

Classification and epidemiology of hypersensitivity drug reactions

Pascal Demoly, MD, PhD^{a,*},
Dominique Hillaire-Buys, MD, PhD^b

^a*Allergy Department, Maladies Respiratoires and INSERM U454 – IFR3,
Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France*

^b*Drug Monitoring Department, Pharmacologie Médicale,
Centre Régional de Pharmacovigilance du Languedoc-Roussillon and INSERM U454 – IFR3,
Hôpital Lapeyronie, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France*

Hypersensitivity drug reactions are adverse effects of drugs taken at a dose that is tolerated by normal subjects that clinically resemble allergy. Although they are a frequent and almost constant worry for prescribing physicians, extensive epidemiologic studies are lacking, because numerous reactions with symptoms suggestive of an allergy are often considered real drug allergies. Only when immunologic mechanisms are involved should these reactions be classified as drug allergy [1]. The vast majority of allergic drug reactions are found to be IgE-mediated or T-cell mediated. Unfortunately, allergic drug reactions may not be differentiated easily from nonimmunologic hypersensitivity drug reactions or from another diagnosis such as an infectious exanthema. Many persons who experience a hypersensitivity drug reaction are cataloged as being allergic to the drug without further investigation [2–5]. The diagnostic work-up of a hypersensitivity drug reaction is difficult [5]. Reasons for this include the following: (1) the reaction itself is rarely documented; (2) the clinical presentation is heterogeneous, mirroring many distinct pathophysiologic events; (3) several drugs are often taken simultaneously; (4) many factors besides the drug can be involved; and (5) when the reaction occurred a long time ago, sensitivity could be lost. Another problem is the lack of consensual diagnostic procedures for many drugs [6], although efforts are underway to overcome this deficiency [6–10]. Indeed, test reagents are not standardized for in vitro or in vivo (skin) tests, and provocation tests are cumbersome and possibly harmful for the patient.

Many physicians (and epidemiologic references) rely on the clinical history without attempting to prove the relationship between drug intake and symptoms

* Corresponding author.

E-mail address: demoly@montp.inserm.fr (P. Demoly).

or clarifying the underlying pathophysiology of the reaction. Such an attitude leads to a misunderstanding of the epidemiology and pathophysiology of this highly relevant field. Additionally, the frequency of drug hypersensitivities may be affected by changes in the output of pharmaceutical industry and prescription patterns. Before considering the importance of hypersensitivity drug reactions as a public health problem, one must define as precisely as possible what is meant by drug hypersensitivity.

Classification of hypersensitivity drug reactions

Predictable (type A) and unpredictable (type B) reactions

Adverse reactions to drugs are classified according to their mechanism and are divided into predictable (type A) and unpredictable (type B) reactions [11]. Toxic reactions are caused by an overdose, whereas pharmacologic reactions include the adverse effects to the normal doses administered. Both types of reactions are predictable. Unpredictable reactions include immune (allergic) or nonimmune hypersensitivity reactions and those reactions related to genetic susceptibilities or undefined mechanisms (sometimes called idiosyncratic and intolerance reactions). Examples of the latter include a rapid acetylation profile (favoring hepatotoxic effects of isoniazide) or a deficiency in IgA (responsible for anaphylaxis during blood transfusions containing IgA).

Immune and nonimmune hypersensitivity drug reactions

A drug allergy is always associated with an immune mechanism for which evidence can be shown of drug-specific antibodies or activated T lymphocytes. This mechanism holds true for reactions to myorelaxants [12] and proteins such as insulin or β -lactams [13]. Schematically, several criteria characterize an allergic reaction:

The reaction is not an expected pharmacologic effect.

A period of sensitization precedes the reaction.

The reaction may occur at a dose much lower than that required for a pharmacologic effect.

The clinical symptoms are characteristic of an allergic reaction.

Resolution occurs within an expected interval, usually days, after discontinuation of the offending agent.

Chemical cross-reactivity may occur.

