

Understanding Adverse Drug Reactions and Drug Allergies: Principles, Diagnosis and Treatment Aspects

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Received: October 5, 2007; Accepted: November 9, 2007; Revised: November 15, 2007

Abstract: Adverse Drug Reactions (ADRs) and drug allergies- as a subset of ADRs- make a significant public health concern, complicating 5 to 15% of therapeutic drug courses. They may result in diminished quality of life, increased physician visits, health care costs, hospitalizations, and even death. The incidence of serious ADRs in hospitalized patients was estimated to be 6.7% and for fatal ADRs to be 0.32%, so recognizing and taking action on ADRs is an important aspect of medication management. Allergic reactions to drugs refer to those ADRs that involve immune mechanisms which account up to 15% of ADRs and can be identified as being a type I through IV immune reaction that the most common immunologic mechanism is IgE-mediated- type I reaction. Clinical manifestations of allergic reactions range from pruritus and rash to serious reactions such as systemic anaphylaxis and cardiovascular emergencies and they are responsible for 2-3% of hospitalized patients.

Health professionals should be aware of the ADRs presenting clinical features and the risk factors and should be able to differentiate between allergic and non-allergic adverse drug reactions. This will lead to increased opportunities to review drug selection and prescribing practices affecting patients' outcome.

This article will review the definition and estimated incidence, the features, classification and types of ADRs and drug allergies and related patents. It will highlight the role of detecting, reporting, and assessing suspected ADRs and drug allergies in the most clinically relevant drugs group. Priorities in the evaluation and management of the conditions of patients who have experienced allergic and non-allergic drug reactions also will be discussed.

Keywords: Adverse drug reaction (ADR), drug allergy, drug hypersensitivity, adverse drug reaction reporting systems, drug monitoring, diagnostic tests, skin tests, basophil activation test (BAT), beta-lactams, sulfonamides, non-steroidal anti-inflammatory agents, local anesthesia, immunologic desensitization.

INTRODUCTION

Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. Adverse reactions are a cost of modern medical therapy [1]. They are the most common cause of iatrogenic disease [2]; one that confronts primary care physician on daily basis [3]. Although the mandate of the Food and Drug Administration (FDA) is to ensure that drugs are safe and effective, these terms are relative. The anticipated benefit from any therapeutic decision must be balanced by the potential risks [1].

The terminology of adverse drug reactions (ADRs), adverse drug events (ADEs), adverse events (AEs) and medication errors may cause confusion, as several definitions exist and overlap [4]. The term "adverse effect" is preferable to other terms such as "toxic effect" or "side effect". A toxic effect is one that occurs as an exaggeration of the desired therapeutic effect, and which is not common at normal doses. A toxic effect is always dose-related. On the other hand, an unwanted side effect occurs via some other mechanisms and may be dose-related or not. A WHO definition says ambiguously that a side effect "is related to the pharmacological properties of the drug"; [5] however, this definition was

formulated to include side effects that, although not the main aim of therapy, may be beneficial rather than harmful. Such an effect may or may not occur through the pharmacological action for which the drug is being used. The term "adverse effect" encompasses all unwanted effects; it makes no assumptions about mechanism, evokes no ambiguity, and avoids the risk of misclassification [6].

Generally, the first step in setting up a system to monitor adverse drug reaction (ADR) is to establish a working definition to determine what parameters will be recorded and reported. There are two most commonly cited definitions. The World Health Organization (WHO) defines ADR as "any response to drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [7]. Karch & Lasagna defines it as "any response to a drug which is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose [8].

ADRs include any reactions that result from the use of a certain medication. Allergic reactions (ARs) or hypersensitivity reactions to drugs are adverse reactions that do not result from known toxicological properties of the drug, but dependent on one or more immunological mechanisms from the drug or its metabolites [9, 10]. Although drug reactions are in most cases not declared, it is possible to

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conclude that Drug Hypersensitivity Reactions (DHRs) represent up to one third of ADRs [11].

Patients and physicians commonly refer to all ADRs as being “allergic” but the term drug allergy or drug hypersensitivities should be applied only to those reactions that are known to be mediated by an immunologic mechanism. ADRs that clinically resemble an allergy, but an immunological process is not proven, should be classified as non-immune drug hypersensitivities [12]. They comprise allergic and so-called pseudoallergic reactions. The latter is characterized by having the features of an allergic reaction without detectable reactions of the adaptive immune system. DHRs can become manifest in a great variety of clinical symptoms and diseases, some of which are quite severe and even fatal. The most common allergic reactions occur in the skin and are observed. Any drug is assumed to be able to elicit hypersensitivity reactions. Antibiotics and antiepileptics are the drugs most frequently causing those [11].

We aim to review the epidemiology, risk factors, classification, diagnosis, management and other important aspects of ADRs and drug allergies in this article. Each followed part will explain different aspects of ADRs and will be continued by drug allergy points.

EPIDEMIOLOGY

ADRs are a major health care problem and contribute significantly to a patient's morbidity and mortality [13]. The percentage of patients experiencing an ADR during hospitalization has been reported to range from 1.5% to 35% [14]. Also, the reported frequencies of hospital admissions attributed to ADRs vary from 0.1% to 16.8% [15]. In a meta-analysis by Lazarou *et al.* of 39 prospective USA studies from 1966 to 1996 showed that 15.1% of hospitalized patients suffered an ADR [16]. In another meta-analysis study, has been reported ADR incidence among hospitalized children from 4.37% to 16.78%, with an estimated mean of 9.53%. This study also reported incidence of pediatric hospital admissions related to ADRs from 0.59% to 4.1%, with a weighted mean of 2.09% [17].

However, the magnitude of the problem of ADRs to marketed drugs is difficult to quantify. In the United States it has been estimated that 3% to 5% of all hospitalizations can be attributed to ADRs, resulting in 300,000 hospitalizations annually [1]. In a large study of more than 10,000 emergency room patients, 293 (2.9%) had drug-related illness, with 71 (24%) requiring hospitalization [18]. In a study of more than 20,000 hospital records, nearly 4% of patients received disabling injuries caused by medical treatment [2]. Drug complications were the most common cause for injuries, accounting for 19% of the total. A recent retrospective case-control study from Singapore by Kidon and See [19] using the hospital inpatient electronic medical record found 222 (2.6%) patients reporting a previous ADR among 8437 hospitalized children. Almost 70% of them involved the use of antibiotics (especially β -lactam antibiotics (45%) and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) (18.5%) were the second most implicated group. Of all reactions; 98% of the reactions were cutaneous [19]. Also in Iranian studies on ADR, anti-infectives were reported as the most common cause [20-23].

In a wide study on hospitalized patients in Iran, ADR frequency was 35.9% in adult infectious ward [23], 65% among patients with co-infection HIV and TB [24], 12.1% in department of pediatric infectious diseases (20), 3.7% in department of pediatric surgery [25]. The ADR rate was 11.6% in department of allergy [26].

Over the past few years, several published reports have addressed the problem of drug-related morbidity in various practice settings. The incidence of serious ADRs in hospitalized patients was estimated to be 6.7% and for fatal ADRs to be 0.32%. By considering serious and non-serious ADRs, the percentage more than doubled, to 15.1% of hospitalized patients [16].

Trying to determine the prevalence of ADRs in the outpatients setting is difficult due to the different methods used to collect data. Reported rates range from 2.6-50.6%, with the lower rates coming from physician data collection and the higher rates coming from surveys [27]. The elderly are at special risk because of number of medications they consume and the complicated clinical states they often present. An estimated 75% of elderly patients are receiving prescription drugs, while 82% use nonprescription drugs regularly; polypharmacy is a particular problem in this age group [28].

There are few true epidemiological data on DHRs. The overall incidence of ADRs is difficult to estimate accurately due to the wide spectrum of disorders that encompass lack of standardized test for many of these drugs and limited use of drug provocation test, so most of the available epidemiological studies to date refer to ADRs in general terms than drug allergy. The label of ‘drug allergy’ needs to be applied with caution after the occurrence of an ADR. Patients should understand that unnecessarily labeling themselves as ‘allergic’ when it is not the case can result in the use of less appropriate medication in the future, as the ‘allergic’ label will restrict the prescriber’s choice. Even when the patient has suffered a true allergic reaction subsequent investigations may show that this was not caused by the drug thought to be responsible at the time [29].

Data of drug allergy in children are more limited. A 12-year survey at a French pediatric center reported 68 cases of children who suffered anaphylaxis during general anesthesia [30]. Through allergologic diagnostic procedures (skin tests and specific IgE assays), an IgE-mediated mechanism was demonstrated in 51 patients: 31 (60.8%) reacted to NMBAs (Neuromuscular Blocking Agents), 14 (27%) to latex, 7 (14%) to colloids, 5 (9%) to opiates and 6 (12%) to hypnotics. The estimated frequency of IgE-mediated anaphylactic reactions was 1 in 2,100 operations. Epidemiological data on drug hypersensitivity in non-hospitalized subjects and the general population are even scarcer and are limited mainly to studies on antibiotic use.

Taken in the broadest context, most studies have found that the incidence of self reported drug allergy is in the order of between 25 and 39 % [31-33].

It is generally accepted that penicillins are the most common cause of allergic drug reactions and anaphylaxis, with an incidence across the population as a whole of between 1 and 10% [34] and the frequency of life-threa-

tening anaphylaxis estimated at 0.01% to 0.05% [35]. Another large scale prospective study showed that of 1790 people with claimed penicillin allergy, only 57 (3.2% patients and 0.01% injections) demonstrated true penicillin allergy of which 4 were anaphylactic in nature (0.2% patients) [36].

Although drug reactions are in most cases not declared, it is possible to conclude that DHRs represent up to one third of ADRs, which may affect 7% of the general population and up to 20% of hospitalized patients besides being responsible for as much as 8% of hospital admissions [12].

RISK FACTORS

Several characteristics have been suggested as risk factors for the development of ADRs which have been discussed in below:

Age: Relationship between age and ADR is controversial. Some studies suggested the very young and very old populations are more susceptible to having adverse reactions. This reflects age related differences in body composition and in activity of metabolic pathways. The ability of the liver to metabolize certain drugs may be reduced in the very young and the very old. A drug's volume of distribution varies greatly between infant, child, adult, and elderly patients [37]. Several risk factors, including differences in drug metabolism, which can produce increased susceptibility to certain drugs, may account for the severity and specificity of ADRs in children. In this case, some organs may be very sensitive to side effects. Moreover, developmental process in children may be susceptible to certain agents, and a number of drugs used in pediatric diseases can produce specific ADRs [38]. Age younger than 12 months was mentioned as a risk factor for ADR in children [39]. On the other hand, some studies showed adult are affected with ADRs more than Children [40, 41].

Some authors showed advanced age has been suggested as risk factor for the development of ADRs [42, 43]. The elderly are more likely to be taking multiple drugs, therefore increasing the possibility of drug interactions. Moreover, renal function tends to decrease with increasing age [37].

