin findings (26). The majority of cutaneous T cells are primed memory-effector cells that respond quickly when immunogenic substances cross the skin barrier or diffuse into the skin from the bloodstream (27).

The following are examples of recognized cutaneous involvement patterns:

Contact dermatitis: An adverse medication reaction known as contact dermatitis is characterized by erythema, edema, and vesicles or bullae that frequently burst, leaving a crust. (28). Lichenification, erythema, and scaling are characteristics of subacute and chronic contact dermatitis.

Maculopapular eruptions (such as morbilliform): One of the most frequent types of delayed drug reactions, maculopapular eruptions can result from type IV

immunologic reactions as well as other mechanisms. They are frequently referred to as "rashes," a term that encompasses exanthems with various levels of cell infiltrations and, consequently, papular components ("maculopapular").

SDRIFE: A distinctive drug eruption known as "Symmetrical drug-related intertriginous and flexural exanthem" (SDRIFE), formerly known as "baboon syndrome," typically appears hours to days after drug exposure and manifests as demarcated, V-shaped erythema in the gluteal/perianal or inguinal/perigenital areas, frequently with involvement of at least one other flexural area, such as the axillae, elbows, or knee.

Some types of SDRIFE, including acute generalized exanthematous pustulosis, may be connected to neurophilic inflammations (AGEP).

Acute generalized exanthematous pustulosis: A uncommon reaction known as AGEP is characterized by superficial pustules that typically emerge 24 hours after taking the offending medication. The most often reported AGEP triggers include antimicrobial medications (such as amoxicillin), antimalarials, and calcium channel blockers. Separately, this disease is covered in more detail.

Drug fever: Drug hypersensitivity symptoms can include fever as the only symptom or the most noticeable symptom, with nonurticarial rash or other organ involvement occurring in a small percentage of patients. Azithromycin, sulfasalazine, minocycline, trimethoprim-sulfamethoxazole, sirolimus, and tacrolimus are among the drugs linked to drug fever. Antiretroviral medication and piperacillin-tazobactam drug fever rates are greater in patients with cystic fibrosis and active HIV infection, respectively (29).

Stevens-Johnson syndrome and toxic epidermal necrolysis: The symptoms of severe blistering dermatitides, such as SJS and TEN, include fever, mucocutaneous sores that cause the skin to slough off and necrosis.

Drug-induced hypersensitivity syndrome: A severe drug hypersensitivity reaction known as DiHS, sometimes known as DRESS, includes rash, fever (38 to 40°C), and multiorgan failure. In DiHS/DRESS, the liver, kidneys, heart, and/or lungs are most frequently impacted. Here, it is briefly discussed, while elsewhere, it is reviewed in more detail.

Given that only roughly 70% of individuals have peripheral eosinophilia, there is ongoing discussion regarding the most appropriate nomenclature for this disease (eg, those caused by abacavir or lamotrigine typically do not). A more frequent result is the presence of activated CD8+ atypical lymphocytes, which can last for months following medication cessation.

Several antiepileptic medications, such as carbamazepine, phenytoin, lamotrigine, and phenobarbital, as well as minocycline, allopurinol, dapsone, abacavir, and nevirapine, have been linked to DRESS/DiHS.

HLA associations: Since the drugs have been shown to bind to the specific HLA-allele itself predominantly (e.g., allopurinol/oxypurinol to the HLA-B*58:01) or exclusively (abacavir and HLA-B*57:01) (30), a phenomenon that is also seen in SJS and TEN, some DiHS/DRESS reactions occur more frequently in patients with certain human leukocyte antigen (HLA) types.

Particular instances include:

- HLA-B*58:01 is linked to DiHS/DRESS and SJS/TEN to allopurinol (31). In Caucasians (about 60%), where other alleles are also involved in SJS/TEN owing to allopurinol, this B*58:01 relationship is less strong. (32).
- Several groups are disproportionately impacted by DiHS/DRESS to carbamazepine, and in some cases SJS/TEN as well. HLA-B15:02 is present in Han Chinese individuals (33), as well as patients from Thailand, Malaysia, and India (34–36). HLA-A*31:01-carrying patients from Japan and Europe (37,38).
- Only individuals with the HLA-B*57:01 allele experience DiHS/DRESS to abacavir; lesser side effects to this medication are not linked to a particular HLA-allele.
- Chinese individuals with HLA-B*13:01 are disproportionately affected by dapsone hypersensitivity syndrome (39).

