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Literature Review

Drug Hypersensitivity in Daily Practice

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ABSTRACT

Adverse drug reactions can affect up to 25% of outpatients and 10–20% of hospitalized patients. They are an important public health issue due to the potential of fatal outcomes. They are increasingly common in daily practice, but ascertaining whether the adverse reaction is a true allergic reaction to the drug is not easy. Drug hypersensitivity encompasses a spectrum of immunologically and non-immunologically-mediated reactions with varying mechanisms and clinical presentations. Factors associated with an increased risk of developing a drug hypersensitivity include patient-related factors, treatment regimen-related factors, and drug-related factors. Diagnosis of drug hypersensitivity relies on a careful history and physical examination and, in some instances, in vivo and in vitro testing and drug provocation tests. The most effective strategy for the management of drug allergy is avoidance and discontinuation of the offending drug(s). Alternative medications with unrelated chemical structures should be given. Additional therapy is largely supportive which includes nutritional support, fluid replacement, and symptomatic which may include topical corticosteroids, oral antihistamines and, in severe cases, systemic corticosteroids. This article will discuss the classification of adverse reactions to drugs, professional steps that can be taken by a physician in prescribing drugs, minimizing the risk of adverse drug reactions, approach to diagnosis, and managing drug hypersensitivity cases in daily practice.

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ABSTRAK

Reaksi efek samping obat dapat mengenai sekitar 25% pasien rawat jalan dan 10-20% pasien rawat inap. Reaksi efek samping obat adalah masalah kesehatan masyarakat yang penting karena berpotensi fatal. Hal tersebut semakin umum dijumpai dalam praktek sehari-hari, tetapi memastikan apakah reaksi efek samping tersebut adalah reaksi alergi yang sebenarnya terhadap obat itu tidaklah mudah. Hipersensitivitas obat mencakup spektrum reaksi yang dimediasi secara imunologis dan non imunologis dengan berbagai mekanisme dan presentasi klinis. Faktor-faktor yang terkait dengan peningkatan risiko terjadinya hipersensitivitas obat meliputi faktor terkait pasien, faktor terkait regimen pengobatan, dan faktor terkait obat. Diagnosis hipersensitivitas obat bergantung pada anamnesis dan pemeriksaan fisik yang cermat dan, dalam beberapa kasus, tes in vivo dan in vitro dan tes provokasi obat. Strategi yang paling efektif untuk pengelolaan alergi obat adalah penghindaran dan penghentian obat-obatan tersebut. Obat-obatan alternatif dengan struktur kimia yang tidak terkait harus diberikan. Terapi terapi suportif yang mencakup dukungan nutrisi, penggantian cairan, dan gejala yang mungkin termasuk kortikosteroid topikal, antihistamin oral dan, dalam kasus yang parah, kortikosteroid sistemik dapat diberikan. Artikel ini akan membahas klasifikasi reaksi efek samping terhadap obat, langkah profesional yang dapat diambil oleh dokter dalam meresepkan obat, meminimalkan risiko reaksi efek samping obat, pendekatan untuk diagnosis, dan manajemen kasus hipersensitivitas obat dalam praktik sehari-hari.

Kata kunci: Reaksi obat, hipersensitivitas obat, alergi obat

INTRODUCTION

Nowadays, changes in the patterns of people's behavior in society have led to an increase in the incidence and prevalence of cardiovascular metabolic diseases (Misra & Khurana, 2009). Increasing life expectancy has also contributed to the increased incidence of degenerative diseases. In line with these changes, more and more classes of drugs are available on the market and being used by the community. Facing patients who suffer from multi pathologic diseases, doctors often use several different types of drugs at the same time in a patient, a condition coined as polypharmacy. Increased use of drugs contributes to the increased cases of unwanted reactions due to drugs and medicaments (Rodrigues & de Oliveira, 2016). All of those reactions are called adverse drug reactions. Adverse drug reaction is reported to be of 16.5% to 25% in an ambulatory care setting (Taché et al., 2011), while in hospitalized patients the figures ranged from 14.7% up to 30% (Classen et al., 2005; Davies et al., 2009).

Drug reactions are increasingly common, but ascertaining whether the adverse reaction is a true allergic reaction to the drug is not easy. Several factors may complicate the determination of the type of reaction, among others: variability of clinical symptoms, the complex interactions between the host and drugs are not fully understood, and the limited laboratory tests available to support the diagnosis of drug allergy. As a result, the diagnosis of drug allergy is often only based on clinical findings. On the other hand, the general public, with the help of a group of law-conscious members of the community, becomes increasingly aware of their rights and demand the attending physician(s) who prescribe the drug(s) to be responsible and even asking for financial compensation. The position of the physician who originally only wanted to help or reduce the patient's suffering had turned to become the accused and cornered (Rothschild et al., 2002).

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This paper will discuss the classification of adverse reactions to drugs, professional steps that can be taken by a physician in prescribing drugs, minimizing the risk of adverse drug reactions, approach to diagnosing adverse reactions (especially those based on allergic reactions), and managing drug hypersensitivity cases.

DEFINITION AND CLASSIFICATION OF ADVERSE DRUG REACTION

The terms 'drug allergy', 'drug hypersensitivity', and 'drug reactions' are often used interchangeably. For the patients and the general public, drug allergy means all adverse reactions arising from drugs, no matter what the mechanism. But medically these terms actually refer to several different things. The term 'drug reaction' refers more to all adverse reactions to drugs in general; the term 'drug hypersensitivity' refers to a reaction based on immunological response to a drug; while the term 'drug allergy' is only limited to reactions mediated by IgE. The definition of adverse drug reaction (ADR) as proposed by Edward is: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards & Aronson, 2000).