Gender: Women are perceived to be more prone to ADRs than men due to the hormonal environment [42, 44]. Such a propensity may result from gender-associated differences in drug exposure, in the number of drugs prescribed, in drug pharmacology, as well as from possible differences in the way the adverse reaction is perceived. The overall death rate does not greatly differ between genders, but the incidence pattern does, partly due to the protective effects of estrogens against heart disease before menopause. Generally ADRs were more frequently reported in females for some classes of drugs (such as genito-urinary, sex hormone, antineoplastic, antiparasitic and respiratory drugs) [44].

Multiple drug therapy: Incidence of ADRs from drug interactions increase sharply with the number of drugs taken so polypharmacy was considered as a risk factor [20, 39, 45, 46].

Current disease: Drug handling may be altered in patients with impaired metabolism such as renal or liver

impairment [41, 42]. Allergy and atopy although are not important major risk factors [47] but had been also mentioned as predisposing factors for ADRs [41, 48]. Diseases in which multiple drug treatment occurs are associated with greater likelihood of ADRs too [49].

Ethnic and Genetic Differences: Ethnic genetic or dietary differences may increase the risk of ADRs. Examples include interaction of diet with glucose 6-phosphate dehydrogenase deficiency; and iron overload resulting from giving iron supplements to sickle cell patients when they do not need it. Genetic polymorphisms are a source of variation of drug response in the human body [49].

Pharmaceutical Factors: Examples include differences in pharmacokinetics (processes by which a drug is absorbed, distributed, metabolized, and eliminated by the body) resulting from different delivery systems; and reactions to drug excipients (e.g. binding agents, solvents, anti-bacterial agents) [49].

Incomplete Medicines Reconciliation: Medicines reconciliation refers to the checking of medicines patients are taking, either prescribed, over the counter, folk medicines, or from other sources. High risk settings where medicines reconciliation is a problem include acute presentation to the Accident and Emergency Department and new interactions within parts of the NHS (National Health Service) which may currently hold separate clinic records e.g. HIV services [50].

Other: Several characteristics, such as a history of previous of ADR, duration of hospital stay [44], concomitant infection such as HIV [51], dose and route of drug administration and duration of therapy [37], personality and habits such as alcoholic, smoking, diet, drug addict, nicotine, compliance have been suggested as other intrinsic risk factors for the development of ADRs [42].

On the other hand some risk factors related to drugs, treatment regimens, and patients (such as age, gender, concurrent illnesses, and previous reactions to related drugs), have been identified as having an important role in drug hypersensitivities [11] which were explained in Table 1 [11, 40-62].

Pharmacogenomics will likely play an increasing role in identifying individuals at risk for certain drug reactions. Genetic risk factors for drug hypersensitivity reactions were shown in Table 2 [63-73].

IMPORTANCE OF REPORTING

The need for reporting ADRs should be considered as important as treatment and overall care of the patient [74]. An ongoing ADR-monitoring and reporting program can provide benefits to the organization, pharmacists, other health care professionals, and patients. These benefits include (but are not limited to) the following:

1. Providing an indirect measure of the quality of pharmaceutical care through identification of preventable ADRs and anticipatory surveillance for high-risk drugs or patients.
2. Complementing organizational risk-management activities and efforts to minimize liability.

Table 1. Risk Factors of Drug Allergy/Hypersensitivity Reactions

Drug and treatment regimens	Patients
Type of Drug: The β -lactams are the most common cause ¹¹ Dosage (high dose ⁴⁸) Mode of administration Intermittent and repeated > uninterrupted ¹¹ Route of administration Topical and parenteral > Oral ^{11, 62} Previous exposure or reactions ⁴⁴	Gender: female > male ⁵²⁻⁵⁵ Age: Adult > Child? ⁴⁰ Atopy: Is not a major risk factor ⁴⁷ (except for NSAID ⁴⁸ & RCM ⁴¹) Genetic background (table-2) - Drug allergy in an parent lead to 15-fold increase his/her child ⁵⁶ Specific illness - Systemic Lupus Erythematosus (SLE) ⁵⁵ - Asthma (for NSAID ⁵⁷ & RCM ⁴⁷)* Concomitant infections - HIV Infection (Co-trimoxazol ⁵⁸ and antiretroviral agents ⁵⁹) - Infectious Mononucleos (IMN) ⁴¹ - Herpes ⁶⁰ - CF ⁶¹

*NSAID: Non-steroidal anti-inflammatory drug, RCM: Radiocontrast media.

Table 2. Genetic Risk Factors of Drug Hypersensitivity Reactions

Culprit Drug	HLA Association	Drug Hypersensitivity	References
Carbamazepin	HLA-B*1502, HLA-B44	SJS (Stevens–Johnson Syndrome)/TEN (Toxic Epidermal Necrolysis)	63-66
Carbamazepin	HLA-A*0301	Maculopapular Eruption (MPE)	63, 64
Carbamazepin	TNF2-DR3 DQ2 haplotype	Hypersensitivity Syndrome (HSS)	65-67
Allopurinol	HLA-B*5801	SJS/TEN/HSS	68
Sulfonamides	A2a, B12, DR7	SJS/TEN	68
Penicillamine	DR3	Penicillamin Toxicity	68
Hydralazin	DR4	SLE (Systemic Lupus Erythematosus)	68
Abacavir	HLA-B*5701, HLA-DR7	HSS/MPE	69
ASA	HLA-DRB1*1302, HLA-DRB1*0609	Urticaria/Angioedema	70
Penicillin	IL-4Ra, IL-4-TL-13-SNP Polymorphism	IgE-Mediated Allergy	71, 72
β -lactam	IL4Ra, IL13 Polymorphism	Immediate Allergic Reaction	73

- Assessing the safety of drug therapies, especially recently approved drugs.
- Measuring ADR incidence.
- Educating health care professionals and patients about drug effects and increasing their level of awareness regarding ADRs.
- Providing quality-assurance screening findings for use in drug-use evaluation programs.

- Measuring the economic impact of ADR prevention as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability [75].

Especially ADR reporting is an important when new agent with limited clinical experience entering the marketplace [74].

REPORTS' METHODS

Some guidance should be given to those health care providers monitoring patients' drug therapies as to what ADRs should be reported. All reactions that fit the clinician's working definition should be reported within the institution's ADR monitoring system [37].

The initiative of an international reporting system for ADRs came in the wake of the thalidomide tragedy in the early 1960s [76]. Although the FDA in the United States had been established some years previously, this disaster was the catalyst for the initiation of systematic collection of data on ADRs primarily through the Hospital Reporting Programme. In 1968, ten countries operating a national reporting system decided to collaborate under the auspices of the WHO and initiated the WHO Pilot Research Project for International Drug Monitoring [77]. The FDA legally mandates that pharmaceutical manufacturers report all ADRs. In instances of death, unexpected, or serious reactions, ADRs must be reported to the FDA within 15 days. In order to consolidate and streamline the ADR reporting process, the FDA initiated the Medwatch program (a voluntary reporting of ADRs which enables practitioners to use a single telephone number to report reactions) (www.fda.gov/medwatch) [74, 78].

Through membership of the WHO programme, one country can know if similar reports are being made elsewhere (The European Union also has its own scheme).

Member countries send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database. When there are several reports of adverse reactions to a particular drug this process may lead to the detection of a signal- an alert about a possible hazard communicated to members' countries. This happens only after detailed evaluation and expert review [7, 76].

Spontaneous reporting is the core data-generating system of international pharmacovigilance, relying on healthcare professionals (and in some places consumers) to identify and report any suspected ADR to their national pharmacovigilance centre or to the manufacturer. Spontaneous reports are almost always submitted voluntarily [1, 51].

In most countries, manufacturers are required to submit reports they receive from healthcare providers to the national authority. This reporting scheme, as exemplified by the yellow card system in the United Kingdom, from the cornerstone of post-marketing drug safety surveillance [51, 79]. The yellow card scheme for reporting suspected ADRs was introduced in 1964 and over 400,000 reports have now been received by the Committee on Safety of Medicines (CSM).

The four critical pieces of information that must be included on the yellow card are:

1. Suspected drug(s) - brand name of medicine(s) (or name and manufacturer for herbal medicines) and batch number if known, route of administration, dosage, dates of administration and indication.
2. Suspected reaction(s) - a description of the reaction(s) and any treatment given, together with the dates the reaction started and stopped, and whether the reaction

was considered to be serious. There are also tick boxes to give information on the outcome, and why the reaction was considered to be serious.

3. Patient details - the essential details are patient's sex and age, and their weight (if known). Information that would identify the patient should not be used (for reasons of confidentiality) although their initials and a local identification number are helpful in case it is necessary to refer back to the patient. It is not necessary to obtain the patient's consent to report an ADR, although this should be discussed with the patient.
4. Reporter details - the name and full professional address of the reporter, so that the report can be acknowledged and contact made for further information, if necessary. Additional information supplied may include other medicines taken, and diagnostic test results and known allergies [80].

However, there are other schemes/forms for reporting suspected ADR with the different colors throughout the world. Generally existing of an intensive system to report any suspected ADR for using health professionals, researchers, the pharmaceutical industry and prescribing physicians is advisable and crucial in all countries.

CLASSIFICATION

Some drug reactions occur in anyone, known as Augmented reactions or type A and include side effects and drug interaction. Others occur in susceptible patients, known as Bizarre reactions or type B and include intolerance, allergies or pseudo allergic reaction [81]. Type A and B were proposed in the 1970s [82] by Rawlins & Thompson and the other types were proposed subsequently when the first two proved insufficient to classify ADRs [6, 83, 84]. This classification is shown in Table 3, with examples of adverse drug reactions in each category [6, 85].

Up to one third of side effects after drug treatment are type B reactions [85], which are not related to the pharmacological activity of the drug and are non-predictable. The majority of type B reactions are immune-mediated side-effects like hypersensitivity reactions. Clinically, these immune-mediated side-effects are very heterogeneous and can be subdivided according to different pathomechanisms [85-87].

Drug reactions can be also classified into immunologic and non-immunologic etiologies. Nonimmunologic drug reactions can be predictable or unpredictable (Table 4) [3, 62].

CLASSIFICATION AND PATHOGENESIS OF DRUG ALLERGY

Drug hypersensitivity reactions are one form of type B or idiosyncratic drug reactions.

