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The Final thesis

Drug-Induced Skin Hypersensitivity Reactions: A Review of Clinical Cases and Literature

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1. Summary

Drug-induced skin hypersensitivity reactions are classified as a subset of adverse drug reactions, categorized into Type A (predictable) and Type B (unpredictable) reactions. Type B reactions encompass drug allergy, which presents the focus of this thesis, and non-immunological drug hypersensitivity, further subdivided into drug intolerance, drug idiosyncrasy and pseudo-allergies. Cutaneous adverse drug reactions are the most common adverse drug reactions, affecting 45% of cases. They can range from mild to severe manifestations like morbilliform eruptions, urticarial toxidermia, fixed pigmented erythema, toxic epidermal necrolysis and acute generalized exanthematous pustulosis. The key principle of the diagnosis of drug-induced skin hypersensitivity reactions involves a detailed patient history, the chronology of reactions, and the physical examination. Various diagnostic tools are employed, including drug provocation tests, skin tests (skin prick, intradermal, patch tests), and in vitro tests (lymphocyte transformation, basophil activation, Enzyme-linked ImmunoSpot assays). Laboratory investigations support diagnosis and monitoring, but results may not always confirm drug-induced reactions conclusively. Treatment involves discontinuation of the offending drug and supportive care tailored to reaction severity. Mild to moderate reactions may be managed with antihistamines, nonsteroidal anti-inflammatory drugs, or topical corticosteroids. Severe cases may require systemic steroids or immunosuppressive agents, with hospitalization warranted for specific signs of severity.

2. Introduction

Drug-induced skin hypersensitivity reactions represent a significant and challenging issue in clinical practice, posing risks to patient safety and complicating therapeutic management. With the widespread use of medications across diverse patient populations, the incidence of these reactions continues to rise, necessitating a comprehensive understanding of their underlying mechanisms and diagnostic approaches. The scope of this thesis is meticulously designed to elucidate and highlight this pertinent information for the medical practice. It sets out to dissect the multifaceted nature of drug-induced skin hypersensitivity reactions by closely examining their clinical manifestations, underlying mechanisms, and the current state of diagnostic techniques. Such an exploration is poised to traverse the breadth of existing academic discussions, while also injecting novel insights through the analysis of contemporary case studies and the latest research findings.

The potential contributions of this research are multifaceted. Primarily, it seeks to enhance the clinical acumen of healthcare providers, equipping them with the knowledge and tools

necessary to identify drug-induced skin hypersensitivity reactions swiftly and accurately. Such advancements in diagnostic precision are anticipated to foster more targeted and efficacious therapeutic strategies and minimizing the risk of adverse reactions. Furthermore, by offering a clearer understanding of the pathophysiological mechanisms at play, this thesis may serve as a catalyst for the development of novel preventative and management approaches, reducing the overall burden of these reactions on patients and healthcare systems alike.

3. Literature selection strategy

An electronic literature search was performed from April 1, 2023, to February 29, 2024, with keywords "Drug-induced Skin Hypersensitivity Reactions", "Cutaneous adverse drug reactions", "Adverse drug reactions", "Drug Hypersensitivity" and "Arzneimittelreaktionen" using Pubmed and Google Scholar. A German Book "Duale Reihe Dermatologie. Moll I, Hrsg. 8, published by Thieme; 2016 was included, as well as Articles since 2002 written in English and German were included. Inclusion criteria were to use only suitable papers published as full articles in the English and German language. Exclusion criterium was articles publishes before the year 2000. Full texts of the relevant articles were extracted after being screened for titles and abstracts.

4. Definition

Drug-induced skin hypersensitivity reactions are exaggerated and/or pathological immune responses caused by the administration of medications (1,2) which manifest on the skin (3). Drug-induced hypersensitivity reactions are a type of adverse drug reactions (ADRs) (4), which are defined by the World Health Organization as "any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment" (5). The Rawlins and Thompson classification system, introduced in 1977, delineates ADRs into two major categories: Type A and Type B reactions (6). Type A reactions, also known as augmented reactions, typically result from the pharmacological actions of the drug at therapeutic doses and are predictable based on the drug's known pharmacology. For example, side effects such as gastrointestinal bleeding occurring because of the treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (11), sedative effects of older antihistamines or hair loss caused by certain cytostatic drugs are typical manifestations of type A reactions. In contrast, type B reactions, referred to as bizarre reactions, occur unpredictably and are not related to the pharmacological actions of the drug. These bizarre reactions can be further classified into drug allergy and non-immunological drug hypersensitivity. Drug allergy involves an immunological reaction. On the other hand, non-immunological drug hypersensitivity lacks an identifiable

immunological mechanism. Non-immunological drug hypersensitivity is subdivided into drug intolerance, where typical symptoms of the pharmacological effects (toxicity) occur already at low doses, which are usually tolerated and drug idiosyncrasy, an unusual response to a drug that is not explained by its pharmacological effect (4,7,8). Reactions resembling allergic responses but are independent of antigen-specific immune responses are termed pseudo-allergies. (4,9,10)

In clinical practice the differentiation between drug allergy and intolerance may be very difficult, but carries significant clinical consequences, particularly concerning future drug exposure or avoidance. In instances of allergy, complete avoidance of the specific drug and closely related compounds, regardless of dose, is essential. (11) Conversely, for intolerance, it is generally advised to avoid the specific drug and other pharmacologically related medications, but the risk can potentially be managed by adjusting the dosage, changing the formulation, or using alternative medications. While allergy is often perceived as more severe, intolerance can also pose life-threatening risks. Therefore, the severity of the reaction may be a more crucial factor than the specific mechanistic classification in clinical practice. (11)

