

Epidemiology and Causes of Drug Hypersensitivity

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Abstract

Drug hypersensitivity reactions (DHRs) are the adverse effects of drugs, taken at a dose which is tolerated by normal subjects, which clinically resemble allergy. There are few true epidemiological data on DHRs. The available information requires a cautious interpretation because the pathogenic mechanism has not been demonstrated by diagnostic tests. Both under- and over-diagnosis must be taken into account. DHRs may represent up to one third of adverse drug reactions, be life-threatening, require or prolong hospitalization, and entail changes in drug prescription. They concern more than 7% of the general population, and therefore are an important public health problem. A few risk factors have been pinpointed. Future progress in genetics, as well as well-designed epidemiological studies on hypersensitivity drug reactions, will be helpful in identifying patients at risk of developing such reactions, in particular severe ones, and in implementing early preventive measures. This review describes current data on the incidence, prevalence, mortality, and risk factors of these reactions.

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Introduction

Drug hypersensitivity reactions (DHRs) represent adverse effects of drugs, taken at a dose which is tolerated by normal subjects, which clinically resemble allergy. Numerous reactions with

symptoms suggestive of an allergy are often erroneously considered to be real drug allergies. In any case, although DHRs are a frequent, almost constant worry for the prescribing physicians, there is no extensive epidemiological study.

DHRs belong to type B adverse drug reactions (ADRs) [1–7]. The classical pharmacological classification of ADRs by Rawlins and Thompson [7] divides these into two major subtypes: type A reactions, which are dose-dependent and predictable, and type B, which are neither. The majority of ADRs are type A reactions. Type B reactions constitute approximately 10–15% of all ADRs (up to one third for some authors) and include DHRs. This classification was further extended to include other subtypes [8–11]. Although more accurate, the latter is too complex to use in everyday clinical practice.

Drug allergic reactions, according to the Nomenclature Review Committee of the World Allergy Organization, refer to DHRs where a definite immunological mechanism, either IgE- or T-cell-mediated, is demonstrated [12]. ADRs that clinically resemble an allergy, but where an immunological process is not proven should be classified as non-immune DHRs [12]. This is impor-

tant because most of the available epidemiological studies to date refer to ADRs in general terms rather than drug allergy. In addition, drug allergy studies rely on clinical histories of a temporal relationship between administration of the suspect drug and symptoms/signs without in vivo or in vitro tests demonstrating drug-specific IgE- or T-cell-mediated mechanisms. This is due to the lack of standardized tests for many of these drugs and the limited use of drug provocation tests.

Prevalence and Incidence of Drug Hypersensitivity Reactions

DHRs are responsible for significant morbidity, mortality and socioeconomic costs that have yet to be fully calculated. Current epidemiological data have to be carefully evaluated as different studies use different populations (either adult or pediatric populations or both, inpatients or outpatients), different definitions of ADRs/drug allergy, and different methodologies and methods of data analysis. It should also be kept in mind that causality assessment (or drug imputability) relies mostly on clinical histories that are not accurate enough for the firm diagnosis of DHRs and cannot replace drug allergy testing [13].

Data on Hospital-Based Populations

The Boston Collaborative Drug Surveillance Program collected information on all ADRs in 4,031 hospitalized patients during a 6-month period: 247 reactions were declared (an incidence of 6.1%), of which 41.7% were severe and 1.2% led to the patient's death [14]. The majority (61.7%) of these reactions were unpredictable and therefore possibly allergic reactions, although this is not stated in the paper. The use of an automatic detection system in the LDS Hospital in Salt Lake City allowed the identification of 731 reactions among 36,653 hospitalized patients (only 12.3% were reported by the doctors in the hospital) during an 18-month period [15]. The incidence

(1.8%) was lower than in the previous study; 13.8% were severe and 32.7% of an allergic nature. However, if the criteria for inclusion had been similar to those used in the Boston study, the incidence (2.8%) would still have been quite similar. Lazarou et al. [16] showed in a meta-analysis of 39 prospective USA studies from 1966 to 1996 that 15.1% of hospitalized patients suffered an ADR (6.7% severe) and that the incidence of drug-related hospital admissions ranged from 3.1 to 6.2%. Although Kvasz et al. [17] raised some questions about the methodology and the validity of the meta-analysis, many subsequent studies have reported similar data. A study by Fattinger et al. [18] analyzed 4,331 hospitalizations in two Swiss departments of internal medicine and found that clinically relevant ADRs occurred in 11% of the patients and that ADRs were the cause of admission in 3.3%. In the prospective French pharmacovigilance study by Olivier et al. [19], data from 671 patients admitted to an emergency department during a 4-week period led to the identification of 44 ADRs involving 41 patients, an incidence of 6.1% (table 1).

In Singapore, a 2-year prospective study by Thong et al. [20] using a network-based electronic notification system where each case was verified by a trained allergist, detected 366 cases of reported drug allergy in a total of 90,910 inpatients. After review, 210 were classified as drug allergy. Cutaneous eruptions were the most common clinical manifestations (95.7%), systemic symptoms occurred in 30% of the cases, and serious adverse reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and general exfoliative dermatitis occurred in 11 patients (5.2%). Antibiotics and anti-epileptic drugs accounted for 75% of the reactions. Thong et al. concluded that the incidence of drug allergy in hospitalized patients was 0.42%. In a Swiss paper by Hardmeier et al. [21], 481 (7.5%) ADRs occurred among 6,383 inpatients (4 allergic reactions to antibiotics in patients with known allergy to the same drug) and there were 2.9% ADR-re-

Table 1. Epidemiological data on hospital-based populations

Ref.	Patients	ADRs	Incidence of ADRs %	Period	Type of ADRs	Culprit drugs	Remarks
14	4,031	247	6.1	6 months	B (61.7%)		41.7% severe ADRs 1.2% fatalities
15	36,653	731	1.8	18 months	A (664 ADRs) B	analgesics, anti-infectious and cardiovascular agents	13.8% severe ADRs 32.7% allergic ADRs
16	62,480		15.1 (ADRs) 6.7 (severe ADRs) 0.32 (fatalities)	1966–1996	A (76.2%) B		
18	3,624	4,331	0.14 (fatalities)	1996–1998	mainly A	cancer chemotherapeutics, iloprost, cyclosporin A	48% possible ADRs 41% possible ADRs disease-unrelated 11% clinically relevant ADRs were the cause of hospitalization in 3.3%
19	671	44 (in 41 patients)	6.1	4 weeks	A (33%)		71% possible ADRs 18% plausible ADRs 11% likely ADRs
20	90,910	366	0.42	1997–1999	210 cases of drug allergy	antibiotics antiepileptics	95.7% (cutaneous symptoms) 30% (systemic symptoms) 5.2% (severe ADRs)
21	6,383	481	7.5	1996–2000	A (0.4%) B (7.2%)	antithrombotics, cardiovascular drugs, antibiotics, hypnotics and NSAIDs	
22	171	7	4	20 days	A B (2 allergic reactions)	antibiotics	
23	18,820	1,225	6.5	6 months	A (95%)	NSAIDs diuretics	
24	13,294	48	0.36	2000–2001	B	antibiotics (penicillins)	all cutaneous ADRs 34% severe ADRs
25	8,437 children	222	2.6	2002	B (98%)	antibiotics NSAIDs	98% cutaneous ADRs
26	789	789	1/13,000 administrations	1999–2000	B	NMBAs, latex antibiotics	all anaphylactic reactions during anesthesia in France 63.6% IgE-mediated
27	83	83		1996–2001	B	NMBAs latex	all anaphylaxis during anesthesia in Norway, 71.1% IgE-mediated
28	68 children	68	1/2,100 surgeries	1989–2001	B	NMBAs, latex, colloids, opiates, hypnotics	cross-reactivity amongst NMBAs in 23 of 30 children (76%)
29	337,647 injections		12.7 (ionic RCM) 3.1 (non-ionic RCM)		A B	RCM	severe ADRs: 0.22% (ionic RCM) and 0.04% (non-ionic RCM), 2 fatalities
31	11,898	132	1.1	1998–2004	mainly A	fluorescein	
32	489,494	110	1–10/10,000 person-years	1998–2001	B	antiepileptics	all ADRs were SJS and TEN, >90% of cases occurred within the first 63 days of therapy