Allergic drug reactions may be classified according to one of four implicated immunological mechanism (the Gell & Coombs classification) [86-88]. While this initial Gell and Coombs classification was somewhat useful in clinical practice, it did not reflect the newly acquired knowledge of

Table 3. Classification of Adverse Drug Reactions

Type of reaction	Mechanism/Example
Type A (Augmented)	Predicted from the known pharmacology of the drug. These reactions are dose-dependent: examples are bleeding with anticoagulants
Type B (Bizarre)	Reactions are not predicted from the known pharmacology of the drug. They appear (but actually are not) relatively dose-independent, as very small doses might already elicit symptoms. They include immune-mediated side-effects like maculopapular exanthema, but also other hypersensitivity reactions, like aspirin-induced asthma
Type C (Chemical/Chronic)	Which are related to the chemical structure and its metabolism, e.g. paracetamol hepatotoxicity.
Type D (Delayed)	Which appear after many years of treatment, e.g. bladder carcinoma after treatment with cyclophosphamide
Type E (End of treatment)	Occur after drug withdrawal, e.g. seizures after stopping phenytoin
Type F (Failure)	Often caused by drug interactions, e.g. inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers

Table 4. Nonimmunologic Drug Reactions

Type	Example
Predictable	
Pharmacologic side effect	Dry mouth from antihistamines
Secondary pharmacologic side effect	Thrush while taking antibiotics
Drug toxicity	Hepatotoxicity from methotrexate
Drug-drug interactions	Seizure from theophylline while taking Erythromycin
Drug overdose	Seizure from excessive lidocaine (Xylocaine)
Unpredictable	
Pseudoallergic	Anaphylactoid reaction after radiocontrast media
Idiosyncratic	Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy
Intolerance	Tinnitus after a single, small dose of aspirin
G6PD: Glucose-6-Phosphate Dehydrogenase	

T-cell heterogeneity. This classification relies on formation of IgE antibodies, which bind to high-affinity IgE receptors on mast cells and basophilic leukocytes, on complement-fixing antibodies and on T-cell reactions, which orchestrate different forms of inflammations. Although these categories seem relatively straightforward, classifying most drug reactions into one or more of them can be quite a challenge because of our lack of mechanistic information regarding these reactions. One should recall that at the time when it was proposed, many critical aspects, such as the pivotal role of T-lymphocytes in immune responses, MHC (major histocompatibility complex) restriction or the cytokines to give only a few examples, were not recognized or even suspected. To better take into account this heterogeneity of T-cell functions, which are important to understand different forms of diseases, the classification of Gell and Coombs has recently been revised [89]. These results have led to the new subclassification of type IV reactions as IVa, IVb, IVc and IVd reactions, which correspond to T-helper 1, T-helper 2, and cytotoxic reactions [87].

Antibody-mediated hypersensitivity reactions to drugs: Although other immune mechanisms can be involved simultaneously, antibodies are the primarily effectors of many hypersensitivity reactions to drugs. This is particularly true for the prototypic Gell and Coombs type-I (IgE-mediated) and type-II and -III (IgM and IgG mediated) reactions.

Importantly, the synthesis of antibodies requires the specific recognition of the antigen by T lymphocytes so that these reactions cannot be considered as exclusively antibody-mediated.

Type I hypersensitivity (immediate type hypersensitivity): Type I hypersensitivity is thought to be responsible for many of the severe adverse reactions associated with drugs; in Type I hypersensitivity, drugs or their metabolites act as haptens, combining covalently with endogenous proteins. The resultant antigenic complex induces the formation of IgE antibodies, which become attached to high-affinity Fc-IgE receptors of mast cells in various tissues of the body.

On subsequent exposure to the antigen, very small amounts of a drug are apparently sufficient to interact and stimulate these receptor-bound IgE molecules, resulting in mast cell degranulation, and the release of various mediators (histamine, tryptase, leukotrienes, prostaglandins, TNF- α , etc.).

IgE-mediated reactions to drugs are usually thought to depend on the prior development of an immune response to a hapten/carrier. Indeed, the majority of drugs able to elicit IgE-mediated allergies are known to be haptens, or they contain foreign antigenic structures occurred during an earlier drug treatment. Haptens are chemically reactive small molecules (mostly <1000 D) that are able to undergo a stable covalent binding to a larger protein or peptide [90-94]. By itself, it is too small to elicit an immune response. Cell-bound or soluble immunoglobulins can recognize the hapten-carrier complex directly, and an immunoglobulin-based response can develop. T cells recognize a peptide fragment of the hapten-carrier complex, which is generated by

intracellular processing of the complex and presented to T cells by MHC molecules. A typical hapten is penicillin G, which tends to bind covalently to lysine groups within soluble or cell-bound proteins, thereby modifying them and eliciting B- and T-cell reactions [93, 94]. It is also possible that the hapten binds directly to the immunogenic peptide presented by the MHC molecule. In this situation, no processing is required [93, 95]. This feature of a hapten, namely, the possibility of binding to many proteins or peptides, may explain the great heterogeneity of immune reactions to it, resulting in a great variety of clinical symptoms [87]. The chemical reactivity of haptens leads to the formation of many distinct antigenic epitopes, which can elicit humoral and cellular immune responses. Examples of a B-cell-mediated immune response are anaphylaxis (IgE) and hemolytic anemia and thrombocytopenia (IgM/IgG). T cell-mediated immune responses include exanthema (maculopapular, bullous, and pustular) and hepatitis, nephritis, pancreatitis, and interstitial pneumonia. In general medical practice, Type I hypersensitivity responses are most commonly seen in patients given penicillins or cephalosporins; this immunologic mechanism is responsible for immediate anaphylactic reactions (anaphylactic shock, urticaria, angioedema, and bronchospasm).

Other drugs are prohaptens, meaning that they require metabolism to become haptens (chemically reactive). The metabolism leads to the formation of a chemically reactive compound (e.g. from sulfamethoxazole [SMX] to the chemically reactive form SMX-NO). It may lead to modification of cell bound or soluble proteins by the chemically reactive metabolite, similar to a real hapten [96].

These drugs or their metabolites can also directly activate T-lymphocyte proliferation [97] which is responsible for delayed type IV allergic reactions in the Gell and Coombs classification (e.g. maculopapular eruptions, contact dermatitis, photosensitization). IgE-mediated reactions can cause mild to very severe, even lethal diseases. In sensitized individuals, the reaction can start within seconds after contact with the parentally applied drug, and minutes after oral drug uptake. Symptoms reach from simple local itch, local wheal and flare reaction upon parenteral drug application, to acute bronchospasm and generalized urticaria and edema, preferentially periorbital, perioral or genital. More severe and complex reactions are called anaphylaxis, whereby in most cases with anaphylaxis some circulatory events with collapse and (transient) unconsciousness are observed together with a generalized redness, itch or urticaria. Anaphylactic shock occurs often within 15 min, and asphyxia due to laryngeal edema often between 15 and 60 min.

Allergic responses may also be produced by the medical use of foreign proteins (e.g. streptokinase, asparaginase, heparin, vaccines, and blood products), desensitization regimens, and latex rubber.

Pseudoallergic reactions (Non-Immune-Mediated Hypersensitivity): Hypersensitivity reactions to drugs do not necessarily involve specific recognition by the immune system, although the generic term 'allergy' is often used to describe all hypersensitivity reactions.

To avoid confusion, the term 'allergy' is recommended for use to strictly describe only those reactions that involve the immunologic memory and highly specific recognition processes. The term 'pseudo-allergy' can be used to describe those reactions that mimic allergy clinically, but in which no specific immune-mediated mechanism is actually involved [98]. 'Pseudoallergic' reactions can be elicited by many drugs, but some drugs seem to elicit them more often (Radiocontrast media (RCM), nonsteroidal anti-inflammatory drugs (NSAIDs), Neuromuscular-blocking agents (NMBAs)) Some drugs might elicit both pseudoallergic and also presumably real allergic reactions, as positive prick skin tests can be detected in very severe reactions (contrast media, neuromuscular-blocking agents). The majority of these reactions imitate the clinical features of milder immediate reactions (erythema, urticaria), but some reactions cause anaphylaxis and can be lethal. Because mediators of anaphylaxis can be released by non specific immunological mechanisms, the clinical symptoms of pseudo-allergic reactions often mimic those of allergic reactions, hence the term 'anaphylactoid' often used to characterize such reactions [99]. The best recognized mechanisms include: Non-immunological activation of the complement system (the anaphylatoxins C3a, C4a and C5a). Alterations in the synthesis and release pathways of arachidonic acid metabolites resulting in intolerance to NSAIDs, particularly aspirin [100]. For NSAID-induced pseudoallergic reactions, it seems that they tend to arise less rapidly (often 10-15 min) than true IgE-mediated allergies and they may require higher drug doses than for true IgE-mediated reactions.

Cytotoxic Mechanism (Type II): In Type II hypersensitivity, drugs typically combine with proteins in erythrocyte, granulocyte or platelet cell membranes. The resultant antigenic complex induces the synthesis of IgG (IgG1, IgG3) or IgM antibodies, which subsequently cross-react with the antigen (and complement), causing cellular lysis. In this type, the antibody can be directed to cell structures on the membrane (rarely) or immune complex activation occurs on the cell surface: The antibody-coated cells will be sequestered to the reticuloendothelial system in liver and spleen by Fc or complement receptor binding.

More rarely, intravascular destruction may occur by complement-mediated lysis.

Type II hypersensitivity reactions include:

- Haemolytic anaemia (penicillin and its derivatives, cephalosporins, levodopa, methyldopa, quinidine and some anti-inflammatory drugs. Today, cephalosporins are the main cause)
- Leucopenia or agranulocytosis (e.g. phenothiazines, carbimazole, clozapine)
- Thrombocytopenia (e.g. heparin, thiazides, quinine, quinidine, sulfonamide antibiotics and many other medications).

Drug-induced immune thrombocytopenia usually develops after 5-8 days of exposure to the sensitizing medication, or after a single exposure in a patient exposed previously to the same drug.

- Pancytopenia. Halothane hepatitis is probably a type II hypersensitivity reaction.

An oxidative metabolite of halothane (trifluoroacetyl chloride) binds covalently to hepatic cell membrane proteins. In susceptible patients, antibodies are synthesized and cross-react with the membrane protein, causing acute hepatic necrosis [96].

Immune Complex Deposition (Type III): Soluble antigens (e.g. bacterial toxins) react with circulating antibodies (IgG) to form precipitin complexes.

Immune complexes will normally be rapidly cleared; either by Fc-IgG-RI or CR1. When excess antigen is present, very high such immune complex levels, a relative deficiency of some complement components, and thus lower capacity to eliminate immune complexes or an aberrant Fc-IgG-R function. An immune complex disease develops. Thus, reduced removal of immune complexes may lead to inappropriate deposition of immune complexes and recruitment of inflammatory cells, in particular PMNs due to immune complex binding to Fc-IgG-R on PMN. In addition, anaphylatoxins C3a and C5a, generated due to local complement activation, may attract PMNs. Type III hypersensitivity reactions are an important factor in serum sickness and certain rheumatic disorders [101].

T-Cell-Mediated, Delayed Drug Hypersensitivity Reactions: delayed hypersensitivity antibody formation is not involved. Macrophage cell membranes complexed with antigens or haptens combine with helper T cells, causing lymphocyte mitosis and the local release of lymphokines (e.g. tumor necrosis factor- α ; interferon- γ). A local inflammatory reaction usually occurs within 24-48 hours, resulting in erythema, induration, blistering and exfoliation, due to the accumulation of macrophages and lymphocytes [102-105].