One can qualify as nonimmune hypersensitivity drug reactions all adverse reactions whose symptomatology brings to mind an allergy but for which the immunologic nature of the reaction cannot be proved [1,11]. These reactions are often unpredictable. Their formal designations as pseudoallergic (or anaphy-

lactoid) reactions have been abolished [1]. They can evoke a pharmacologic effect of the drug and assume most of the criteria listed previously. Numerous nonimmune hypersensitivity reactions occur and are caused by multiple etiologies [11]. Examples include nonspecific histamine release (opiates, radiocontrast media, and vancomycin), an accumulation of bradykinin (angiotensin-converting enzyme inhibitors), complement activation (radiocontrast media, protamine), an activation of leukotriene synthesis (aspirin and nonsteroidal anti-inflammatory drugs), and bronchospasm (by liberation of sulfur dioxide during treatments containing sulfites or by blockage of the β -adrenergic receptors, even when the drug is administered through the eyes). Moreover, β -blockers aggravate every type I hypersensitivity reaction and make treatment by epinephrine difficult.

Drug reactions presumed to be hypersensitivity drug reactions

Almost two thirds of patients who visit a physician for a reaction that is diagnosed as a “drug allergy” sustain events that are not drug related. The probability is inverse for anaphylactic shock (Fig. 1, authors’ personal data, 2003). Usually, the clinical signs are maculopapular cutaneous eruptions that appear during a course of antibiotics for an infection of the respiratory tract. This eruption is frequently (especially in children) related to the pathogenic agent, even though the interaction of the infection and medication is still an unknown factor that may be T-cell mediated. The reactions can also be of a pharmacologic nature (eg, a central effect of narcotics), a subjective symptomatology (anguish,

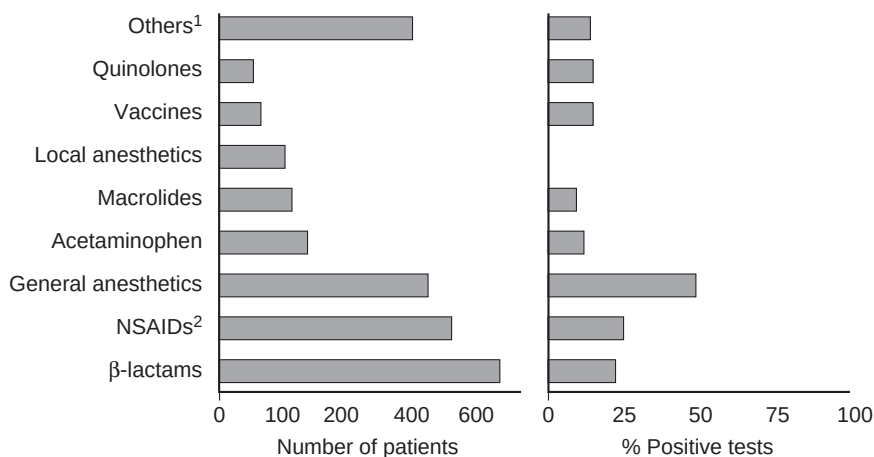


Fig. 1. Personal data concerning the results of 5 years of a drug allergy outpatient consultation. A total of 2150 subjects visited the authors’ department with a clear-cut history of hypersensitivity drug reactions. After a thorough diagnostic procedure (including provocation tests for drugs when skin tests were not validated), only 415 patients (19.3%) had a proven hypersensitivity drug reaction. ¹Including streptogramins, dihydroergotamine, insulin, and HIV drugs; ²including aspirin and all non-steroidal anti-inflammatory drugs (NSAIDs).

hyperventilation syndrome during local anesthesia), or a food allergy (medication is often taken during a meal).