Recently, adverse drug reactions are categorized into several groups according to their reaction profiles: Type A (Augmentation of normal drug effects), type B (Bizarre effects), type C (Chronic effects), type D (Delayed effects), type E (End of drug use), and type F (Failure of therapy) (Edwards & Aronson, 2000; Schatz & Weber, 2015), but for the ease of description for general practitioners, in this article we will only focus on type A and type B adverse drug reactions (Figure 1). Type A reactions are pharmacological effects that are predictable and dose-dependent. Most ADRs (about 80%) are type A reactions, which include side effects; toxic effects; secondary effects; and drug-drug interactions. Type B reactions which comprise about 5-15% of ADRs, are hypersensitivity reactions that are unpredictable and not dose-dependent. They include hypersensitivity reactions that involve an immune mechanism (IgE- or T cell-mediated, or immune complex or cytotoxic reaction), classified as immune (or allergic) hypersensitivity reactions; or other hypersensitivity reactions without an immune mechanism or in which an immunological process is not proven, classified as non-immune (or non-allergic) hypersensitivity reactions (Thien, 2006). Another source of literature mentions that non-immune mediated drug hypersensitivity including idiosyncratic reaction, drug intolerance, and pseudoallergy (Riedl & Casillas, 2003).

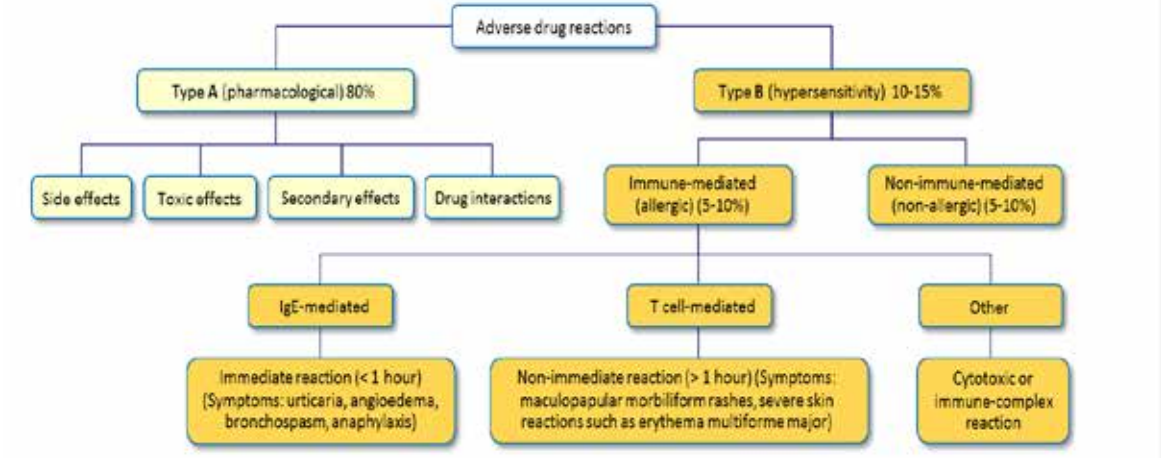

Figure 1. Classification of adverse drug reactions

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Pharmacological side effects

Side effects of a drug is an undesirable effect, but cannot be avoided because it is a pharmacological effect of the drug in normal doses. For example, first-generation antihistamine drugs cause side effects of sedation. Anticholinergic drugs cause side effects of dry mouth, blurred vision, and urine retention. Other drugs have side effects that are not immediately recognizable, including teratogenic or carcinogenic effects.

Secondary pharmacological effects

The secondary effects of a drug are not directly related to the main pharmacological effects of a drug but can be considered as a natural consequence of using the drug. For example, antibiotics can induce a Jarisch-Herxheimer reaction in patients with syphilis or leptospirosis treated with penicillin. Giving certain antibiotics (such as Ampicillin, Clindamycin, or Cephalosporin) can cause excessive growth of Clostridium difficile germs due to the loss of competition between germs. The toxin produced by these germs can cause the emergence of pseudomembranous colitis.

Drug toxic effects

The toxic effect of a drug is related to the local or systemic concentration of the drug in the body and will arise in everyone if the toxic threshold value is passed. Drug toxicity increases in liver disease. Kidney failure can cause drug accumulation and trigger toxic effects.

Drug interactions

Drug interaction is a modification of the effect of a certain drug by other drugs that have been given previously or concomitantly to a patient. The higher the number of the drugs given to a patient, the greater the likelihood of drug interactions. Interactions often involve drugs metabolized by the cytochrome P-450 enzyme system in the liver.

Drug overdose

Each drug has its own margin of safety. The safe dose of a drug is determined based on previous research and is called a therapeutic window. The provision of drugs with excessive doses will obviously increase the toxic effect. Metabolic disorders or abnormal excretion of drugs may also cause overdose even though the drug is given in a standard therapeutic dose.

Drug intolerance

Drug Intolerance is the emergence of a typical pharmacological effect of a drug in certain patients, even if given in small doses. Patients generally have genetic propensity which results in a low therapeutic threshold value for a drug. Certain patients are very sensitive to the effects of antihistamine sedation, while other patients are very sensitive to the coughing effect of an angiotensin-converting enzyme (ACE) inhibitor.

Idiosyncratic reactions

Idiosyncrasy is an unexpected response to a drug. The effects that appear are qualitatively abnormal and different from the pharmacological effects of the drug. This reaction only occurs in patients who have certain enzyme deficiencies. Examples include the emergence of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency which given Primaquine, Sulfonamide, Nitrofuran, or vitamin K analogs; Chloramphenicol can cause aplastic anemia; ACE inhibitors can cause idiosyncratic reactions in the form of angioedema.

Pseudoallergy / Anaphylactoid reactions

Pseudoallergy or anaphylactoid reaction is an immediate type of systemic reaction caused by the release of mast cell mediators through a mechanism that does not involve IgE cross-linking. The clinical manifestations very closely resemble IgE-mediated reactions, but this reaction does not require prior exposure

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to suspected drugs or medicaments. Contrast material for radiological examination is the most common cause; Opiates, Vancomycin, Polymyxin B, and NSAIDs can cause urticaria or angioedema; while Aspirin or NSAIDs may induce asthma or even anaphylactoid reaction.