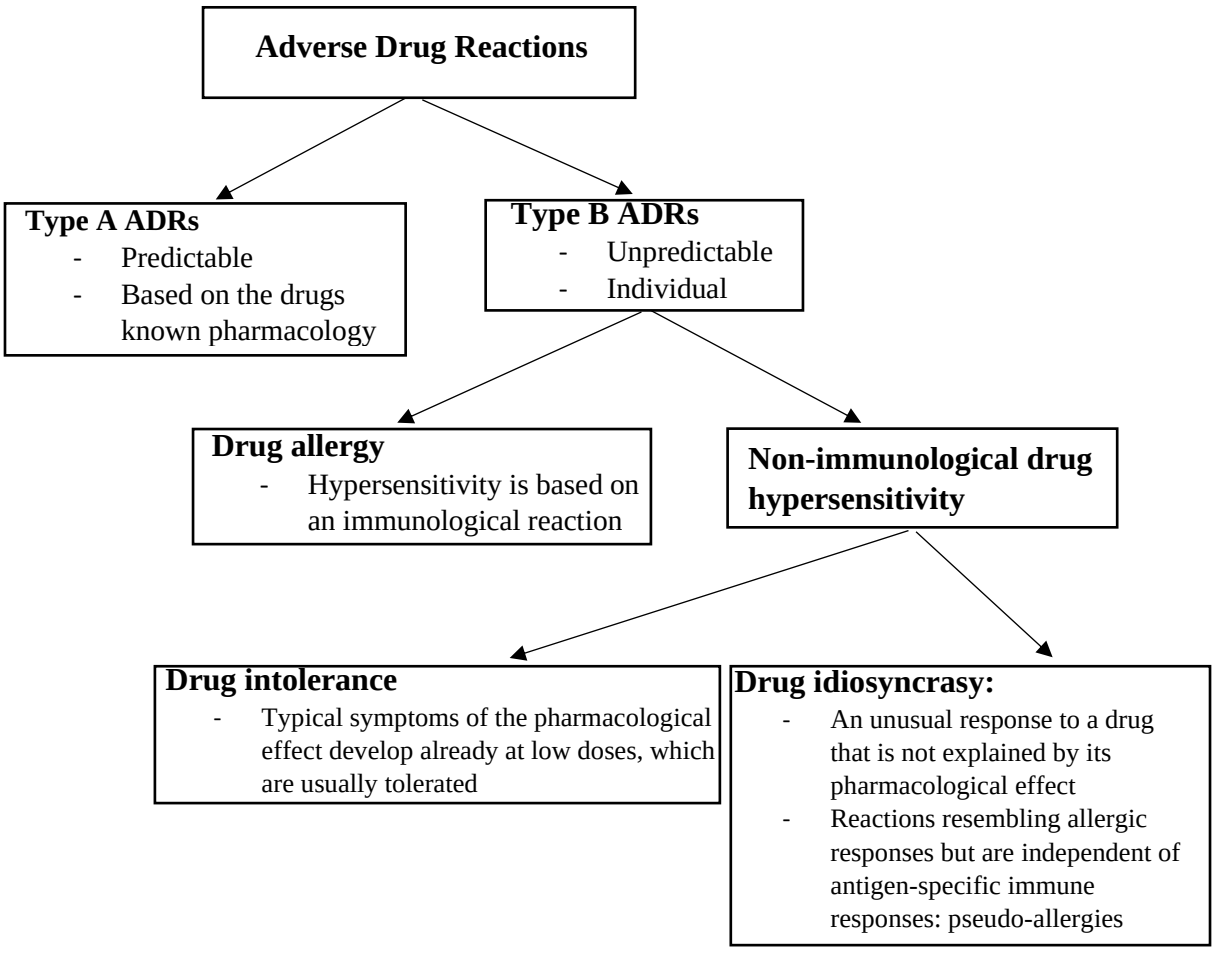

Figure 1: Classification of adverse drug reactions (4)

5. Epidemiology

In General, adverse drug reactions are responsible for 3 to 6% of hospital admissions and manifest in 10 to 15% of patients during their hospital stay. (12) The predictable and dose-dependent Type A ADRs comprise up to 80% of all ADRs. In contrast, Type B ADRs, characterized by unpredictability and dose-independency, comprise 15–20% of all ADRs (13,14) The skin represents the organ most impacted by adverse reactions to drugs, termed Cutaneous Adverse Drug Reactions (CADRs), accounting for 45% of cases. Fortunately, the majority of CADRs are mild or resolve on their own. However, between 2% and 6.7% of cutaneous reactions have the potential to progress into severe and potentially life-threatening clinical syndromes (6). It is important to note that the reported incidence rates of adverse drug reactions are general estimates. Factors such as differences in reporting practices across healthcare settings, variations in drug utilization patterns among diverse patient populations, and regional disparities in healthcare systems can contribute to variations in ADR incidences. Despite these variations, these findings underscore the critical need for ongoing education and training for healthcare professionals. Enhancing their ability to recognize and manage ADRs effectively in clinical practice is essential for improving patient safety and optimizing healthcare outcomes. (6)

In subsequent sections, this thesis will delve deeper into Type B, immunological hypersensitivity reactions.

6. Pathomechanism

Transitioning from the epidemiological overview to the exploration of underlying mechanisms of drug-induced skin hypersensitivity reactions, the focus in the following shifts to a broader understanding of hypersensitivity reactions in general.

The European Academy of Allergy and Clinical Immunology released in 2023 a new classification system for allergic disorders, in which “Hypersensitivity reactions originally described by Gell and Coombs have been extended into nine different types comprising antibody- (I-III), cell-mediated (IVa-c), tissue-driven mechanisms (V-VI) and direct response to chemicals (VII). Types I-III are linked to classical and newly described clinical conditions. Type IVa-c are specified and detailed according to the current understanding of T1, T2 and T3 responses. Types V-VI involve epithelial barrier defects and metabolic-induced immune dysregulation, while direct cellular and inflammatory responses to chemicals are covered in type VII. “(15)

Type I hypersensitivity reactions mediated by IgE are associated with allergic conditions like allergic rhinoconjunctivitis (ARC), asthma, atopic dermatitis (AD), acute urticaria/angioedema, and reactions to food, venom, and drugs. Classical allergens that trigger type I hypersensitivity include pollens, house dust mites, mold spores, animal dander, insect venoms, certain foods, latex, and medications such as penicillin, other beta-lactam antibiotics, vaccines, serums, monoclonal antibodies, insulin, and protein-based drugs (15,16).

The type I response involves two phases: sensitization and effector phases. In the sensitization phase, T2 cell signals regulate the production of allergen-specific immunoglobulin E (sIgE) through interactions between adaptive and innate immune systems. Antigen-presenting cells (APCs) like dendritic cells (DCs), B lymphocytes (B cells), and macrophages (Mφ) capture and present allergen peptides to naïve T cells via major histocompatibility complex class II (MHC class II) molecules (15). DCs primarily activate naïve T cells, while B cells and macrophages also contribute to T-cell differentiation. Cytokines produced by APCs modulate naïve T-cell differentiation into subsets like Th1, Th2, Th17, Tc1, Tc2, Tc17, and regulatory T cells (15). Early production of IL-4 by mast cells (MCs), basophils, and innate lymphoid cells type 2 (ILC2s) amplifies the response, leading to differentiation of naïve T cells into Th2 and Tc2 cells, facilitating immunoglobulin class-switching in B cells and tissue migration of Th2 cells (15).

During the effector phase, mast cells and basophils sensitized by sIgE undergo degranulation upon allergen re-exposure, releasing mediators like histamine, prostaglandins, leukotrienes, and cytokines that cause allergic symptoms. (15,17,18).

Type II hypersensitivity reactions, characterized by antibody-mediated cellular cytotoxicity, are commonly induced by drugs, and implicated in various autoimmune disorders, including immune thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia, among others. In drug-dependent type II allergic reactions, the drug or its metabolite initially binds to cell membrane proteins. (15) Subsequent binding of anti-drug antibodies to the drug-membrane protein complex activates complement or interacts with the Fc fragment gamma receptor (FcγR) on effector cells such as NK cells, eosinophils, macrophages, or neutrophils, ultimately leading to cell lysis. (15) The mechanisms underlying sensitization and IgG development are unclear but may involve molecular mimicry. Likewise, in type II autoimmune reactions, complexes formed by drugs and anti-drug antibodies bind to self-antigens on cell membranes. This binding activates complement or effector cells through Fc receptors,

ultimately leading to cell lysis. (15). IgG and IgM are the primary antibodies implicated in type II allergic reactions. They damage cells through various mechanisms: (15)

1. Activation of the classical complement pathway, generating the cytolytic membrane attack complex C5b-9. (15)

2. Antibody-dependent cellular cytotoxicity, primarily involving NK cells and CD16-expressing CD8+ T cells. In Antibody-dependent cellular cytotoxicity, IgG recognizes antigens (drugs) bound to target cell surfaces, subsequently binding to FcγR on effector cells. Effector cells release cytotoxic substances such as perforin and granzymes, inducing regulated cell death mechanisms like apoptosis, necroptosis, and pyroptosis. (15)

3. Opsonization of the drug-target cell by C3b and iC3b complement fragments or antibodies, followed by phagocytosis by Mφ and neutrophils. (15)

4. Activation of eosinophils through FcγR, leading to the release of major basic protein (MBP) or reactive oxygen species. Activation of the complement system and immune cell recruitment result in the release of inflammatory mediators, proteolytic enzymes, and newly generated mediators, contributing to further tissue damage. (15,18,19)

