

# Epidemiology of hypersensitivity drug reactions

Eva Rebelo Gomes and Pascal Demoly

## Purpose of review

Hypersensitivity drug reactions are but one of the many different types of adverse drug reactions. They may be potentially life-threatening, prolong hospitalization, affect drug prescribing patterns of physicians and result in socioeconomic costs. This review summarizes current knowledge on the incidence, prevalence, mortality and risk factors for these reactions in different populations.

## Recent findings

Hypersensitivity reactions represent about one third of all adverse drug reactions. Adverse drug reactions affect 10–20% of hospitalized patients and more than 7% of the general population. Severe reactions including anaphylaxis, drug hypersensitivity syndromes, Stevens Johnson syndrome and toxic epidermal necrolysis are also associated with significant morbidity and mortality. Although several risk factors have been identified, their clinical importance has not been fully understood. Future progress in immunogenetics and pharmacogenetics may help identify populations at risk for specific types of reactions.

## Summary

Well designed epidemiological studies on hypersensitivity drug reactions are lacking as most studies have been on adverse drug reactions. Such studies will be helpful in identifying patients at risk of developing such reactions, in particular severe reactions, and implementing early preventive measures.

## Keywords

adverse drug reactions, drug hypersensitivity, incidence, prevalence, risk factors

## Introduction

Adverse drug reactions (ADRs) are regarded as an important public health problem as they may be potentially life-threatening. An ADR is defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in man [1]. However many other definitions and different classifications have been proposed [2–5,6\*]. The classical pharmacological classification of ADRs by Rawlins and Thompson [7] separates these into two major subtypes: type A reactions, which are dose dependent and predictable, and type B which are not dose dependent and unpredictable. This classification was further extended to include other subtypes [8–10] in order to facilitate the inclusion of reactions that did not find their place in subtypes A or B. Recently a new classification was proposed by Aronson and Ferner [11] which includes three major parameters (dose responsiveness, time course and susceptibility). Although more accurate, this is somewhat complex to use in everyday clinical practice.

The majority of ADRs are type A reactions. Type B reactions comprise approximately 10–15% of all ADRs and include hypersensitivity drug reactions. According to the Nomenclature Review Committee of the World Allergy Organization, drug allergy refers to a hypersensitivity reaction for which a definite immunological mechanism, either IgE or T-cell-mediated, is demonstrated [12]. ADRs that clinically resemble an allergy but for which an immunological process is not proven should be classified as non-immune hypersensitivity reactions [12]. This is important because most of the available epidemiological studies to date refer to ADRs in general rather than drug allergy. In addition, those that studied drug allergy relied on clinical history of a temporal relationship between ingestion of the putative drug and symptoms/signs without demonstration of drug-specific IgE or T-cell-mediated mechanisms using in-vivo or in-vitro tests. This is due to the lack of standardized tests for many of these drugs and limitations of drug provocation tests.

## Prevalence and incidence of hypersensitivity drug reactions

Hypersensitivity drug reactions are responsible for significant morbidity, mortality and socioeconomic costs that are often underestimated. Current epidemiological data have to be regarded carefully as different studies used different populations (either adult or paediatric populations or both, inpatients or outpatients), different

Curr Opin Allergy Clin Immunol 5:309–316. © 2005 Lippincott Williams & Wilkins.

Allergy Department, INSERM U454 – IFR3, Arnaud de Villeneuve Hospital, University Hospital of Montpellier, Montpellier, France

Correspondence to Pascal Demoly, MD, PhD, Professor of Pulmonology, Head of the Allergy Department, Maladies Respiratoires and INSERM U454 – IFR3, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France  
Tel: +33 467336127; fax: +33 467042708; e-mail: demoly@montp.inserm.fr

Current Opinion in Allergy and Clinical Immunology 2005, 5:309–316

## Abbreviations

|              |                                     |
|--------------|-------------------------------------|
| <b>ACE</b>   | angiotensin-converting enzyme       |
| <b>ADE</b>   | adverse drug event                  |
| <b>ADR</b>   | adverse drug reaction               |
| <b>NSAID</b> | non-steroidal antiinflammatory drug |
| <b>TNF</b>   | tumour necrosis factor              |

© 2005 Lippincott Williams & Wilkins  
1528-4050

definitions of ADRs/drug allergy, different methodologies and methods of data analyses. It should also be kept in mind that the assessment of severity, preventability and drug imputability of reactions relies mostly on clinical history, which can sometimes be ambiguous [13].