Multiple and varied mechanisms of drug allergy

Drugs can induce all of the types of immunologic reactions described by Gell and Coombs [14]. Antibiotics (especially β -lactams) are the principal therapeutic classes involved. An IgE-mediated allergy (type I in the Gell and Coombs classification) is the most common form and results from the interaction between the drug and the specific IgEs presented on the surface of the mast cells and basophils. This immunologic mechanism is responsible for immediate anaphylactic reactions (anaphylactic shock, urticaria, angioedema, and bronchospasm). These drugs or their metabolites can also directly activate T-lymphocyte proliferation [15], which is responsible for delayed type IV allergic reactions in the Gell and Coombs classification (eg, maculopapular eruptions, contact dermatitis, photosensitization). Complement-mediated reactions (Gell and Coombs type II cytotoxicity reactions mediated by antigen-specific IgG or IgM and type III immune complex reactions mediated by antigen-specific IgG antibodies) are less frequent [16]. These reactions are responsible primarily for cytopenia, serum sickness syndrome, glomerulonephritis, prolonged fevers, and certain urticarias. For the most part, the metabolites are unknown, and sometimes several complex allergic mechanisms intervene (eg, types I and IV) [16]. Moreover, nonallergic mechanisms, which are very often toxic in nature, may be associated (eg, the hydroxylamines derived from sulfonamides or those induced by viruses such as Epstein-Barr [17] or HIV [18]). These reactions depend on both the drug and the host. The epidemiologic data are limited; however, intense investigations on the polymorphisms of drug-metabolizing enzymes and inflammatory mediators are being performed (within the scope of the impressive development of pharmacogenetics).

Epidemiology of hypersensitivity drug reactions

Incidence and prevalence

Hypersensitivity drug reactions are responsible for mortality, morbidity, and extra costs that are typically underestimated. Some data are available. In the study by Bates et al [19], nurses and pharmacists participating in the Boston Collaborative Drug Surveillance Program in the United States collected information on adverse drug reactions in 4031 hospitalized patients during a 6-month period. A total of 247 reactions were declared (an incidence of 6.1%), of which 41.7% were severe and 1.2% led to the patient's death. A total of 194 other reactions could also be related to drugs (which increased the incidence to 10.9%). Most of these reactions were unpredictable (61.7%) and, possibly, allergic reactions, although this conclusion was not stated in the article. In a study by Classen et al [20],

pharmacists at the LDS Hospital in Salt Lake City, Utah, studied 36,653 hospitalized patients during an 18-month period by an automatic detection system, identifying 731 reactions. The 1.8% incidence was lower than in the previous study, with only 12.3% of the events reported by the doctors in the hospital. Of the reactions, 13.8% were severe, and 32.7% were of an allergic nature. This system principally detected reactions requiring a biologic assessment or a corrective treatment. If applied to the study of Bates et al [19], their incidence would have been similar at 2.8%. Lazarou et al [21] reported in a recent meta-analysis of 33 prospective US studies from 1966 to 1996 that 15.1% of hospitalized patients sustained an adverse drug reaction (6.7% severe). The incidence of drug-related hospital admissions ranged from 3.1% to 6.2%. A recent French survey conducted for 14 days in a representative sample of teaching and general hospitals confirmed these data; 3.2% of the patients had been admitted to the hospital because of an adverse reaction [22]. The notion of underdeclaration of the undesirable effects of drugs is constantly reported in studies, even at university hospitals, where a maximum of 6% to 12% of these events are declared [20,23]. In general practice, the French Centres of Pharmacovigilance estimate that they are informed of less than 1 effect in 20,000 and less than 1 serious effect in 6000.