Type III hypersensitivity reactions, encompassing immune complex-mediated responses, manifest in conditions like the acute phase of hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness, and the Arthus reaction. These reactions are also linked to autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and post-streptococcal glomerulonephritis (15). In Type III allergic hypersensitivity reactions, IgM and IgG antibodies bind to soluble antigens, such as drugs or venoms, forming antigen-antibody complexes. Due to the reduced clearance stemming from diminished function of the MO activating system or increased production of antigen-antibody complexes (as seen in chronic infections, autoimmune diseases, or cancers), immune complexes are deposited in multiple tissues across the body, including small blood vessels, capillaries, joint synovium, kidney glomeruli, and porous lung alveoli. (15) This deposition triggers inflammation as the porous nature of these tissues allows immune complexes to enter, activating the complement system locally. Complement activation releases chemotactic agents that attract neutrophils, leading to tissue damage and contributing to the observed symptoms through a local inflammatory response. (15) Additionally, complement-independent pathways involve immune complexes interacting with FcγR on immune cells like neutrophils, leading to pathologic phagocytosis. (15) However, some research suggests a minimal role of complement in actual Type III allergic

reactions. For instance, studies on Arthus reaction show a minimal reduction in mice with intact Fc signaling but reduced complement levels, suggesting that MC degranulation may predominantly drive the reaction. Complement, particularly anaphylatoxin C5a, might indirectly influence the reaction by altering the ratio of activating to inhibitory Fc receptors on effector cells. The resulting aggregation of immune complex-related events may lead to local fibrinoid necrosis, potentially exacerbating ischemia, and thrombosis in tissue vessel walls. (15,18,20)

Type IV reactions, historically termed delayed-type reactions, are orchestrated by memory T lymphocytes engaging with innate immune cells like ILCs, NK-T cells, NK cells, neutrophils, eosinophils, and macrophages. These reactions are characterized by symptoms appearing hours to days after exposure. Various subsets of T cells drive Type IV responses through specific pathways, demonstrating significant diversity in memory lymphocyte phenotypes. Some disease mechanisms can only be elucidated by the collaboration of multiple subtypes of Type IV hypersensitivity. (15,18,21)

Type IVa reactions commonly present as allergic contact dermatitis, chronic hypersensitivity pneumonitis (extrinsic allergic alveolitis), and celiac disease. They are also associated with non-T2 endotypes of conditions like asthma, allergic rhinitis, chronic rhinosinusitis, and atopic dermatitis. Type IVa reactions involve T1 responses driven by memory Th1 and Tc1 cells upon exposure to interleukin-12 (IL-12), interleukin-23 (IL-23), and interferon-gamma (IFN-γ) from antigen-presenting cells. (15)

Th1 cells release IFN-γ, lymphotoxin, and tumor necrosis factor-alpha (TNF-α), contributing to granuloma formation, IgG1 and IgG3 synthesis by B cells, and T-cell cytotoxicity. Innate immune cells like ILC1 and classically activated macrophages (M1 macrophages) reinforce the memory immune response in Type IVa reactions, producing inflammatory mediators like reactive oxygen species, proteases, and pro-inflammatory cytokines that contribute to tissue damage. (15)

Type IVb reactions, characterized by a T2 immune response, are prominently observed in classical allergic reactions, such as chronic airway inflammation seen in conditions like Allergic rhinithis, chronic rhinosinusitis, asthma, and atopic dermatitis, often termed the T2 endotype. (15) Additionally, they play a role in food allergy, eosinophilic esophagitis, and protein-contact dermatitis. Th2 cells, ILC2, NK-T cells, eosinophils, and a specific subset of macrophages are key components in orchestrating Type IVb - T2 immune responses. (15,18,23) Th2 cells, activated by IL-4, basophils, or NK-T cells, are pivotal in Type IVb reactions. They release

significant amounts of cytokines like IL-4, IL-5, IL-9, IL-13, IL-31, and eotaxins I-III. IL-4 and IL-13 (15) play crucial roles in inducing IgE class switching in B cells, while IL-13 contributes to tissue remodelling in chronic hypersensitivity. IL-5 facilitates bone marrow expansion of eosinophils, their recruitment to sites of inflammation, and sustains their survival, perpetuating tissue damage. IL-31, primarily produced by Th2 cells but also by Mφ and dendritic cells, is a key mediator of itch. Th2 immune responses often coincide with allergen-specific Th9 cells, induced by IL-4 and TGF-β. Th9 cells significantly contribute to Type IVb hypersensitivity by producing IL-9, which enhances IgE synthesis by B cells and serves as a growth factor for mast cell precursors, eosinophils, and basophils. (15) In Type IVb reactions, innate immune cells like mast cells, basophils, ILC2, eosinophils, and alternatively activated macrophages amplify the memory immune response. ILC2s produce type 2 cytokines in response to IL-33 and/or IL-25, contributing to tissue inflammation and homeostasis. Mast cells and basophils are early sources of IL-4 crucial for Th2 cell differentiation, while a unique subset of NK-T cells (NK-T2) also produce IL-4, contributing to ongoing Type IVb inflammation. (15) Eosinophils play a central role in Type IVb-T2 immune responses, contributing significantly to chronic allergic inflammation. Activated by various cytokines and chemokines, eosinophils migrate to inflamed tissue sites, releasing cytotoxic granules and extracellular traps, which induce tissue damage and exacerbate allergic reactions. (15) Type IVb reactions intersect with type I hypersensitivity in the final stage of IgE synthesis triggered by T2 cells. However, the predominant effector mechanism in Type IVb reactions involves eosinophil activation through IL-5, highlighting their distinct immunopathogenesis compared to other hypersensitivity types. Additionally, Type IVb reactions share similarities with type V hypersensitivity in epithelial cell activation and barrier disruption, facilitating the drainage of inflammation toward the bronchial lumen. (15,18)

In Type IVc responses, involving a T3 immune response, Th17 cells, Tc17 cells, ILC3, and other cells producing IL-17A and IL-17F cytokines, are implicated in driving neutrophilic inflammation, notably in the pathogenesis of atopic dermatitis and neutrophilic asthma. (15) Th17 cells, a subset of helper T-cells, are pivotal in Type IVc reactions. These cells secrete IL-17 family cytokines, which modulate innate immune responses and promote local inflammation by inducing the release of proinflammatory mediators. Memory Th17 cells acquire their characteristic phenotype in response to signals from antigen-presenting cells such as IL-6, IL-21, IL-23, and TGF-β. (15) The primary effector cytokines produced by Th17 cells include IL-17A, IL-17F, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor. (15) IL-17A and IL-17F, produced by various immune cells in response to inflammatory cues, play a

critical role in recruiting neutrophils (NEU) to sites of inflammation. These cytokines activate ILC3 and stromal cells, inducing the production of IL-8, a potent chemoattractant for neutrophils. Consequently, tissue infiltration by neutrophils is a hallmark feature of Type IVc hypersensitivity. (15) Moreover, apart from inducing a "respiratory burst" and enzyme release leading to necrosis, neutrophil extracellular traps, composed mainly of DNA, are associated with tissue damage. (15) The Type IVc response shares similarities with Type IVb hypersensitivity, particularly in the formation of extracellular traps involving eosinophils. Additionally, the T3 response can be augmented by innate immune cells, especially ILC3. Type IVc inflammation often coexists with Type IVa reactions, although in certain pathological conditions, the activation of memory Th17 cells predominates. (15,18)

Additional subtypes of Type IV hypersensitivity reactions can be delineated based on the effector T cells involved. (15) These subtypes may encompass Th9 or Th22 cells. IL-9, a quintessential cytokine, exerts influence on various target cells including T cells, B cells, mast cells, and airway epithelial cells by activating signal transducer and activator of transcription (STAT) proteins 1, 3, and 5. (15) Th9 cells exhibit a multifaceted role in the immune system, as they may foster immune tolerance in certain models, protect against parasitic infections, and also trigger allergic inflammation and asthma. (15) Notably, CD4+ T-cell subsets like Th17 and Th9, along with MCs and innate lymphoid cells type 2, are capable of producing IL-9. Among its diverse effects, IL-9 serves as a pivotal cytokine in Th17 and regulatory T (Treg) cell differentiation, amplifies the production of IgE and IgG by B cells in response to IL-4, and augments the proliferation of bone marrow mast cells and their progenitors in conjunction with stem cell factor. (15) On the other hand, Th22 cells exhibit a protective role in tissue homeostasis during the early stages of asthma and atopic dermatitis, while also participating in tissue remodeling during the chronic phase of these conditions. The hallmark cytokine associated with Th22 cells is IL-22. Primarily targeting non-hematopoietic epithelial and stromal cells, IL-22 promotes cellular proliferation and plays a crucial role in tissue regeneration. (15) Moreover, IL-22 regulates host defense mechanisms at barrier surfaces. However, an alternative proinflammatory role of IL-22 in skin pathology has been proposed, as elevated levels of CD8+ IL-22-secreting cells have been correlated with the severity of AD. (15, 18)

