*ejpmr, 2025, 12(3), 484-496*

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# A REVIEW ON ADVERSE DRUG REACTION AT PRESENT DAY'S AND THEIR CLINICAL CONSEQUENCES

**Mousumi Das[1], Manonayan Singha[1], Mir Irfan Soyel[1]*, Malay Besra[1], Deepayan Kar[1], Biplab Kumar Chakra[1], Nilanjan Adhikari[2]**

[1-2]Assistant Professor, P.G. Institute of Medical Sciences, Chandrakona Town, Paschim Medinipur, West Bengal, India, Pin – 721201.

***Corresponding Author: Mir Irfan Soyel**
Assistant Professor, P.G. Institute of Medical Sciences, Chandrakona Town, Paschim Medinipur, West Bengal, India, Pin - 721201.

**Article Received on 25/01/2025** **Article Revised on 15/02/2025** **Article Published on 07/03/2025**

## ABSTRACT

Significant patient morbidity and death as well as financial strain on the healthcare system are caused by adverse medication reactions. Anaphylaxis and malignant hyperthermia continue to be the two most worrisome adverse medication responses for anesthetists. Anaphylaxis under anesthesia is so common that most anesthetists will handle at least one case during their careers, despite the fact that its incidence is difficult to determine. Numerous medications administered during the preoperative phase and the anesthetized patient's fluctuating presentation might cause delays in diagnosis and treatment, as well as negatively impact the result. Furthermore, because adverse effects may be mediated by mechanisms other than IgE activation, causative medicines can still be challenging to identify despite advancements in testing. Anesthetists' must stay current on new advances because of the rise in allergy reports to newer anesthetic medications like sugammadex and the shift in the most likely causal peri-operative substances during the past few decades. To help reduce the likelihood of a reaction, they should also be aware of patient features, such as pharmacokinetic abnormalities that may predispose to adverse medication reactions. Morbidity and mortality are still high because to the severity of adverse pharmacological reactions to preoperative medications.

**KEYWORDS:** Adverse drug reaction, Risk Factors for ADR, Drug Hypersensitivity Reactions, Diagnostic and Therapy for Drug Hypersensitivity, Penicillin allergy.

## INTRODUCTION

According to the definition of an adverse drug reaction (ADR), "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, specific treatment, alteration of the dosage regimen, or withdrawal of the product.[1]" Since 2012, in addition to the authorized use of a medication in prescribed dosages, the definition has expanded to encompass reactions that arise from mistakes, misuse, or abuse, as well as suspected reactions to medications that are unlicensed or used off-label.[2] Although this shift may affect how manufacturers and medical regulators report and monitor adverse drug reactions, it shouldn't have an impact on how we manage ADRs in clinical practice. ADRs are a prevalent manifestation in clinical practice, including as a cause of unscheduled hospital admissions, happening during hospital admission, and manifesting after discharge, according to groundbreaking research conducted in the USA and the UK in the late 20th and early 21st centuries.[3] Research indicates that between 5% and 10% of patients may experience an ADR upon admission, during hospitalization, or after discharge, despite numerous prevention measures. The frequency of ADRs has stayed largely constant over time. The majority of ADRs do not result in significant systemic symptoms, and the frequency of occurrences is inevitably correlated with the methodology employed to detect them. However, given the related morbidity and mortality, potential adverse effects on the prescriber-patient relationship, and potential financial costs, this frequency of potential damage must be carefully considered.[4]

### Definitions and Classifications

The phrases "drug allergy," "drug hypersensitivity "and" drug reaction" are frequently used synonymously. Drug responses include all unfavorable occurrences associated with the administration of drugs, regardless of their cause. A sensitized patient's immune system reacting to a pharmacological agent is known as drug hypersensitivity. Drug allergies are only limited to an IgE-mediated response.[5] There are two categories of etiologies for drug reactions: immunologic and nonimmunologic. Most adverse medication reactions (75–80%) are brought on

by predictable, nonimmunologic consequences. One Unpredictable side effects, which may or may not be immune-mediated, account for the remaining 20 to 25 percent of adverse medication occurrences.[6] IgE-mediated drug allergies are classified as immune-mediated reactions, which make up 5–10% of all medication reactions and represent real drug hypersensitivity.[7,8] ADRs are traditionally divided into two categories: Type A reactions are "dose-dependent" and predicted based on the drug's pharmacology; they are also known as enhanced reactions.

Type B reactions are peculiar reactions that are unpredictable and idiosyncratic based on pharmacology.[9] This basic classification is still frequently used, but it does not apply to all ADRs. For example, it does not account for withdrawal reactions (such as rebound hypertension with centrally-acting antihypertensive cessation) or chronic adverse effects linked to cumulative drug exposure (such as osteoporosis with long-term corticosteroid treatment). "DoTS" is an alternate and possibly more thorough classification system that groups reactions according to the drug's dose, the reaction's time course, and pertinent susceptibility characteristics (such as genetic, pathological, and other biological.[10] DoTS has the benefit of being useful for practical ADR diagnosis and prevention in addition to classifying reactions.

**Epidemiology**

Globally, immunological and nonimmune processes causing adverse medication reactions are a leading cause of illness and mortality. They are the most prevalent iatrogenic disease, complicating 5–15% of medication regimens.[11,12] Serious adverse medication reactions are responsible for about 100,000 deaths in the US each year.[13] Adverse drug reactions account for 3–6% of all hospital admissions, and 6–15% of hospitalized patients (including 2.2 million people in the US in 1994) had a serious adverse drug reaction.[11-14] Epidemiologic evidence supports the existence of some characteristics, such as female gender, HIV infection, or herpes, that raise the chance of general adverse medication reactions (Table 1).[15-19]

**Table 1: Patient Risk Factors for Adverse Drug Reactions.[15-19]**

| General drug reactions (nonimmune) | Hypersensitivity drug reactions (immune) |
|---|---|
| Female gender | Female gender |
| Serious illness | Adult |
| Renal insufficiency | HIV infection |
| Liver disease | Concomitant viral infection |
| HIV infection | Previous hypersensitivity to chemically-related drug |
| Herpes infection | Asthma |
| Alcoholism | Use of beta blockers |
| Systemic lupus erythematosus | Specific genetic polymorphisms<br>Systemic lupus erythematosus |