Family members of a patient who has been identified as having a high-risk HLA profile should also be warned to steer clear of the pertinent medication because it has been seen that these hypersensitivity reactions can run in families. Before giving patients carbamazepine, oxcarbazepine, abacavir, and allopurinol, it has been advised to check them for particular alleles (40).

Single organ involvement: With T cell-mediated hypersensitivity, organ involvement can occasionally occur without skin symptoms or skin symptoms can be slight and go unnoticed. Examples of presentations include solitary pneumonitis, isolated interstitial nephritis, and isolated drug-induced hepatitis. Allopurinol can cause nephritis (41), flucloxacillin and the medication combination amoxicillin-clavulanate potassium can cause cholestatic hepatitis, and abacavir and nitrofurantoin can cause pneumonitis. It can be difficult to diagnose this symptom as a medication allergy. These illnesses are covered elsewhere.

Influence of viral infections: During generalized viral infections and exacerbations of autoimmune diseases, where T cell reactivity is enhanced by widespread immune activation of T cells, high cytokine levels, and an increased expression of

major histocompatibility complex (MHC) and costimulatory molecules, there is a higher risk of several type IV drug allergic reactions (ranging from simple exanthema to SJS/TEN).

The following viral illnesses can put patients at risk for adverse medication responses:

- Epstein Barr virus (with amoxicillin).
- Cytomegalovirus (with antibiotics) (42).
- Human herpes virus 6 (with anticonvulsants and other agents).
- HIV infection (with trimethoprim-sulfomethoxazol and other agents).
- Amoxicillin medication (and to a lesser extent other antibiotics) frequently causes exanthematous responses in young infants. When given the same medication again later, the majority of these kids tolerate it (43). Although this has not been definitively proven, it is likely that systemic viral infections are also promoting these reactions. Since rhinoviruses exclusively affect the local nasopharynx and respiratory tract, they are unlikely to have this effect because they do not significantly excite the immune system.

Effects of dosage and treatment duration: Dose appears to be crucial in the emergence of delayed hypersensitivity reactions. The majority of delayed drug hypersensitivity events involve medications that are taken daily in doses between 100 and 1000 mg. Lamotrigine and allopurinol are two examples (44–46). Drugs that are dosed less than 10 mg per day, on the other hand, rarely cause delayed hypersensitivity reactions.

Clinical and in vitro evidence regarding allopurinol hypersensitivity imply that the beginning dose may also be important for developing hypersensitivity (44,45). Therefore, smaller beginning doses of medications like allopurinol or lamotrigine may reduce the incidence of hypersensitivity.

In one trial, more than 10 days of gemifloxacin treatment resulted in maculopapular exanthema in almost one-third of the female participants, but this was uncommon with only three days of treatment (16).

Further immunologic responses: Drug-induced autoimmunity and fixed drug eruption are two additional immunologic drug reaction types that cannot be easily categorized within the Gell and Coombs methodology.

Drug-induced autoimmunity: Autoimmune disorders can be brought on by drugs (47). Although the discovery that drug binding to HLA molecules might induce alterations in the given peptides has opened new research avenues, the pathophysiology of these reactions remains a mystery. These discoveries and drug-induced autoimmune disorders have not yet been definitively linked, though.

- The most well-known instance is a condition that resembles lupus and can arise from exposure to drugs including procainamide, phenytoin, isoniazid, sulfasalazine, amiodarone, minocycline, and penicillamine (47–50).
- A condition resembling pemphigus can also be brought on by penicillamine.
- IgA bullous dermatosis has been linked to a number of medications, including metronidazole, ceftriaxone, ciprofloxacin, and vancomycin.

Fixed drug eruption: Fixed drug eruption, which manifests as erythematous and edematous plaques with a grayish center or frank bullae, is a reasonably common reaction. When exposed to drugs again, lesions return to the same locations (usually the lips, tongue, genitalia, face, and acral areas). Pigmentation arises after inflammation at these site(s). Sulfonamides, anticoagulants, and many other medications can cause fixed drug eruption (52). Although T lymphocytes found in the skin produce interferon gamma, the mechanism is uncertain (53,54).

Pseudoallergic Reactions

Pseudoallergic drug reactions are unproven immunologic mechanisms that cause adverse drug reactions with symptoms and indications that resemble immunologic drug allergies (table 2). They are also known as "nonimmune hypersensitivity reactions" and are a subset of type B drug hypersensitivity reactions (DHR) (7).