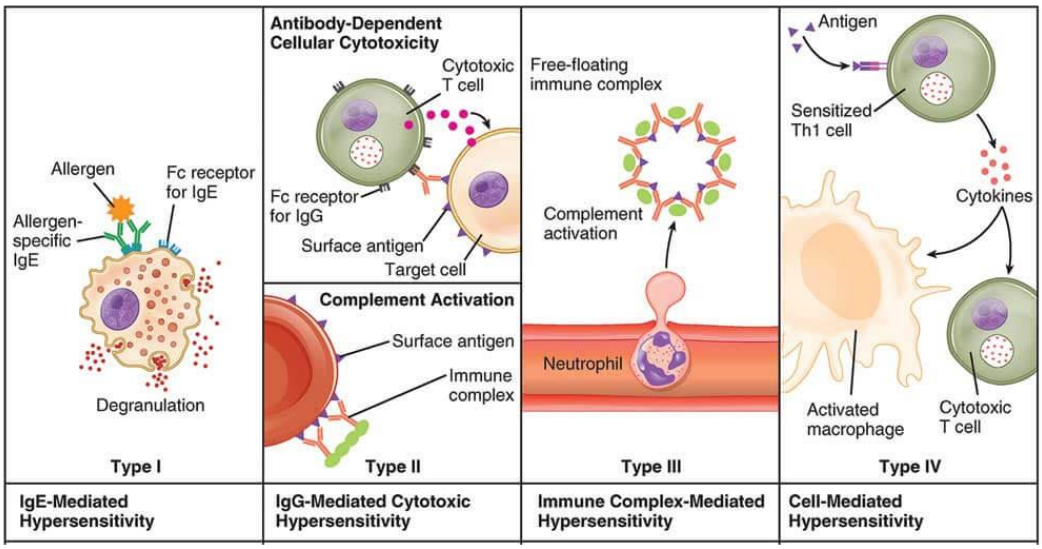

Figure 2: Simplified mechanisms of Type I-IV hypersensitivity reactions (24)

In Type V and Type VI hypersensitivity reactions, there is no direct connection to drug allergy. Hence, these reactions are mentioned briefly to ensure comprehensive coverage.

Type V hypersensitivity encompass epithelial barrier defects. Recent research has made significant strides in understanding mucosal and cutaneous inflammatory disorders like chronic allergic rhinitis/allergic conjunctivitis, chronic rhinosinusitis, atopic dermatitis, asthma, food protein-induced enterocolitis syndrome, eosinophilic esophagitis, and celiac disease, revealing them to be a spectrum of symptoms driven by diverse pathological mechanisms. Some of these disorders stem from compromised barrier function in the skin or mucosal membranes rather than primary immune dysregulation, leading to chronic inflammation. (15) Barrier compromise can result from deficiencies in structural elements, tight junction proteins, antiproteases, ion transport, and other critical components, potentially activating sensory nerves and contributing to allergic symptoms. Intestinal barrier dysfunction, possibly due to mucus erosion from low-fiber diets, highlights the importance of considering type V hypersensitivity in understanding disease processes and developing personalized treatments. (15)

Type VI hypersensitivity, associated with metabolic-induced immune dysregulation, has gained attention in the context of increasing obesity rates, particularly seen in the rising prevalence of asthma among obese individuals. Obesity plays a defining role in asthma subtypes, impacting adult-onset asthma, corticosteroid resistance, and disease severity, often leading to higher rates of hospitalization. The mechanisms linking obesity and asthma are complex, involving changes in chest wall dynamics and direct or indirect effects on inflammatory responses. Elevated body mass index correlates with increased levels of circulating inflammatory mediators, along with

higher blood neutrophil and eosinophil counts. (15) Obesity is characterized by elevated serum acute phase reactants, reactive oxygen species, chemokines, and innate proinflammatory cytokines, including adipose tissue-derived factors like leptin. (15)

Type VII hypersensitivity reactions, characterized by direct cellular and inflammatory responses to chemical substances, manifest across a spectrum of conditions including allergic rhinitis, allergic rhinitis with conjunctivitis, asthma, atopic dermatitis, acute urticaria/angioedema, and drug allergies. Idiosyncratic reactions encompass hypersensitivity to nonsteroidal anti-inflammatory drugs, exhibiting distinct phenotypes depending on the presence or absence of underlying respiratory or cutaneous diseases. (15) These include NSAIDs-exacerbated respiratory disease in patients with rhinitis and/or asthma, NSAIDs-exacerbated cutaneous disease in those with chronic spontaneous urticaria, and NSAIDs-induced acute urticaria/angioedema in otherwise healthy individuals. (15) Recently, additional phenotypes presenting concurrent cutaneous and respiratory symptoms after NSAID intake have been extensively documented. These reactions stem from the inhibition of cyclooxygenase (COX)-1, leading to the release of eicosanoid mediators in susceptible individuals. (15) Aspirin-exacerbated respiratory disease (AERD), previously known as Samter's disease, represents a chronic inflammatory condition characterized by asthma, recurrent nasal polyps, and hypersensitivity to aspirin and other NSAIDs. (15) Dysregulation in the metabolism of arachidonic acid, a precursor to prostaglandins and leukotrienes, leads to overproduction of cysteinyl leukotrienes and decreased anti-inflammatory prostaglandins in AERD. Inhibition of COX-1 and COX-2 by aspirin and NSAIDs exacerbates this imbalance, intensifying the inflammatory response. Cysteinyl leukotrienes play a pivotal role in AERD pathogenesis, inducing bronchoconstriction, increased vascular permeability, mucus production, and inflammatory cell recruitment. (15) Moreover, airway epithelial remodeling in AERD involves dysregulated inflammatory pathways and epithelial changes sustaining type 2 inflammation. Pharmacological interactions in these reactions involve G protein-coupled receptors (GPCRs) expressed in mast cells.

The activation of Mas-related GPCR X2 (MRGPRX2), stimulated by cationic ligands, triggers anaphylactoid reactions independent of antibodies. MRGPRX2 activation occurs with certain drugs, including non-depolarizing neuromuscular blockers and fluoroquinolones, leading to MC degranulation and release of inflammatory mediators. Additionally, MCs can be activated by various compounds through GPCRs, ion channels, hyperosmolar stimuli, and pattern

recognition receptors, among others, further highlighting the complexity of type VII hypersensitivity reactions. (15,18)

Furthermore, in the context of drug hypersensitivity, the P-I concept has developed. The P-I concept refers to the interplay between pharmacological (P) properties of a drug and the individual's immune response (I). The P-I concept proposes that certain drugs form noncovalent bonds (such as van der Waals forces, hydrogen bonds, and electrostatic interactions) directly with immune receptor proteins (HLA and TCR), leading to T-cell-mediated reactions that exhibit features of hypersensitivity, alloimmune, and/or autoimmune responses. (25) This concept distinguishes between drug binding to HLA (p-i HLA) or TCR (p-i TCR), with some drugs being capable of interacting with both types of receptors. This concept serves as a bridge between pharmacology and immunology. (25)