Based on the types of immunologic drug reactions, Gell and Coombs classify the dominant immunological mechanisms underlying the hypersensitivity reaction to the drug (Table 1). However, there are several adverse reactions to the drug that cannot be classified into this classification because the immunological mechanism is not yet known, for example, erythroderma, maculopapular rash, exfoliative dermatitis, fixed drug eruption, lupus-like syndrome, and specific drug hypersensitivity syndrome (Riedl & Casillas, 2003; Warrington et al., 2018).

Based on the modifications proposed by Werner J Pichler, type IV reactions of the original Gell and Coombs classification are further divided into 4 sub-categories: type IVa which involves activation and deposition of monocytes; type IVb which involves activation of eosinophils; type IVc which involves activation of CD4 or CD8 T lymphocytes; and type IVd which involves neutrophil activation (Figure 2) (Pichler, 2013). A certain drug may cause several types of reactions. Penicillin, for example, may cause anaphylaxis and urticaria (type I reaction), hemolytic anemia (type II reaction), serum-sickness reaction (type III reaction), and contact dermatitis due to topical Penicillin administration (type IV reaction). Immune response to a drug antigen is very diverse and the reaction that occurs is complex. It is very likely that there is more than one mechanism involved in a reaction to a particular drug (Riedl & Casillas, 2003; Warrington et al., 2018).

Table 1. Classification of drug hypersensitivity reactions according to Gell & Coombs

Immune reaction	Mechanism	Clinical manifestation	Time of occurrence
Type I (IgE-mediated)	The drug binds to specific IgE on the mast cell surface, triggering the release of histamine and other inflammatory mediators	Urticaria, angioedema, bronchial smooth muscle spasm, pruritus, nausea and diarrhea, anaphylaxis	A few minutes to several hours (but mostly under 1 hour) after drug exposure,
Type II (cytotoxic)	Specific of IgG or IgM which attacks cells that bind to the drug / hapten	Hemolytic anemia, neutropenia, thrombocytopenia	Variable
Type III (immune complex)	Deposition of drug-antibody complex in the tissue, triggering activation of the complement system and inflammation	Serum sickness, drug fever, rash, arthralgia, lymphadenopathy, glomerulonephritis, vasculitis	1 to 3 weeks after exposure to the drug
Type IV (*delayed, cell-mediated*)	Presentation of drug molecules via MHC to T lymphocytes, triggering the release of cytokines and inflammatory mediators	Contact sensitivity, skin rashes, organ-tissue damage	2 to >20 days after exposure to the drug

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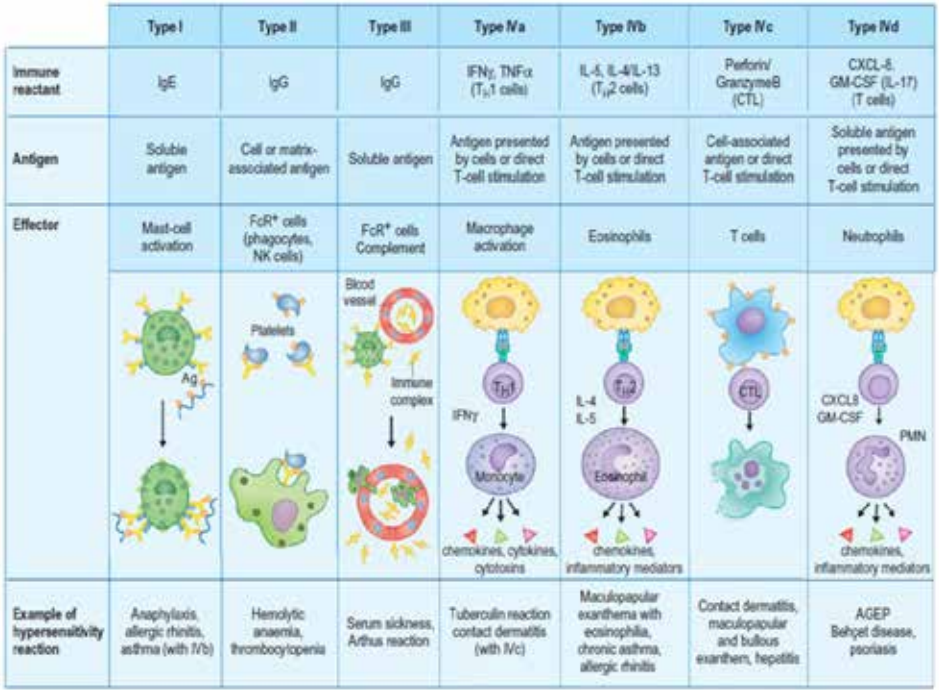

Figure 2. Revised Gell and Coombs classification of drug reactions

RISK FACTORS FOR DRUG HYPER-SENSITIVITY

Epidemiological data indicate that there are certain risk factors for adverse drug reactions in general and certain risk factors for drug hypersensitivity reactions (Table 2). Risk factors can be classified as drug-related factors, factors related to treatment regimens, and factors associated with the host (Riedl & Casillas, 2003; Demoly & Hillaire-Buys, 2004).

Drug-related risk factors

Drug-related adverse reactions to drugs include the chemical properties of the drug and its molecular weight. Drugs with complex chemical structures, such as heterologous antisera (Diphtheria serum from horses), enzymes (Streptokinase, Chymopapain), and hormones (Insulin) tend to be more immunogenic (more capable to generate immune responses). Similarly, drugs that have a large molecular weight (> 1000 Dalton). Most drugs have a lower molecular weight but can react as a hapten after binding to a carrier protein so that it can induce an immune response (Riedl & Casillas, 2003; Demoly & Hillaire-Buys, 2004; Pichler, 2013). Some types of drugs are intrinsically reactive molecules (eg. Penicillin), other types of drugs require enzymatic or non-enzymatic conversion to become reactive intermediate metabolites (eg. Sulfamethoxazole). According to the 'danger concept', antigens from a drug can generate an immune response if they accompanied by the presence of a 'danger signal' which is a costimulation signal and cytokine that increases and determines the type of elicited immune response (Gomes & Kuyucu, 2017). Whereas according to the 'pharmacologic interaction concept', a drug can cause an immune response if it is able to bind non-covalently to specific receptors on T cells (Pichler, 2013).