DRUG RECOGNITION BY T CELLS

The recognition of small molecules (such as drugs) by B cells and T cells is usually explained by the hapten concept.

Alternatively, if the drug is not chemically reactive itself, it may represent a prohaptens, which becomes reactive during metabolism [102-105]. A third, nonhapten pathway (pharmacologic interaction with immune receptors, also known as the 'p-i concept') does not require covalent association of the drug with the MHC molecule. The participation of T cells in allergic reactions to chemically inert drug structures has been shown in the last few years [106, 107]. According to this hypothesis, the structure of the drug would bind to the peptide-MHC complex on one side and to the T cell receptor on the other side. Thus, the structure of the drug would determine the binding, which albeit labile, would be enough to induce the activation of T-cells. Under physiological conditions, one can suppose that low-affinity T cell receptors prevent any damage that could occasionally result from the presentation of the drug to the cells [107-113]. A signal, known as "danger signal" is necessary for the activation of the immune system, as for instance, damage to kidney cells caused by the toxic effect of a drug metabolite, excessive stimulation of immune response during infections by viruses such as HIV and Epstein-Barr, periods of clinical activity of

autoimmune diseases, such as Sjögren's syndrome or systemic lupus erythematosus [110].

The chemically inert drug seems to bind directly to the T cell receptor (labile interaction with TCR). Full T cell stimulation requires an interaction with the MHC molecule. This type of drug stimulation is restricted to certain drugs that fit into TCRs and results in an exclusive T cell stimulation [10]. This model has been expanded by *in vitro* studies using T-cell clones' specific for such drugs as sulfamethoxazole, lidocaine, mepivacaine, celecoxib, lamotrigine, and carbamazepine [87]. The clinical symptoms elicited by drugs that are immunogenic because of their chemical (happen or pro hapten concepts) or structural features (*p-i concept*) may well differ. A hapten-like drug (for example, amoxicillin) is able to alter many different proteins, either soluble or cell-bound, and can even modify different MHC molecules and their embedded peptides directly.

These distinct antigenic determinants can stimulate T cells and B cells and elicit more or less all types of immune reactions. Indeed, penicillins are reported to cause different antibody-mediated diseases, such as anaphylaxis or hemolytic anemia, but also various T-cell-mediated reactions, such as maculopapular exanthema, drug-induced hypersensitivity syndrome, acute generalized exanthematous pustulosis, the Stevens-Johnson Syndrome (SJS), and even Toxic Epidermal Necrolysis (TEN).

Some these reactions are severe and life-threatening and often the onset of hypersensitivity syndrome occurs with a mean of 2-weeks from the onset of drug exposure [114, 115].

SUBCLASSIFICATION OF TYPE IV REACTIONS

Since different subpopulations of drug-specific T cells can be found in inflammatory skin lesions, Pichler *et al.* [87] proposed a subclassification of Gell and Coombs type IV reactions. According to them, type IVa would predominantly be determined by a Th1 pattern, similarly to what occurs in the response to tuberculin. Type IVb would comprise the Th2 pattern, with high levels of IL-5, which is responsible for eosinophilia. Type IVc would include cytotoxic CD4+ T cells that contain cytolytic factors found in maculopapular exanthema, and CD8+ T cells, which contain cytolytic factors and, when activated, express FasL, as occurs in bullous exanthema.

And finally, type IVd, which would include IL-8 producing T cells, chemotactic factor for neutrophils. In the latter case, there would be accumulation of neutrophils in the lesions and keratinocytes would present IL-8 production, without increasing the expression of MHC molecules class II.

The term delayed hypersensitivity reactions, originally coined to describe T-cell reactions to tuberculin, became an umbrella term for various T-cell-mediated immune mechanisms.

ADRS DIAGNOSIS

Adverse Drug reactions Assessment

An accurate medical history is an important first step in evaluating a patient with a possible adverse reaction.

Suspected drug need to be identified with dosages, route of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. For past reactions, a detailed description may yield clues to the nature of the ADR. The propensity for particular drug to cause the suspected reaction can be checked with information in the Physicians' Desk Reference (available in printed form and online; www.pdr.net), the Drug Eruption Reference Manual, or directly from the drug manufacture [41, 61].

If a patient is taking medicines, the differential diagnosis should include the possibility of an ADR. The first problem is to find out whether a patient is taking a medicinal product, including: over-the-counter formulations; products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse); and long-term treatments that the patient may forget (such as oral contraceptives).

The next step is to find out whether the effect could be due to a medicine. If the patient is taking several medicines, the problem is to distinguish which, if any, is causative. This problem is complex, because some of the patient's complaints might be due to other diseases or to one or more of the drugs. There are numerous schemes for assigning probability of causation to a suspected adverse drug reaction [6] which have been proposed and are used in different countries. There are two most commonly classification for the causality evaluation; WHO Probability Scale [5, 6, 20] and Naranjo nomogram [116] which were explained in the below panel and Table 5 retrospectively.

Table 5. Adverse Drug Reaction Assessment Algorithm

	<i>Adverse Drug Reaction (ADR)</i>	
	<i>Yes</i>	<i>No</i>
Appropriate temporal sequence	+2	-1
A known ADR	+1	0
Alternative explanation available	-1	+2
Objective evidence of ADR	+1	0
Appropriate serum level or laboratory value	+1	0
Dechallenge improvement	+1	0
Rechallenge relapse	+2	-1*

- If rechallenge was not done, value assigned was 0.
- Scoring: doubtful< 1; possible= 1-4; probable= 5-8; definite= 9-10.

WHO Criteria for Causality Assessment

Certain: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/unclassifiable: a report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

The time relation between the use of the drug and the occurrence of the reaction should be also assessed. Are they plausibly linked? For example:

- Does the reaction occurs or get worse as the dose of the drug reaches steady state or when the steady-state dose is increased (for dose-related reactions)?
- Does the reaction abates or disappears as the dose of the drug is reduced or the drug is withdrawn (for dose related reactions)?
- If a drug interaction is suspected, does the timing of introduction or withdrawal of the interacting drug fit?
- If there are features of an allergic reaction, has the patient previously been exposed? Lack of previous exposure does not rule out an allergic reaction, but previous exposure is consistent with such a reaction.
- If the effect is a congenital abnormality, did drug exposure occur at the appropriate gestational time?
- If the effect is a tumor, was the time lag sufficiently long for the tumor to have grown? The answer to this will depend on knowledge of tumor kinetics.

Symptoms that occur soon after a drug is taken are often easily connected with use of a drug. However, diagnosing symptoms due to chronic drug use requires a significant level of suspicion and is often complicated. Stopping a drug is sometimes necessary but is difficult if the drug is essential and does not have an acceptable substitute. When proof of the relationship between drug and symptoms is important, rechallenge should be considered, except in the case of serious allergic reactions.

Finally, rechallenge with the drug should be considered, particularly if the patient is likely to benefit directly from the

knowledge gained. It should be possible to attribute causality.

CLINICAL FINDINGS

The accepted international terminology for reporting of adverse drug reactions is WHO's Adverse Reaction Terminology (WHO-ART) [117]. This terminology contains more than 1700 unique terms and has been developed over more than 30 years to serve as a basis for rational coding of adverse reaction terms. The structure of WHO-ART is hierarchical, beginning with the body system/organ level (within which terms) and including preferred terms (to provide precise identification of drug problems) [118]. WHO-ART classification included a large spectrum of clinical reactions, which are summarized in Table 6 with the identification code. This variability in manifestations means that clinicians always have to consider that the drug may be the cause of the patients' symptoms. With the completion of the human genome project and the anticipated increase in drug targets, it is likely that new challenges will be faced as new drugs are introduced, which will have to be detected through clinical evaluation of patients [119]. Drug reactions commonly manifest with dermatologic symptoms caused by

the metabolic and immunologic activity of the skin. The most common dermatologic manifestation of drug reaction is morbilliform rashes. Typically, an erythematous, maculopapular rash appears within one to three weeks after drug exposure, originates on the trunk, and eventually spreads to the limbs [62, 120].

Reaction severity is assessed subjectively based upon the need for treatment and outcome [20, 121]. Table 7 shows the definition used to describe the severity of an ADR.

Table 7. Definitions Used to Assess the Severity of Adverse Drug Reactions

Mild: uncomplicated primary disease, does not require treatment or prolongation of hospital stay and drug discontinuation not necessary
Moderate: treatment or prolongs hospitalization by at least 1 day (or both) may be required, but not necessarily drug discontinuation; some but not all of the mild criteria and none of the severe criteria
Severe: an ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR is permanently disabling, requires intensive medical care, or takes longer than 14 days to recover
Fatal: an ADR directly or indirectly contributes to a patient's death

Table 6. System Organ Classes According to WHO-ART Classification

Code	System Organ Class Name
0100	Skin and appendages disorders
0200	Musculo-skeletal system disorders
0300	Collagen disorders
0400*	Nervous system and especial sense
0500	Psychiatric disorders
0600	Gastrointestinal system disorders
0700	Liver and biliary system disorders
0800	Metabolic and nutritional disorders
0900	Endocrine disorders
1000*	Cardiovascular system
1100	Respiratory system disorders
1200*	Haemic and lymphatic system
1300	Urinary system disorders
1400*	Reproductive system
1500	Foetal disorders
1600	Neonatal and infancy disorders
1700	Neoplasms
1800*	Body as a whole
2000	Secondary terms-events
2100	Poison specific terms

* Includes some System Organ Classes

The other used term is "Seriousness". FDA defined Serious ADR as one of the below items: [16, 75]:

1. Result in death, 2. Life-threatening, 3. Require hospitalization, 4. Prolong hospitalization, 5. Cause disability, 6. Cause congenital anomalies, 7. Require intervention to prevent permanent injury.

DRUG ALLERGY DIAGNOSIS

Clinical history

The history and the physical examination are the most important diagnostic Procedures and critical in the evaluation of drug allergy. Data should be taken in a uniform format. A specific questionnaire [122] has been developed by the ENDA (European Network for Drug Allergy) and is available in many different languages.

The history is the primary tool in trying to discern a drug reaction [123] and in distinguishing allergic reactions from other adverse reactions. A complete list of drugs is obtainable for hospitalized patients (the chart notes should be available) and can be confirmed with the hospital pharmacy. For outpatients, it can be difficult to have a complete list, and it is especially important to inquire about over-the-counter medications, health supplements, or any other type of ingested, because the patient will often not report these as medications. Once the list is complete the most important component on clinical assessment of true allergy are as follows [61]:

Pharmacologic actions of the drug: The Physicians' Desk Reference provides information about the non-immune adverse reactions of many prescription drugs (toxicity, side effects, secondary effects, and drug interactions).