The pharmacological aspect arises from the drug's unintended interaction with immune receptors, known as an off-target effect. For instance, a drug designed to block an ion channel protein may also bind to specific HLA or TCR proteins. (25) This "off-target" interaction between the drug and immune receptors follows typical rules of pharmacological ligand/protein interactions, including dose dependence and predictability if the off-target receptor is identified. The functional outcome of the drug-immune receptor interaction depends on several factors, including the location and affinity of drug binding on the immune receptor protein, the orientation of the binding, and the state of T-cell activation. (25)

The immunological aspect of the P-I concept leads to unconventional T-cell stimulation involving CD4+ and/or CD8+ cells, and sometimes double-positive CD4+/CD8+ T cells. Notably, according to the alloimmune model for drug hypersensitivity reactions, a strong T-cell reaction can occur without the need for a second signal, although the origin of danger/second signals in drug hypersensitivity reactions (DHRs) remains a subject of ongoing investigation. (25)

For further research it is important to mention, that several concepts of p-i are often derived from analyzing a single drug or a small number of patients. However, each drug appears to exhibit unique characteristics. To generalize these findings, it is imperative to confirm them with additional drugs and a larger patient cohort. (25)

Based on the pathomechanisms of hypersensitivity reactions the diagnostic approach for drug-induced skin hypersensitivity reactions is structured as followed, as the type of immune stimulation determines the procedures for diagnostic testing.

7. Diagnostic approach

First and foremost, it's imperative to acknowledge that the probability of precisely diagnosing hypersensitivity reactions notably rises when a patient undergoes assessment by an allergist or dermatologist during the acute phase of a suspected drug reaction. This early evaluation enables a more precise differentiation of potential diagnoses, classification of the clinical presentation, monitoring of symptom progression, and a more accurate determination of a drug's involvement. (26)

7.1 Patient history

The initial step in addressing any suspected cutaneous adverse drug reaction begins with a comprehensive patient history, which should encompass documentation related to the use of medications at the time of the reaction, covering the reasons for use, trade names, modes of application, ingredients, duration and dosage of treatment, any prior exposures to the same drug (indicative of sensitization) and history of tolerance. The chronology of the hypersensitivity reaction is meticulously assembled, detailing the timing in relation to drug application, the first occurrence, the course and resolution of the reaction, and the therapeutic measures taken and their outcomes. (26,27) The context of the reaction also requires examination, including any acute illnesses at the time of the reaction and factors that might lower the threshold for an allergic or non-allergic response, such as stress, physical exertion, and exposure to certain foods, alcohol, UV light, or menstrual cycles. A comprehensive medical and allergy history is gathered, documenting known hypersensitivities, reactions in the absence of drug exposure, atopic diseases, food allergies, predisposing diseases, and other relevant medical conditions, including psychological health. Exposure to potential noxious agents like nicotine, alcohol, and drugs is recorded, along with a list of current medications. (26,27)

7.2 Physical examination

After the history-taking phase, the physical examination assumes paramount importance, serving as a valuable adjunct in the evaluation of drug hypersensitivity. Of particular significance is the thorough assessment of clinical signs and symptoms, especially in instances of immediate generalized reactions, which have the potential to manifest as severe or life-threatening drug-induced reactions. An indispensable component of the assessment protocol is an exhaustive examination of the skin. (6,27,28) This entails a comprehensive scrutiny of the location or distribution pattern of the cutaneous eruption, characterization of the morphology

(e.g., papular, macular, vesicular, pustular, desquamative) and configuration of the skin lesions (e.g., annular, arcuate, confluent, linear), alongside an appraisal of accompanying symptoms such as pruritus, pain, or burning sensation. Photographic evidence of acute-phase skin alterations can greatly aid in identifying the type of clinical reaction. A meticulous differentiation between various types of cutaneous lesions holds significant diagnostic value, offering substantial insights into the underlying mechanism and classification of the drug reaction. (6,27,28)

The selection of planned diagnostic procedures is determined by an initial classification, which considers factors such as the chronology or time course of the reaction, the clinical presentation, and the suspected trigger, elaborated in the patient's history and physical examination:

Drug allergy phenotypes are typically categorized as either immediate onset or delayed onset. Immediate-onset drug allergy involves symptoms that manifest within 1 to 6 hours following exposure. Immediate reactions are predominantly IgE-mediated. On the other hand, delayed-onset drug allergy may emerge days to weeks after exposure to the allergen. This type of allergy can present with a diverse range of symptoms, ranging from isolated single-organ involvement to systemic multiorgan involvement. (4,29)

7.3 Clinical presentation

The most common clinical presentations of allergic reactions encompass the following. Morbilliform or erythematous maculopapular eruptions, also known as exanthematous eruptions, represent the most prevalent form of drug reaction, constituting approximately 40% of all cases. (3) Typically, the rash emerges within a timeframe ranging from one day to three weeks after the initiation of the causative drug, although this interval may vary in individuals previously sensitized to the medication. Clinically, these eruptions manifest as diverse maculopapular lesions devoid of mucosal involvement, resembling viral exanthems. Initially, lesions often emerge on the trunk or areas subject to pressure or injury, subsequently spreading to involve the extremities in a typically symmetrical pattern. (3) Commonly implicated drugs encompass antibiotics such as beta-lactams and sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics including carbamazepine and hydantoins, and allopurinol. (3,6,30)

Urticaria commonly manifests in two distinct manners. Immediate urticaria typically arises swiftly, occurring within 1 or 2 hours, in exceptional cases, it can also occur after a latency period of 6-12 hours, (26) following the initiation of treatment and presents as wheals or hives

that can emerge on various body parts such as the face, trunk, or extremities, sometimes accompanied by angioedema, characterized by swelling in the deeper layers of the skin. (31) Three key characteristics define hives: a central swelling surrounded by erythema, accompanied by itching or burning sensations, and their transient nature. Typically, individual lesions vanish within 30 minutes to 24 hours without leaving any lasting mark or hyperpigmentation. The underlying mechanism involves the release of inflammatory mediators from mast cells and basophils, often triggered by immune mechanisms such as type I hypersensitivity reactions. (32) Such immediate reactions necessitate the cessation of the medication due to the risk of anaphylaxis development. The presentation commonly associates with NSAIDs, sulfonamides, phenytoin, morphine, codeine, penicillin, and cephalosporins as the most prevalent drugs. In contrast, delayed urticaria typically emerges several days post-medication administration. Given its association with the pharmacological characteristics of the drug, continued use of the medication is not contraindicated in cases of delayed urticaria. (6)

Fixed pigmented erythema, or fixed drug eruption, typically emerges within 24 hours to a few days following the intake of the causative medication. (3) The typical presentation involves single or multiple circular to oval-shaped macules, ranging in color from red to brown. These lesions may progress to form plaques with vesicles or blistering. The upper limbs and lips are commonly impacted areas, although any region of the body, including the genital area and other mucous membranes, can also be affected. (6) Following the resolution of acute inflammation, it is common for post-inflammatory hyperpigmentation to persist for weeks to months. (33) Medications associated with FPE are Tetracycline, NSAIDs, and carbamazepine. (29)

Toxic epidermal necrolysis (TEN), also referred to as Lyell syndrome, along with Stevens-Johnson syndrome (SJS), represents the most severe manifestations of toxidermia, with a mortality rate of 25%. SJS and TEN form a spectrum, distinguished by the extent of skin involvement (<10% in SJS, >30% in TEN, and 10% to 30% in SJS-TEN overlap syndrome). (30) Symptoms typically manifest 21 days after the initiation of the causative medication. Following the onset of the rash, the progression of skin lesions varies from a few hours to several days. These lesions often appear as a dark red or purpuric macular rash with pseudo-cockades merging into a detached dermis composed of large shreds exposing the underlying dermis. Initially, the eruption commonly begins on the face and gradually spreads symmetrically to other body regions. A key clinical sign of SJS or TEN is a positive Nikolsky sign, characterized by the detachment of the epidermis from the dermis upon gentle pressure. (6,30,34) Additionally, the presence of painful erosions affecting at least two mucous

membrane sites (such as the conjunctiva, nose, mouth, anus, or genital area) is indicative of SJS or TEN. (35) Patients often experience significant systemic effects, including high fever, rapid dehydration, and the risk of skin lesion superinfection. Respiratory decline marked by tachypnea and hypoxia may signal underlying bronchial tree necrosis, which correlates with a poor clinical prognosis. Drugs commonly associated with TEN include anti-epileptics, cotrimoxazole, sulfonamides and allopurinol. (30, 36)