ADRs = Adverse drug reactions; NMBAs = neuromuscular blocking agents; NSAIDs = non-steroidal anti-inflammatory drugs; RCM = radio contrast media; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

lated hospital admissions. In a 20-day observational prospective study from an Italian university hospital, among 171 inpatients undergoing antibiotic treatment, 7 (4%) patients experienced an ADR, of which 2 (28%) (angioedema from piperacillin; skin rash from ceftriaxone) may have been allergic reactions [22]. Pirmohamed et al. [23] conducted a prospective study in two National Health Service hospitals in Merseyside, UK, comprising 18,820 patients aged >16 years admitted over a 6-month period, which found 1,225 (6.5%) admissions related to an ADR. Most ADRs (95%) were classified as type A reactions, and thus not related to drug hypersensitivity. However, non-steroidal anti-inflammatory drugs (NSAIDs) were again the most commonly implicated drugs (causing hemorrhagic complications, wheezing and dermatological reactions), followed by diuretics. In a 6-month prospective survey of cutaneous drug reactions in hospitalized patients from a French general hospital, a total of 48 cases assessed by dermatologists as cutaneous allergic reactions from drugs resulted in an incidence of 3.6 per 1,000 patients. Of these, 34% were considered severe and antibiotics, mainly penicillins, were the most commonly implicated drug [24]. A recent retrospective case control study from Singapore by Kidon and See [25] using the hospital inpatient electronic medical record found 222 (2.6%) patients reporting a previous ADR among 8,437 hospitalized children. Almost 70% of them involved the use of antibiotics (β -lactams in 45%) and NSAIDs (18.5%); 98% of the reactions were cutaneous and could have been allergic in nature.

When considering more specific clinical settings it is possible to find more accurate data. The French registry of anaphylaxis during general anesthesia identified 789 cases during a 2-year survey, giving an incidence of 1/13,000 administrations of general anesthesia. 518 (66%) were IgE-mediated, with neuromuscular blocking agents (NMBAs) (58.2%) (incidence of 1/6,500 NMBA injections) and antibiotics (15.1%) being

the most common etiologic agents [26]. The latter are now a rising cause of anaphylaxis during general anesthesia. Similarly, a high prevalence (71.1%) of IgE-mediated reactions has been reported in a 6-year survey performed by a single allergy center in Norway. Among 83 cases of anaphylaxis related to general anesthesia, 93.2% were caused by NMBAs [27]. Suxamethonium was the most frequently involved substance, followed by rocuronium and vecuronium. The few reactions in which other allergies could be detected were mainly linked to latex (3.6%). Data in children are scarce. A 12-year survey at a French pediatric center reported 68 cases of children who suffered anaphylaxis during general anesthesia [28]. 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, 14 (27%) to latex, 7 (14%) to colloids, 5 (9%) to opiates, and 6 (12%) to hypnotics. The NMBA vecuronium caused the largest number of reactions. Cross-reactivity among the NMBAs available in France was observed in 23 of 30 children (76%), particularly to vecuronium, atracurium and pancuronium. The estimated frequency of IgE-mediated anaphylactic reactions was 1 in 2,100 operations. In the study by Katayama et al. [29], of 337,647 injections of radio contrast media (RCM) in Japan, the incidence of adverse reactions was 12.7% (0.22% of severe reactions for ionic products and 0.04% for non-ionic products); two reactions were fatal (incidence of 0.0006%). The data concerning RCM have been reviewed recently [30]. It would appear that mild immediate reactions occur in 3.8–12.7% of patients receiving intravenous injections of high-osmolar, ionic RCM and in 0.7–3.1% of patients receiving low-osmolar non-ionic RCM. Severe immediate reactions have been reported to occur with a frequency of 0.1–0.4% for ionic RCM and with a frequency of 0.02–0.04% for non-ionic ones. The frequency of non-immediate adverse reactions ranges from 0.5 to 23%. This large variation may be due to the difficulty

in verifying whether symptoms occurring hours or days after RCM exposure are actually caused by the RCM. When radiological examinations with use of RCM were compared with examinations without RCM, most non-immediate symptoms, except skin reactions, were found to be unrelated to the RCM administration. Thus, various types of exanthema seem to account for the majority of the RCM-induced non-immediate hypersensitivity reactions. Such eruptions have been reported to affect some 1–3% of RCM-exposed patients.

With regard to fluorescein, an Australian review reported 132 adverse reactions among a total of 11,898 fluorescein angiograms performed between 1998 and 2004 [31]. Reactions were mainly nausea and vomiting, but dizziness, fainting, localized reactions, and urticaria also occurred. There were no serious adverse reactions or deaths recorded.

As far as antiepileptic drugs are concerned, a recent study evaluated the risk of hospitalization for SJS and TEN in new users and estimated that it was low for carbamazepine, lamotrigine, phenytoin, and phenobarbital (ranging between 1 and 10 per 10,000 new users) and significantly lower for valproic acid. Furthermore, more than 90% of cases occurred within the first 63 days of antiepileptic use [32].

Data on Outpatients and General Population

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 (table 2). A prospective study of patients receiving monthly injections of penicillin G (for rheumatic fever) found 57 reactions in 1,790 patients (incidence of 3.2% of patients and 0.19% of injections), 4 cases of anaphylaxis (incidence of 0.2% of patients and 0.01% of injections), and 1 fatality (incidence of 0.05% of patients and 0.003% of injections) [33]. Apter et al. [34] led a retrospective cohort study using the UK General Practice Research Database. Records

of patients who received at least two prescriptions for penicillin at least 60 days apart were selected and examined for hypersensitivity reactions. A penicillin prescription was given to 3,375,162 patients (all ages), of which 6,212 (0.18%) experienced an allergic-like event. Of these, 48.5% were given a second prescription after the event and only 1.89% had another event, suggesting that penicillin hypersensitivity is less frequent in outpatients than in hospitalized patients and that most reactions resembling drug allergy are not drug related. On the other hand, although the difference in incidence is small in the group reporting a previous reaction, the risk of a second event increased 11.2 times. However, higher numbers are reported in the meta-analysis by Impicciatore et al. [35], where the reported incidence of ADRs in pediatric outpatients was 1.46%. In another review of 5,923 records from a private group pediatric practice in northern Virginia, cutaneous eruptions occurred in 7.3% of children who were given common oral antibiotics [36]. With regard to quinolones, 3 out of 3,200 students treated with ciprofloxacin to prevent meningococcal carriage experienced an anaphylactic reaction [37]. A cross-sectional survey of a general adult population from Porto, Portugal, found a global 7.8% (181/2,309) prevalence of self-reported drug allergy; 4.5% to penicillins or other β -lactams, 1.9% to aspirin or other NSAIDs and 1.5% to other drugs. Most of the reported reactions were immediate (43%), occurred on the first day of treatment (78.5%), and involved the skin (63.5%), and thus could have been immune-mediated [38]. Similar results were found among university students using a comparable methodology [39]. Between 2003 and 2004, a subsample of 282 general practitioners in the BEACH (Bettering the Evaluation and Care of Health) data collection program in Australia recorded patient responses to questions about ADRs [40]. From 8,215 encounters, doctors reported that 852 patients (10.4%) had experienced an ADR in the previous 6 months. Patients aged >45 years (ver-