The chronology of drug administration: The timing of the use of the medications in relationship to the reaction is important, as is a history of how long the patient has been on each of the medications is not pharmacologically mediated, immediate reactions (occurring from several minutes to 1 hour after drug administration) suggest an IgE-mediated event caused by pre-formed IgE antibodies. Non-immediate reactions (occurring more than 1 hour after drug administration) suggest a drug-specific T cell-mediated mechanism [11]. Reactions in this category include eczematous, maculopapular, bullous, and pustular exanthems. Most immunologically mediated drug reactions occur within 8 to 21 days of initiating a new medication. Knowledge of the half-lives of the respective medications is also important. Drug eruptions should resolve with removal of the offending agent; however, for medications with long half-lives, this can be several weeks.

The nature of the reaction: Reactions that occur with the first dose either are not immunologically mediated or are an indication of previous sensitization. It is not uncommon for a patient to be tolerant to the first course of a drug (during which they are sensitized) and then to experience a reaction on taking the first dose of the next course some weeks or months later.

Urticaria, angioedema, bronchospasm and anaphylaxis signify mast cell activation, and usually indicate an immune mechanism mediated by drug-specific IgE antibodies. These sign and symptoms require a period of sensitization (i.e., do not occur with the first dose). However, some drugs (e.g. radiocontrast media, aspirin or vancomycin) may activate

mast cells directly, or through non-immune mechanisms, without previous exposure and may occur with the first dose.

Maculopapular exanthems such as morbilliform, fixed drug eruptions and other non-specific rashes are mediated by T cells.

Host risk factors: Host risk factors can also be helpful (Table 1) concurrent medications at the time of the reaction are important. Antibiotics are usually first to be blamed for a reaction, but other medications, such as narcotics or NSAIDs, are frequently co administered and may be responsible.

An underlying condition that favors reactions to certain medications? Examples of such conditions include ampicillin induced morbilliform rash in patients with mononucleosis and trimethoprim/sulfamethoxazole reactions in patients infected with HIV, the cause of an adverse drug reaction is often difficult.

Previous exposure: It is important to determine whether the patient has had prior exposure to the same or structurally related medications, the effect of drug discontinuation, treatment of the reaction to date, and the response to treatment. Patients with a history of previous allergic reactions appear to be at increased risk for subsequent ADRs, even to medications that are chemically dissimilar indication.

In according to various clinical presentations of drug allergies, risk of subsequent reaction has been estimated and some examples of high-, moderate-, and low-risk situations were presented Table 8 [124].

Table 8. Examples of High -Moderate- and Low- Risk Situations Involving Drug Hypersensitivity Reactions

Higher- risk situations (estimated to be from 50% to 95%) 1. Administration of a β-lactam antibiotic to a patient within 1 year of a convincing allergic reaction to penicillin 2. Penicillin skin test reactions are positive, and the patient receives a bolus infusion of a β-lactam antibiotic 3. Cross-reactivity between penicillin and imipenem 4. Cross-reactivity between phenytoin and carbamazepine in terms of SJS or TEN 5. Readministration of Phenobarbital to a patient who had experienced a blistering rash from phenobarbital 6. Cross-reactivity or acute angioedema reactions among angiotensin- converting enzyme inhibitors in susceptible patients 7. A clinical setting in which opportunities for patient safety are overlooked Moderate- risk situations (estimated to be from 30% to 50%) 1. An aspirin- intolerant patient with asthma receiving an initial full dose of a nonselective NSAID 2. Administration of a β-lactam antibiotic to a patient with a convincing history of penicillin allergy 5 years previously Lower- risk situations (estimated to be from 0% to 5%) 1. Patient with penicillin allergy has negative skin test reactions to major and minor penicillin determinants and receives a β-lactam or cephalosporin 2. Administration of a β-lactam antibiotic to a patient with a convincing history of a penicillin allergy 25 years previously (skin testing and test dosing still are indicated) 3. A patient with SJS from phenytoin or carbamazepine receives valproic acid 4. A patient with nonselective NSAID- induced asthma or urticaria receives a COX-2 antagonist 5. A patient with acute angioedema from an angiotensin- converting enzyme inhibitor receives an angiotensin receptor blocker 6. A patient who experienced anaphylactic shock from radiographic contrast medium who is pretreated with prednisone (-13, -7 and -1 hour) and diphenhydramine (-1 hour) and receives a lower osmolality contrast medium 7. A patient with sulfamethoxazole- induced maculopapular rash who receives furosemide or other nonantibiotic sulfonamide

PHYSICAL EXAMINATION

A complete physical examination is helpful in categorizing the drug reaction; the physical examination may provide further information to support drug hypersensitivity.

A prudent initial step is an evaluation for signs and symptoms of an immediate generalized reaction, because this is the most severe life-threatening form of an ADR. A detailed skin examination is essential, because the skin is the organ most frequently and prominently affected by ADRs.

The most common skin finding is a maculopapular or morbilliform eruption. The maculopapular eruption consists of red/pink macules and papules that are distributed in a symmetric pattern throughout the body, often sparing the face. This eruption tends to be mildly pruritic. The pathogenesis is unknown but most likely T-cell mediated, not IgE mediated, in contrast to urticaria. In addition to a detailed skin examination, a complete physical examination can reveal more clues. Vital signs should be monitored. Tachycardia, tachypnea, and hypotension can be seen with an anaphylactic reaction. Fever, alone or in combination with other signs and symptoms, can be seen with a drug reaction.

Other critical components of the physical examination include an assessment of the lymph nodes, lungs, liver, spleen, and joints. These areas should be examined in every patient when evaluated during a reaction.

Finally, clinical picture of drug allergy is very heterogeneous, mirroring many distinct pathophysiological events. Thus, many doctors only rely on history and some reference manuals for drug allergy diagnosis, without attempting to prove the relationship between drug intake and symptoms or to clarify the underlying pathomechanism of the reaction. Such an attitude leads to a misunderstanding of drug hypersensitivity.

DIAGNOSTIC TESTS FOR DRUG HYPERSENSITIVITY

Diagnosis of drug hypersensitivity is difficult, as an enormous amount of different drugs can elicit various immune-mediated diseases with distinct pathomechanism. Although diagnostic testing methods exist, overall they are still of limited practical value for the clinician who is evaluating a patient with a suspected drug allergy. In selecting diagnostic tests, it is important to consider whether the reaction is immediate or non-immediate, as summarized in Table 9 [125].

DIAGNOSTIC TESTS FOR TYPE I REACTIONS

Skin test

Although standardized skin tests are commonly used by allergists in diagnosis of allergic reactions to aeroallergens and Hymenoptera venom, evaluation of a drug allergy is hampered by the relative unavailability of relevant drug metabolites and appropriate multivalent testing reagents. Skin testing with skin prick test (SPT), intradermal test (IDT) and/or patch test is especially recommended in adverse drug reactions to β -lactam antibiotics (mainly penicillins, cephalosporins). SPT and IDT are often positive to myorelaxants, insulin, protamine, heparin, streptokinase and chymopapain. It is also recommended to perform patch

tests and IDT in delayed local or exanthematic adverse reactions to other antibiotics, carbamazepine, practolol, pyrazonolines and tetrazepam.

Skin tests and provocation tests to local anesthetics should be performed; however, in this case the purpose is to exclude a reaction to a preparation under test conditions, rather than to confirm drug allergy [126].

In both ENDA protocols [127] —as well as in the American practice parameters [128]— skin testing with penicilloyl polylysine (PPL) and minor determinant mixture (MDM) represents the first-line method for diagnosing hypersensitivity reactions to β -lactams. Such protocols recommend the use of benzylpenicillin, amoxicillin, ampicillin and any other suspect β -lactam. Testing with major and minor determinants is done with a skin prick test, followed by an intradermal test if the skin prick test is negative. The commercial product Pre-Pen [Hollister- Stier] and Allergopen (Allergopharma), which contains the major determinant of penicillin, is currently unavailable anywhere, but alternatives may be available. Penicillin reagents (PPL and MDM) have been sold in Spain by Diater (DAP, Madrid, Spain) since 2003 as an allergen for prick and intradermal tests. In a recent study [129], Romano *et al.* observed a good concordance between Allergopharma reagents (Allergopen, Hamburg, Germany) and the DAP ones. Also Amoxycillin and ampicillin should be included in the skin test array to improve the diagnostic value [127]. This is because, with changes in drug prescription patterns. Regarding skin tests for major and minor determinants of penicillin, negative predictive values of 97 and 99% are respectively estimated, which means that if the test yields a negative result, the patient can tolerate the drug without being exposed to immediate allergic reaction [128]. Skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism. There are other diseases where immunological reactions to drugs could be involved, but skin testing has generally not been found helpful. For example, renal or hepatic manifestations may occur as a part of a generalized allergic reaction (e.g., in Drug Reaction with Eosinophilia and Systematic Symptoms). However, the value of skin tests in hematological (anemia, thrombocytopenia, leukopenia), renal (e.g., glomerulonephritis) or hepatic manifestations (e.g., hepatitis) has not been proven. Also skin testing is not considered to be helpful in autoimmune diseases like systemic lupus erythematosus, bullous pemphigoid, pemphigus vulgaris, and interstitial lung disease [130].

Skin test methods: A SPT is done by pricking the skin percutaneously with a prick needle through an allergen solution. It is the safest and easiest test, but only moderately sensitive, for immediate drug reactions. An intradermal test is accomplished by injecting 0.02-0.05 ml of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. The IDT is more sensitive than the SPT, but also carries a higher risk for inducing an irritative, falsely positive reaction and might even lead to an anaphylactic reaction in IgE-dependent reactions. Readings should be taken after 15-20 min if immediate reactions are analyzed, and after 24 and 72 h for evaluation of non-immediate (late) reactions (Intradermal tests). In selected cases, additional readings

(e.g. after 96 h) are sometimes recommended, as time intervals between testing and positive test reactions may vary. Immediate reactions are documented by measuring the mean diameter of the wheal (and erythema) of the test preparations and the negative control directly after the injection and after 15-20 min. Reactions are considered positive when the size of the initial wheal increases by 3 mm or greater in diameter after 15-20 min and is associated with a flare [130].

SERUM SPECIFIC IgE

Serum specific IgE assays (radioallergosorbent tests, RASTs (Radio-Allergo-Sorbent Tests) and immunoenzymatic assays, or enzyme-linked immunosorbent assays) are still the most common *in vitro* methods for evaluating immediate reactions [125]. RAST testing was first developed in 1974 after the discovery of the IgE antibody by Johansson and Ishizaka in 1967. It is now best performed utilizing the more refined ImmunoCAP system that employs allergen in a small container (cap) which latches onto the patient's serum-specific IgE. After a fluorescent enzyme 'labelled' anti-IgE is added (radio isotopes are no longer used), the amount of specific IgE can then be accurately quantified. The ImmunoCAP results are graded from negative 0 (<0.35 kU/l) to positive grade 1 (>0.35 kU/l) up to grade 6 (>100 kU/l) [131].

For most drugs RAST and RAST analogues are performed by linking the allergen (i.e. drug) to a solid phase (i.e. carbohydrate particle, paper disk, or the wall of polystyrene test tubes or plastic microtiter) solid-phase immunoassays have been developed to detect serum IgE antibodies directed against the some β -lactams, muscle relaxants, and insulin. Like other *in vitro* tests, they are generally more specific but less sensitive than skin tests. Hence, they have poor negative predictive values but better positive predictive values, and are used in conjunction with clinical evaluation and skin tests [127].