Acute generalized exanthematous pustulosis (AGEP) presents as a scarlatiniform erythematous rash accompanied by small pustules, primarily concentrated in the major skin folds such as the axillary and inguinal regions. (30,37) These pustules may merge, leading to superficial desquamation of the skin. While mucosal involvement can occur, it is typically limited. AGEP is commonly triggered by antibiotics, particularly aminopenicillins and macrolides. The eruption typically manifests abruptly, appearing within 24 hours to 4 days following initiation of the causative medication. Symptoms often include burning sensations and pruritus. (30, 38) The rash typically resolves within ten days. It is essential to differentiate AGEP from generalized pustular psoriasis, which shares similar dermatological features but differs in clinical evolution and histopathological characteristics. Distinguishing AGEP is crucial due to its potential for severe outcomes and a mortality rate of approximately 5%. (6,30,39)

Multi-organ reactions encompass for example drug reaction with eosinophilia and systemic symptoms (DRESS), alternatively termed drug-induced hypersensitivity syndrome. (30) DRESS is characterized by a delayed onset skin eruption occurring 2 to 6 weeks following the initiation of the medication. The eruption typically presents as a nonspecific pruritic maculopapular exanthem or a febrile erythroderma, with approximately 30% of cases exhibiting facial edema. (30) In rare instances, small pustules, purpura, or lesions resembling erythema multiforme may develop. DRESS is distinguished from other drug-induced eruptions by its association with significant adenopathy involving multiple lymph nodes and visceral organs. Commonly affected organs include the liver (resulting in hepatitis), kidneys (leading to interstitial nephritis), lungs, heart, and pancreas. (30,35,40,41) Clinical manifestations of DRESS are often accompanied by eosinophilia (> 1500 PNN / mm3) and a mononucleosis-like syndrome. Visceral complications of DRESS may persist for several weeks and can emerge after the onset of the skin eruption. Additionally, eosinophilia may not be evident during the early stages of the disease. The precise underlying mechanisms of DRESS remain unknown. Patients experiencing severe cutaneous manifestations of DRESS should be hospitalized and undergo thorough clinical monitoring both during and after hospitalization. (6,30)

Serum sickness (SS) is a type III hypersensitivity reaction mediated by immune complexes, characterized by the onset of fever, skin rash, and joint inflammation. Initially documented in 1906 among individuals administered nonhuman-derived antiserum, symptoms typically manifest 1 to 2 weeks post-exposure to the triggering agent, which may include the rabies vaccine, immune-modulating medications, or antivenoms. (6) The rash associated with SS is often described as urticarial but can also manifest as a maculopapular or vasculitic eruption. Joint involvement predominantly presents as arthralgias affecting the hands, feet, ankles, knees, and shoulders, although arthritis may also occur. Additional symptoms may encompass lymphadenopathy, headache, neuropathy, or vasculitis. (6) Laboratory assessments may reveal decreased complement levels (CH50, C3–4), elevated serum creatinine, and either leukopenia or mild leukocytosis. Fortunately, SS is a self-limiting condition that typically resolves within several weeks following cessation of the causative agent. (6,42)

The spectrum of drug-induced lupus encompasses systemic involvement, referred to as drug-induced systemic lupus erythematosus (DI-SLE), and a form limited to the skin, known as drug-induced subacute cutaneous lupus (DI-S-CLE). Clinical manifestations of DI-SLE deviate from those seen in SLE. Specifically, DI-SLE typically presents with fever, arthralgia/arthritis, myalgia, and serositis, with infrequent involvement of internal organs such as lupus nephritis and central nervous system disease. (6,43) Classic cutaneous manifestations of SLE, including malar rash and discoid rash, are uncommon in DI-SLE. Conversely, DI-SCLE manifests as annular-polycyclic or psoriasiform lesions distributed in photosensitive areas, often accompanied by anti-SSA antibodies. (44) ANAs are universally detected, and anti-histone antibodies are present in 75% of DI-SLE patients. Symptoms typically resolve within days to weeks following discontinuation of the offending drug. (6)

Drug-induced vasculitis is characterized by inflammation affecting blood vessels, primarily targeting the skin and subcutaneous tissue, with potential involvement of the kidneys and lungs. (45) Clinical presentations vary, ranging from localized small vessel hypersensitivity vasculitis to more systemic forms resembling severe vasculitis like Churg-Strauss syndrome, Wegener's granulomatosis and polyarteritis nodosa. (6) Leukocytoclastic vasculitis represents the most common type of cutaneous vasculitis (30%), typically manifesting as a palpable purpuric or petechial rash predominantly on the lower extremities. Severe cases may exhibit systemic symptoms such as arthralgias, gastrointestinal issues, or nephropathy. Frequently implicated drugs include penicillin, sulfonamides, quinolones, allopurinol, propylthiouracil, anti-TNFα

agents, NSAIDs, and hydralazine. Discontinuation of the offending medication often leads to symptom resolution. (6)

Immediate reactions (IgE -mediated)	**Delayed reactions** (non-IgE mediated)
- Appear < 1hour - Occasionally <6 hours	- >3->12 days - In re-exposure >1 day
Presentation: urticaria, angioedema, anaphylaxis	Presentation: maculopapular/morbilliform exanthems, AGEP, SJS, TEN, DRESS, vasculitis, SS

Figure 3: Overview Immediate reactions vs. Delayed reactions

Laboratory investigations and allergy testing play a pivotal role in complementing clinical evaluations to confirm suspected diagnoses accurately. The selection of diagnostic tools is contingent upon the specific nature of the reaction and its potential mechanisms. These assessments can be broadly categorized into in vivo and in vitro testing methods.

7.4 Test methods

In vivo tests are typically conducted after several weeks or months following the resolution of the reaction to prevent any potential flare-ups. Patients are advised to discontinue antihistamines or steroids before undergoing these tests to avoid any interference with the results.

The drug provocation test, also known as a challenge test, involves administering a controlled dose of a drug to identify a drug hypersensitivity reaction, applicable to both nonimmune and immune-mediated reactions. While regarded as the gold standard for determining causality in drug reactions, its use is circumscribed due to the potential risk of recurrent reactions, particularly in severe cases. Therefore, only proficient healthcare professionals must conduct this test especially in cases where the patient's history or previous allergy tests do not definitively indicate hypersensitivity or the patient’s history indicates hypersensitivity but only with mild or nonspecific symptoms. Careful consideration of the risks and benefits is essential before proceeding with a drug provocation test, which may serve to confirm a diagnosis or rule out cross-reactivity with related drugs in established hypersensitivity cases. (6,27,32,46,47),

Dermatological tests, also known as skin tests, encompass various procedures such as the skin prick test, intradermal test, and patch test. The interpretation of results for skin prick and intradermal testing to identify IgE-mediated immediate hypersensitivity typically occurs within

15–20 minutes, whereas patch tests necessitate a longer observation period (24–96 hours). Assessment involves measuring the diameter of wheals and/or erythema at the application site, with negative and positive controls employed for result comparison. Sensitivity of these tests varies depending on factors such as the drug, its concentration, and the nature of the reaction. (6,27,32)