Clinically, it can be challenging to discern between pseudoallergic reactions and actual allergic reactions because of how similar or identical they present. The pathophysiology and resulting clinical symptoms of some pseudoallergic reactions are identical to those of allergic reactions because they originate from direct (as opposed to immunologic) activation of immune and inflammatory cells. Most of them have unknown, comprehensive mechanisms that may vary from one another (table 2).

For IgE-independent, direct mast cell stimulation, it was discovered that a single receptor, known as Mrgprb2 (Mas-Related G-Protein Coupled Receptor Member B2) in mice and MRGPRX2 (Mas-Related G-Protein Coupled Receptor Member X2 in humans), was essential (13). It is known that fluoroquinolone antibiotics and neuromuscular blocking drugs (NMBA) bind to this receptor and work through this mechanism to produce systemic, nonallergic (pseudoallergic, anaphylactoid) reactions. Some of the medications on the list below (common culprit medications) may function in this manner.

It is yet unknown why some patients only have pseudoallergic symptoms.

The diagnosis, prognosis, and prevention of pseudoallergy may differ from those of actual allergic reactions, which is important to note. In particular, skin or in vitro allergy tests cannot be used to diagnose pseudoallergic reactions, and they do not get worse with repeated exposure.

Reactions that resemble anaphylaxis: One of the most crucial things for doctors to comprehend is idiosyncratic reactions that resemble IgE-mediated, type I allergic reactions. Nonimmunologic stimulation of mast cells and basophils results in the release of vasoactive mediators, just like IgE-mediated responses. The intensity of these fictitious allergic reactions might range from minor to severe. As a result, immunologic anaphylaxis and acute nonimmunologic anaphylaxis should be treated similarly.

Anaphylactoid is a term used frequently to describe nonimmunologic events that resemble anaphylaxis. Unfortunately, the term "anaphylactoid" has been incorrectly used to describe reactions comparable to anaphylaxis but less severe, which has resulted in the undertreatment of patients with nonimmunologic anaphylaxis. As a result, the term "anaphylactoid" is no longer recommended and "nonimmunologic anaphylaxis" is now favored. Clinicians need to be aware that any kind of anaphylaxis has the potential to be fatal.

Uncertain medications may cause these reactions for unknown reasons. Some of the affected patients have dermographism as an underlying condition and exhibit an apparent "instability" of their mast cells, which degranulate upon pressure or following exposure to certain tiny chemicals.

Commonly used medications: The following is a list of medications that can result in nonimmunologic anaphylaxis, and separate reviews of each clinical condition are provided:

- Radiocontrast agents
- Chemotherapeutic agents
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Vancomycin
- Local anesthetic agents
- Opiates
- Monoclonal antibodies and other biologic therapies used in cancer therapy

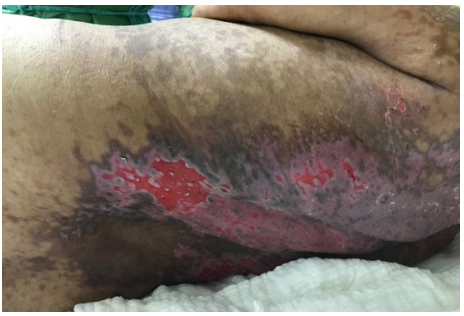

Figure 1. Toxic epidermal necrolysis

CONCLUSİON

Types A and B adverse drug reactions can be used as general classifications. The majority of reactions are Type A, which can happen to anyone and are predictable based on a drug's recognized pharmacologic qualities. Less frequently occurring Type B responses can rarely be predicted by a drug's recognized pharmacologic qualities because they only affect sensitive patients.

A subgroup of type B reactions are immunologic or allergic drug reactions. The Gell and Coombs classification system can be used to categorize immunologic drug reactions into four groups. In clinical practice, types I and IV are much more prevalent than types II and III. Clinically, the various types of reactions have distinctive signs and symptoms, and timing of symptom onset may also be useful in differentiating between types. But there is a considerable clinical overlap between them. Other immunologic drug reactions outside of the Gell and Coombs classification include drug-induced autoimmunity and fixed drug eruption.

Type B (hypersensitivity) drug reactions with signs and symptoms that resemble immunologic drug allergies but are not immunologic are known as pseudoallergic drug reactions. Due to their potential to show similarly to or identically to genuine allergic reactions, pseudoallergic reactions are particularly challenging to differentiate clinically. Pseudoallergic reactions, however, have different diagnosis, prognosis, and preventative procedures.

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