Although these *in vitro* tests appear to be less sensitive than skin testing, in order to avoid provocation tests, at least in cases with the most severe reactions have been recommended [125].

BASOPHIL ACTIVATION TEST (BAT)

Flowassisted allergy diagnosis relies upon quantification of alterations in the expression of particular basophilic activation markers. Actually, upon challenge with a specific allergen, basophils not only secrete quantifiable bioactive mediators but also upregulate the expression of deferent markers which can be detected efficiently by flow cytometry using specific monoclonal antibodies.

Currently, the technique has been applied in the investigation of IgE-mediated allergy caused by classical inhalant allergens, food, Hevea latex, hymenoptera venoms and drugs. It is also appreciated; the technique proves valuable in the diagnosis of non-IgE-mediated (anaphylactoid) reactions such drug hypersensitivity and the detection of autoantibodies in certain forms of chronic urticaria [132].

Basophils are a minor fraction of blood leukocytes (less than 0.2%), able to release histamine and several mediators, particularly in IgE-mediated allergic process. Flow cytometry allows the analysis of large numbers of cells and permits the simultaneous quantification of several parameters such as membrane markers. At present, the most commonly used antigens in BATs are CD63 (gp53) and CD203c. The CD63 molecule is a 53-KD protein expressed on cytoplasmic granules of resting basophil, monocyte, macrophages and platelets that moves to the cellular surface upon cell activation [133].

On activated basophils (e.g. by allergen, anti-IgE and anti-Fc ϵ RI), as a result of the fusion between the granule and cell membrane, CD63 is expressed with high density and allows the quantitative determination of basophil degranulation by flow cytometry detection. This technique can be used in the diagnosis of immediate allergic reactions to β -

Table 9. Diagnostic Tests of Hypersensitivity Reactions to Drugs

Immunologic testing	Immune mechanisms	Type of reaction
Skin tests Drug provocation tests Specific IgE assays Flow cytometric Basophil activation tests	Immediate hypersensitivity; IgE-mediated	I
Drug-specific antibody; Coombs test	Cytotoxic reaction; mediated by IgG/IgM and complement	II
Circulating immune complex; and complement C3, C4, CH50; immunohistopathology for immunofluorescence studies	Immune complex disease; mediated by IgG/IgM	III
Lymphocyte transformation tests Intradermal tests (Delayed-reading) Patch tests Drug provocation tests	Delayed or cell-mediated hypersensitivity	IV

lactams [134], NMBA (rocuronium) [135], and NSAID [136].

The BAT is more sensitive and specific than other *in vitro* diagnostic techniques in drug allergy. In various studies, its sensitivity in allergy to musclerelaxant drugs ranges between 36 and 97.7%, with a specificity of around 95%. For β -lactam antibiotics, BAT sensitivity is 50% and its specificity 90%. For NSAIDs, sensitivity varies between 66 and 75%; specificity is about 93%. BAT is also a useful technique in the diagnosis of isolated cases of hypersensitivity to various drugs [133].

DIAGNOSTIC TESTS FOR TYPE IV REACTIONS

Patch Test and Delayed Intradermal Skin Testing

in vivo T cell assays, like delayed intradermal skin tests and patch tests, are attractive because they can easily be performed in a clinical setting. In the diagnostic work-up, the patient's history is fundamental; patch testing is useful, together with delayed-reading intradermal testing.

Patch tests are done by making a 5% concentration of the relevant drug in a vehicle such as petrolatum, applying it to the skin (back of the patient) and measuring the reaction after 48-72 hours.

Scoring is done according to international standards [137]. Patch test positivity has been reported in nonimmediate cutaneous reactions to systemically administered β -lactams [138].

Romano *et al.* reported both patch and intradermal tests are useful in evaluating nonimmediate reactions to Aminopenicillins. Positive patch test and delayed intradermal responses together indicate delayed hypersensitivity [139]. Generally, intradermal testing appears to be somewhat more sensitive than patch testing and Patch tests appear to be more specific than delayed reading intradermal tests [138].

Although the specificity is generally very high with no false positive cases if the recommended concentrations for skin testing are used, the sensitivity was never higher than 50-60% [140]. Overall, patch testing has a good positive predictive value for delayed cutaneous reactions to drugs [101]. Sensitivity of patch testing is estimated to be 30-60%, which means that a negative patch test does not always exclude a hypersensitivity reaction. However, in AGEP (acute generalized exanthematous pustulosis) the percentage of positive patch tests is higher than for other drug-induced exanthems [141]. Moreover, in patients with hypersensitivity reactions to radiocontrast media, intradermal testing with delayed reading was found to be more sensitive than patch testing [89].

For evaluating patients who have suffered severe skin reactions (e.g. TEN, severe bullous exanthems, AGEP, SJS) or systemic reactions (e.g. DRESS; drug rash eosinophilia and systemic signs), patch tests should be used as the first line of investigation; in case of positive results, intradermal testing may be avoided. In case of patch test negativity, for intradermal testing, the drug should be initially tested with the highest dilution [130]. Provocation tests must not be performed [142].

LYMPHOCYTE TRANSFORMATION TEST (LTT)

The lymphocyte transformation test (LTT) measures *in vitro* T cell proliferative responses to antigens or mitogens. In the LTT peripheral blood mononuclear cells are obtained from a sensitized patient and cultured in the presence of the suspected drug. Sensitized lymphocytes undergo blastogenesis and generate lymphokines such as IL-2, followed by a proliferative response that can be measured by means of the incorporation of ³H-thymidine during DNA synthesis. The result can be expressed as stimulation index (SI) which is the relation between the cell proliferations.

A retrospective evaluation of the sensitivity and specificity of the LTT with a high amount of LTT reactions to β -lactam antibiotics revealed a sensitivity of 78% and compared to the patch test the same specificity of 85% whereas the sensitivity of the patch test (64%) was lower than the sensitivity (78%) of the LTT [97]. The LTT has a general sensitivity of 60-70%, and the overall specificity of this test is at least 85%. Its sensitivity is limited (for β -lactam allergy it is in the range of 60-70%); although it is higher than of other tests for drug hypersensitivity diagnosis. Dependent on the drug and clinical pictures of disease, different tests systems might be required, Table 10 shows the diseases, in which the lymphocyte transformation test (LTT) has been found to be positive [143].

Table 10. Diseases, in which the Lymphocyte Transformation Test (LTT) has been Found to be Positive

Frequently positive (>50%)

Generalized maculopapular exanthema

Bullous exanthema

Acute generalized exanthematous pustulosis (AGEP)

DHS (drug hypersensitivity syndrome)/drug rash with eosinophilia and systemic symptoms (DRESS)

Anaphylaxis (generalized, severe symptoms)

Occasionally positive

Hepatitis (dependent on type of drug)

Nephritis (dependent on type of drug)

Urticaria, angioedema

Interstitial lung disease*

Pancreatitis*

Rarely positive (<10%)

Toxic epidermal necrolysis (TEN)

Vasculitis

Macular exanthema (without T-cell infiltration)

Guillain-Barre*

Blood dyscrasia-like idiopathic thrombocytopenic purpura (ITP),

Haemolytic anemia

Fixed drug eruption

* Rarely investigated.

DRUG PROVOCATION TEST (DPT)

A drug provocation test is the controlled administration of the drug to a patient with a history suggesting a drug allergy. This drug is either an alternative, structurally or pharmacologically related drug or the suspected drug itself.

DPT is sometimes termed controlled challenge or re-exposure, drug challenge, graded or incremental challenge, test dosing, rechallenge, or testing for tolerance [142].

This test is the gold standard for the identification of drug hypersensitivity. However, provocation testing carries a clear risk of a reaction similar to the previous immediate hypersensitivity reaction, although subsequent reactions are generally milder and briefer than the original reaction. In one study, the overall rate of such reactions during provocation testing was 17.6 percent [144]. Thus such testing should be performed only by experienced personnel in a setting in which equipment for cardiopulmonary resuscitation is available. DPT is often the only reliable way to establish a diagnosis, if other diagnostic procedures such as *in vivo* skin testing and *in vitro* laboratory tests do not lead to conclusive results. Absolute contraindications to rechallenge with medication include patients who have had severe life threatening reactions, such as vasculitis, the SJS, TEN, DRESS, and organ involvement.

In conclusion, as the pathogenesis of drug hypersensitivity reactions is complex - its diagnosis is complex as well, only a combined approach using:

- An exact history (which is the most important component);
- Skin tests (immediate and delayed);
- LTT;
- Determination of specific IgE, if available; and
- Provocation tests (mainly to rule out a hypersensitivity reaction), seems to be appropriate.

PREVENTION AND TREATMENT OF NON-IMMUNOLOGIC DRUG REACTIONS

Prevention: It should be an essential part of routine clinical work. Prevention of ADRs requires familiarity with the drug and potential reactions to it. Computer-based analysis should be used to check for potential drug interactions; analysis should be repeated whenever drugs are changed or added. Drugs and initial dosage must be carefully selected for the elderly. If patients develop nonspecific symptoms, ADRs should always be considered before beginning symptomatic treatment. Some adverse drug reactions are by their nature predictable, and therefore, preventable. For dose-related ADRs, modifying the dose or eliminating or reducing precipitating factors may suffice. Increasing the rate of drug elimination is rarely necessary. However, dose adjustment according to the needs of individual patients may help to minimize ADRs. Pharmacokinetic parameters such as volume of distribution and elimination rate, as well as pharmacodynamic responses, tend to vary from patient to patient. Giving a standard dose of a drug to all patients under such circumstances may give rise to inappropriately high serum concentrations in some patients, resulting in toxic

effects. Therapeutic drug monitoring can help to minimize these ADRs, and pharmacogenetics has the potential to identify patients at an increased risk of such problems [145].

The importance of identifying and understanding preventable adverse drug reactions was first discussed in an article in 1971 [146]. The author estimated that 70% to 80% of ADRs that occurred could be prevented. Some literatures suggest that preventable ADRs occur at a rate between 5% to 80% [147, 148].

The following list of questions used to assess the preventability of an ADR, adapted from Schumock and Thornton (6). Answering "yes" to one, or more of the following questions suggest that an ADR may have been preventable [149]:

Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?

Was the dose, route and frequency of administration not appropriate for the patient's age, weight and disease state?

Was required therapeutic drug monitoring or other necessary lab tests not performed?

Was there a history of allergy or previous reaction to the drug (or drug class)?

Was a drug interaction involved in the reaction?

Was a toxic serum drug level (or lab test) documented?

Was poor compliance involved in the reaction?

Preventability categories were tallied for both in- and outpatient ADRs. For those ADRs that occurred prior to admission, the presence of a documented toxic serum drug concentration or lab test was the most common preventable event [121].