#### Data on hospital based populations

The classical study of Bates [14] used data from the Boston Collaborative Drug Surveillance Program, which collected information on all ADRs in 4031 hospitalized patients during a 6-month period. Two hundred and forty-seven ADRs were reported (an incidence of 6.1%), of which 41.7% were severe and 1.2% led to the patient's death. In the study by Classen [15], 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. The incidence was lower than the previous study at 1.8%; 13.8% were severe and 32.7% of an allergic nature. If, however, similar criteria for inclusion were used as in the Boston study, the incidence would have been quite similar at 2.8%. Lazarou [16] showed in a meta-analysis of 33 prospective studies from the USA between 1966 and 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 [17] raised some questions about the methodology and the validity of the meta-analysis, many other studies that followed reported similar data. A study by Fattinger [18] analysed 4331 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 [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 resulting in an incidence of 6.1% hospital admissions for ADRs. In Singapore, a 2-year prospective study by Thong [20], using a network-based electronic notification system for which each case was verified by a trained allergist, detected 366 cases of reported drug allergy from a total of 90 910 inpatients. After review, 210 were classified as drug allergy. Cutaneous manifestations were the most common clinical presentation (95.7%), systemic manifestations 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. They concluded that the frequency of drug allergy in hospitalized patients was 4.2 per 1000 hospitalizations and mortality attributable to drug allergy

was 0.09 per 1000 hospitalizations. A 13-month prospective pharmacoepidemiological survey in Germany by Dormann [21] showed that in 78 (8.5%) of 915 admissions, 102 community-acquired ADRs were detected (thought mostly related to secondary pharmacological effects) and in 3.8% of all admissions ADRs led directly to hospitalization (interestingly, 56.9% of the ADRs were not recognized by the attending physician on admission). The most commonly implicated drugs were diuretics, non-steroidal antiinflammatory drugs (NSAIDs) and sedatives. In Australia, 2–4% of all hospital admissions were considered to be medication-related and this figure substantially increases with the patients' age [22]. Again, NSAIDs were the second on the list of implicated drugs after anticoagulants. In a recent Swiss paper by Hardmeier [23] 457 (7.2%) ADRs occurred among 6383 inpatients (four allergic reactions to antibiotics in patients with known allergy to the same drug) and there were 2.9% ADR-related 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 whom two (28%) may have been allergic reactions (angioedema from piperacillin; skin rash from ceftriaxone) [24].

Pirmohamed [25\*\*] conducted a prospective study in two UK National Health Service hospitals in Merseyside, UK comprising 18 820 patients aged more than 16 years admitted over a 6-month period, which found 1225 (6.5%) admissions related to an ADR with an overall fatality rate of 0.15%. Most ADRs (95%) were classified as type A reactions, so these were probably not related to hypersensitivity. However, NSAIDs were again one of 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 general French hospital, a total of 48 cases assessed by dermatologists to be cutaneous allergic reactions from drugs resulted in a prevalence of 3.6 per 1000 patients. Of these, 34% were considered severe and antibiotics, mainly penicillins, were the most commonly implicated drug [26]. A recent retrospective case–control study from Singapore by Kidon [27] using the hospital inpatient electronic medical record found 222 (2.6%) patients reporting a previous ADR among 8437 hospitalized children. Almost 70% of them involved the use of antibiotics (especially  $\beta$ -lactam antibiotics, 45%) and NSAIDs (18.5%) were the second most implicated group. Of all reactions, 98% were cutaneous.