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Tabel 2. Risk factors for adverse drug reactions

Risk factors for adverse drug reaction in general
• Female gender • Critical illness • Renal insufficiency • Liver disease • Polypharmacy • HIV infection • Other viral infections (eg. Herpes virus) • Alcoholism • Systemic lupus erythematosus (SLE)
Risk factors for drug hypersensitivity reaction (immunologic mechanism)
• Female gender • HIV infection • Other viral infections • Previous history of hypersensitivity to similar or the same group of drugs • Uncontrolled asthma • Person with beta blocker medication • Certain gen polymorphisme • Systemic lupus erythematosus (SLE)

Treatment regiment-related risk factors

The dose of the drug and the route of administration determine the frequency of occurrence of adverse reactions to the drug. Drugs that are given in high doses or given frequently will increase the occurrence of sensitization. Drugs that are given continuously cause fewer reactions than drugs given periodically or intermittently. Drugs that are given through the oral route are less likely to cause adverse reactions than drugs that are given topically or intramuscularly because antigen presentation by immune cells in the skin is more efficient or there is an adjuvant effect of drug preparation. Parenteral administration (intravenous) is the most immunogenic route because a high concentration of drug antigens in circulation can be achieved quickly (Demoly & Hillaire-Buys, 2004; Pichler, 2013; Warrington et al., 2018).

Host-related risk factors

The gender and the age of the patient determine the risk of adverse reactions to the drug. Almost all epidemiological studies show that women experience drug adverse reactions more often than men (65-70% compared to 30-35%) (Demoly & Hillaire-Buys, 2004; Pichler, 2013). Women generally have a lower body mass, a reduced hepatic drug clearance, have a different activity of cytochrome P450 (CYP) enzymes (40% increase in CYP3A4, varied decrease in CYP2D6, CYP2C19 and CYP1A2), and metabolize drugs at different rates than men. Other factors should also be considered as there are also gender differences in drug metabolites conjugation, absorption, protein binding, and renal excretion, but how these differences result in an increased risk of DHR is still not clear (Rademaker, 2001; Soldin et al., 2011). Infant and children are less likely to experience adverse reactions than adults probably due to the immaturity of the

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immunologic apparatus. The history of atopy does not increase the risk of adverse reactions to the drug but may exacerbate clinical manifestations if the adverse reaction occurs, so that atopic patients may suffer from more severe reactions (Demoly & Hillaire-Buys, 2004; Pichler, 2013).

The tendency to experience adverse drug reactions is also genetically determined. Certain MHC haplotype pairs are known to correlate with hypersensitivity reactions to certain drugs, for example, haplotype A2, DRw52 with Penicillin drugs; haplotype DQ7, DR11 with Pyrazolone drugs; B57 haplotype, DR7DQ3 with Abacavir; or DR3 haplotype, DQ2 with Carbamazepine. Some of the enzymes involved in drug metabolisms (biotransformation and detoxification of drugs) such as the CYP-450 enzyme, N-acetyl-transferase, and glutathione-S-transferase are also genetically regulated. The gene polymorphism that encodes the enzyme leukotriene C4 synthase determines the risk of aspirin-induced asthma. Variation in the allele -308TNFalpha is associated with the occurrence of hypersensitivity to Carbamazepine (Demoly & Hillaire-Buys, 2004; Pichler, 2013; Alfirevic et al., 2011; Fan et al., 2017).

CLINICAL MANIFESTATIONS

The skin is the organ most frequently and prominently affected by drug-induced hypersensitivity reactions. A generalized maculopapular rash is the most common cutaneous manifestation, which is characterized by raised, pink or erythematous lesions that appear within days to 3 weeks after drug exposure. These lesions typically originate in the truncal area and then spread to the limbs. The maculopapular rash can be mistaken with viral exanthema. Urticaria with/without angioedema is also common and may result from both IgE-mediated and non-IgE-mediated mechanisms. The most severe forms of cutaneous adverse drug reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS usually begins with a maculopapular rash that often progresses to bullae, accompanied by mucous membrane ulcerations, conjunctivitis, fever, sore throat, and fatigue. TEN is similar to SJS, but it involves a larger percentage of the epidermis to detach from the layers below, leading to extensive skin exfoliation and a scalded skin appearance. Nikolsky's sign is positive (Edwards & Aronson, 2000; Riedl & Casillas, 2003; Thien, 2006; Warrington et al., 2018).

Although skin reactions are the most common physical manifestation of drug-induced allergic reactions, many other organ systems may be involved, such as the renal, hepatic and hematologic systems. Multi-organ reactions may also occur and include anaphylaxis, serum sickness, drug fever, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, serum sickness, drug-induced lupus erythematosus (DILE) and hypersensitivity vasculitis that worth a special mention and description (Riedl & Casillas, 2003; Demoly & Hillaire-Buys, 2004; Pichler, 2013; Gomes & Kuyucu, 2017).

Serum sickness and serum sickness-like reaction

Serum sickness arises from the administration of heterologous antisera. While reactions that resemble serum sickness can be caused by non-protein drugs, specifically β-lactam antibiotics. Anti-snake venom serum, black widow spider anti-serum, anti-diphtheria serum, and rabies are examples of heterologous antisera. Some drugs that can cause serum sickness-like reactions to include Ciprofloxacin, Metronidazole, Streptomycin, Sulfonamide, Allopurinol,

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Carbamazepine, Methimazole, Thiouracil, and Propanolol. Symptoms of fever, lethargy, skin eruption, joint pain, and lymphadenopathy appear 6-21 days after drug exposure. The latent period explains the time needed for the formation of antibodies. The onset of clinical symptoms coincides with the production of immune complexes. In patients who have been previously sensitized the reaction can arise 2-4 days after exposure to the drug (Thien 2006; Warrington et al., 2018).