Another used term is "avoidability" which is defined as the impact that a preventive measure would have had on the likelihood of an ADR. This was determined from charts and information obtained from the family practitioner using a specific ten-item questionnaire developed for this purpose and displayed in below [150]:

1. Indication for treatment is recognized for cure, palliation, symptom, improvement, or prevention of disease.
2. Duration of treatment was adequate according to symptoms or treatment requirement
3. Prescribed dose were adequate
4. Prescribed dose were adapted to patient's characteristics
5. Drug monitoring was applied when indicated
6. Known interactions were taken into account
7. Absolute or relative concentrations were respected
8. Previous intolerance was checked
9. Warning signs was taken into account
10. Preventive treatment against drug toxicity was prescribed

A good ADR team should include clinicians, clinical pharmacologists and pharmacists. Hospital pharmacists can

play very important roles in identifying and preventing ADRs.

These include providing an effective Drug Information Service, promoting close liaison between wards and pharmacy, giving advice as an active member of the ward team and playing a direct role in national reporting schemes. A thorough knowledge of ADRs and a well-established ADR reporting system will help to reduce the occurrence and, thus, the costs of avoidable ADR-related admissions [145].

Consequently to minimize ADRs, physicians and prescribers should use drugs only when indicated, be wary of new drugs, and know the relationship between drugs. Drug interactions should be anticipated, and patients should be warned against self-medication. Concurrent use of two or more drugs should be avoided unless definitely indicated.

Management & Treatment: Successful management of an adverse reaction hinges on early recognition and prompt withholding of the drug in question [151]. Sometimes rapid action is important because of the serious nature of a suspected ADR, for example anaphylactic shock [6]. A new symptom or sign may be caused by the underlying disease process and not be iatrogenic at all; in such situations knowledge of the adverse reactions produced by each drug used can be very helpful. When a severe adverse reaction occurs it may be prudent to stop all the drugs which patient is receiving and then reintroduce them one at a time, watching for re-emergence of symptoms. Certain adverse reactions can be terminated rapidly by means of a specific antidote. An example is the dystonic posturing induced in children by prochlorperazine and metoclopramide. This dramatic clinical presentation is immediately reversed by slow intravenous injection of biperiden 1 to 2mg [151].

If several medicines could be causative, the non-essential medicines should be withdrawn first, preferably one at a time, depending on the severity of the reaction. If the reaction is likely to be dose-related, dose reduction should be considered. The patient should be observed during withdrawal. If the patient is not doing well after withdrawal of the first drug, the next most likely culprit should be considered, and the process repeated. On the other hand, the patient may be suffering through being deprived of the medicine withheld. In that case, either another suitable drug should be substituted (remembering the possibility of cross-sensitivity), or the same drug should be tried at a lower dosage (for a dose-related reaction). The latter approach should be tried if more than one drug was withheld, for instance if an interaction was suspected or if the seriousness of the reaction made it wise to withhold several possible drugs. Reintroduce apparently essential medicines one at a time, starting with the one least likely to be the culprit.

If the patient cannot manage without a medicine that has caused an adverse reaction, provide symptomatic relief while continuing the essential treatment. For example, severe nausea and vomiting are routinely treated symptomatically in patients receiving anti-cancer drugs. However, when treating an adverse drug reaction, it is important not to introduce more medicines than are essential [6].

A majority of adverse reactions are a minor nature and will resolve spontaneously within a few days of withdrawal

of the drug responsible. Therapy for ADRs is almost exclusively symptomatic. Symptomatic relief in the form of antipruritics, analgesics and histamine H1-receptor antagonists may be necessary on an individual basis. Antihistamines often bestow added benefit through their sedative effect. Calamine has a soothing effect on inflamed skin; in severe cases a steroids in high dosage are required for the treatment of SJS. Skin rash, sore eyes and developing stomatitis should alert the clinician to this diagnosis [151].

However, when treating an adverse drug reaction, it is important not to introduce more medicines than are essential. Always have a clear therapeutic objective in mind, do not treat for longer than is necessary, and review the patient regularly and look for ways to simplify management.

Notes on the management of ADRs by the reaction type are as shown below in summary [6]:

Type A: Reduce dose or withhold, Consider effects of concomitant therapy

Type B: Withhold and avoid in future

Type C: Reduce dose or withhold; withdrawal may have to be prolonged

Type D: Often intractable

Type E: Reintroduce and withdraw slowly

Type F: Increase dosage, Consider effects of concomitant therapy

EVALUATION AND MANAGEMENT OF SPECIFIC DRUG HYPERSENSITIVITY

β -Lactam Antibiotics

Penicillin: Due to their favorable risk-benefit ratios, β -lactams are still antibiotics of first choice for many infections. Allergic reactions to β -lactams are the most common cause of adverse drug reactions mediated by specific immunological mechanisms [127]. In addition to immediate reactions β -lactams can elicit delayed-appearing urticaria/angioedema, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), more severe bullous exanthems like the SJS and TEN [152].

Penicillin is the most prevalent medication allergy, with approximately 10% of patients reporting being penicillin-allergic [153]. However, when patients with a history of penicillin allergy are evaluated, more than 90% of them are found not to be allergic and are able to tolerate the drug [154, 155]. Amoxicillin (AX) is considered nowadays the most commonly consumed and frequent case of anaphylaxis to β -lactam in many countries [156-158]. Consumption of cephalosporins is increasing and both β -lactams are therefore gaining importance as a cause of allergy [127]. Frequently prescribed aminopenicillins more commonly lead to delayed reactions, while penicillin G and penicillin V tend to cause immediate reactions [152]. After administration, penicillin is degraded (in the absence of an enzymatic process) to major determinants (95% of transformation) and minor determinants (5% of transformation). These determinants serve as immunogenic haptens for binding to albumin or IgG. The use of reagents known as major and minor determinants has allowed allergists-immunologists to demonstrate anti

penicillin (determinant) IgE antibodies to identify which patients have anti-penicillin IgE and which patients do not [124].

The minor determinants, penicilloate and penilloate are the most important in inducing allergic responses. Less commonly, the R-group side chain, which distinguishes different penicillin compounds, may also serve as an allergenic determinant [158].

This finding suggests that different penicillins may be cross reactive, not only by virtue of their shared β -lactam and thiazolidine rings but also by virtue of shared or similar side-chain determinants [159]. After its identification, penicilloyl determinants were coupled to a weakly immunogenic polylysine carrier to form penicilloyl polylysine (PPL), and in addition to the penicilloyl determinant, several other minor penicillin determinants (MDM) are formed.

The most reliable approach for evaluating allergic reactions to β -lactams is a detailed description of the symptoms which can be obtained from the patients. Because an accurate diagnosis of penicillin allergy cannot be made clinically, any patient with a history of a possible IgE-mediated reaction to penicillin is a candidate for skin testing.

The penicillin skin test procedure is analogous to other immediate-type allergy skin testing [160]. Penicillin skin testing with both major and minor determinants is the most reliable tool for diagnosing a penicillin allergy mediated by IgE. However, penicillin skin testing is not predictive of reactions mediated by non-IgE mechanisms such as IgG- or IgM-mediated immune complex diseases, hemolytic anemia, EM (Erythema Multiform), SJS, and TEN. Patients with a clear history of serious non-IgE-mediated penicillin reactions, such as SJS, TEN, or interstitial nephritis, should not undergo skin testing. Penicillin skin testing has a low risk of systemic reactions and fatalities if correct reagents and proper techniques are used [161].

When appropriate major and minor determinants are used, a negative skin test essentially rules out the potential for a serious immediate-type reaction.

In large-scale studies, 1% to 3% of skin test-negative patients developed mild and self-limiting reactions on being challenged with the drug. On the other hand, the predictive value of a positive test indicated that 50% of the patients could develop another clinical reaction after re-exposure while the predictive value of a negative test indicated that in the event of further administration of BP (benzylpenicillin), there would be good tolerance, or at least just a minimal clinical response. In addition to skin testing, various *in vitro* methods are also available for the diagnosis of immediate hypersensitivity to β -lactam. Although the new biological tests can give useful complementary information, skin testing remains the method of choice and the first to perform, unless otherwise indicated [162].

In order to provide a practical approach for patient evaluation some algorithms have been described, in immediate reactions the ENDA recommends. In the allergological workup, the first step which could be recommended is to use PPL and MDM and, if negative, to undertake a drug-provocation test with benzylpenicillin. If this is negative, skin testing with amoxicillin and possibly with other β -

lactams, is necessary to complete the diagnosis. Thus, after following these steps in this order, cross-reacting or selective responders are separated. An alternative work up is to perform all skin tests in parallel and a drug provocation test with the culprit drug if they are all negative [127].

In evaluating non-immediate reactions to β -lactams, ENDA group proposed combines skin tests and patch tests with a common panel of reagents - including penicillin determinants (PPL, MDM, and BP) and the two most used aminopenicillins (AM and AX) - as well as the suspect β -lactam; in selected cases, provocation tests with the latter are also suggested [152].

At the time of writing this article, the major determinants (PrePen[®]) for penicillin skin testing is no longer available commercially, however some medical center are able to produce own major and minor determinants Diater (DAP, Madrid, Spain). In a Commentary by ENDA, the following measures were recommended [163]:

1. Use an equivalent kit for skin testing
2. Otherwise, use benzylpenicillin, amoxicillin, ampicillin plus the culprit β -lactam, if this can be identified.

After diagnosis, the most important and effective therapeutic measure in managing drug hypersensitivity reactions is the discontinuation of the offending medication.

Acute management of an anaphylactic drug reaction can be lifesaving. The initial steps in the management of anaphylaxis are the same as for all life-threatening events, that is, the control of airway, breathing, and circulation. A sometimes overlooked step is the need to start oxygen at the outset of the resuscitation.

The most critical medication is epinephrine. In children or adults in an office setting, intramuscular or subcutaneous administration can be used. The intramuscular or subcutaneous dose for adults, using 1:1000 epinephrine, is 0.2 to 0.5 ml. In children, the dose is 0.01 mg/kg (maximum, 0.3 ml per dose). Histamine receptor antagonist therapy can be used with epinephrine. Corticosteroids are available for intravenous infusion if the clinical situation warrants. Other supportive care includes fluid resuscitation and the use of vasopressors depending on the clinical scenario. Patients should be observed after stabilization for at least 2 hours with mild episodes and probably for 24 hours after severe anaphylaxis [101].

Patients may undergo drug desensitization if that drug is necessary for treatment. Penicillin desensitization is commonly performed, and either the oral or the intravenous route may be used and acute drug desensitization involves the administration of incremental doses of a drug.

Cephalosporins: Cephalosporins share a common four-member β -lactam ring with penicillin, (cephalosporins also have a unique dihydrothiazine ring). Cephalosporins appear to be less allergenic than penicillins, particularly in causing IgE-mediated reactions. The incidence of anaphylaxis as a reaction to cephalosporins [164] is about an order of magnitude lower than it is to penicillin. Unlike penicillin, cephalosporin has no validated diagnostic skin test reagents available. Skin testing using nonirritating concentrations of native cephalosporins has been performed [158], and data

suggest a high negative predictive value using parenteral cephalosporins at 2 mg/ml [165].