*HIV = human immunodeficiency virus.*

A higher risk of hypersensitive medication reactions is associated to conditions including asthma, systemic lupus erythematosus, or use of beta blocker(Table 1).[15-19] Atopic patients are more likely to experience severe allergic reactions even when they do not have a greater percentage of drug sensitization.[20] The most significant drug-related risk factors for drug hypersensitivity relate to the chemical characteristics and molecular weight of the drug; larger drugs with more structural complexity (such as nonhuman proteins) are more likely to be immunogenic; complex antigens that can cause hypersensitivity reactions include insulin, streptokinase, and heterogonous antisera; most drugs have a molecular weight (less than 1,000 daltons), but they can still become immunogenic by coupling with carrier proteins, like albumin, to form simple chemical-carrier complexes (hapten).The method used to administer the medication—topical, intramuscular, and intravenous administrations are more likely to result in hypersensitivity reactions—also influences the frequency of these reactions.

These effects are brought on by the rapid achievement of high concentrations of circulating drug antigen by intravenous therapy, the effectiveness of antigen presentation in the skin, and the adjuvant effects of repository drug formulations. Drug hypersensitivity is less common with oral treatments.[20] Some adverse medication reactions might result in permanent impairment or death, while others are mild and go away without any after effects. Although ADRs happen frequently, estimates of their occurrence vary widely. This is because ADRs are significantly underreported, and there are variations in study designs, populations examined, and ADR criteria. In the US, adverse medication responses are responsible for between 2.9% and 15.4% of all hospital admissions.[21,22] The elderly and other vulnerable groups might have the highest incidence. ADRs cause hospitalization for around 16% of nursing home residents.[23] Co-administration of seven or more drugs is a substantial risk factor for hospitalization. According to estimates, ADRs rank between the fourth and sixth most common cause of death for hospitalized patients. A study suggests that an estimated 6.7% of hospitalized patients experience serious adverse drug reactions.[24] A review of over 30,000 medical records revealed that an adverse drug reaction was responsible for 19.4% of the 1133

medication-related adverse events that were documented [25]. According to reports, 20% of hospitalized HIV-infected patients experience ADRs.[26] The majority of patients receive an average of nine medications during each hospital stay, and up to 30% of patients may have an adverse drug reaction (ADR), with 3% of those cases potentially being life-threatening.[27] According to reports, adverse medication reactions can lengthen hospital stays by 2.2 to 4.6 days and raise expenses by more than $2500 each incident.[28] It has been estimated that ADRs cost the economy billions of dollars per year.[29]

**Clinical Manifestations**

Any organ system may be affected by true hypersensitivity adverse medication responses, which can mimic disease and include systemic events like anaphylaxis (Table-2). Drug reactions frequently present as dermatological symptoms brought on by the skin's immunologic and metabolic processes. Morbilliform rashes are the most prevalent dermatological sign of a medication reaction. An erythematous, maculopapular rash usually develops on the torso and gradually spreads to the limbs one to three weeks following medication contact. Although it can also occur with Type III or pseudoallergic reactions, urticaria usually indicates a really allergic Type I reaction. Because severe nonallergic, hypersensitive cutaneous reactions are linked to substantial morbidity and mortality, they should be recognized right away as bullous skin disorders. The most frequent cause of eczematous rashes is topical medication, and they typically indicate contact dermatitis, a Type IV reaction to drug exposure.[30,31]

**Table 2: Gell and Coombs Classification of Drug Hypersensitivity Reactions.[30,31]**

| Immune Reaction | Mechanism | Clinical manifestations | Timing of reactions |
|---|---|---|---|
| **Type I (IgE-Mediated)** | Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators | Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis | Minutes to hours after drug exposure |
| **Type II (Cytotoxic)** | Specific IgG or IgM antibodies directed at drug-hapten coated cells | Hemolytic anemia, neutropenia, thrombocytopenia | Variable |
| **Type III (Immune Complex)** | Tissue deposition of drug-antibody complexes with complement activation and inflammation | Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis | 1 to 3 weeks after drug exposure |
| **Type IV (Delayed, CellMediated)** | MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release | Allergic contact dermatitis, maculopapular drug rash | 2 to 7 days after cutaneous drug exposure |

**Clinical evaluation**

Drug hypersensitivity reactions must be considered in the differential diagnosis of patients presenting with typical allergic manifestations, such as anaphylaxis, urticaria, and asthma. Additionally, they should be evaluated in cases exhibiting serum sickness-like symptoms, dermatologic rashes, fever and pulmonary infiltrates with eosinophilia, hepatitis, acute interstitial nephritis and lupus-like syndromes. The diagnosis of drug hypersensitivity is predicated upon the identification of clinical symptoms and physical findings that align with an immune-mediated drug reaction. A thorough patient history should encompass a detailed account of all prescription and over-the-counter medications ingested within the past month, including specific dosages and the timing of administration. The temporal correlation between the initiation of drug therapy and the onset of symptoms is of paramount importance. In the absence of prior sensitization to a specific drug, the interval between exposure and the manifestation of adverse reactions typically ranges from one week to one month. Comprehensive inquiry into prior drug exposures and any previous hypersensitivity reactions is essential. Physical examination can provide pivotal clues to support the diagnosis of drug hypersensitivity. A critical first step involves evaluating for signs of an immediate generalized allergic reaction, given that this represents the most severe, potentially life-threatening manifestation of an adverse drug reaction. Alarm bells for imminent cardiovascular collapse include urticaria, laryngeal or upper airway edema, wheezing, and hypotension. Other signs indicative of serious drug-induced reactions may encompass fever, mucous membrane lesions, lymphadenopathy, joint tenderness and swelling, or abnormal pulmonary findings.