Drug fever

Drug fever is a drug hypersensitivity reaction that is suspected to have an immunological mechanism. Patients usually experience high fever accompanied by shivering. The fever immediately falls within 48-72 hours after the drug is stopped, but re-appears within a few hours if the drug is re-administered. The presence of skin rash supports the suspicion of a drug reaction. Laboratory tests show leukocytosis (shift to the left), and increased erythrocyte sedimentation rate (resembling an infection). Abnormalities of liver function tests are also often found. Autopsy in patients who die from drug fever showed arteritis and focal necrosis in some organs such as the heart, lung and liver muscles. Aromatic anticonvulsants such as Carbamazepine and Phenytoin, Phenobarbital and Primidone are important causes of drug fever (Patel & Gallagher, 2010).

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

This is a potentially life-threatening condition characterized by a widespread rash, fever, lymphadenopathy (swollen/enlarged lymph nodes) and hepatic dysfunction. It usually begins 2–6 weeks after drug exposure. The prodromal stage including fever, lymphadenopathy, influenza-like symptoms, burning pain, or pruritus, can precede the skin eruption by up to 2 weeks. DRESS syndrome-specific organ involvement results from specific eosinophil or lymphocyte tissue infiltration. Liver involvement is observed in more than 80% of patients: mainly hepatic cytolysis, sometimes cholestasis, or both, while fulminant hepatic failure is rare. The involvement of the kidney generally characterized by interstitial nephritis. The lungs are affected in up to 15% of cases, manifested by dyspnoea, cough, eosinophilic pneumonitis, but respiratory failure is rare (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006; Warrington et al., 2018).

Drug-induced Lupus Erythematosus (DILE)

This condition can be caused by several types of drugs including Hydralazine, Procainamide, Isoniazid, Chlorpromazine, Methyldopa, Quinidine, Beta-blockers, anti-thyroid drugs, anticonvulsants, Penicillamine, and Sulfasalazine. Fever, malaise, joint and muscle pain, pleuritis, and weight loss can occur immediately after exposure, but generally, only appear a few months after drug exposure. Pleuropericardial manifestations are more common, whereas classic features such as malar rash, discoid lesions, oral cavity ulceration, Raynaud's phenomenon, alopecia, kidney abnormalities, and central nervous system are rare. The clinical symptoms usually disappear within a few days after cessation of the drug, but sometimes it persists or recurs for several months before finally disappearing (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006; Warrington et al., 2018).

Hypersensitivity vasculitis

This reaction is characterized by inflammation and necrosis of the blood vessels. Organ or tissue that has a lot of blood vessel flow is the main predilection site. This disorder can occur in all age groups, but most often in the fifth decade. Some drugs that are often related include diuretics, Penicillin, Sulphonamides, Thiouracil, Iodide, and Allopurinol. The

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most common clinical features are palpable purpura on the skin of the lower extremity and sacral area. Fever, malaise, muscle pain, and anorexia accompany skin lesions. Sometimes glomerular inflammation, joint pain, and arthritis, abdominal pain, gastrointestinal bleeding, pulmonary infiltrate, and peripheral neuropathy are also encountered. Symptoms gradually disappear after the drug is stopped (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006; Solensky et al., 2010; Warrington et al., 2018).

DIAGNOSTIC APPROACH

The diagnosis of adverse reactions to drugs is indeed difficult. Some reasons for this include: (1) adverse reactions to the drug are often not recorded, both by the patient and the attending physician; (2) the clinical manifestations vary greatly, resembling the clinical picture of other diseases; (3) more than one drug consumed simultaneously by the patient; (4) many other non-drug-related factors are involved; (5) if the previous reaction has been very long time ago in the past, the sensitivity to the drug at this moment may be reduced or even lost. Supporting examinations in the form of in vivo and in vitro tests are not yet standardized, while provocation tests must go through complicated procedures and may endanger patients (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006; Solensky et al., 2010).

A diagnosis of drug hypersensitivity depends on identifying symptoms and physical findings that are compatible with an immune drug reaction. If there is a high probability of a causal relationship and reaction is not pharmacologically mediated, the following steps are to distinguish between immune-mediated (allergic) from non-immune-mediated hypersensitivity. If the patient is taking several medicines, the problem is to distinguish which, if any, is causative. This problem is complex as some of the patient's complaints might be caused by one or more of the drugs or due to other diseases (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006).

Clinical history

A thorough and detailed history is a fundamental component in evaluating patients with suspected adverse reactions to drugs. A history of the nature of reaction experienced by the patient helps the clinicians to determine what diagnostic tests to choose, whether is it safe to reintroduce the suspected drug. For outpatients, it may be difficult to obtain a record of the drug's reaction on the medical record. For hospitalized patients, the medical records should be easily obtained, and if possible, the original medical record that describes the drug reaction should be reviewed. Some important things that need to be asked are as follows (Edwards & Aronson, 2000; Riedl & Casillas, 2004; Thien, 2006; Solensky et al., 2010; Khan & Solensky, 2010) :

- ***Did the observed reaction occur on first exposure to the drug?***

Immune-mediated drug hypersensitivity requires previous exposure and sensitization period before it develops. So, they do not usually occur on the first exposure to the drug. The patient usually tolerant of the first course of a drug and then become sensitized, and experience a reaction when taking the first dose of the next course later on. Cross-reacting drugs may elicit a reaction when there is the previous sensitization to another drug with common antigenic determinants. The non-immune-mediated reaction usually occurs on the first exposure to the drug.