When considering more specific clinical settings it is possible to find more accurate data. The French registry of anaphylaxis during general anaesthesia identified 789 cases during a 2-year survey, giving a prevalence of one in

13 000 episodes of general anaesthesia. Five hundred and eighteen (66%) had a demonstrated immune mechanism, of which neuromuscular blocking agents (58.2%) (prevalence of one in 6500 myorelaxant injections) and antibiotics (15.1%) were the most common causes [28]. In the study by Katayama [29], of 337 647 injections of radio contrast media in Japan, the incidence of adverse reactions was 12.6%, (0.22% of severe reactions for ionic products and 0.04% for non-ionic products) of which two deaths were reported (incidence of 0.0006%).

#### Data on outpatients and general population

Epidemiological data on drug hypersensitivity in non-hospitalized subjects and the general population is even more scarce and are limited mainly to studies on antibiotic use. A prospective study of patients receiving monthly injections of penicillin G (for rheumatic fever) found 57 reactions in 1790 patients (incidence of 3.2% of patients and 0.19% of injections), four cases of anaphylaxis (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) [30].

Apter [31•] 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) and from those 6212 (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 is markedly increased. Higher numbers are, however, reported in the meta-analysis by Impicciatore [32] in which the reported incidence of ADRs in paediatric outpatients was 1.46%. In another review of 5923 records from a private group paediatric practice in northern Virginia, USA, cutaneous eruptions occurred in 7.3% of children who were given common oral antibiotics [33]. With regard to quinolones, three out of 3200 students treated with ciprofloxacin to prevent meningococcal carriage experienced an anaphylactic reaction [34].

To evaluate the prevalence of drug hypersensitivity in the general population, we carried out a cross-sectional survey of a general adult population from Porto, Portugal and found a 7.8% (181 of 2309) prevalence of self-reported drug allergy, of which 4.5% were to penicillins or other  $\beta$ -lactams, 1.9% to aspirin or other NSAIDs and 1.5% to other drugs. The term 'allergy' was used because

it was the most recognized by people in general. Most of the reported reactions were immediate (43%), occurred on the first day of treatment (78.5%) and involved the skin (63.5%) so these could have been immunologically mediated [35•]. Similar results were found among university students using a comparable methodology [36].

It is possible to conclude that hypersensitivity drug reactions represent about one third of adverse drug reactions which can affect 7% of the general population and up to 20% of hospitalized patients besides being responsible for as many 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

Drug hypersensitivity reactions can be serious and potentially life-threatening. In the USA, the study by Lazarou [16] showed that 0.32% of hospitalized patients died from ADRs, making up 106 000 estimated deaths for the year 1994 (that would be the fourth cause of death in this country). The proportion of allergic reactions in this study was not evaluated, but could be estimated to be around 23.8% (all severities). Pirmohamed [25••] found that the overall fatality related to ADRs was 0.15%, and calculated that ADRs causing hospital admissions are responsible for 5700 deaths per year in England.

In the study of Fattinger [18] the estimated incidence of possible ADR-related deaths was similar at 0.14%. In the study by Hardmeier [23] among 6383 inpatients, 10 adverse drug event (ADE)-related fatalities were reported (0.16% of the included patients) corresponding to 3% of all deaths. A similar number was reported by Juntti [37] with 5% ADE-related deaths in a study evaluating 1511 in-hospital fatalities. In the study by Moore [38] 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 four of them (13%). Thong [20] found that the attributable mortality due to drug allergy was 0.09 per 1000 hospitalizations.

Anaphylactic shock is one of the severe reactions commonly associated with drug allergy fatalities. It is usually an IgE-mediated reaction and is the most frightening and potentially lethal allergic event. However, non-IgE-mediated anaphylaxis, like many NSAID-induced reactions may also be equally dangerous. In the retrospective study by Kemp [39] from 266 reported cases of anaphylaxis from a private allergy practice in Memphis, drugs (20%) were the second most recognizable cause of reactions with NSAIDs responsible for half of those. Based on a medical literature review to obtain prevalence estimates of anaphylaxis in the general population, Neugut [40]

calculated a rate of 0.7–10% for penicillins (USA population at risk would be 1.9–27.2 million) and 0.22–1% for radiocontrast media (USA population at risk would be 22 000–100 000). Matasar and Neugut reported about 1500 annual deaths from anaphylaxis in the USA [41].