Table 2. Epidemiological data on outpatients and general population

Ref.	Patients	Patients with ADRs	Incidence of ADRs %	Period	Type of ADRs	Culprit drugs	Remarks
33	1,790 (32,430 injections)	57	3.2 (ADRs) 0.2 (anaphylaxis) 0.05 (fatality)	1988–1990	B	benzathine penicillin	patients with long-term drug prophylaxis for rheumatic fever 4 anaphylaxis, 1 fatality
34	3,375,162 (1st prescription) 2,017,957 (2nd prescription)	6,212 3,509	0.18 1.89 with previous reactions 0.17 without	1987–2001	B	penicillin	risk of DHRs is markedly increased in subjects with a previous reaction
35	11,513 children	192	1.46		not specified		64 reactions definite/probable 1 severe ADR
36	5,923 children records	472 erythemas	7.3	1996	B	antibiotics	none were severe
37	3,200	8	1:1,000		B	ciprofloxacin	3 anaphylaxis 3 erythemas 2 nausea and vomiting
38	2,309	181	7.8	2002	B	mainly β -lactams	63.5% cutaneous ADRs
39	2,150		7.7	2001	B	antibiotics NSAIDs	mainly cutaneous ADRs
40	8,215	852	10.4	2003–2004	A B		>50% mild ADRs 35.8% moderate ADRs 10% severe ADRs risk factors: old age and female gender

ADRs = Adverse drug reactions; DHRs = drug hypersensitivity reactions; NSAIDs = non-steroidal anti-inflammatory drugs.

sus <45 years), children aged 1–4 years (versus older children), and female patients (versus male patients) were significantly more likely to have experienced an ADR. Most patients (83.5%) had experienced only one ADR, while 10.7 and 5.8% had experienced two or more events, respectively. For 71.9% of the patients, one reason for the most recent event was a recognized side effect, followed by drug sensitivity (12.4%) and allergy (11.0%). Over half of the patients were rated as having a ‘mild’ event, with 35.8% rated as ‘moderate’ and 10.0% as ‘severe’. General practitioners classified 23.2% of events as preventable, and 7.6% of events resulted in hospitalization.

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. Reactions are in most cases not declared, but reported numbers can also be inflated by the lack of a definite diagnosis.

General Data on Mortality

DHRs can be serious and life-threatening. All routes of administration are potentially lethal: oral, injectable (i.v., i.m., s.c., intralymphatic, intra-articular), inhaled, topical (intrauterine, rectal, cutaneous). The study by Lazarou et al. [16]

showed that 0.32% of hospitalized patients in the USA died from ADRs, an estimated 106,000 deaths for the year 1994, which would make them the fourth most frequent cause of death in that country. The proportion of allergic reactions in this study was not evaluated, but could be estimated to be around 23.8% (all severities). Pirmohamed et al. [23] found that the overall fatality rate related to ADRs was 0.15%, and calculated that ADRs that had led to hospital admissions were responsible for 5,700 deaths per year in England. In the study by Fattinger et al. [18] the estimated incidence (0.14%) of possible ADR-related deaths was similar. In the study by Hardmeier et al. [21], among 6,383 inpatients, 10 ADR-related fatalities were reported (0.16% of the included patients), corresponding to 3% of all deaths. A similar percentage (5%) of ADR-related deaths was reported by Juntti-Patinen and Neuvonen [41] in their study evaluating 1,511 in-hospital fatalities. In the study by Moore et al. [42] of 329 patients admitted to an internal medicine ward over 6 months, there were 31 patients (9.4%) with at least one ADR and a fatal reaction occurred in 4 of them (13%). Thong et al. [20] found that the mortality due to drug allergy was 0.09 per 1,000 hospitalizations.

Anaphylactic shock is one of the severe reactions commonly associated with drug allergy fatalities. It is usually an IgE-mediated reaction and it is the most frightening and potentially lethal allergic event. Non-IgE-mediated anaphylactic shocks can also be drug related and equally dangerous. In the retrospective study by Kemp et al. [43], of 266 cases of anaphylaxis described by a private allergy practice in Memphis, drugs (20%) were the second most recognizable cause of reactions, with NSAIDs responsible for half of them. The lethal risk related to penicillin anaphylaxis has long been known. There is renewed interest in this subject because injectable antibiotics are responsible for a large percentage (15%) of anaphylaxis during anesthesia, making them the third most important cause after NMBAs and

latex [26]. Antibiotics take the first position in cases declared to the French Allergovigilance Network [44]. Based on a medical literature review to obtain prevalence estimates of anaphylaxis in the general population, Neugut et al. [45] calculated a rate of 0.7–10% for penicillins (the USA population at risk would be 1.9–27.2 million) and 0.22–1% for RCM (the USA population at risk would be 22,000–100,000). Matasar and Neugut [46] reported about 1,500 annual deaths from anaphylaxis in the USA. In the UK, where hospital admissions for acute anaphylaxis are increasing (from 56 per million in 1991 to 102 per million in 1995) [47], the work by Pumphrey [48] on deaths from anaphylaxis (1992–2001) shows that drugs are the leading cause (88 deaths out of 202) followed by food allergy and insect stings. In the complete 1992–1998 UK registry of fatal anaphylaxis, there were 164 fatalities, of which drug-induced anaphylaxis constituted 39% of the cases, with 27 cases from anesthetics, 16 from antibiotics, and 8 from RCM [49]. In another recent analysis by Peng and Jick [50] using a general practice research database (1994–1999), 675 cases of anaphylaxis were reported; thus, the estimated incidence of 8.4 per 100,000 persons/year of anaphylaxis in the UK, with oral medicines being the second most common cause after insect stings. The recent 3-year Swiss study by Helbling et al. [51] led to the identification of 226 individuals diagnosed with 246 episodes of life-threatening anaphylaxis and 3 deaths. The authors calculated an annual incidence of 7.9–9.6 cases per 100,000 inhabitants per year of anaphylaxis and identified drugs as the second most common cause (18.1%) after hymenoptera stings. Van der Klauw et al. [52] analyzed 345 cases of probable anaphylaxis and 485 cases of possible anaphylaxis associated with drugs over a 20-year period in the Netherlands. In this study, the mortality from anaphylactic shock was 2.5% (21 cases of 830) and the implicated drugs were: RCM (8 deaths), dextran (3), glafenin (2), immunotherapy for allergy (2), protamine (1), penicillin (1), tetracosac-

tide (1), metoprolol (1), erythromycin (1), and butylscopolamine with metimazole (1). In Italy, Cianferoni et al. [53] carried out a retrospective review of the clinical features of 113 episodes of anaphylaxis regarding 107 patients and resulting in admission to hospital. Drugs (NSAIDs and antibiotics) were the most frequent cause of reactions (49%), followed by hymenoptera stings (29%). From 1968 to 1990 the Danish Committee on Drug Administration [54] recorded 30 cases of fatal anaphylaxis, of which 8 were caused by RCM, 6 by penicillins, 5 by allergen extracts, 2 by NSAIDs and 1 by a NMBA (incidence of 0.3 cases of fatal anaphylaxis per million inhabitants per year).