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- ***What was the nature of the reaction?***

The clinicians must explore which systems (eg. cutaneous, respiratory, or gastrointestinal) were involved in the reaction and asked the patient to describe the characteristics. If a cutaneous eruption occurred, what kind was it (eg. urticarial, morbilliform, bullous, or exfoliative). Urticaria, angioedema, bronchospasm, and anaphylaxis signify IgE-mediated reaction and mast cell activation. Maculopapular rashes such as morbilliform, fixed drug eruptions and other non-specific rashes are mediated by T cells. Detailed history and documentation (sometimes the patient took a photo of the rash) can often help to elucidate the nature of the reaction and guide appropriate testing and management.

- ***What was the time course of the reaction?***

Immediate reactions occur from several minutes to 1 hour after drug exposure. It suggests an IgE-mediated reaction. Non-immediate reactions occur more than 1 hour after drug exposure, suggesting a T cell-mediated reaction. It is important to know whether the reaction occurs during the course of medication, or the onset of symptoms appear after the course of medication was completed. Patients often accuse a particular drug as a culprit drug, but if the reaction emerges several days after the course of the medication had completed, it might be that the reaction is not caused by that particular drug.

- ***What is the name of the suspected drug?***

Although obvious, it is not uncommon that patients are unable to recall the name of the suspected drug. Many reasons for this which include passage of time and the fact that the names of many drugs sound similar and sometimes difficult to be memorized. A patient who was given multiple drugs also might confuse which drug caused which reaction. Be sure to get information about all of the medications the patient is taking concomitantly, including over-the-counter medications, herbal products or traditional remedies, or drugs of abuse, and long-term treatment that the patient had and may forget. Antibiotics are usually blamed for the reactions, but drugs such as opiates and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently co-administered and might be responsible instead.

- ***How long ago did the reaction occur?***

The time elapsed is important because some allergies, such as an allergy to Penicillin, may wane over time.

- ***Why was the drug prescribed?***

The indication of the medication is important because symptoms of the underlying disease might be misattributed to the medication. Viral exanthema may be misattributed to the drug taken at that moment; a truncal rash during streptococcal pharyngitis can be misattributed to Penicillin therapy for that illness.

- ***Had the patient taken the same or a cross-reacting drug in the past?***

Most allergic or immune-mediated reactions require a period of sensitization, typically during a previous course of medication that was tolerated by the patient.

- ***Has the patient received the same or similar drug since the reaction?***

Some patients with a history of Penicillin allergy report that later they tolerated a course of Amoxicillin-clavulanate, not realizing that the latter is a Penicillin-class compound.

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- ***Has the patient experienced similar symptoms of reaction without the drug?***

The most common situation is chronic recurrent idiopathic urticaria which can be confused for drug hypersensitivity or food allergy.

- ***Does the patient have an underlying condition that may increase the tendency for drug hypersensitivity?***

As has been described in the host-related risk factors section, patient with infectious mononucleosis has an increased tendency to have reactions to Ampicillin; HIV-infected patients tend to have higher propensity to experience hypersensitivity reactions to Trimethoprim-sulfamethoxazole.

Physical examination

The physical examination may provide further information to support the diagnosis of drug hypersensitivity. The initial step is an evaluation for signs and symptoms of an immediate generalized reaction. It is one of the warning signs of severe life-threatening adverse drug reaction. Other warning signs of impending cardiovascular collapse include urticaria, laryngeal or upper airway edema, wheezing, and hypotension. Several signs suggestive of serious adverse drug reactions include the presence of fever, mucous membrane lesions, lymphadenopathy, joint tenderness, and swelling, or an abnormal pulmonary examination. A detailed skin examination is very important, as the skin is the most commonly affected organ by adverse drug reactions. It is also very important to distinguish between various types of skin lesions, because this may provide substantial clues to the possible immune-mediated mechanism of the drug reaction. Lymph nodes, the lungs, liver, spleen, kidneys, and joints must also be examined and evaluated (Riedl & Casillas, 2004; Thien, 2006; Solensky et al., 2010; Khan & Solensky, 2010; Warrington et al., 2018). All of the data from the patient's history and physical findings should be recorded in a uniform format. The Drug Allergy Interest Group of EAACI (EAACI-DAIG) and its core group, the European Network of Drug Allergy (ENDA), have developed a questionnaire that has been translated into various languages and can be downloaded from the literature (Demoly et al., 1999).

Laboratory evaluation

The diagnosis of drug hypersensitivity is usually based on clinical judgment, as definitive, confirmatory drug-specific testing is often difficult in daily practice. The goal of laboratory testing is to confirm the presence of biochemical or immunologic markers that explain the activation of a particular immunopathologic pathway in a particular drug hypersensitivity reaction. The selection of the laboratory or diagnostic tests should consider whether the reaction is immediate or non-immediate, as summarized in Table 3. All information gained from the patient's history and physical examination is very important for diagnostic planning in order to assess the likelihood of which drug has caused a reaction. Diagnostic allergy testing should be performed 4-6 weeks after the resolution of symptoms and within 6 months period after the last reaction. Investigations should be performed by an experienced allergist or at a specialized allergy center (Romano et al., 2011; Brockow et al., 2015).

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Tabel 3. Diagnostic tests of drug hypersensitivity reactions

Type of reaction		Type of tests
Immediate	*In vivo*	Skin prick test
		Intradermal test
		Drug provocation test
	In vitro	Drug-specific IgE assays
		Flow cytometric Basophil Activation Test (BAT)
Non-immediate	*In vivo*	Delayed-reading intradermal tests
		Patch test
		Drug provocation test
	In vitro	Lymphocyte Transformation Test (LTT)
		Flow cytometric Lymphocyte Activation Test (LAT)
		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells

Skin tests are an essential part of drug hypersensitivity reaction investigation. However, currently, there is no uniform standard for skin testing with drugs. Test substances in high concentrations can cause reactions even in healthy subjects. Optimal test concentrations for many drugs are not known, but The European Network on Drug Allergy (ENDA) methods and non-irritant test concentrations can be considered and reviewed elsewhere (Brockow et al., 2013; Brockow et al., 2015).