In the UK where hospital admissions for acute anaphylaxis are increasing (from 56 per million in 1991 to 102 per million in 1995) [42], the work by Pumphrey [43] on deaths from anaphylaxis (1992–2001) showed that drugs were the leading cause (88 out of 202 fatalities) followed by food-related anaphylaxis and insect stings. In the UK register of all fatal anaphylactic reactions between 1992 and 1998, there were 164 fatalities, of which drug induced anaphylaxis comprised 39% of the cases with 27 cases from anaesthetics, 16 from antibiotics and eight from radiocontrast media [44]. In another recent analysis by Peng [45•] using a general practice research database (1994 to 1999), 675 cases of anaphylaxis were reported, and thus the estimated incidence of 8.4 per 100 000 person-year of anaphylaxis in the UK with oral medicines is the second highest after insect stings. The recent 3-year Swiss study by Helbling [46•] led to the identification of 226 individuals diagnosed with 246 episodes of life-threatening anaphylaxis and three deaths. The authors calculated an annual incidence of 7.9–9.6 cases per 100 000 inhabitants per year of anaphylaxis and attributed drugs as the second most common cause (18.1%) after hymenoptera stings. Van-der-Klaauw [47] analysed 345 cases of probable anaphylaxis to drugs and 485 possible cases 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 glafenin (two deaths), NSAIDs, sulfonamides, dextran (three deaths), floctafenin, allergen extracts for specific immunotherapy (two deaths) and amoxicillin. In Italy, Cianferoni [48] carried out a retrospective review of clinical features of 113 episodes of anaphylaxis, resulting in admission to hospital of 107 patients. Drugs (NSAIDs and antibiotics) were the most frequent cause of reactions (49%) followed by hymenoptera stings (29%). The Danish Committee on Drug Administration revealed from 1968 to 1990 30 cases of fatal anaphylaxis of which eight were caused by radio contrast media, six by penicillins, five by allergen extracts, two by NSAIDs and one by myorelaxants (an incidence of 0.3 cases of fatal anaphylaxis per million inhabitants per year) [49].

Anaphylaxis is not, however, the only cause of mortality due to allergic drug reactions. The serious, mostly drug-related, dermatological conditions SJS (5% mortality) and TEN (30% mortality) with estimated incidence of 0.4–1.2 and 1.2–6 per million people/year, respectively [50] are other examples of life-threatening events. They occurred in 5.2% of the 210 drug allergic patients

in Thong's study [20]. Besides, multisystem organ hypersensitivity syndrome and organ specific involvement can also contribute to drug hypersensitivity-related mortality.

### **Risk factors for hypersensitivity drug reactions**

Some drug-related, treatment regimen-related, and patient-related risk factors (such as age, sex, concurrent illnesses and previous reactions to related drugs), have been identified as having an important role in drug hypersensitivity.

### **Drug-related aspects**

A large variety of drugs are currently used in everyday practice. Those implicated in allergic reactions are, however, a much smaller group. In order to be immunogenic or a complete allergen, a substance must have a sufficient molecular weight (more than 1000 D), so most drugs behave as haptens and have to bind to carrier proteins to induce a specific immune response. Beta-lactams are intrinsically reactive (hapten concept); other drugs like sulfamethoxazole require previous conversion to a reactive intermediate (pro-hapten concept). Drug-related cytotoxicity may also be of importance to enhance the immune response (danger concept). Some other drugs although not reactive, can still be immunogenic by direct noncovalent binding to immune receptors, T-cell receptors and major histocompatibility complex peptides (pharmacological interaction concept) [51]. The notion that the drug itself is an important risk factor for drug allergy even among the same therapeutic group can be illustrated by the review by Ibia [33]. Based on the number of patients for whom each group of antibiotic 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 [52]. In this survey, the authors analysed the incidence of cutaneous drug reactions in 15 438 hospitalized patients, which provided the majority of data regularly used to obtain the incidence of hypersensitivity drug reactions. There were 358 reactions reported and confirmed by a dermatologist with an overall frequency of 2.3%. The number of reactions over the number of administrations for each drug was reported as 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 specially demonstrated with  $\beta$ -lactams. Traditionally reactions to  $\beta$ -lactams concerned mostly penicillin G but in recent years reactions to amoxicillin and to cephalosporins have been increasing and the prevalence seems to differ among different populations. These changes which can

be partially explained by changes in prescribing patterns are addressed in the recent review by Blanca [53].