Although hypersensitivity drug reactions represent up to one third of adverse drug reactions and can affect 10% to 15% of hospitalized patients, in most cases, these reactions are not declared [19–23]. Inversely, because a precise diagnosis is rarely made, and based on the authors' personal experience (Fig. 1), these reactions could also be overestimated. The Comprehensive Hospital Drug Monitoring Program of Bern and Saint Gallen in Switzerland found 2.7% of cutaneous allergic reactions documented by a dermatologist in 48,005 patients hospitalized over a 20-year period [24]; however, the diagnosis was one of probability without re-challenge. This rate is supported by another survey of the Boston Collaborative Drug Surveillance Program [25] in which the investigators provided most of the data regularly used to calculate the incidence of hypersensitivity drug reactions. The incidence of cutaneous drug reactions in 15,438 hospitalized patients was analyzed over a 7-year period. A total of 358 reactions were collected and confirmed by a dermatologist. For each of the 51 drugs studied, the number of reactions versus the number of administrations has been reported, with a global incidence of 2.3%. Specific rates are 5.1% for amoxicillin, 3.4% for co-trimoxazole, 3.3% for ampicillin, 2.2% for blood derivatives, 2.1% for cephalosporins, 2% for erythromycin, 1.8% for penicillin G, and 0.4% for gentamycin. A prospective study in patients receiving monthly injections of penicillin G (for rheumatic fever) reported similar data, with 57 reactions in 1790 patients (incidence of 3.2% of patients and 0.19% of injections) [26]. A more recent study is the French registry of adverse reactions during general anesthesia. The sixth recently published survey identified 789 cases (518 with a demonstrated immune mechanism) [27]. The incidence of such reactions was 1 event per 13,000 general anesthetics and 1 event per 6500 myorelaxant injections.

The great majority of drugs are prescribed for outpatients, and few studies have looked at this population. The incidence of drug reactions in a population of

nonhospitalized subjects or even in the general population is mostly unknown. In a recent cross-sectional survey of a general adult population in Porto, Portugal, the prevalence of self-reported drug allergy was 7.8% (181/2309). Rates were 4.5% for penicillins or other β -lactams, 1.9% for aspirin or other nonsteroidal anti-inflammatory drugs, and 1.5% for other drugs (P. Demoly, MD, PhD, personal data, 2003). In a review of almost 6000 medical records in a private group pediatric practice in northern Virginia, cutaneous eruptions occurred in 7.3% of the children who were given common oral antibiotics [28]. The rates were 12.3% for cefaclor, 8.5% for sulfonamides, 7.4% for penicillins, and 2.6% for other cephalosporins. In another study, 3 of 3200 students given ciprofloxacin to prevent meningococcal carriage experienced an anaphylactic reaction [29]. In the study by Katayama et al [30] of 337,647 injections of radiocontrast media in Japan, the incidence of adverse reactions was 12.6%. The rate of severe reactions was 0.22% for ionic products and 0.04% for nonionic products. Other useful information is the incidence of these reactions in exposed subjects during clinical trials; however, drug monographs do not always reflect the safety profile of the drug once it is commercialized, especially when the drug (eg, an anti-HIV drug) is rapidly launched.

Mortality

Drug hypersensitivity reactions can be serious and potentially life threatening. In the United States, the study by Lazarou et al [21] analyzed 33 prospective studies from 1966 to 1996 and showed that 0.32% of hospitalized patients died of adverse drug reactions. The 106,000 deaths estimated for the year 1994 comprised the fourth leading cause of death. The proportion of allergic reactions in the study was not evaluated but was estimated to be 23.8% (all severities). Anaphylactic shock is an IgE-mediated reaction that is the most frightening and potentially lethal; non-IgE-related anaphylactic shock can also be drug related. Although these events are rare, the extremely rapid onset of the symptoms and the possibility of death make them a major threat for patients and physicians. Other causes of mortality owing to allergic drug reactions are toxic epidermic necrolysis (30% mortality), Stevens-Johnson syndrome (5% mortality), multi-system organ hypersensitivity syndrome (10% mortality), and other vasculitis or liver, lung, or kidney involvements.

Anaphylactic shock has been studied specifically in some cohorts. Yocum et al [31] reported that drug anaphylaxis represented 12.8% of 179 anaphylactic cases collected at the Mayo Clinic, Rochester, over a 3-year period. van-der-Klaauw et al [32] reported 345 cases of probable anaphylaxis to drugs and 485 possible cases over a 20-year period from 1974 to 1994 in the Netherlands. The nonnarcotic analgesic drug glafenine was responsible for 326 cases, in which there were 2 deaths, followed by nonsteroidal anti-inflammatory drugs (101 cases), sulfonamides (23 cases), dextran (20 cases, 3 deaths), floctafenine (12 cases), allergens (12 cases, 2 deaths) and amoxicillin (11 cases). The mortality rate for anaphylactic shock was 2.5% in that study (21 deaths in 830 cases). The Danish Drug Administration reported 30 cases of fatal anaphylactic shock from 1968 to 1990,