Drug provocation

Drug provocation test remains the gold standard for the identification of an eliciting drug when allergiologic test results are negative, not available, or not validated. This procedure not only allows drug hypersensitivity to be confirmed but also allows it to be ruled out in a large percentage of reactions reported by the patients in which the in vivo and in vitro test results are negative. Thus, drug provocation tests can be used to exclude a hypersensitivity in patients with non-suggestive histories or to provide safe alternatives in allergic patients and thereby prove tolerance. This tool can be used both in allergic or non-allergic drug hypersensitivity reactions, but contraindicated in non-controllable and/or severe life-threatening drug hypersensitivities reactions, such as SJS, TEN, DRESS, vasculitis, and AGEP (Romano et al., 2011).

With the above step by step approach, clinicians might come to the diagnosis of drug hypersensitivity reactions. We construct a simple algorithm to assess patients with drug hypersensitivity reactions as seen in Figure 3 below (Soegiarto, 2015).

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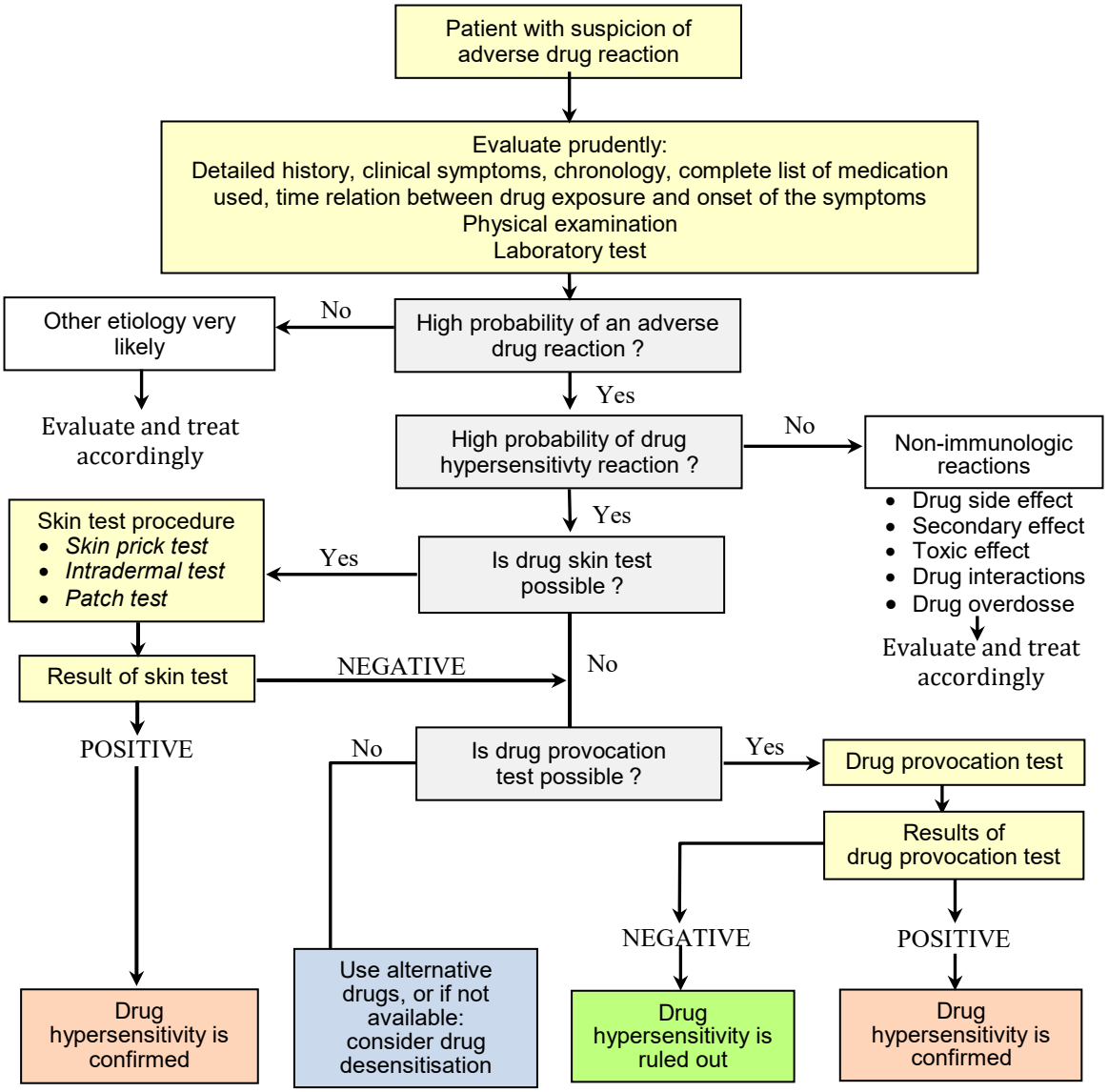

Figure 3. Algorithm for the evaluation of drug reactions

Drug causality assessment

It is very important to determine which drug causing the hypersensitivity reaction experienced by the patient. In most instances, it is difficult to do so, particularly if the patient taking multiple drugs concomitantly. Identifying the culprit drug or drugs can be lifesaving or helpful in preventing further damage caused by the drug to the body. Drug reintroduction may cause more severe reactions, but on the other hand, overdiagnosis and unnecessary drug avoidance in non-hypersensitive patients are also improper. Currently, there are many criteria or algorithms available to establish a causal relationship in cases of adverse drug reaction, such as the WHO–UMC Probability Scale, Liverpool causality assessment tool, the French causality assessment method, or the Naranjo Probability Scale (Table 4) (Naranjo et al., 1981).