A meticulous dermatologic examination is indispensable, as the skin is the organ most commonly affected in adverse drug reactions. Discriminating between various types of cutaneous lesions is crucial, as this can offer significant insight into the underlying immune-mediated mechanisms driving the drug hypersensitivity (table 3).[32]

**Table 3: Cutaneous Symptoms of Drug Hypersensitivity Reactions.**[32]

| Type of skin lesion | Associated immune-mediated mechanism of the drug reaction |
|---|---|
| Exanthematous or morbilliform eruption originating on trunk | Classic "drug rash"; most common |
| Urticaria | IgE antibody-mediated or direct mast cell stimulation |
| Purpura | Vasculitis or drug-induced thrombocytopenia |
| Maculopapular lesions with distribution on the fingers, toes, or soles | Serum sickness |
| Blistering lesions with mucous membrane involvement | Stevens-Johnson syndrome or toxic epidermal necrolysis |
| Eczematous rash in sun-exposed areas | Photoallergic reaction |
| Solitary circumscribed erythematous raised lesion | Fixed drug eruption |
| Papulovesicular, scaly lesion | Contact dermatitis |

The comprehensive assessment of drug hypersensitivity reactions necessitates a meticulous evaluation of both patient history and physical examination, as these remain the cornerstone of diagnostic accuracy. The primary investigative modalities encompass specific drug provocation testing and a spectrum of laboratory assays designed to elucidate the immunopathological mechanisms underlying the hypersensitivity response. Among these, immediate-type hypersensitivity skin testing constitutes the most rapid and diagnostically robust methodology for the detection of drug-specific immunoglobulin E (IgE) antibodies. However, the applicability of skin testing is predominantly constrained to high-molecular-weight proteinaceous antigens and the major and minor antigenic determinants of β-lactam antibiotics, notably penicillin. The radioallergosorbent test (RAST) serves as an alternative in vitro diagnostic tool for identifying IgE-mediated sensitization, albeit its utility remains largely restricted to penicillin major determinants.

Beyond these modalities, additional in vitro assays such as leukotriene release tests, basophil activation markers, and basophil histamine release assays have been explored as surrogate indicators of type I hypersensitivity. Nevertheless, the widespread clinical implementation of these assays is impeded by their limited availability, suboptimal standardization, and ambiguous sensitivity and specificity profiles. For hypersensitivity reactions classified under Gell and Coombs types II and III, diagnostic methodologies remain less well established. Drug-induced hemolytic anemia, a prototypical type II hypersensitivity reaction, can be initially screened using the direct Coombs test, with subsequent confirmation via drug-specific autoantibody assays when available.

Delayed-type hypersensitivity (type IV) reactions necessitate distinct diagnostic approaches, with patch testing and delayed intradermal drug testing being the principal investigative tools. Additionally, the lymphocyte transformation test (LTT), an in vitro assay measuring antigen-specific T-cell proliferation, has demonstrated potential in characterizing morbilliform drug eruptions, although its accessibility remains limited. Complementary laboratory investigations facilitating hypersensitivity reaction characterization include serum tryptase quantification, complement level assessments, and immune complex assays. The detection of elevated serum tryptase within 1 to 2 hours post-anaphylaxis serves as a reliable biomarker implicating mast cell degranulation. Conversely, complement component depletion is a hallmark of serum sickness reactions but is not observed in serum sickness-like syndromes. Immune complex assays may further substantiate the diagnosis of serum sickness. Despite advancements in immunodiagnostic methodologies, significant gaps persist in the standardization, sensitivity, and specificity of these assays, necessitating further research to enhance their clinical applicability in drug hypersensitivity diagnostics.[33]

**Laboratory Evaluation**

Only drugs approved by the Food and Drug Administration (FDA) are considered safe and effective for sale in the United States. In other words, all known hazards must be outweighed by the medication's advantages. However, there are drawbacks to both prescription and over-the-counter (OTC) medications. The degree of adverse effects might vary, ranging from minor annoyances like a runny nose to serious conditions like myocardial infarction and, in some cases, deaths.A number of variables such as age, concomitant medication use, vitamin intake, dietary supplements, drug dosage, and delivery route, can influence the severityof side effects. Compared to the oral method, adverse effects appear more quickly and intensely when given intravenously (IV) or intramuscularly (IM). Several laboratory procedures have been carried out toascertain the effects of a drug on the body.Drug-induced liver failure is characterized by increased levels of liver enzymes, such as aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). Patients with renal failure had higher levels of

lipase and amylase, according to laboratory studies. Laboratory tests detect high-cholesterol drugs at concentrations greater than 200 mg/dL, such as beta-adrenaline, anabolic steroids, and prednisone. Drugs that raise blood glucose levels above what is regarded as normal include beta-adrenergic blockers, corticosteroids, and statins.Laboratory techniques can also be incorporated into analytical methods since they have been used in scientific labs to help separate and identify chemicals (e.g., spectrophotometry, high performance liquid chromatography).[34]

In order to determine the cause of the suspected adverse drug effect, diagnostic testing aims to assess biochemical or immunologic markers that validate activation of a certain immunopathologic pathway. Laboratory evaluation is leaded by the suspected pathologic mechanism (Table 4).[35]

**Table 4: Diagnostic Testing and Therapy for Drug Hypersensitivity.[35]**

| Immune reaction | Laboratory tests | Therapeutic considerations |
|---|---|---|
| Type I (IgE-mediated) | Skin testing<br>RAST<br>Serum tryptase | Discontinue drug.<br>Consider epinephrine, antihistamines,corticosteroids, bronchodilators. Inpatient monitoring, if severe |
| Type II (cytotoxic) | Direct or indirect Coombs' test | Discontinue drug.<br>Consider systemic corticosteroids.<br>Transfusion in severe cases |
| Type III (immunecomplex) | ESR<br>C-reactive protein Immune complexes Complement studies Antinuclearantibody, antihistone antibody Tissue biopsy for immunofluorescence studies | Discontinue drug. complex)<br>Consider NSAIDs, antihistamines, or systemiccorticosteroids; or plasmapheresis if severe. |
| Type IV (delayed, cell-mediated) | Patch testing<br>Lymphocyte proliferation assay* | Discontinue drug.<br>Consider topical corticosteroids, antihistaminesor systemic corticosteroids if severe. |

RAST = radioallergosorbent test; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal anti-inflammatory drugs*—This is an investigational test