of which 8 were caused by radiocontrast media, 6 by penicillins, 5 by allergen extracts, 2 by nonsteroidal anti-inflammatory drugs, and 1 by myorelaxants [33] (incidence of 0.3 cases per 1 million inhabitants per year). A recent survey in the United Kingdom identified an almost twofold increase in hospital admissions for acute anaphylaxis between 1991 (56 cases per million) and 1995 (102 per million). When the etiology was recorded (51%), the most common cause was a therapeutic drug (62%) [34]. In France, a register of all fatal anaphylactic reactions has been established since 1992. The latest report details 164 fatalities during 1992 to 1998 [35]. Drug anaphylaxis represented 39% of the cases. The cause was anesthetics in 27 cases, antibiotics in 16, and radiocontrast media in 8.

For certain drugs, such as general anesthetics, penicillins, or radiocontrast media, the statistics are more precise. In the previously cited study of patients receiving weekly injections of penicillin G (for rheumatic fever) [26], four anaphylactic events (incidence of 0.2% of patients and 0.01% of injections) and one fatality (incidence of 0.05% of patients and 0.003% of injections) are described. In the study by Katayama et al [30] of 337,647 injections of radiocontrast media in Japan, two deaths were reported (incidence of 0.0006%).

Drug-related risk factors

Drug-related, treatment regimen–related, and patient-related risk factors have a major role in determining drug hypersensitivities. To be immunogenic in a native state, a substance must have a sufficient molecular weight (>1000 D). Examples include complete allergens such as heterologic sera, certain enzymes (chymopapain), and hormones (insulin). Most other drugs have an insufficient molecular weight but can react as haptens by covalent binding to a carrier protein (possibly a major histocompatibility complex [MHC]–associated peptide) [16] to induce a specific immune response [11]. Some drugs (eg, penicillins) are intrinsically reactive (hapten concept), whereas other drugs require enzymatic or nonenzymatic conversion to a reactive intermediate (pro-hapten concept). Sulfamethoxazole, for which the hydroxylamine derivative is a reactive metabolite, illustrates the pro-hapten concept. The inherent chemical reactivity of drugs or drug metabolites is critical [6,16]. In addition, drug-related cytotoxicity may be of importance to enhance the immune response (danger concept) [6]. According to this concept, the immune response to a drug-derived antigen requires the presence of co-stimulatory signals and cytokines, which propagate and determine the type of immune response. The “danger signal” might result from chemical, physical, or viral stress. On the other hand, many drugs are not reactive and can still be immunogenic by direct noncovalent binding to MHC peptides (pharmacologic interaction concept) [16].

Treatment regimen–related risk factors

The dosage of the drug and the mode of administration influence the frequency of the reactions. Certain drugs given at high doses or frequency are

associated with increased rates of sensitization. In an allergy to penicillin or insulin, intermittent and repeated administrations are more sensitizing than is an uninterrupted treatment. The parenteral route is the most immunogenic, but topical administration (ointments, creams, eye drops) also can be immunogenic and a source of sensitizations and reactions (probably owing to a local inflammation).

Host-related risk factors

Several host-related factors can influence how a drug is processed and can predispose the host to drug allergy. Most studies show that women are affected more often than men (65% to 70% versus 30% to 35%, respectively) [36–38], and it is often reported that children are less affected than adults. This is also the authors' experience, but systematic and thorough studies are lacking. Atopic patients do not seem to be predisposed [37–39], but their reactions can be more severe. This notion is regularly debated, and atopy could have a role for certain drugs, such as nonsteroidal anti-inflammatory drugs [40] and chymopapain [41]. In the study by Haddi et al [37], the percentage of subjects with specific serum IgE (globally evaluated by the positivity of Phadiatop) was not higher in 303 subjects with a history of allergic reactions to drugs (17.6%) when compared with 1764 subjects without this history.