Anaphylaxis is not, however, the only cause of mortality due to allergic drug reactions. The serious, mostly drug-related delayed dermatological conditions SJS (ca. 10% mortality) and TEN (30% mortality), with estimated incidences of 0.4–1.2 and 1.2–6 per million people/year, respectively [55], are other examples of life-threatening reactions [56]. They occurred in 5.2% of the 210 drug-allergic patients in the study by Thong et al. [20]. The multisystem organ hypersensitivity syndrome (10% mortality) and organ-specific involvement, including hepatitis, can also contribute to drug hypersensitivity-related mortality.

Risk Factors for Drug Hypersensitivity Reactions

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.

Drug-Related Aspects

A large variety of drugs are currently used in everyday practice. However, those implicated in allergic reactions are a much smaller group. In order to be immunogenic or a complete allergen, it

is believed that a substance must have a sufficient molecular weight (>1,000 daltons); thus, most drugs behave as haptens and have to bind to carrier proteins to induce a specific immune response. β -Lactams are intrinsically reactive (supporting the hapten concept of the pathophysiology of drug allergy), other drugs, like sulfamethoxazole, require previous conversion to a reactive intermediate (pro-hapten concept). Drug-related cytotoxicity may also be of importance in enhancing the immune response (danger concept). Although not reactive, some other drugs can still be immunogenic by direct non-covalent binding to immune receptors, mostly T-cell receptors (pharmacological interaction concept) [57]. The notion that the type of drug itself is an important risk factor for drug allergy even among the same therapeutic group can be illustrated by the review by Ibia et al. [36]. Based on the number of patients for whom each group of antibiotics was prescribed, the documented frequencies of reactions were: 12.3% for cefaclor, 8.5% for sulfonamides, 7.4% for penicillins, and 2.6% for other cephalosporins. This is also shown in another survey from the Boston Collaborative Drug Surveillance Program [58]. In this survey, which provided most of the data regularly used regarding the incidence of DHRs, the authors analyzed the incidence of cutaneous drug reactions in 15,438 hospitalized patients. There were 358 reactions reported and confirmed by a dermatologist, with an overall incidence of 2.3%. The number of reactions over the number of administrations for each drug was 5.1% for amoxicillin, 3.4% for cotrimoxazole, 3.3% for ampicillin, 2.1% for cephalosporins, 2% for erythromycin, 1.8% for penicillin G, and 0.4% for gentamycin. Another interesting aspect is the changing pattern of reactivity to certain drugs over time, which has been especially demonstrated with β -lactams [59]. Traditionally, reactions to β -lactams concerned mostly penicillin G, but in recent years reactions to amoxicillin and to cephalosporins have been increasing and their prevalence seems

to differ among populations and/or countries (e.g., anaphylaxis associated with β -lactams appears to be rare in Central Europe and common in Southern Europe).

Treatment Regimen

The dosage of the drug and the mode of administration influence the frequency of reactions. It appears that intermittent and repeated administrations can be more sensitizing than an uninterrupted treatment [60]. This is supported by a recent publication by Cetinkaya and Cag [61] who studied 147 children who had received β -lactams at least 3 times in the preceding 12 months without allergic reaction. A 10.2% frequency of positive skin tests to penicillin was found and the authors concluded that frequent use of β -lactam antibiotics leads to sensitization. Pichichero and Pichichero [62], however, found no difference in the frequency of previous β -lactam treatments in skin-test-negative and skin-test-positive children.

With regard to the route of administration, the parenteral route is considered the most immunogenic, although strong data showing that the parenteral route is more immunogenic than the oral route are lacking. Topical administration to the skin (and not the mucosa) is an important sensitization pathway [63, 64].

Host-Related Factors

Host-related factors can predispose patients to drug allergy, especially by acting on the way the drug is processed. Most studies show that women are more often affected than men (65–70 vs. 30–35%) [65–67]. Differences can, however, depend on the age group [25], on the type of reaction (cutaneous reaction rates were 35% higher in females than males in the Bigby et al. [58] review), and on the culprit drug [38]. In a gemifloxacin unpublished study, 30% of women in child-bearing age reacted as compared to only 4% of males (<http://www.fda.gov>). Estrogen production or use possibly plays a role. Subgroup analysis of the study

of Thong et al. [20] showed that hospitalized female patients were statistically significantly more likely to develop drug allergy than males, although there were no significant differences in the clinical manifestations and mortality between both genders. In addition, patients >65 years of age did not appear to be more at risk of developing drug allergy than those <65 years and there was no increase in the severity of allergic reactions or drug-related mortality [pers. commun., unpubl. data].

It is often reported that children are less affected than adults [68]. In the study on pediatric patients by Temple et al. [69], 565 ADRs were reported by a hospital surveillance program over a 6-year period (1994–1999), with an ADR rate of 0.85 per 100 admissions. Antibiotics were the most frequently implicated drug class (26.4%), although 2.8% of patients had a documented allergy to the medication suspected of causing the reaction. However, other studies on ADRs in pediatric populations report incidences similar to the ones in adults [35, 36]. In the 20-day observational prospective study of Mazzeo et al. [22], the rate of reactions (most of them probably not due to allergy) to antibiotics in inpatients was higher in children than in adults. An 8-month survey of ADR in a pediatric isolation ward by Weiss et al. [70] showed that among 68 ADRs detected in 46 (21.5%) of 214 patients, 7 (10%) were classified as severe and 50% were antibiotic-associated. Of all the ADRs, 14 (20.6%) were considered to be of an immunologic nature.

The role of atopy is still under debate, but it does not seem to be a major risk factor [66, 67, 71]. The influence of atopy may, however, depend on the drug in question and it was reported to be a risk factor for NSAID hypersensitivity, especially when cutaneous reactions are present [72].