In order to confirm suspected Type I hypersensitivity reactions, antigen-specific IgE must be detected. For these patients, an effective diagnostic method is skin testing. Skin testing procedures are well-defined for muscle relaxants and local anaesthetics, and they are standardized for penicillin.[36,37] Furthermore, it could provide useful information for analyzing high-molecular-weight protein compounds including insulin, vaccinations, streptokinase, latex, and polyclonal or monoclonal antibodies[38,39].In the proper clinical context, a positive skin test for such reagents supports the diagnosis of a Type I hypersensitivity reaction and validates the presence of antigen-specific IgE. Because the test specificity has been well established, negative skin testing is solely useful in penicillin skin testing[40].With other drug agents, a negative skin test does not effectively rule out the existence of specific IgE. For a small number of medications, IgE can be tested in vitro using radioallergosorbent tests, which are traditionally less sensitive than skin testing for identifying particular IgE levels[38]. Additionally, many medications have unknown immunogenic factors, which reduces the prognostic usefulness of in vitro testing[41].Measuring mast cell activation by laboratory tests may be helpful if acquired within four hours of onset of the suspected allergic reaction. Serum striptease levels peak one hour after anaphylaxis and stay increased for two to four hours following the incident, whereas serum histamine levels peak five minutes after the event and fall to baseline within thirty minutes[42]. It has been proved that, histamine, striptease, and beta-striptease levels are helpful in confirming acute IgE-mediated reactions, but negative results do not eliminate acute allergic reactions[43,44]. Haemolytic anaemia, thrombocytopenia, or neutropenia are symptoms of type II cytotoxic drug reactions that are visible on a full blood count. A positive direct and/or indirect Coombs' test, which indicates the presence of complement and/or drug-hapten on the red cell membrane, can confirm haemolytic anaemia. Erythrocyte sedimentation rate and C-reactive protein are two examples of nonspecific inflammatory markers that may rise in Type III immune complex reactions to a medication. If available, more precise laboratory tests for circulating immune complexes or complement levels (CH50, C3, C4) can be carried out. While negative testing do not rule out the diagnosis of immune complex illness, positive tests aid in confirming the clinical diagnosis. Autoantibody assays, such as antinuclear antibody or anti-histone antibody, can identify systemic vasculitides brought on by medication[45]. Typically, type IV immunological reactions manifest as topical medication-induced allergic

contact dermatitis. Patch testing for certain medication agents is a suitable diagnostic step in these situations. The diagnosis of a Type IV immunological reaction is supported by symptoms such as erythema, induration, and a pruritic vesiculopapular rash that appears 48 hours after the patch is applied. The initial laboratory evaluation is also include such as a complete blood count performance using a Coulter (Coulter Electronics, Inc., Hialeah, Fla.) counter; erythrocyte sedimentation rate determination by the Westergren technique; blood chemistries performed by using of a continuous flow-automated multiple channel analysis system; sequential multiple analyses, computerized (SMAC Technicon Instrument Corp., Tarrytown, N. Y.); determination of quantitative immunoglobulins G, A, and M with the use of the Beckman Auto immunochemistry System, Beckman Instruments, Brea, Calif. and measurement of immunoglobulin E with the Phadebas IgE PRIST radioimmunoassay kit, Pharmacia Diagnostics, Piscataway. N. J.[46]

**Use of a Laboratory Alert System for the detection Adverse Drug Reactions in Hospitalized Patients: Hyponatremia and Rhabdomyolysis**

Analysis of the laboratory signal "hyponatremia" is more successful than analysis of the signal "rhabdomyolysis" since fewer cases need to be looked at in order to detect an adverse drug reaction. ADR is found to be common for all of the signals, with "hyponatremia" accounting for 39.3% and "rhabdomyolysis" for 3.3%. In both cases, it has been impossible to determine a relationship between the degree of the laboratory value change and the probability that drugs were the cause.Automated laboratory signals can be used to analyse adverse medication reactions and extract information that can be missed during clinical examination. To do this correctly, medical professionals must carefully fill out a patient's clinical history, making sure that no important details are missed that can come in handy later.[47]

**Diagnosis and attribution of causality**

A patient's overall diagnosis includes the diagnosis of an adverse medication reaction. The likelihood of an adverse drug reaction should be considered in the differential diagnosis if the patient is on medication. Finding out whether a patient is taking a medication is the first challenge. This includes over-the-counter formulations, products that might not be considered medications (like herbal or traditional remedies, recreational drugs, or drugs of abuse), and long-term treatments that the patient might forget (like oral contraceptives). The next step is to determine whether a medication may be to blame for the impact. It can be difficult to determine which medication, if any, is the cause when the patient is taking multiple prescriptions. This issue is complicated since some of the patient's concerns may be brought on by one or many medications or by other illnesses. There are numerous formal techniques for determining the likelihood that a suspected adverse medication reaction is caused.[48,49] Since conclusive, confirmatory drug-specific testing is frequently challenging, the diagnosis of drug hypersensitivity is typically made using clinical judgment.

Following the establishment of the diagnosis, the medical record should have the necessary paperwork outlining the medicine that caused the side effect and its type. With repeated drug exposure, immune-mediated drug hypersensitivity reactions usually present a foreseeable, more significant health risk. Reactions to nonimmune drugs are typically milder and less consistent. If there is no adequate alternative and the danger of not treating the underlying disease outweighs the risk of stopping the drug, then continuing to use the offending drug may be prudent. In these situations, a skilled doctor's constant supervision of the patient is crucial. A list of alternative medications for future use should be given to the patient when they stop taking a medication.[51,52]

***The timing of reaction occurrence***

It is important to evaluate the temporal relationship between drug use and reaction occurrence. Are they convincing relationship?

As an illustration,

- Does the reaction happen or worsen when the drug's dose reaches steady state or, in the case of dose-related reactions, when the steady-state dose is raised?
- For dose-related reactions, does the reaction lessen or go away when the drug's dosage is lowered or stopped?
- Does the timing of the interacting medicine's introduction or withdrawal make sense if a drug interaction is suspected?
- Has the patient been exposed before, if there are signs of an allergic reaction? While prior exposure is associated with an allergic reaction, lack of prior exposure does not rule it out.
- Did drug exposure happen at the right gestational time if the impact is a congenital abnormality?
- Was the time lag long enough if the consequence was a tumor?
- Wished the tumor had expanded? Understanding tumor dynamics will be necessary to respond to this question.