The skin prick test involves pricking the skin with a sterile lancet or similar device, allowing a specific allergen-containing solution to penetrate the epidermodermal junction zone. This test is commonly utilized for immediate (IgE-mediated) drug adverse reactions due to its practicality and widespread availability. (6,27,32,48) Conversely, the intradermal test entails injecting a small volume (0.02–0.05 mL) of allergen intradermally, typically using nonirritating concentrations. (6,49) Limited to sterile liquid drug formulations, this test can diagnose both immediate and delayed drug hypersensitivity reactions. On the other hand, patch testing involves applying a specific concentration of the antigen onto small plates affixed to the patient's back for a period ranging from several days to a couple of days. Although primarily used for diagnosing contact dermatitis, its application has expanded to encompass other nonimmediate CADRs, including maculopapular rash, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis. (6,50)

In vitro testing offers valuable assistance in elucidating diagnoses and establishing causality without the risk of triggering reaction reactivation. Nonetheless, these tests may entail higher costs and may not be universally accessible. (6)

Regarding skin biopsy, the histopathological features observed in CADRs may lack complete specificity; however, they can offer valuable indications and contribute to establishing a definitive diagnosis but may not conclusively rule out alternative causes or other underlying conditions. (6,51)

Tests for specific IgE antibodies offer an objective assessment of circulating drug specific IgE antibodies. While these tests are recommended for diagnosing immediate IgE-mediated reactions triggered by β-lactam drugs, their utility remains a topic of debate with unclear determinants. The sensitivity may vary between 19% and 75%, while specificity ranges from 67% to 100%. It's noteworthy that positive predictive values tend to be lower than negative predictive values. (6)

The lymphocyte transformation test assesses the expansion of T cells in vitro in response to a particular drug, relying on the activation and proliferation of drug-specific memory T cells when the patient's peripheral mononuclear cells are cultured with the suspected drug (27,52) This test is applicable to various drugs and immune responses. In individuals with delayed hypersensitivity reactions like DRESS, its sensitivity and specificity have been evidenced to reach up to 73% and 95%, respectively. (6)

The lymphocyte toxicity assay (LTA), akin to the lymphocyte transformation test, employs peripheral mononuclear cells to determine the causality of a specific drug in T-cell mediated adverse drug reactions. However, LTA primarily assesses the viability of the patient's T-cells when exposed to varying concentrations of the suspected drug compared to T-cells from a healthy control. Its sensitivity, specificity, negative predictive value, and positive predictive value appear to fluctuate depending on the drug implicated in the reaction. Nonetheless, LTA has demonstrated utility as a diagnostic tool for delayed hypersensitivity reactions to numerous drug classes, encompassing aromatic anticonvulsants, sulfonamides, and β-lactam antibiotics. (6)

The basophil activation test employs flow cytometry to assess the allergen-induced activation of basophils. It has undergone validation for IgE-mediated allergies, including severe anaphylaxis. The sensitivity and specificity of this test vary depending on the drug being evaluated. In the case of β-lactam drugs, the sensitivity and specificity of the basophil activation test may reach up to 78–97%, respectively. (6,52)

The Enzyme-linked ImmunoSpot assay detects cytokine molecules, such as interferon-γ, secreted locally, utilizing antibody-coated plates for both qualitative and quantitative measurement of specific proteins. It quantifies cytokine production on a per-cell basis and is utilized in determining drug causality in severe DHRs like SJS/TEN, DRESS, and AGEP. Recent research indicates that the performance of the enzyme linked ImmunoSpot test depends on the drug type or the DHR phenotype. Its sensitivity may increase if conducted within 30 days of DHR onset or during the acute phase. Although the sensitivity and specificity of this test vary, overall sensitivity is approximately 52%, while specificity can range from 86% to 100%. Similar to the lymphocyte transformation test and LTA, the enzyme linked ImmunoSpot test is not routinely available for diagnostic use in most centers. (6,54,55)

7.5 Laboratory tests

Additionally, several laboratory tests, including complete blood count and differential, liver function tests, inflammatory markers, complement, tryptase, and creatinine, are valuable tools for supporting a potential diagnosis and monitoring disease progression and treatment response. (6) However, negative or normal results do not definitively rule out a drug-induced adverse reaction. While eosinophilia often indicates a drug-induced allergic reaction, its absence does not definitively rule out such a cause since most patients with these reactions do not exhibit eosinophilia. (6) Autoantibodies can aid in diagnosing drug-induced vasculitis (e.g., antinuclear cytoplasmic antibody) and drug-induced lupus erythematosus (DILE). In systemic DILE cases, positive antihistone antibody levels are common, while in cutaneous DILE, positive anti-Ro/SSA, anti-La/SSB, or both levels are frequent. (57) For suspected anaphylaxis cases, the diagnosis can involve identifying increased serum total tryptase levels above baseline or serum mature tryptase (β-tryptase) levels. These levels typically peak 0.5 to 2 hours post-drug administration and then decline with a half-life of around 2 hours. Additional methods to detect systemic mast cell mediator release include collecting 24-hour urine samples to assess major urinary metabolites of histamine or prostaglandin D2. (5,6,55-57)

Following the comprehensive evaluation, the findings are reviewed with the patient and documented accordingly. Ideally, an allergy passport is provided, serving as an official medical document. This passport contains details about the type of reaction experienced, specific substances or medications that are not tolerated, and potential cross-reactivities to be mindful of in the future. (26)

8. Treatment

For the sake of completeness, a brief overview of the treatment will be touched upon. Typically, the management of these conditions begins with discontinuing the suspected trigger drug. (58) Supportive care is tailored according to the severity of the reactions. For mild to moderate reactions, antihistamines, NSAIDs, and topical corticosteroids may be necessary. In cases of severe reactions, consideration should be given to systemic steroids (e.g., prednisone at a dosage of 0.5–1 mg/kg/d) or other immunosuppressive agents (such as cyclosporine, TNF inhibitors, or other biologic therapies); however, their efficacy remains controversial, as little evidence- based recommendations exist.(6) Hospitalization is warranted when certain signs of severity are present in CADRs, which may include cutaneous manifestations (e.g., extensive skin involvement, confluent erythema, facial edema, skin pain, purpura, skin necrosis, blistering, or epidermal detachment, positive Nikolsky's sign, mucosal erosions, urticaria,

and/or tongue swelling), general symptoms (e.g., high fever, lymphadenopathy, arthralgia or arthritis, expiratory dyspnea or difficulty breathing, cardiovascular involvement, or hypotension), (30) and biological abnormalities (e.g., eosinophilia >1000/μL, lymphocytosis with atypical lymphocytes, abnormal liver function, kidney, or cardiac parameters)(6,58-60). Reasons for hospitalization in those manifestations encompass ensuring the integrity of the skin barrier, preserving fluid balance, safeguarding the airway, and addressing infections. Also monitoring and replacing fluids and electrolytes are essential tasks, as well as providing nutritional support is vital to combat the body's heightened catabolic state. Additionally, managing body temperature and ensuring adequate pain relief are typically necessary. Multisystem involvement also requires early initiation of multidisciplinary care. (61)

9. Conclusion

In conclusion, this thesis on drug-induced skin hypersensitivity reactions traversed a comprehensive path through the intricate landscape of these adverse drug reactions. Through an exhaustive review of the literature and analysis of case studies, this study has shed light on the complex clinical presentations, underlying pathophysiology, and the critical diagnostic approaches necessary for identifying and managing these reactions effectively. The objectives set forth at the outset of this research endeavour have been met, contributing valuable insights, and enhancing the existing body of knowledge on drug-induced skin hypersensitivity reactions. Especially, the presentation of the new nomenclature for allergic diseases holds significant promise for the future of this field, especially with its potential to drive endotype-based thinking, fostering the development of innovative diagnostic tools, enhancing therapeutic strategies, and optimizing disease management. Moreover, this approach can guide future translational and clinical research towards more innovative methodologies. The primary advantage of adopting this immune response and tissue-based allergy nomenclature lies in its contribution to advancing precision and personalized medicine.