Some ethnic groups and genetic backgrounds seem to facilitate certain types of ADRs (table 3). Easterbrook et al.'s [73] study on epidemiological risk factors for hypersensitivity reactions to abacavir found the Caucasian race to be a risk factor

Table 3. Genetic risk factors for drug hypersensitivity reactions

Ref.	Population	Genetic predisposition	Drug-related clinical symptoms
25	222 hospitalized children	old age, male gender, Chinese descent, asthma and associated chronic illness	ADRs due to mainly β -lactams and NSAIDs
73		white race and a high CD8 cell count at therapy initiation	abacavir hypersensitivity
74	2,225	East Asians were more likely to develop cough and hyperkalemia, and African-Americans to develop angioedema	ADRs associated with ACE inhibitors
76		African and Asian people	ACE inhibitors-induced cough
77	Maputo, Mozambique	more frequently in Blacks (18.0%) than in Non-Blacks (3.2%)	self-reported chloroquine allergy
78		abnormal des-Arg(9)-BK degradation	ACE inhibitors-induced angioedema
79	Australian	HLA-B*5701, HLA-DR7 and HLA-DQ3 incidence of HLA-B*5701 allele = 94.4%	abacavir hypersensitivity
80	Australian	HLA-B*5701 and Hsp70-Hom M493T alleles haplotypic polymorphism within the TNF promoter region (TNF α -238A)	abacavir hypersensitivity
83	USA	HLA-B*5701 (incidence = 22.2%)	abacavir hypersensitivity
84		TNF α promoter polymorphism (-308 position)	severity of CBZ hypersensitivity
85	English	HSP70 gene variants	CBZ-induced SJS/TEN
86 [#] , 87	Han Chinese	HLA* 1502 gene, [#] incidence of this allele = 100%	CBZ-induced SJS/TEN
89	European	HLA* 1502 allele and Asian ancestry in 4/12 cases	CBZ-induced SJS/TEN
92	Han Chinese	HLA-B*5801	allopurinol-induced severe cutaneous allergic reactions
94		LTC4S promoter polymorphism	ASA-induced asthma
95		familial aggregation inheriting the LTC4S -444C allele deletion of GSTM1	ASA-induced urticaria
96	Japanese	promoter -1993T>C polymorphism in the TBX21 gene, coding for T-bet	ASA-induced asthma
97	Korean	HLA-alleles DRB1*1302 and DQB1*0609, promoter polymorphisms of ALOX5 (-1708A>G), CysLTR1 (-634C>T) and Fc ϵ R1 α (-344C>T, -95T>C)	ASA-induced urticaria/angiodema
98		Fc ϵ R1 β (-190T>C) polymorphism of MS4A2 gene	ASA-induced asthma
99	Korean	CysLTR1 variants	ASA-induced asthma
100		ALOX5 Sp1 repeat polymorphism	severity of ASA-induced asthma
101	Chinese	E237G variant of Fc ϵ R1 β gene	IgE-mediated penicillin allergy
102	Chinese	IL-4R α Q576R polymorphism	IgE-mediated penicillin allergy
103	Chinese	IL-4-IL-13-SNP polymorphisms	IgE-mediated penicillin allergy
104	Italian	polymorphisms of IL-13 (R130Q and -1055C>T variants) and IL-4RA (I50 V, S478P, and Q551R variants)	immediate allergic reactions to β -lactams
105	Caucasian	Ile75Val variant of IL-4R α gene two linked IL-10 promoter gene polymorphisms (-819C>T and -592C>A)	immediate allergic reactions to β -lactams

ACE = Angiotensin-converting enzyme; ADRs = adverse drug reactions; ALOX5 = 5-lipoxygenase; BK = bradykinin; CBZ = carbamazepine; CYP2C9 = cytochrome P₄₅₀2C9; CysLTR1 = cysteinyl LT receptor 1; GSTM1 = glutathione S-transferase M1; Fc ϵ R1 α = high-affinity IgE receptor α chain; Fc ϵ R1 β = high-affinity IgE receptor β chain; HSP = heat-shock protein; LTC4S = leukotriene C4 synthase; NSAIDs = non-steroidal anti-inflammatory drugs; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

for reactions. In a recent cohort study evaluating risk factors for ADRs associated with angiotensin-converting enzyme (ACE) inhibitors involving 2,225 people, of whom 19% had to discontinue therapy due to ADRs, African-Americans were found to be more susceptible to developing ACE-related angioedema than other ethnic groups [74]. This confirmed the results of other authors [75]. African and Asian people also appear to be at an increased risk for ACE inhibitor-induced cough [76]. In the study by Lunet et al. [77], self-reported chloroquine allergy in Maputo, Mozambique, was more frequent in Blacks (18.0%) compared with Non-Blacks (3.2%). In the study by Kidon et al. [25], Chinese descent, asthma, and associated chronic illness were all considered as independent risk factors for ADRs. These differences may be due to genetic polymorphisms that alter drug metabolism or immune responses in some individuals, leading to an increased susceptibility to certain drugs or to certain ADRs. For example, individuals with ACE genotype II are reported to have an increased risk for ACE inhibitor-induced cough [76] and in those with angioedema an abnormal degradation of some bradykinin metabolites has been described [78].

With regard to abacavir hypersensitivity, Mallal et al. [79, 80] demonstrated that it is linked to HLA-B*5701 and to its combination with a haplotypic Hsp70-Hom M493T variant. The authors also suggest that in Whites, genotyping for HLA-B*5701 should be performed before prescription of abacavir [79] and this strategy appears to reduce the incidence of abacavir hypersensitivity in their clinic [81]. An alternative flow cytometry method for HLA-B57 phenotyping using commercially available B17 monoclonal antibodies has been developed and represents a sensitive, rapid and cost-effective alternative to HLA typing as a screening assay prior to abacavir prescription [82]. The incidence of this allele in abacavir hypersensitive persons is high (94.4%) [79] in the Australian cohort, but

in other studies [83] it is lower (22.2%), but still significantly higher than average. A haplotypic polymorphism within the TNF promoter region (TNF-238A) may also affect the levels of TNF production influencing the severity of abacavir reactions [80]. Another TNF α promoter polymorphism (-308TNF α) was associated with a more severe course of carbamazepine hypersensitivity reactions [84]. Concerning carbamazepine hypersensitivity, recent studies have also found an association between SJS and TEN and the heat-shock protein (HSP70) gene variants [85], as well as the HLA-B*1502 gene [86, 87]. The incidence of this allele is high (100%) in the Han Chinese with carbamazepine-induced severe bullous skin reactions [86], but it is not in Whites [88, 89]. Interestingly, although only 4 out of 12 carbamazepine-induced SJS/TEN cases of the European study RegiSCAR had the HLA-B*1502 allele, it is remarkable that all 4 had an Asian ancestry [89]. This shows that although this HLA region may contain important genes for SJS/TEN, this allele is not universal and ethnicity matters. In vitro data have suggested that these patients may have a detoxification defect [88]. The work by Bavdekar et al. [90] proposes that accumulation of toxic arene oxide metabolites, due to a defect in epoxide hydrolase-mediated detoxification, contributes to anticonvulsant hypersensitivity. However, no specific polymorphisms have been pinpointed in the epoxide hydrolase gene [88, 91]. Chen's group [92] also demonstrated a strong association in Han Chinese between the genetic marker HLA-B*5801 allele and allopurinol-induced severe cutaneous allergic reactions. With regard to NSAID ADRs, it was recently suggested that NSAID-related gastrointestinal bleeding could be associated with two polymorphisms of cytochrome P₄₅₀2C9 [93]. As far as NSAID hypersensitivity is concerned, a few gene polymorphisms have been found. In bronchial biopsies of patients with aspirin-induced asthma, an overexpression of leukotriene C4 synthase was reported. This could