***Identification of patterns of ADR***

The adverse effect pattern may correspond to a suspected medication's known pharmacology or allergy pattern, or it may be related to or pharmacologically similar substances. For instance, in a patient on digoxin, a combination of heart block and an ectopic arrhythmia is almost probably caused by the medication. Some patterns are pathognomonic, or nearly so. However, as a negative drug reaction could not be known or even anticipated from the pharmacology, this information shouldn't be used to rule out a relationship, especially

with a new medication. For example, corticosteroids, which are frequently used to decrease immunological responses, have the potential to trigger allergic reactions.

The event's background frequency and how frequently it is linked to drugs should then be taken into account. Since headaches are somewhat common, their correlation with a Medicine might be a coincidence. Aplastic anemia, on the other hand, is more likely to be an adverse drug reaction because it has a low background occurrence and is frequently linked to medications.

***Monitoring of ADR***

Biopsies, allergy testing, and plasma concentration measurements are examples of investigations that can help with diagnosis, set baselines for organ function (such as liver, kidney, or thyroid function), and offer a way to monitor what occurs following therapeutic modifications. They might also exclude other possible conditions. In order to prepare for an adverse drug reaction, it can occasionally be cautious to set baseline functions at the beginning of therapy. For instance, baseline thyroid function tests are frequently ordered prior to administering amiodarone, which can not only cause thyroid disease but also alter thyroid function tests, even when thyroid function is normal, making interpretation challenging. Such anticipation is useless in other situations. For instance, neutropenia cannot be detected until it manifests itself, and the white-cell count during carbimazole or methimazole medication does not forecast it.

Lastly, retaking the medication should be taken into account, especially if the patient would likely learn something from the new information. After completing this task, causation ought to be able to be established. Several causality classification schemes have been put forth and are employed in various nations.[48,50]

**Therapy and Management**

In the management of drug-induced hypersensitivity reactions, the foremost and most efficacious intervention is the immediate discontinuation of the culpable pharmaceutical agent. When clinically feasible, the offending medication should be supplanted with an alternative compound possessing a divergent chemical structure to minimize cross-reactivity. The subsequent clinical sequelae following medication cessation or substitution necessitate vigilant and continuous monitoring to preempt potential adverse outcomes. Empirical evidence suggests that, in the majority of cases, the resolution of hypersensitivity manifestations transpires within approximately two weeks, thereby substantiating the initial diagnosis of drug hypersensitivity.

Adjunctive therapeutic measures are predominantly supportive and aimed at ameliorating symptomatic distress. In scenarios characterized by pronounced hypersensitivity, the administration of systemic corticosteroids may expedite recovery, while topical corticosteroids in conjunction with oral antihistamines can significantly attenuate cutaneous symptoms. Moreover, in the context of severe cutaneous adverse reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, the clinical management paradigm shifts towards the deployment of intensive, multifaceted therapeutic strategies to mitigate morbidity and enhance patient outcomes.[53]

**Penicillin allergy:** The immunologic cross-reactivity inherent to the beta-lactam moiety has profound clinical implications, particularly in the context of penicillin-allergic patients.[54] Specifically, the structural homology between penicillins and carbapenems precipitates a significant risk of cross-reactivity, thereby generally contraindicating the use of carbapenems in this patient subset [Evidence level B, nonrandomized clinical trial]. In contrast, aztreonam (Azactam) exhibits an exceptionally low propensity for cross-reactivity, rendering it a viable alternative when therapeutic intervention is required.[55,56] Moreover, the literature documents variable degrees of cross-reactivity between cephalosporins and penicillins, with epidemiological data since the 1980s indicating that the incidence of cross-reaction with second- and third-generation cephalosporins remains at or below 5 percent.[57] Notably, first-generation cephalosporins appear to demonstrate a comparatively higher likelihood of eliciting immunologic cross-responses.[58] Although the absolute incidence of clinically significant cross-reactivity is relatively low, the potential for severe adverse outcomes, including fatal anaphylaxis, necessitates judicious clinical decision-making.[59] Consequently, a conservative management strategy is advocated, which may include penicillin skin testing prior to the initiation of cephalosporin therapy, particularly in patients with a documented history of severe penicillin hypersensitivity.[60,61]

**Radiocontrast media reactions:** In patients exhibiting severe adverse reactions to radiocontrast media, it is imperative to conduct a comprehensive and methodologically rigorous patient history that meticulously documents prior hypersensitivity episodes, reaction phenotypes, and any pertinent risk factors. Such an in-depth anamnesis not only facilitates the accurate identification and risk stratification of individuals predisposed to radiocontrast-induced hypersensitivity but also informs the development of tailored prophylactic and therapeutic strategies. For a detailed, evidence-based treatment algorithm specific to this high-risk cohort, please refer to Table 6, which delineates the recommended clinical management protocols.[62,63]

**Therapeutic plan:** Upon definitive characterization of a drug-induced hypersensitivity reaction, targeted therapeutic interventions may be promptly instituted as delineated in subsequent sections corresponding to the specific immunopathological phenotype. In addition to

the exigencies of immediate management, considerations regarding the prospective use of the implicated agent—or pharmacologically and structurally analogous compounds—warrant meticulous evaluation. Specifically, in the context of Gell and Coombs type I (IgE-mediated) reactions, re-administration of the offending drug is generally contraindicated due to the inherent risk of eliciting severe anaphylactic responses. In circumstances where clinical imperatives necessitate the use of the causative agent, a rigorously controlled desensitization protocol may be employed. This protocol involves the systematic, incremental augmentation of drug dosage under closely monitored conditions, thereby transitioning the patient from a hypersensitive state to a temporary state of immunological tolerance—provided that the therapeutic regimen remains uninterrupted.

It is imperative to underscore that such desensitization strategies are exclusively reserved for type I hypersensitivity reactions. For alternative immunologically mediated adverse reactions—encompassing Gell and Coombs types II through IV, as well as conditions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and the hypersensitivity syndrome (HSS)/ Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)—the future use of the culprit medication is unequivocally contraindicated. In these instances, beyond the cessation of the offending agent, a comprehensive approach involving patient education and the dissemination of critical information to the broader clinical team is essential. This approach is particularly salient in scenarios that necessitate the avoidance of cross-reactive agents, such as the exclusion of all aromatic anticonvulsants in patients diagnosed with HSS/DRESS.