#### Treatment regime

The dosage of the drug and the mode of administration influence the frequency of the reactions. It appears that intermittent and repeated administrations can be more sensitizing than an uninterrupted treatment [54]. This is supported by a recent publication from Cetinkaya [55<sup>•</sup>] who studied 147 children who had received  $\beta$ -lactams at least three times in the preceding 12 months without allergic reaction. A 10.2% frequency of positive skin tests to penicillin was found and the author concluded that frequent use of  $\beta$ -lactam antibiotics leads to sensitization. Pichichero [56], however, found no difference in the frequency of previous  $\beta$ -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, but topical administration has also shown to be an important source of sensitizations for many reported reactions [57,58].

#### Host-related factors

Host-related factors can predispose 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% against 30–35%) [59–61]. Differences can, however, depend on the age group considered [27], on the type of reaction (cutaneous reaction rates were 35% higher in females than males in the Bigby [52] review) and on the culprit drug [35<sup>•</sup>]. Subgroup analysis of Thong's [20] study 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 the sexes. In addition, elderly patients above 65 years of age did not appear to be more at risk of developing drug allergy than the non-elderly and there was no increase in the severity of allergic reactions or drug-related mortality (personal communication, unpublished data).

It is often reported that children are less affected than adults [62]. In the study by Temple [63<sup>•</sup>] on paediatric patients, 565 ADRs were reported to a hospital surveillance programme 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 to cause the reaction. Other studies on ADRs in paediatric populations, however, report incidences similar to the ones in adults [32,33]. In the 20-day observational prospective study of Mazzeo [24] the rate of reactions (most of them deemed probably not due to allergy) to antibiotics in inpatients were higher

in children than in adults. An 8-month survey of ADRs in a paediatric isolation ward by Weiss [64] showed that among 68 ADRs detected in 46 of 214 patients (21.5%), seven (10%) were classified as severe and 50% were antibiotic associated. Among all ADRs 14 (20.6%) were considered to be immunologically induced.

The role of atopy is still under debate, but it does not seem to be a major risk factor [60,61,65]. 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 [66].

#### Genetic background

Some ethnic groups seem to be prone to certain types of ADRs. Easterbrook's [67] study on epidemiological risk factors for hypersensitivity reactions to abacavir found the Caucasian race as a risk factor for reactions. In a recent cohort study evaluating risk factors for ADEs associated with angiotensin-converting enzyme (ACE) inhibitors involving 2225 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 [68]. This confirmed the results of other authors [69]. African and Asian people also appear to be at an increased risk for ACE inhibitor induced cough [70]. In the study by Kidon [40], Chinese descent, asthma, and associated chronic illness, were all considered as independent risk factors for reported 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. Individuals with ACE genotype II are reported to have an increased risk for ACE inhibitor induced cough [70] and in those with angioedema an abnormality of degradation of some bradykinin metabolites has been described [71].

The work by Martin [72] shows that predisposition to abacavir hypersensitivity was linked to HLA-B5701, and its combination to a haplotypic Hsp70-Hom variant seems to be highly predictive of hypersensitivity (the authors even suggest that prospective genetic testing should be done to identify patients at risk). A haplotypic polymorphism within the tumour necrosis factor (TNF) promoter region (TNF-238A) may also affect the levels of TNF production influencing the severity of abacavir reactions [72]. Another TNF polymorphism (–308TNF- $\alpha$ ) was associated with severe carbamazepine hypersensitivity reactions [73]. The work from Bavdekar [74] proposes that accumulation of toxic arene oxide metabolites due to a defect in epoxide hydrolase-mediated detoxification contributes to anticonvulsant

hypersensitivity. Regarding NSAIDs, it was recently suggested that NSAID-related severe reactions could be associated with two polymorphisms of cytochrome P450C9 [75]. 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 [76].