A familial concentration of cases is sometimes reported in the literature. Certain MHC haplotypes seemed to be implicated in delayed hypersensitivity reactions to aminopenicillins (A2, DRw52) [42], pyrazolone (DQ7, DR11) [43], abacavir (B57, DR7DQ3) [44], and carbamazepine hypersensitivity (DR3, DQ2) in one study [45] but not in another [46]. The genetic control of cytochrome P-450 enzymes and N-acetyl-transferases (ensuring the biotransformation of drugs) and glutathione-S-transferases (detoxification enzymes of cytochrome P-450–derived reactive metabolites) can also be the cause, and studies of the sulfonamides are ongoing. A case-control study suggests that patients with systemic lupus erythematosus have a two to five times greater risk for reactions (principally cutaneous) after the absorption of β -lactams, sulfonamides, and erythromycin [47]. A syndrome of multiple drug hypersensitivities (IgE-dependent for subjects allergic to penicillins) has been described [38,48] and challenged [49]. These descriptions suggest the genetic controls already mentioned but should not be mistaken for reactions to diverse drugs of an identical structure (cross-reactivities).

Patients with AIDS sustain more cutaneous reactions to drugs when compared with other persons and have 10 to 50 times more reactions to co-trimoxazole [50]. These reactions can be explained by a slow acetylator phenotype for N-acetyltransferase 2 and a deficiency in glutathione frequently observed in these patients [50,51]. Allelic differences in the activity of phase I and phase II enzymes can affect the level at which reactive metabolites are generated and how quickly these metabolites are removed. Other enzymatic polymorphisms may participate in the pathophysiology of some hypersensitivity drug reactions. An overexpression of the key enzyme in cysteinyl-leukotriene biosynthesis was reported in bronchial biopsy specimens of aspirin-induced asthma patients. This

finding could be explained, in part, by a genetic polymorphism of the leukotriene C4 synthase [52]. The variant allele $-308\text{TNF}\alpha$ was associated with severe carbamazepine hypersensitivity reactions in one study [45]. β -blockers act in the same way as the presence of asthma as risk factors for hypersensitivity reactions during radiocontrast media injections, multiplying the risk by 2.5 and 4.5, respectively [53].

Socioeconomic impact

The socioeconomic impact of drug allergies has never been precisely evaluated. One must take into account not only the direct costs (treatment of the reactions, hospitalizations, and prolongations of hospitalization) but also the indirect costs (sick leave, invalidity, excessive cost of the choice of alternatives, which are not always medically satisfactory). As an example, Preston et al [2] questioned 97 patients with a clinical history of allergy to penicillins who needed treatment with antibiotics for a classic infection treated initially with penicillins. They found that less than 10% of the patients had been given an allergy test for penicillin, more than 50% had been given an alternative but more expensive antibiotic, and more than 10% had used penicillins since their incident without any problems.

Data obtained from national cross-sectional incidence studies on hospital admissions caused by adverse drug reactions [21,22,54] can be extrapolated for the whole country and the extra cost calculated (if one knows the duration of the hospitalization of the patient). In the meta-analysis of Lazarou et al [21] of 33 prospective studies from 1966 to 1996, 4.7% of the hospitalizations were for adverse drug reactions, including a total of 1,547,000 hospitalizations for the year 1994 in the United States. It was not possible to calculate the percentage of hypersensitivity drug reactions, but this rate was estimated to be 23.8% of the adverse reactions of hospitalized patients. In another case-control study by Classen et al of the LDS Hospital [55], 1580 patients having adverse drug reactions during hospitalization were compared with 20,197 controls. The patients were hospitalized for 1.91 days more than the controls, incurring additional costs of \$2262 per patient. The role of drug allergy was not evaluated with precision.