Given the extensive spectrum of drug-induced hypersensitivity reactions affecting diverse organ systems, the remainder of this article is dedicated to the clinical evaluation and management of the most prevalent immune-mediated adverse drug reactions. The discussion encompasses a range of reactions—including the complete array of Gell and Coombs classifications (types I–IV), morbilliform eruptions, erythema multiforme, Stevens-Johnson syndrome, TEN, anaphylactoid reactions, and HSS/DRESS—thereby providing a comprehensive framework for both clinical practice and future research initiatives (Table 1).[64]

**Table 6: Identification and future management of the most common drug reactions.[64]**

| Reaction type | Clinical characteristics | Laboratory testing | Future use of medication |
|---|---|---|---|
| Gell and Coombs Type 1 | Urticaria, angioedema, wheezing, hypotension, nausea, vomiting, abdominal pain, diarrhea | Skin testing, radioallergosorbent testing | Desensitization |
| Gell and Coombs Type 2 | Hemolytic anemia, granulocytopenia, thrombocytopenia | Complete blood count | Contraindicated |
| Gell and Coombs Type 3 | Fever, urticaria, arthralgias, lymphadenopathy 2– 21 days after therapy initiated | Complement levels | Contraindicated |
| Gell and Coombs Type 4 | Skin erythema, skin blistering | Patch testing | Likely contraindicated |
| Morbilliform | Maculopapular rash becoming confluent | Possibly patch testing, intradermal skin testing (delayed reaction) | Use with caution |
| Erythema multiforme | Distinctive target lesions | None | Contraindicated |
| Stevens-Johnson/TEN | Target lesions, mucous membrane involvement, skin desquamation | None | Contraindicated |
| Anaphylactoid | Urticaria, wheezing, angioedema, hypotension | None | Pretreatment with prednisone and Benadryl for radiocontrast sensitivity |
| HSS/DRESS | Exfoliative dermatitis, fever, lymphadenopathy | Complete blood count, liver enzymes, creatinine, urinalysis | Contraindicated |

**Management:** When a hypersensitivity reaction ensues, the immediate and unequivocal cessation of the inciting agent is universally recognized as the most judicious initial intervention. In the absence of a definitive, causally targeted therapeutic modality, management is predominantly supportive, as detailed in Table 7.

Historically, drug-induced exanthems have been managed with systemic glucocorticoids, notwithstanding the ongoing debate regarding their clinical efficacy. Moreover, severe mucocutaneous syndromes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have demonstrated a suboptimal and inconsistent response to both glucocorticoids and other anti-inflammatory agents. Emerging evidence suggests that cyclosporine A may confer a reduction in mortality within this patient population; however, further validation through controlled studies is warranted. Additionally, the administration of high-dose intravenous immunoglobulins (IVIG) has been adopted in the therapeutic armamentarium for conditions including DRESS, SJS, and TEN. The purported mechanism underlying IVIG efficacy is hypothesized to involve the neutralization of apoptosis pathways via antibodies directed against key regulatory molecules, namely the Fas receptor (first apoptosis signal receptor) and its ligand, FasL.[65]

**The avoidance of hypersensitivity reactions:** Given the estimated mean cost of €2700 per adverse event in Germany.[66] the prevention of such occurrences transcends mere ethical considerations and emerges as a critical economic imperative. A significant proportion of these adverse events are, in fact, preventable (see Table 7).[64] Accordingly, when a patient self-reports a history of "allergy," this should instigate a thorough allergological re-evaluation—unless unequivocal documentation, such as an allergy passport, is already available. In many instances, the diagnostic confirmation or exclusion of the suspected hypersensitivity reaction necessitates the employment of multiple, complementary testing modalities to enhance diagnostic accuracy. Moreover, in scenarios where re-exposure to the implicated agent is either clinically necessary or unavoidable, patients who have previously exhibited immediate-type hypersensitivity responses may be considered for a carefully monitored desensitization protocol, thereby mitigating the risk of subsequent adverse immunologic events.

**Table 7: The classification, frequencies, mechanisms, and manifestations of undesired events, with examples and treatment options (frequencies in relation to the overall number of undesired events).[64]**

| Group | Type | Frequency (Reference) | Mechanism | Example | Treatment options aside from discontinuation of the offending substance |
|---|---|---|---|---|---|
| Medication error | | 20% | Medical appropriateness index too high, e.g., double prescriptio | Prescription of the same drug with generic name and trade name | – regular checking (computer-assisted if possible) of medications and of the patient‘s adherence to treatment |
| ADR | pharmacological (type A) | 72% | PK: pharmacogenetic variants or PK-DI | Irinotecan in carriers of the UGT1A1 variant | – regular checking (computer-assisted if possible) of DI<br>– therapeutic drug monitoring (TDM) |
| | | | PD: multidimensional effects | Cutaneous reaction to EGFR antagonists such as cetuximab | – immune modulation with doxycycline |
| | hypersensitivity (type B) | 6% | Not allergic (pseudoallergy) | Red man syndrome in response to vancomycin | – H1 blockers (e.g., dimenhydrinate 62 mg i. v.)<br>– H2 blockers (e.g., ranitidine 150 mg i. v.) – glucocorticoids (e.g., prednisolone 500 mg i. v.)<br>– volume/norepinephrine as indicated<br>– epinephrine (e.g., 0.5 mg i. m.) as indicated<br>– ventilation/coniotomy as indicated |
| | | 0.4% | Type I (IgE) | Anaphylaxis in response to penicillins | |
| | | rare | Type II (IgG/IgM) | Hemolytic anemia or thrombocytopenia in response to penicillins | – substitution of blood components |
| | | rare | Type III (IgG/IgM) | Nephritis in response to penicillins | – glucocorticoids or other anti-inflammatory substances/ immune modulators<br>– volume |