be partially explained by a genetic polymorphism in the promoter region of this enzyme [94]. In aspirin-induced urticaria, a familial aggregation inheriting this -444C allele of the leukotriene C4 synthase gene has also been found, as well as a deletion of the glutathione S-transferase M1 [95]. A Japanese study demonstrated that the promoter -1993T>C polymorphism in the TBX21 gene, coding for T-bet, a Th1-specific transcription factor, is associated with a risk of aspirin-induced asthma [96]. The Korean cohort of aspirin hypersensitivity showed that HLA alleles DRB1*1302 and DQB1*0609 may be genetic markers of aspirin-induced urticaria/angioedema. The promoter polymorphisms of the 5-lipoxygenase (-1708A>G), cysteinyl leukotriene receptor 1 CysLTR1 (-634C>T) and high-affinity IgE receptor α chain Fc ϵ R1 α (-344C>T, -95T>C) genes were also described [97]. Other studies of the same group suggest that the genetic variants of Fc ϵ R1 β (-190T>C) [98], CysLTR1 [99] and tandem repeat in 5-lipoxygenase promoter are associated with aspirin-induced asthma [100]. Finally, concerning β -lactam hypersensitivity, Qiao's group showed that the E237G variant of Fc ϵ R1 β [101], IL-4R α Q576R [102], IL-4-IL-13-SNP polymorphisms [103] may participate in the development of IgE-dependent penicillin allergy in a Chinese population. A recent study performed on an Italian population evaluated the association between immediate allergic reactions to β -lactams, specifically penicillins and cephalosporins, and the polymorphisms of IL-13 (R130Q and -1055C>T variants) and IL-4RA (I50V, S478P, and Q551R variants). The combination of the less frequent allele of the IL-13 R130Q polymorphism with any of the predominant homozygous genotypes of the three polymorphisms of IL-4RA was more significantly associated with the risk of β -lactam allergy ($p = 0.0006, 0.0077, \text{ and } 0.0041$, respectively) than any other polymorphism considered alone ($p = 0.1745, 0.0268, 0.1812, 0.0152$, respectively). The same associations were ob-

served with serum IgE levels (IL-13/IL-4RA variant combinations: $p = 0.0009, 0.0007, 0.0020$, respectively and each variant: $p = 0.0201, 0.0021, 0.0531, \text{ and } 0.0417$, respectively). The combination of IL-4RA variants with 1055C>T polymorphism produced similar associations [104]. In a Caucasian population, Guglielmi et al. [105] found among atopic subjects two significant associations between immediate β -lactam allergy in women and the Ile75Val variant of IL-4R α gene and two linked IL-10 promoter gene polymorphisms (-819C>T and -592C>A). The time has now come to identify and analyze all relevant gene polymorphisms involved in drug hypersensitivity.

Drug hypersensitivity appears to be more frequent in certain diseases and therefore, concomitant pathologies might play a role. For example, hypersensitivity reactions to NSAIDs are particularly frequent in some populations, such as asthmatics [106]. Interestingly, Ventura et al. [107] describe hypersensitivity to aspirin as a risk factor, along with female gender and atopy, for immediate reactions to glucocorticoids. HIV-infected patients suffer 10–100 times more from cutaneous reactions to drugs, especially to cotrimoxazole [108]. The frequency of drug hypersensitivity in this population ranges from 3 to 20%. A recent review by Temesgen and Beri [109] on drug allergy in HIV patients showed comprehensive data on reactions associated with antiretroviral drugs as well as with cotrimoxazole. Aminopenicillin-induced exanthema in florid infectious mononucleosis may result from specific sensitization to the drug, although the exact role of Epstein Barr virus remains unknown [110, 111].

Finally, many factors can combine to lead to an ADR: drugs [26], infection [112], exercise, and food allergy [113] may interact with each other to induce a hypersensitivity reaction or increase its severity.

Conclusion

There are few epidemiological data on DHRs which affect up to 20% of hospitalized patients and up to 7% of outpatients. The available information, based predominantly on the epidemiology of ADRs, requires cautious interpretation, because these reactions are rarely accurately classified or definitively diagnosed. Both under-diagnosis (due to under-reporting [114, 115]) and over-diagnosis (due to the over-use of the term 'allergy' [116]) have also to be considered. Mis-

classification based on drug allergy histories may have consequences on individual treatment choices and lead to the use of more expensive and less effective drugs. Multicenter studies, both in hospital-based populations and in general populations, using the same methodologies and definitions would also be of great value in order to have an accurate global perspective about risk factors and possible regional differences and to allow the implementation of better preventive measures for patients.

References

- 1 WHO: International drug monitoring: the role of national centres. Tech Rep Ser No 498. Geneva, WHO, 1972.
- 2 Edwards IR, Aronson JK: Adverse drug reactions: definitions, diagnosis and management. *Lancet* 2000;356:1255–1259.
- 3 Meyboom RH, Lindquist M, Egberts AC: An ABC of drug-related problems. *Drug Saf* 2000;23:99–105.
- 4 Stephens MDB: Definitions and classifications of adverse reaction terms; in Stephens MDB, Talbot JCC, Routledge PA (eds): *The Detection of New Adverse Reactions*, ed 4. London, Macmillan, 1998, pp 32–44.
- 5 Ross SD: Drug-related adverse events: a readers' guide to assessing literature reviews and meta-analyses. *Arch Intern Med* 2001;161:1041–1046.
- 6 Nebeker JR, Barach P, Samore MH: Clarifying adverse drug events: a clinician's guide to terminology, documentation and reporting. *Ann Intern Med* 2004;140:795–801.
- 7 Rawlins MD, Thompson JW: Pathogenesis of adverse drug reactions; in Davies DM (ed): *Textbook of Adverse Drug Reactions*. Oxford, Oxford University Press, 1977, p 10.
- 8 Aronson JK: Drug therapy; in Haslett C, Chilvers ER, Boon NA, Colledge NR, Hunter JAA (eds): *Davidson's Principles and Practice of Medicine*, ed 19. Edinburgh, Elsevier Science, 2002, pp 147–163.
- 9 Grahame-Smith DG, Aronson JK: Adverse drug reactions; in *The Oxford Textbook of Clinical Pharmacology and Drug Therapy*. Oxford, Oxford University Press, 1984, pp 132–157.
- 10 Hartigan-Go KY, Wong JQ: Inclusion of therapeutic failures as adverse drug reactions; in Aronson JK (ed): *Side Effects of Drugs*, Annual 23. A Worldwide Yearly Survey of New Data and Trends in Adverse Drug Reactions. Amsterdam, Elsevier, 2000.
- 11 Aronson JK, Ferner RE: Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003;327:1222–1225.
- 12 Johansson S, Bieber T, Dahl R, et al: Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832–836.
- 13 Hayward RA, Hofer TP: Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *JAMA* 2001;286:415–420.
- 14 Bates DW, Cullen DJ, Laird N, et al: Incidence of adverse drug events and potential adverse drug events. *JAMA* 1995;274:29–34.
- 15 Classen DC, Pestotnik SL, Evans RS, Burke JP: Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991;266:2847–2851.
- 16 Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA* 1998;279:1200–1205.
- 17 Kvasz M, Allen E, Gordon MJ, et al: Adverse drug reactions in hospitalized patients: a critique of meta-analysis. *Med Gen Med* 2000;2:E3.
- 18 Fattinger K, Roos M, Vergeres P, et al: Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol* 2000;49:158–167.
- 19 Olivier P, Boulbes O, Tubery M, et al: Assessing the feasibility of using an adverse drug reaction preventability scale in clinical practice: a study in a French emergency department. *Drug Saf* 2002;25:1035–1044.
- 20 Thong BY, Leong KP, Tang CY, Chng HH: Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 2003;90:342–347.
- 21 Hardmeier B, Braunschweig S, Carvalaro M, et al: Adverse drug events caused by medication errors in medical inpatients. *Swiss Med Wkly* 2004;134:664–670.
- 22 Mazzeo F, Capuano A, Avolio A, Filippelli A, Rossi F: Hospital-based intensive monitoring of antibiotic-induced adverse events in a university hospital. *Pharmacol Res* 2005;51:269–274.