Perspectives

Epidemiologic data on hypersensitivity drug reactions are scanty, and available information requires a cautious interpretation. Underdiagnosis because of a lack of time to declare cases to regulatory agencies seems to be as frequent as overdiagnosis owing to a common fear of anaphylaxis. These events are globally presented as adverse drug reactions and rarely individualized and proven. Misclassification based on drug allergy history may have a consequence on individual treatment choices. Choosing second-line drugs may result in greater costs, less effective treatment, and more frequent adverse effects. A better un-

understanding of the frequency of these reactions and the development of testing to establish a firm diagnosis should result in improved knowledge of this subject and should improve the diagnosis, treatment, and protection of patients. A national US task force [6] recently emphasized the importance of research to improve prevention and management of hypersensitivity drug reactions. This effort, in turn, should allow us to reduce morbidity and mortality and, consequently, health care costs.

Summary

Adverse drug reactions affect 10% to 20% of hospitalized patients, and up to one third of these events are hypersensitivity reactions. Allergic reactions are unpredictable reactions caused by immunologic mechanisms. Nonimmune hypersensitivity reactions are unpredictable adverse reactions that are clinically similar to allergic reactions for which no drug-specific antibodies or T lymphocytes are identified. Few tools allow a definite diagnosis, and most of the available ones need to be validated. True epidemiologic data are limited, and most of the available information on incidence, mortality, and socioeconomic impact should be discussed with caution.

Acknowledgments

The authors thank Dr. Eva Gomes, in Porto, Portugal, for sharing her survey on hypersensitivity drug reactions in a general adult population.

References

- [1] Johansson S, Hourihane J, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56(9):813–24.
- [2] Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am J Hosp Pharm* 1994;51(1):79–84.
- [3] Demoly P, Bousquet J. Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol* 2001;1(4):305–10.
- [4] deShazo R, Kemp S. Allergic reactions to drugs and biological agents. *JAMA* 1997;278(22):1895–906.
- [5] Vervloet D, Durham S. Adverse reactions to drugs. *BMJ* 1998;316(7143):1511–4.
- [6] Adkinson Jr NF, Essayan D, Gruchalla R, Haggerty H, Kawabata T, Sandler JD, et al. Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. *J Allergy Clin Immunol* 2002;109(3):S461–78.
- [7] Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity questionnaire. *Allergy* 1999;54(9):999–1003.
- [8] Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57(1):45–51.
- [9] Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation

- testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58(9):854–63.
- [10] Torres MJ, Blanca M, Fernandez J, Romano A, de Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;58(10):961–72.
- [11] Patterson R, DeSwarte RD, Greenberger PA, et al. Drug allergy and protocols for management of drug allergies. 2nd edition. Providence (RI): OceanSide Publications; 1995.
- [12] Vervloet D, Arnaud A, Senft M, Dor P, Bongrand P, Charpin J, et al. Leukocyte histamine release to suxamethonium in patients with adverse reactions to muscle relaxants. *J Allergy Clin Immunol* 1985;75(3):338–42.
- [13] Brander C, Mauri-Hellweg D, Bettens F, Rolli H, Goldman M, Pichler WJ. Heterogeneous T cell responses to lactam-modified self-structures are observed in penicillin-allergic individuals. *J Immunol* 1995;155(5):2670–8.
- [14] Gell PGH, Coombs RRA, Lachmann PJ. Clinical aspects of immunology. 3rd edition. Oxford: Blackwell; 1975.
- [15] Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1996;27(2):175–81.
- [16] Britschgi M, von Greyerz S, Burkhart C, Pichler WJ. Molecular aspects of drug recognition by specific T cells. *Curr Drug Targets* 2003;4(1):1–11.
- [17] Webster AW, Thompson RA. The ampicillin rash. *Clin Exp Immunol* 1974;18(4):553–64.
- [18] Battegay M, Opravil M, Wütrich B, Lüthy R. Rash with amoxicillin-clavulanate therapy in HIV-infected patients. *Lancet* 1989;334(8671):1100.
- [19] Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. *JAMA* 1995;274(1):29–34.
- [20] Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991;266(20):2847–51.
- [21] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279(15):1200–5.
- [22] Pouyanne P, Haramburu F, Imbs JL, Bégaud B. Admissions to hospital caused by adverse drug reactions: cross-sectional incidence study. *BMJ* 2000;320(7241):1036.
- [23] Smith CC, Bennett PM, Pearce HM, Harrison PI, Reynolds DJ, Aronson JK, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. *Br J Clin Pharmacol* 1996;42(4):423–9.
- [24] Hunziker TH, Künzi U-P, Braunschweig S, Zehnder D, Hoigne R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy* 1997;52(4):388–93.
- [25] Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA* 1986;256(24):3358–63.
- [26] International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991;337(8753):1308–10.
- [27] Mertes PM, Laxenaire MC, Alla F, Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003;99(3):536–45.
- [28] Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children. *Arch Dermatol* 2000;136(7):849–54.
- [29] Burke P, Burne SR. Allergy associated with ciprofloxacin. *BMJ* 2000;320(7236):679.
- [30] Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;175(3):621–8.
- [31] Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994;69(1):16–23.
- [32] van der Klauw MM, Wilson JH, Stricker BH. Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974–1994) and review of the literature. *Clin Exp Allergy* 1996;26(12):1355–63.