PENICILLIN/CEPHALOSPORIN CROSS-REACTIVITY

Varying degrees of cross-reactivity between cephalosporins and penicillins have been documented. When a patient with penicillin allergy requires a cephalosporin, the risk of a cephalosporin reaction is much lower going from the first generation (5% to 16.5%) to the second generation (4%) and the third or fourth generation (1% to 3%) [124]. The patient with penicillin allergy does experience more cephalosporin-induced allergic reactions (up to an 8-fold increase) than do patients without penicillin allergy [166].

A more conservative approach includes penicillin skin testing before initiation of cephalosporin therapy, particularly for patients with a history of serious allergic reactions to penicillin. Patients with penicillin allergy with negative skin test responses to major and minor penicillin determinants can tolerate a cephalosporin without an allergic reaction [124].

The principles of allergenic cross-reactions between cephalosporins are similar to those that pertain to the penicillins. If IgE antibodies are directed toward the core ring structures, cross-reactivity may exist among all the cephalosporins. If antibodies exist to the R1 or R2 side-chain group, (McBride, *et al.* disclosed the formula) [167] however, the situation becomes much more complex. If a patient who has a history of a cephalosporin allergy requires another cephalosporin, one of two approaches may be considered.

- (1) Perform a graded challenge with a cephalosporin that does not share side-chain determinants with the original cephalosporin. Challenges were begun with 0.01 followed by 0.1 and full doses of the cephalosporin administered hourly in patients with negative cephalosporin skin test responses [165].
- (2) Perform cephalosporin skin testing, although such skin testing is not standardized and the negative predictive value is unknown [128].

SULFONAMIDES

A sulfonamide is any compound that contains a sulfonamide (SO₂NH₂) moiety [159]. Sulfonamide antimicrobial agents are different from other sulfonamide-containing medications, such as furosemide, thiazide diuretics, and celecoxib. This difference is important when considering the potential cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides. Cross-reactivity between sulfonamide antibiotics and other sulfonamide derived drugs is only a theoretical concern that has not been borne out in clinical practice, and need not necessarily exclude their use if clinically indicated [168].

Oxidation of sulfonamides into nitrosometabolites also can participate in sulfonamide-induced allergic reactions [124].

Reactions to sulfonamide antimicrobial agents are usually cutaneous in nature, and they occur in approximately 1% to 3% of healthy persons but in as many as 40% to 80%

of patients with AIDS (Acquired Immune Deficiency Syndrome) [127]. The clinical reactions exhibited are diverse and include anaphylaxis, urticaria, erythroderma, fixed drug eruption, EM, macular exanthems, and even more severe cutaneous reactions, such as SJS and TEN [159] by far the most common reactions are delayed maculopapular and morbilliform eruptions [158]. At this time, we have few diagnostic tools for evaluating patients with sulfonamide-induced reactions. The LTT has proven to be a useful test for the diagnosis of sulfanamides hypersensitivity reactions [143].

Over the last 2 decades, numerous protocols have been devised in an attempt to administer TMP-SMX safely to HIV (Human Immunodeficiency Virus) positive patients who have a history of previous reactions to the antibiotics [169].

The term desensitization is commonly used to describe these procedures, but it is imprecise, because IgE antibodies are not implicated in these reactions. All the protocols start with a low, subtherapeutic dose of TMP-SMX, which is incrementally increased until the full dose is reached. The reported desensitization success rates range from 60% to 100% [158]. Desensitization protocols should not be attempted in patients who have had severe drug-induced cutaneous reactions, such as SJS or TEN [159].

ASPIRIN AND OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Hypersensitivity reactions to aspirin and other NSAIDs may have a number of clinical manifestations (Table 11).

It is estimated that approximately 5% to 10% of adult asthmatics have Aspirin-exacerbated respiratory disease (AERD), whereas the prevalence increases to about a third in adult patients who have asthma and nasal polyposis (158). AERD is rare in prepubescent children. However, there are other clinical syndromes in which there is no history of asthma or rhinitis and the patient has an isolated sensitivity to a specific NSAID [170]. This may have an immunological basis with a putative IgE mechanism. There is no specific diagnostic test to identify sensitive patients. Clarifying the history and recognising the clinical patterns can allow specific provocation challenges to ascertain safe alternatives and prevent unnecessary avoidance of aspirin or other NSAIDs of Patients with reactions to NSAIDs, especially those with asthma and/or rhinitis, benefit from the discontinuation of drug treatment, and from the continuous use of cysteine leukotriene receptor antagonists [171]. In special cases in which the continuous use of NSAIDs is necessary and there is no substitute, desensitization is recommended. However, Hellstrom disclosed methods and compositions for reducing the risks of adverse cardiovascular (CV) events associated with the administration of non-steroidal anti-inflammatory drugs (NSAIDs) [172].

In this case, the patient is exposed to increasing doses of NSAIDs, at regular intervals of 20 minutes, until symptoms appear or the desired therapeutic dose is achieved, which should be then maintained uninterruptedly. Bova disclosed if NSAIDs are given in combination with nicotinic acid the flush reaction is decreases [173].

Table 11. Major type of Hypersensitivity Reactions to ASA and other NSAIDs

Reaction type	Underlying disease	Drugs involved	Cross-reactions	Mechanism
Respiratory	Rhinitis, polyps, asthma	ASA, NSAIDs	All except COX-2	COX-1 inhibition
Multiple-drug urticaria/angioedema	Chronic urticaria	ASA, NSAIDs	All except COX-2	COX-1 inhibition
Single-drug urticaria/angioedema	None	ASA, NSAIDs COX-2	None	IgE (probable)
Anaphylaxis	None	ASA, NSAIDs COX-2	None	IgE (probable)
Aseptic meningitis	None	NSAIDs	None	T cell (probable)
Hypersensitivity pneumonitis	None	NSAIDs	None	T cell (probable)

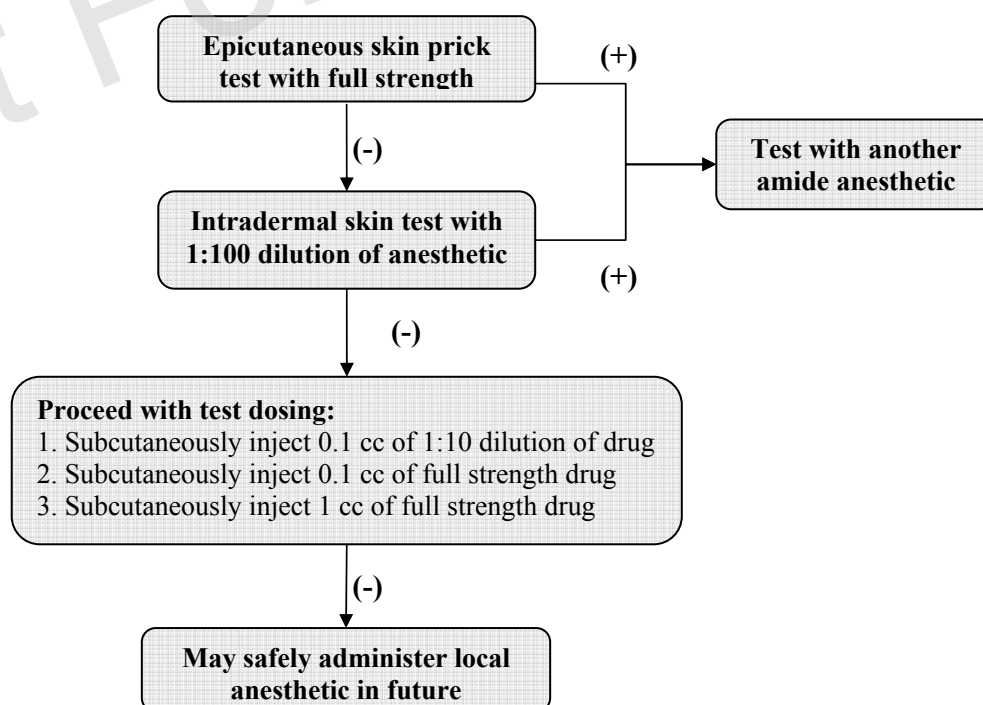
LOCAL ANESTHETICS

Despite the perception that many patients are allergic to local anesthetics, true IgE-mediated reactions are extremely rare, and usually consist of delayed contact dermatitis [174]. Reported reactions are most likely due to other reasons, including hyperventilation, vasovagal reactions, toxic reaction, numbness of the pharynx from extravasated anesthetic, or inadvertent intravascular injection of epinephrine (added to most local anesthetics to vasoconstrict the area). Large-scale studies have found that, following full evaluation, virtually all patients with a history of allergy to local anesthetics are able to tolerate these drugs. Local anesthetics belong to two chemical groups: benzoic acid esters (e.g. Procaine), and amides (e.g. Lidocaine). There is cross-reactivity among the benzoate esters but not among the amides [158].

Unfortunately, patients who experience any adverse reaction to local anesthetics are frequently labeled allergic and told to avoid all “-caines” in the future. The patient should undergo skin prick and intradermal skin tests with the same agent that will subsequently be used by the dentist or physician, and using incremental doses (test dosing). It serves to alleviate dentists’ or physicians’ legal concerns regarding use of a drug to which a patient is listed as being allergic (Fig. 1) [158].

CURRENT & FUTURE DEVELOPMENTS

Adverse drug reactions (ADRs) and drug hypersensitivity reactions (DHRs) continue to be a major public health problem. Knowledge increasing in the context of identifying, understanding, predicting, and ultimately reducing the burden of ADRs is essential for health care providers such as physicians, clinicians, pharmacists, pharmacologists, ...

**Fig. (1).** Management of patients with previous reactions to local anesthetics.

Encouragingly they are advised to keep their information on ADRs up to date. The present review article will give opportunities to achieve this aim by means of preparing and collecting useful information on ADRs and especially drug hypersensitivity from the definition to the treatment.

Drug hypersensitivity is a complex and still widely neglected topic. The diagnosis of DHRs is difficult and often relies on clinical histories, skin tests, and a few validated in-vitro tests, such as serum specific IgE assays, which are available only for a few drugs. New diagnostic tools, however, such as the BAT, have been developed and are under validation. An important breakthrough is the identification of extremely high HLA-B associations with certain drugs and diseases which already results in the possibility of effective prevention of some forms of drug hypersensitivity reactions. If this knowledge is combined with rapid progress of cellular diagnostic test using flow cytometry and growing knowledge of the human genome, we will undoubtedly not only identify genetic predisposing factors of DHRs but also have new tests available to identify relevant drug. Together, these developments consequently can lead to a reduced incidence of DHRs.

Consequently, we believe the addressing these issues will aid physicians and prescribers in the better diagnosis, prevention and therapeutic monitoring of ADRs and DHRs.

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