| | | | | | |
|---|---|---|---|---|---|
| | | 1.6% | Type IV | DIA | – reverse isolation (protection of the patient from microorganisms)<br>– prophylactic antibiotic and antimycotic coverage (e.g., ampicillin + sulbactam 4 g/d + 0.5 g/d, ciprofloxacin 750 mg/d, fluconazole 200 mg/d)<br>– growth factors such as filgrastim |
| | | | | DILI | – H1 blockers for pruritus |
| | | | | DRESS (type IVb) | – antipyretic drugs for fever<br>– H1 blockers for pruritus<br>– glucocorticoids, plasmapheresis and/or high-dose intravenous immunoglobulins |
| | | | | SJS/TEN (type IVc) | – reverse isolation as indicated<br>– local treatment as an artifical cutaneous barrier, possibly with the addition of glucocorticoids and antimicrobial drugs<br>– systemic glucocorticoids, cyclosporine, intravenous immunoglobulins<br>– antibiotics if there is any evidence of infection<br>– wound treatment analogous to that of burns (no early debridement!)<br>– electrolyte and volume substitution<br>– analgesia |
| | | | | AGEP (type IVd), MPR | – H1 blockers for pruritus<br>– in the early phase, glucocorticoids |

**ADR:** Adverse drug reactions, AGEP: acute generalized exanthematous pustulosis, DI: drug interactions, DIA: drug-induced agranulocytosis, DILI: drug-induced liver injury, DIRI: drug-induced renal injury, DRESS: drug reaction with eosinophilia and systemic symptoms, EGFR: epidermal growth factor receptor, IgG: immunglobulin G, IgM: immunglobulin M, i.m.: intramuscular; i.v.: intravenous, MPR: makulopapular rash, PD: pharmacodynamics, PK: pharmakokinetics, SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis, UGT: UDP-glucuronyltransferase.

## CONCLUSION

We've covered ADR identification, administration, and reporting here. We have discussed the ways in which contemporary technology is altering the predictive, preventive, detection, and management of ADRs, as well as the ongoing efforts to enhance these procedures through technological advancements. With the combination of phenotypic data and pharmacogenetics, prescribers can now generate patient-specific recommendations, increasing the likelihood of individualized therapy. A favorable benefit-to-harm ratio can be attained during the course of a pharmaceutical product's lifecycle with the use of such regulatory science at the national and international levels. ADR risk avoidance or mitigation continues to be a barrier in our daily clinical practice, thus for individual clinicians, getting the greatest results from medicines remains a top priority

## ACKNOWLEDGEMENT

We are grateful to the P.G. Institute of Medical Science for providing the necessary resources and facility.

### Author's Contribution

Mir Irfan Soyel, Malay Besra, Mousumi Das, Deepayan Kar, Manonayan Singha, Design this study, conducted the data analysis and prepares manuscript.
Biplab Kumar Chakra have done Proof reading.
Nilanjan Adhikari, have supply resource compilations.
All authors read and approved the final manuscript.

### Funding

This work was supported by the P.G. Institute of Medical Science.

### Data availability

The data that support the findings of this study are available from the corresponding author, Mir Irfan Soyel, upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**REFERENCE**


1. Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug safety, Oct. 2005; 28: 851-70.
2. Mammì M, Citraro R, Torcasio G, Cusato G, Palleria C, Paola ED. Pharmacovigilance in pharmaceutical companies: An overview. Journal of Pharmacology and Pharmacotherapeutics, Dec. 2013; 4(1): S33-7.
3. Coleman JJ, Pontefract SK. Adverse drug reactions. Clinical Medicine, Oct. 1, 2016; 16(5): 481-5.
4. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. British journal of clinical pharmacology, Apr. 2008; 65(4): 573-9.
5. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. American family physician, Nov. 1, 2003; 68(9): 1781-91.
6. Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA, Dykewicz MS. Disease management of drug hypersensitivity: A practice parameter: Preface. Annals of Allergy, Asthma and Immunology, 1999; 83(6 III): viii-700.
7. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. Jama, Dec. 10, 1997; 278(22): 1895-906.
8. Anderson JA, Adkinson NF. Allergic reactions to drugs and biologic agents. Jama, Nov. 27, 1987; 258(20): 2891-9.
9. Rawlins MD. Pathogenesis of adverse drug reactions. Text book of adverse drug reactions, 1977.
10. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. Bmj, Nov. 20, 2003; 327(7425): 1222-5.
11. Ditto AM. Drug allergy. In: Grammer LC, Greenberger PA, eds. Patterson's Allergic diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 295.
12. Jick H. Adverse drug reactions: the magnitude of the problem. Journal of Allergy and Clinical Immunology, Oct. 1, 1984; 74(4): 555-7.
13. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Jama, Apr. 15, 1998; 279(15): 1200-5.
14. Einarson TR. Drug-related hospital admissions. Annals of Pharmacotherapy, Jul. 1993; 27(7-8): 832-40.
15. Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy, 1998; 28(4): 61-2.
16. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. J Acquir Immune Defic Syndr, 1992; 5: 1237-57.
17. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol, 2001; 137: 301-4.
18. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann Intern Med., 1991; 115: 270-6.
19. Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. J Rheumatol, 1992; 19: 265-9.
20. Adkinson NF Jr. Risk factors for drug allergy. J Allergy Clin Immunol, 1984; 74: 567-72.
21. Beard K. Adverse reactions as a cause of hospital admission in the aged. Drugs & aging, Jul. 1992; 2(4): 356-67.
22. Prince BS, Goetz CM, Rihn TL, Olsky M. Drug-related emergency department visits and hospital admissions. American Journal of Hospital Pharmacy, Jul. 1, 1992; 49(7): 1696-700.
23. Cooper JW. Adverse drug reaction-related hospitalizations of nursing facility patients: a 4-year study. Southern medical journal, May 1, 1999; 92(5): 485-90.
24. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA, 1998; 279: 1200–5.
25. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med., 1991; 324: 377–84.
26. Harb G, Alldredge B, Coleman R, Jacobson M. Pharmacoepidemiology of adverse drug reactions in hospitalized patients with human immunodeficiency virus disease. J Acquir Immune Defic Syndr, 1993; 6: 919–26.
27. Jick H. Adverse drug reactions: The magnitude of the problem. J Allergy Clin Immunol, 1984; 74: 555–7.
28. Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA, 1997; 277: 307–1.
29. Johnson JA, Bootman JL. Drug-related morbidity and mortality: A cost-of-illness model. Arch Intern Med., 1995; 155: 1949–56.
30. Hertl M, Merk HF. Lymphocyte activation in cutaneous drug reactions. Journal of investigative dermatology, Jul. 1, 1995; 105(1): S95-8.
31. Yawalkar, Egli, Hari, Nievergelt, Braathen, Pichler. Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. Clinical & Experimental Allergy, Jun. 2000; 30(6): 847-55.
32. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. American family physician, Nov. 1, 2003; 68(9): 1781-91.