- [33] Lenler-Petersen P, Hansen D, Andersen M, Sorensen HT, Bille H. Drug-related fatal anaphylactic shock in Denmark 1968–1990: a study based on notifications to the Committee on Adverse Drug Reactions. *J Clin Epidemiol* 1995;48(9):1185–8.
- [34] Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *BMJ* 2000; 320(7247):1441.
- [35] Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30(8):1144–50.
- [36] Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. *Clin Exp Allergy* 1998;28(Suppl 4):S61–2.
- [37] Haddi E, Charpin D, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP, et al. Atopy and systemic reactions to drugs. *Allergy* 1990;45(3):236–9.
- [38] Asero R. Detection of patients with multiple drug allergy syndrome by elective tolerance tests. *Ann Allergy Asthma Immunol* 1998;80(2):185–8.
- [39] Astarita C, Harris RI, De Fusco R, Franzese A, Biscardi D, Mazzacca FR, et al. An epidemiological study of atopy in children. *Clin Allergy* 1988;18(4):341–50.
- [40] Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000;84(1):101–6.
- [41] Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C. Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs. *Allergy* 1998;53(9):880–4.
- [42] Romano A, De Santis A, Romito A, Di Fonso M, Venuti A, Gasbarrini GB, et al. Delayed hypersensitivity to aminopenicillins is related to major histocompatibility complex genes. *Ann Allergy Asthma Immunol* 1998;80(5):433–7.
- [43] Kowalski ML, Woszczek G, Bienkiewicz B, Mis M. Association of pyrazolone drug hypersensitivity with HLA-DQ and DR antigens. *Clin Exp Allergy* 1998;28(9):1353–8.
- [44] Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002;359(9308):727–32.
- [45] Pirmohamed M, Lin K, Chadwick D, Park BK. TNFalpha promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 2001;56(7):890–6.
- [46] Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; 155(21):2285–90.
- [47] Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. *J Rheumatol* 1992;19(2):265–9.
- [48] Smith JW, Johnson JE, Cluff LE. Studies on the epidemiology of adverse drug reactions. II. An evaluation of penicillin allergy. *N Engl J Med* 1966;274(18):998–1002.
- [49] Khoury L, Warrington R. The multiple drug allergy syndrome: a matched-control retrospective study in patients allergic to penicillin. *J Allergy Clin Immunol* 1996;98(2):462–4.
- [50] Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993;328(23):1670–4.
- [51] Buhl R, Jaffe HA, Holroyd KJ, Wells FB, Mastrangeli A, Saltini C, et al. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet* 1989;334(8675):1294–8.
- [52] Sanak M, Simon HU, Szczeklik A. Leukotriene C4 synthase (LTC4s) promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997;350(9091):1599–600.
- [53] Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on β -adrenergic blockers or with asthma. *Ann Intern Med* 1991; 115(4):270–6.
- [54] Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993;27(7–8):832–40.
- [55] Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol* 1998;102(2):281–5.