- 23 Pirmohamed M, James S, Meakin S, et al: Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004; 329:15–19.
- 24 Fiszenson-Albala F, Auzerie V, Mahe E, et al: A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003;149:1018–1022.
- 25 Kidon MI, See Y: Adverse drug reactions in Singaporean children. *Singapore Med J* 2004;45:574–577.
- 26 Mertes PM, Laxenaire MC, Alla F, Groupe d'Etudes des Réactions Anaphylactoides Peranesthésiques: Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003;99: 536–545.
- 27 Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E: Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005;102:897–903.
- 28 Karila C, Brunet-Langot D, Labbez F, et al: Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. *Allergy* 2005;60:828–834.
- 29 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: 621–628.
- 30 Brockow K, Christiansen C, Kanny G, et al: Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150–158.
- 31 Kwan AS, Barry C, McAllister IL, Constable I: Fluorescein angiography and adverse drug reactions revisited: the Lions Eye experience. *Clin Experiment Ophthalmol* 2006;34:33–38.
- 32 Mockenhaupt M, Messenheimer J, Tenis P, Schlingmann J: Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;64:1134–1138.
- 33 International Rheumatic Fever Study Group: Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991;337:1308–1310.
- 34 Apter AJ, Kinman JL, Bilker WB, et al: Represcription of penicillin after allergic-like events. *J Allergy Clin Immunol* 2004;113:764–770.
- 35 Impicciatore P, Choonara I, Clarkson A, et al: Incidence of adverse drug reactions in paediatric in-/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77–83.
- 36 Ibia EO, Schwartz RH, Wiedermann BL: Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol* 2000;136:849–854.
- 37 Burke P, Burne SR: Allergy associated with ciprofloxacin. *Br Med J* 2000;320: 679.
- 38 Gomes E, Cardoso MF, Praça F, et al: Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;34:1597–1601.
- 39 Falcao H, Lunet N, Gomes E, et al: Drug allergy in university students from Porto, Portugal. *Allergy* 2003;58:1210.
- 40 Miller GC, Britth HC, Valenti L: Adverse drug events in general practice patients in Australia. *Med J Aust* 2006; 184:321–324.
- 41 Juntti-Patinen L, Neuvonen PJ: Drug-related death in a university central hospital. *Eur J Clin Pharmacol* 2002;58: 479–482.
- 42 Moore N, Lecointre D, Noblet C, Mabile M: Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 1998;45:301–308.
- 43 Kemp SF, Lockey RF, Wolf BL, Lieberman P: Anaphylaxis. A review of 266 cases. *Arch Intern Med* 1995;155:1749–1754.
- 44 Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G: Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005;60: 443–451.
- 45 Neugut AI, Ghatak AT, Miller RL: Anaphylaxis in the United States: an investigation into epidemiology. *Arch Intern Med* 2001;161:15–21.
- 46 Matasar MJ, Neugut AI: Epidemiology of anaphylaxis in the United States. *Allergy Asthma Rep* 2003;3:30–35.
- 47 Sheikh A, Alves B: Hospital admissions for acute anaphylaxis: time trend study. *Br Med J* 2000;320:1441.
- 48 Pumphrey R: Anaphylaxis: Can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol* 2004;4: 285–290.
- 49 Pumphrey RS: Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144–1150.
- 50 Peng MM, Jick H: A population-based study of incidence, cause and severity of anaphylaxis in the United Kingdom. *Arch Intern Med* 2004;164:317–319.
- 51 Helbling A, Hurni T, Mueller UR, Pichler WJ: Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss canton Bern. *Clin Exp Allergy* 2004;34:285–290.
- 52 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;26:1355–1363.
- 53 Cianferoni A, Novembre E, Mugnaini L, et al: Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). *Ann Allergy Asthma Immunol* 2001;87:27–32.
- 54 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; 48:1185–1188.
- 55 Roujeau JC, Stern RS: Severe cutaneous adverse reactions to drugs. *N Engl J Med* 1994;331:1272–1285.
- 56 Wolf R, Orion E, Marcos B, Matz H: Life-threatening acute adverse cutaneous drug reactions. *Clin Dermatol* 2005;23:171–181.
- 57 Britschgi M, von Greyerz S, Burkhart C, Pichler WJ: Molecular aspects of drug recognition by specific T cells. *Curr Drug Targets* 2003;4:1–11.
- 58 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;256:3358–3363.
- 59 Blanca M, Torres MJ, Mayorga C, et al: Immediate allergic reactions to β -lactams: facts and controversies. *Curr Opin Allergy Clin Immunol* 2004;4: 261–266.
- 60 De Weck AL: Pharmacologic and immunochemical mechanisms of drug hypersensitivity. *Immunol Allergy Clin North Am* 1991;11:461–474.
- 61 Cetinkaya F, Cag Y: Penicillin sensitivity among children without a positive history for penicillin allergy. *Pediatr Allergy Immunol* 2004;15:278–280.