33. Volcheck GW. Clinical evaluation and management of drug hypersensitivity. Immunology and Allergy Clinics, Aug. 1, 2004; 24(3): 357-71.
34. Hameed Manahi RA. Laboratory Tests for the Early Detection of Adverse Drug Reaction. Saudi J Med Pharm Sci., 2023; 9(12): 835-8.
35. Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. Annals of Pharmacotherapy, Jan. 2002; 36(1): 130-47.
36. deShazo RD, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. Journal of Allergy and Clinical Immunology, Jun. 1, 1979; 63(6): 387-94.
37. Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. Journal of allergy and clinical immunology, Sep. 1, 1990; 86(3): 325-32.
38. Patterson r. Drug allergy and protocols for management of drug allergies, 1994; 15: 252. Inallergy proceedings, Jan. 1, 1995; 16(1): 53-53. 95 pitman st, providence, ri 02906: ocean side publications inc.
39. Hamilton RG, Adkinson Jr NF. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. Journal of allergy and clinical immunology, Nov. 1, 1996; 98(5): 872-83.
40. Sogn DD, Evans R, Shepherd GM, Casale TB, Condemi J, Greenberger PA, Kohler PF, Saxon A, Summers RJ, VanArsdel PP, Massicot JG. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Archives of internal medicine, May 1, 1992; 152(5): 1025-32.
41. Gruchalla RS, Sullivan TJ. In vivo and in vitro diagnosis of drug allergy. Immunology and allergy clinics of North America, Aug. 1, 1991; 11(3): 595-610.
42. Schwartz LB. Tryptase, a mediator of human mast cells. Journal of allergy and clinical immunology, Oct. 1, 1990; 86(4): 594-8.
43. Shepherd GM. Allergy to β-lactam antibiotics. Immunology and allergy clinics of North America, Aug. 1, 1991; 11(3): 611-33.
44. Annè S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology, Feb. 1, 1995; 74(2): 167-70.
45. Adams LE, Hess EV. Drug-related lupus: incidence, mechanisms and clinical implications. Drug Safety, Nov. 1991; 6(6): 431-49.
46. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients: I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. Journal of allergy and clinical immunology, Mar. 1, 1985; 75(3): 348-55.
47. Valdés-Garicano M, Mejía-Abril G, Campodónico D, Parra-Garcés R, Abad-Santos F. Utility of a Laboratory Alert System for Detecting Adverse Drug Reactions in Hospitalised Patients: Hyponatremia and Rhabdomyolysis. Frontiers in Pharmacology, Jul. 6, 2022; 13: 937045.
48. Stephens MD. The diagnosis of adverse medical events associated with drug treatment. InThe detection of new adverse drug reactions, 1988; 73-114. Palgrave, London.
49. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The lancet, Oct. 7, 2000; 356(9237): 1255-9.
50. Meyboom RH, Royer RJ. Causality classification at pharmacovigilance centres in the European Community. Pharmacoepidemiology & Drug Safety, Mar. 1, 1992; 1(2): 87-97.
51. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. American family physician, Nov. 1, 2003; 68(9): 1781-91.
52. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). InSeminars in cutaneous medicine and surgery, Dec. 1, 1996; 15(4): 250-257.
53. Craven NM. Management of toxic epidermal necrolysis. Hospital Medicine, Nov. 2000; 61(11): 778-81.
54. Saxon A, Adelman DC, Patel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. Journal of allergy and clinical immunology, Aug. 1, 1988; 82(2): 213-7.
55. Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson Jr NF. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. Journal of Infectious Diseases, Jan. 1, 1984; 149(1): 16-22.
56. Adkinson Jr NF. Immunogenicity and cross-allergenicity of aztreonam. The American journal of medicine, Mar. 23, 1990; 88(3): S12-5.
57. Shepherd GM. Allergy to β-lactam antibiotics. Immunology and allergy clinics of North America, Aug. 1, 1991; 11(3): 611-33.
58. Lin RY. A perspective on penicillin allergy. Archives of Internal Medicine, May 1, 1992; 152(5): 930-7.
59. Pumphrey RS, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. The Lancet, Apr. 3, 1999; 353(9159): 1157-8.
60. Eker N, Kutluk G, Cetinkaya F. Evaluation of Cross-Reactivity Between Penicillins and Cephalosporins in Children with a History of Cephalosporin Allergy. The Medical Bulletin of Sisli Etfal Hospital, Jun. 28, 2024; 58(2): 155.
61. Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA, Dykewicz MS. Disease management of drug

hypersensitivity: A practice parameter: Preface. Annals of Allergy, Asthma and Immunology, 1999; 83(6 III): viii-700.
62. Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. Journal of allergy and clinical immunology, Sep. 1, 1990; 86(3): 325-32.
63. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. Journal of allergy and clinical immunology, Apr. 1, 1991; 87(4): 867-72.
64. Volcheck GW. Clinical evaluation and management of drug hypersensitivity. Immunology and Allergy Clinics, Aug. 1, 2004; 24(3): 357-71.
65. Böhm R, Proksch E, Schwarz T, Cascorbi I. Drug hypersensitivity: diagnosis, genetics, and prevention. Deutsches Ärzteblatt International, Jul. 2018; 115(29-30): 501.
66. Athanasiou MC, Dettling M, Cascorbi I, Mosyagin I, Salisbury BA, Pierz KA, Zou W, Whalen H, Malhotra AK, Lencz T, Gerson SL. Candidate gene analysis identifies a polymorphism in HLA-DQB1 associated with clozapine-induced agranulocytosis. The Journal of clinical psychiatry, Sep. 21, 2010; 71(4): 2240.