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Tabel 4. Naranjo adverse drug reaction probability scale

Questions		Yes	No	Don't know
1.	Are there previous conclusive reports on this reaction?	+1	0	0
2.	Did the adverse event appear after the suspect drug was administered?	+2	-1	0
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4.	Did the adverse reaction reappear when drug was re-administered?	+2	-1	0
5.	Are there alternate causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6.	Did the reaction reappear when a placebo was given?	-1	+1	0
7.	Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10.	Was the adverse event confirmed by objective evidence?	+1	0	0

Scoring for Naranjo algorithm: >9 = definite; 5–8 = probable; 1–4 = possible; 0 = doubtful.

Overall assessment

The final assessment should be made after considering all of the evidence, including the history of the clinical reaction, results of in vivo, in vitro, and drug provocations tests. In some cases, however, drug hypersensitivity cannot be ruled out reliably although we had applied all available test methods. The overall assessment should be discussed with the patient and/or family member and documented in the patient's medical record. An allergy passport should then be issued, which provides information about the drug(s) which conclusively or highly suspected to cause the reaction and the type of the reaction. If it is possible, the information about possible cross-reactivities could also be included (Brockow et al., 2015).

MANAGEMENT

General principles

The first action that must be taken is to stop the offending medication(s). For some allergic drug reactions, withdrawal of the drug may be all that is required for treatment. In general, the symptoms of an allergic reaction will resolve within a few days or weeks. This proves presumptively that the reaction that arises is indeed caused by one or more drugs obtained by the patient. Drugs with not very strong indications (not so needed by patients) should also be stopped. Medications that are essential for the patients should be substituted with alternative substances with different or unrelated chemical structures to avoid cross-reaction whenever possible. The clinical consequences of medication cessation or substitution should be closely monitored. If

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the drug is essential for the patient and an alternative medication cannot be found, while the risk of not treating the underlying disease is significant, the other method that can be taken is to do the drug desensitization (Riedl & Casillas, 2004; Solensky et al., 2010).

Symptomatic treatment

Additional therapy for drug hypersensitivity reactions is largely supportive and symptomatic. Symptomatic treatment is intended to eliminate the clinical manifestations of drug allergy until the reaction subsides. Mild reactions usually do not require treatment. Oral antihistamines and topical steroids may improve dermatologic symptoms. Treatment for more severe reactions depends on the degree of skin eruption and systemic symptoms that arise. Anaphylaxis, anaphylactoid (pseudo-allergy) reactions, requires prompt emergency treatment with appropriate protocols.

Oral antihistamine is usually sufficient for patients with serum sickness or serum sickness-like reactions. More severe reactions require corticosteroids (Prednisone) with an initial dose of 40-60 mg per day and gradually reduced in 7-10 days. Sometimes plasmapheresis is needed to remove the remaining immune complexes.

Stevens-Johnson syndrome and toxic epidermal necrolysis require additional intensive therapy. Severe cases must be hospitalized; nutritional support and infusion should be given to replace lost fluids and correction of electrolyte disturbance; open skin lesions are closed with a sterile dressing and given a physiological saline solution or Burowi's solution and treated like a burn injury; oral cavity lesions are treated with mouthwash. Although some centers are reluctant to give, systemic corticosteroids may speed recovery in a severe case of drug hypersensitivity reactions. Pulse dose intravenous dexamethasone or methylprednisolone at disease onset and tapered gradually when clinical improvement occurs (Kardaun & Jonkman, 2007; Araki et al., 2009). Cyclosporine and intravenous immunoglobulin are also suggested in the literature (French et al., 2006). Underlying diseases and secondary infections must also be addressed. Sepsis is the main cause of death for patients. If health care facilities and patient care in your clinic or hospital are inadequate, immediate referral of severe drug hypersensitivity patients to hospitals with better equipment and treatment capabilities is advisable.

PREVENTION

To prevent the occurrence of drug allergic reactions physician should avoid polypharmacy. Medication should only be given if there are clear indications. Before prescribing medication to a patient it is necessary to ask carefully whether the patient has a history of allergies to certain drugs. The drugs that are currently being consumed by the patients should also be put into consideration because interactions between several drugs can increase the occurrence of hypersensitivity or adverse reactions. If the patient is allergic to a certain drug, cross-reactive drugs should be avoided. Special attention needs to be given to certain drugs which are known to be frequently associated with hypersensitivity reactions (Table 5) (Riedl & Casillas, 2004; Solensky et al., 2010).

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Tabel 5. Drugs that frequently associated with hypersensitivity reactions

Drug name or category	
Aspirin and other NSAIDs	Cisplatin and other platinum-based drugs
β-lactam antibiotics	Radiocontrast media (iodinated)
Sulfonamide	Antihypertensive (ACE inhibitor, Methyldopa)
Anti-tuberculosis drugs (Isoniazid, Rifampicin)	Antiarrhythmic (Procainamide, Quinidine)
Nitrofurantoin	Drugs containing heavy metals (Gold salt)
Anticonvulsant (Carbamazepine, Phenytoin)	Hormones (insulin, other hormones)
Anesthetics (neuromuscular blocking agents)	Enzym (Streptokinase, Chymopapain)
Allopurinol	Vaccines (egg-based)

CONCLUSION

Drug hypersensitivity encompasses a spectrum of immunologically and non-immunologically-mediated reactions with varying mechanisms and clinical presentations. Diagnosis of drug hypersensitivity relies on a careful history and physical examination and, in some instances, in vivo and in vitro testing and drug provocation tests. The most effective strategy for the management of drug allergy is avoidance and discontinuation of the offending drug(s). Physicians should also aware and understand the properties, mechanisms of action, indications, contraindications, and possible side-effects of a drug that will be prescribed to the patient. It's good for physicians to give prior warning of possible side-effects that can happen to the patients. This is necessary to avoid miscommunication with the patients that often lead to prosecution in the court or compensation claims that are burdensome to the physicians.

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