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11. Attachments

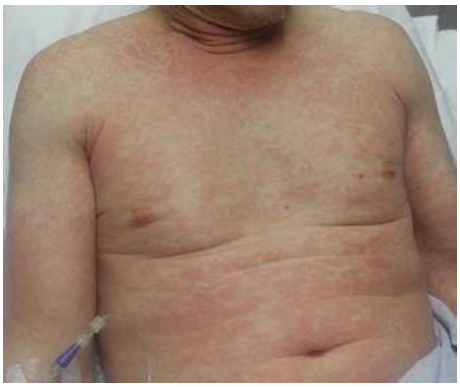

Figure 4: Mobilliform Drug Eruptions (62)

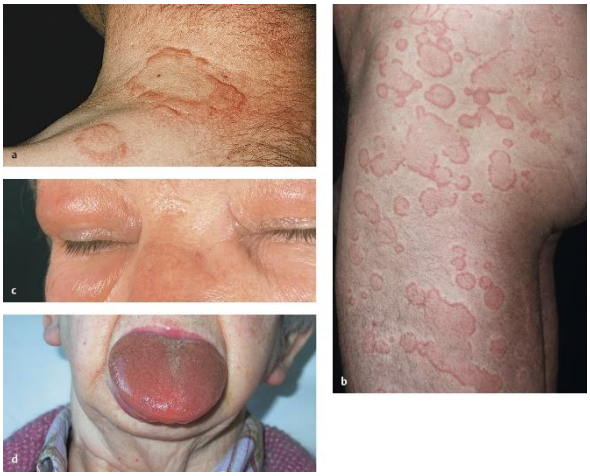

Figure 5: Urticaria and angioedema (32)
a. Marginal wheals, centrally pale due to pressure-induced edema (here left shoulder and neck).
b. Extensive confluent wheals, resembling geographical urticaria.
c. Edema of the eyelids (angioedema of the eyelids).
d. Angioedema with massive tongue swelling.

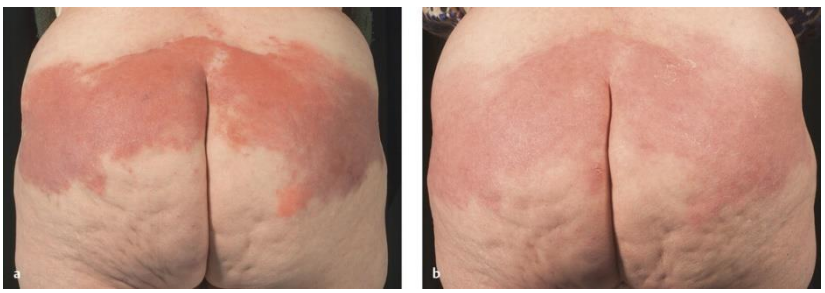

Figure 6: Fixed pigmented erythema: Well-demarcated, extensive, brownish-red fixed drug eruption on the buttocks (32)
a. in the acute phase.
b. After 3 weeks.

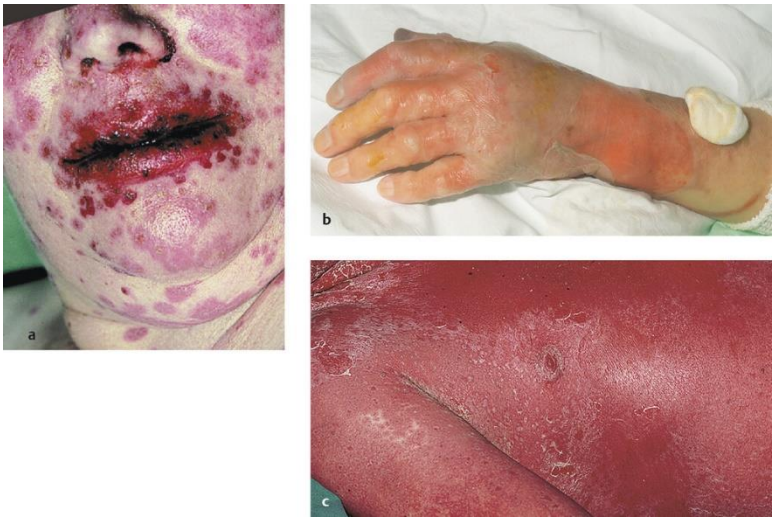

Figure 7: Stevens-Johnson syndrome and Toxic epidermal necrolysis (32)

a. Stevens-Johnson syndrome with extensive mucosal involvement.
b. + c. Toxic epidermal necrolysis: syndrome of "scalded skin" with widespread detachment of the epidermis.

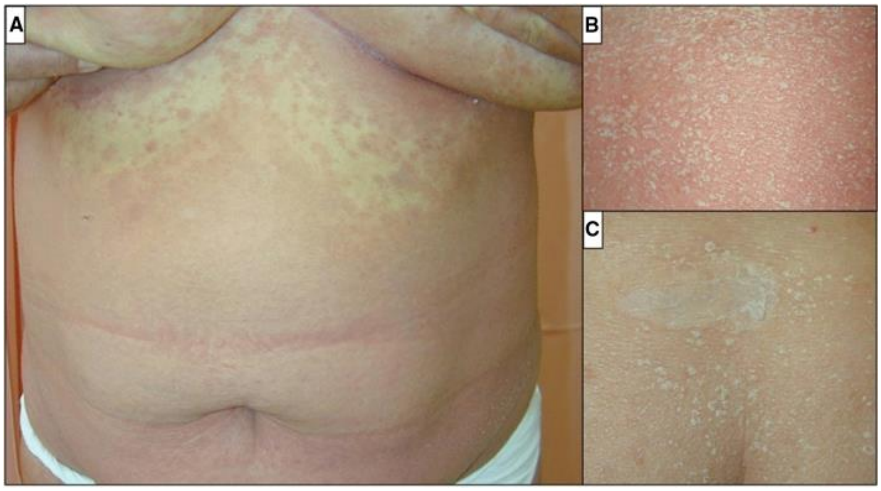

Figure 8: Generalised exanthematous pustulosis in a patient 3 days after oral clindamycin initiation: (63)

a. 3 days of intertriginous erythema followed by
b. pustules overlying the erythema for 2–3 days, followed by
c. subsequent desquamation of the affected skin approximately 1 week after appearance of the rash

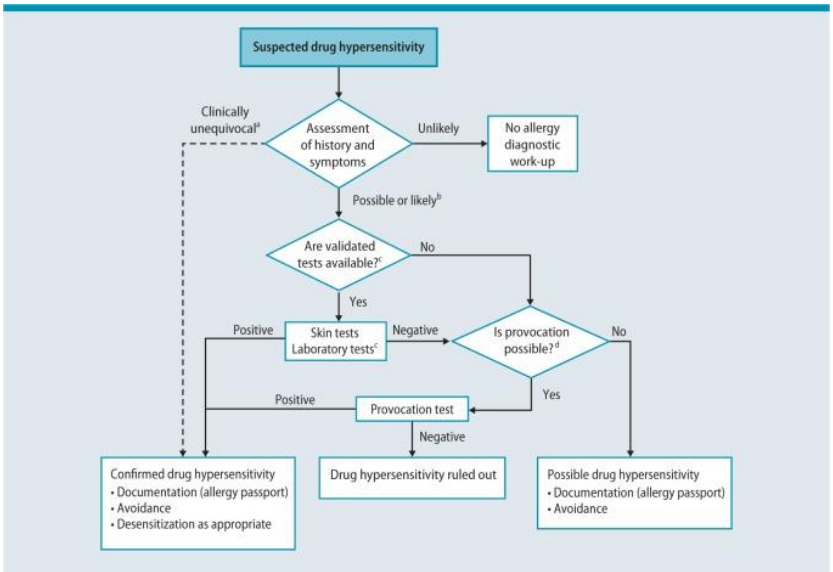

Figure 9: Diagnostical approach to suspected drug hypersensitivity reactions (4)

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