- 62 Pichichero ME, Pichichero DM: Diagnosis of penicillin, amoxicillin and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr* 1998;132:137–143.
- 63 Juan WH, Yang LC, Hong HS: Acute generalized exanthematous pustulosis induced by topical lindane. *Dermatology* 2004;209:239–240.
- 64 McIlwain M, Primosch R, Bimstein E: Allergic reaction to intranasal midazolam HCL: a case report. *Pediatr Dent* 2004;26:359–361.
- 65 Barranco P, Lopez-Serrano MC: General and epidemiological aspects of allergic drug reactions. *Clin Exp Allergy* 1998;28(suppl 4):S61–S62.
- 66 Haddi E, Charpin D, Tafforeau M, et al: Atopy and systemic reactions to drugs. *Allergy* 1990;45:236–239.
- 67 Asero R: Detection of patients with multiple drug allergy syndrome by elective tolerance tests. *Ann Allergy Asthma Immunol* 1998;80:185–188.
- 68 Demoly P, Bousquet J: Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol* 2001;1:305–310.
- 69 Temple ME, Robinson RF, Miller JC, et al: Frequency and preventability of adverse drug reactions in paediatric patients. *Drug Saf* 2004;27:819–829.
- 70 Weiss J, Krebs S, Hoffmann C, et al: Survey of adverse drug reactions on a pediatric ward: a strategy for early and detailed detection. *Pediatrics* 2002;110:254–257.
- 71 Ponvert C, Le Clainche L, de Blic J, et al: Allergy to β -lactam antibiotics in children. *Pediatrics* 1999;104:45.
- 72 Sanchez-Borges M, Capriles-Hulett A: Atopy is a risk for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000;84:101–106.
- 73 Easterbrook PJ, Waters A, Murad S, et al: Epidemiological risk factors for hypersensitivity reactions to abacavir. *HIV Med* 2003;4:321–324.
- 74 Morimoto T, Gandhi TK, Fiskio JM, et al: An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. *J Eval Clin Pract* 2004;10:499–509.
- 75 Brown NJ, Ray WA, Snowden M, Griffin MR: Black Americans have an increased rate of angiotensin-converting enzyme inhibitor associated angioedema. *Clin Pharmacol Ther* 1996;60:8–13.
- 76 Dykewicz MS: Cough and angioedema from angiotensin-converting enzyme inhibitors: new insights into mechanisms and management. *Curr Opin Allergy Clin Immunol* 2004;4:267–270.
- 77 Lunet N, Falcao H, Sousa M, Bay N, Barros H: Self-reported food and drug allergy in Maputo, Mozambique. *Public Health* 2005;119:587–589.
- 78 Molinaro G, Cugno M, Perez M, et al: Angiotensin-converting enzyme inhibitor-associated angioedema is characterized by a slower degradation of desarginine(9)-bradykinin. *J Pharmacol Exp Ther* 2002;303:232–237.
- 79 Mallal S, Nolan D, Witt 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;359:727–732.
- 80 Martin AM, Nolan D, Gaudieri S, et al: Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA* 2004;101:4180–4185.
- 81 Rauch A, Nolan D, Martin A, et al: Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006;43:92–102.
- 82 Martin AM, Krueger R, Almeida CA, et al: A sensitive and rapid alternative to HLA typing as a genetic screening test for abacavir hypersensitivity syndrome. *Pharmacogenet Genomics* 2006;16:353–357.
- 83 Stekler J, Maenza J, Stevens C, et al: Abacavir hypersensitivity reaction in primary HIV infection. *AIDS* 2006;20:1269–1274.
- 84 Pirmohamed M, Lin K, Chadwick D, Park BK: TNF α promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 2001;56:890–896.
- 85 Alfirevic A, Mills T, Harrington P, et al: Serious carbamazepine-induced hypersensitivity reactions associated with the HSP70 gene cluster. *Pharmacogenet Genomics* 2006;16:287–296.
- 86 Chung WH, Hung SI, Hong HS, et al: Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004;428:486.
- 87 Hung SI, Chung WH, Jee SH, et al: Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16:297–306.
- 88 Pirmohamed M: Genetic factors in the predisposition to drug-induced hypersensitivity reactions. *AAPS J* 2006;8:E20–E26.
- 89 Lonjou C, Thomas L, Borot N, et al: A marker for Stevens-Johnson syndrome...: ethnicity matters. *Pharmacogenomics J* 2006;6:265–268.
- 90 Bavdekar SB, Muranjan MN, Gogtay NJ, et al: Anticonvulsant hypersensitivity syndrome: lymphocyte toxicity assay for the confirmation of diagnosis and risk assessment. *Ann Pharmacother* 2004;38:1648–1650.
- 91 Gaedigk A, Spielberg SP, Grant DM: Characterization of the microsomal epoxide hydrolase gene in patients with anticonvulsant adverse drug reactions. *Pharmacogenetics* 1994;4:142–153.
- 92 Hung SI, Chung WH, Liou LB, et al: HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102:4134–4139.
- 93 Martinez C, Blanco G, Ladero JM, et al: Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. *Br J Pharmacol* 2004;141:205–208.
- 94 Sanak M, Simon HU, Szczeklik A: Leukotriene C4 synthase (LTC4s) promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997;350:1599–1600.
- 95 Mastalerz L, Setkowicz M, Sanak M, Rybarczyk H, Szczeklik A: Familial aggregation of aspirin-induced urticaria and leukotriene C synthase allelic variant. *Br J Dermatol* 2006;154:256–260.
- 96 Akahoshi M, Obara K, Hirota T, et al: Functional promoter polymorphism in the TBX21 gene associated with aspirin-induced asthma. *Hum Genet* 2005;117:16–26.
- 97 Kim SH, Ye YM, Lee SK, Park HS: Genetic mechanism of aspirin-induced urticaria/angioedema. *Curr Opin Allergy Clin Immunol* 2006;6:266–270.
- 98 Kim SH, Bae JS, Holloway JW, et al: A polymorphism of MS4A2 (-109T>C) encoding the β -chain of the high-affinity immunoglobulin E receptor (Fc ϵ R1 β) is associated with a susceptibility to aspirin-intolerant asthma. *Clin Exp Allergy* 2006;36:877–883.

- 99 Kim SH, Oh JM, Kim YS, et al: Cysteinyl leukotriene receptor-1 promoter polymorphism is associated with aspirin-intolerant asthma in males. *Clin Exp Allergy* 2006;36:433–439.
- 100 Kim SH, Bae JS, Suh CH, et al: Polymorphism of tandem repeat in promoter of 5-lipoxygenase in ASA-intolerant asthma: a positive association with airway hyperresponsiveness. *Allergy* 2005;60:760–765.
- 101 Qiao HL, Yang J, Zhang YW: Specific serum IgE levels and FcεRIβ genetic polymorphism in patients with penicillins allergy. *Allergy* 2004;59:1326–1332.
- 102 Qiao HL, Yang J, Zhang YW: Relationships between specific serum IgE, cytokines and polymorphisms in the IL-4, IL-4Rα in patients with penicillins allergy. *Allergy* 2005;60:1053–1059.
- 103 Yang J, Qiao HL, Dong ZM: Polymorphisms of IL-13 and IL-4-IL-13-SNPs in patients with penicillin allergies. *Eur J Clin Pharmacol* 2005;61:803–809.
- 104 Guéant-Rodriguez RM, Romano A, Béri-Dexheimer M, et al: Gene-gene interactions of IL-13 and IL-4RA variants in immediate allergic reactions to β-lactam antibiotics. *Pharmacogenetics* 2006 (in press).
- 105 Guglielmi L, Fontaine C, Gougat-Barbera C, et al: IL-10 promoter and IL-4Rα gene polymorphisms are associated with immediate β-lactam allergy in atopic women. *Allergy* 2006;61:921–927.
- 106 Fahrenholz JM: Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 2003;24:113–124.
- 107 Ventura MT, Muratore L, Calogiuri GF, et al: Allergic and pseudoallergic reactions induced by glucocorticoids: a review. *Curr Pharm Des* 2003;9:1956–1964.
- 108 Coopman SA, Johnson RA, Platt R, Stern RS: Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993;328:1670–1674.
- 109 Temesgen Z, Beri G: HIV and drug allergy. *Immunol Allergy Clin N Am* 2004;24:521–531.
- 110 Webster AW, Thompson RA: The ampicillin rash. Lymphocyte transformation by ampicillin polymer. *Clin Exp Immunol* 1974;18:553–564.
- 111 Renn CN, Straff W, Dorfmueller A, Al-Masaoudi T, Merk HF, Sachs B: Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. *Br J Dermatol* 2002;147:1166–1170.
- 112 Mizukawa Y, Shiohara T: Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: with emphasis on EB virus, human herpesvirus 6 and hepatitis C virus. *J Dermatol Sci* 2000;22:169–180.
- 113 Moneret-Vautrin DA, Morisset M: Adult food allergy. *Curr Allergy Asthma Rep* 2005;5:80–85.
- 114 Backstrom M, Mjorndal T, Dahlqvist R: Under-reporting of serious adverse drug reactions in Sweden. *Pharmacoepidemiol Drug Saf* 2004;13:483–487.
- 115 Mittmann N, Knowles SR, Gomez M, et al: Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Saf* 2004;27:477–487.
- 116 Messaad D, Sahla H, Benahmed S, et al: Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;140:1001–1006.

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