### Concomitant pathology

Hypersensitivity reactions to NSAIDs are particularly frequent in some populations such as asthmatics [77]. Interestingly Ventura [78] describes hypersensitivity to aspirin as a risk factor to immediate reactions to glucocorticoids along with female sex and atopy. Patients with AIDS suffer 10–100 times more from cutaneous reactions to drugs especially from cotrimoxazole [79]. The frequency of drug hypersensitivity in this population ranges from 3 to 20%. A recent review on drug allergy in HIV patients published by Temesgen [80] showed comprehensive data on reactions reported for antiretroviral drugs that are currently licensed, as well as to cotrimoxazole.

### Conjugated factors

Finally, many factors can conjugate among themselves to lead to an ADR: drugs [28], infection [81], exercise and food allergy [82] may synergize with each other to precipitate a hypersensitivity reaction or increase its severity.

### Conclusion

There are few epidemiological data on hypersensitivity drug reactions. They affect 10–20% of hospitalized patients and up to 7% of outpatients. The available information based predominantly on the epidemiology of ADR, requires cautious interpretation as these reactions are rarely accurately classified or proven. Both underdiagnosis because of underreporting [83\*,84\*] and overdiagnosis due to the common use of the term ‘allergy’ [85\*\*] have also to be considered. Misclassification based on drug allergy history may have consequences on individual treatment choices and lead to the use of more expensive and less effective drugs. Multicentre 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, possible regional differences and to allow the implementation of better preventive measures for the patients.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 World Health Organization. International drug monitoring: the role of national centres. *World Health Organ Tech Rep Ser* 1972; 498:1–25.
- 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, editors. *The detection of new adverse reactions*. 4th ed. 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.
- The use of a patient clinical history helps to illustrate the use of different terms regarding drug-induced harm.
- 7 Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. *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, editors. *Davidson's principles and practice of medicine*. 19th ed. Edinburgh: Elsevier Science; 2002. pp. 147–163.
- 9 Grahame-Smith DG, Aronson JK. Adverse drug reactions. In: *The Oxford textbook of clinical pharmacology, 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, editor. *Side effects of drugs. Annual 23. A world-wide yearly survey of new data and trends in adverse drug reactions*. Amsterdam: Elsevier; 2000. p. xxvii.
- 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 IE, Gordon MJ, *et al.* Adverse drug reactions in hospitalized patients: a critique of meta-analysis. *MedGenMed* 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 Dormann H, Criegee-Rieck M, Neubert A, *et al.* Lack of awareness of community-acquired adverse drug reactions upon hospital admission: dimensions and consequences of a dilemma. *Drug Saf* 2003; 26:353–362.
- 22 Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. *Int J Qual Health Care* 2003; 15 (Suppl 1): 149–159.
- 23 Hardmeier B, Braunschweig S, Carvallaro M, *et al.* Adverse drug events caused by medication errors in medical inpatients. *Swiss Med Wkly* 2004; 134:664–670.
- 24 Mazzeo F, Capuano A, Avolio A, *et al.* Hospital-based intensive monitoring of antibiotic-induced adverse events in a university hospital. *Pharmacol Res* 2005; 51:269–274.
- 25 Pirmohamed M, James S, Meakin S, *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 2004; 329:15–19.
- This is an important paper in view of the large population studied. Several epidemiological aspects of ADRs are addressed and an attempt is made at classification of the reactions.

- 26 Fiszenson-Albala F, Auzeir 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.
- 27 Kidon MI, See Y. Adverse drug reactions in Singaporean children. *Singapore Med J* 2004; 45:574–577.
- 28 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; 99:536–545.
- 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 International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991; 337:1308–1310.
- 31 Apter AJ, Kinman JL, Bilker WB, *et al.* Represcription of penicillin after allergic-like events. *J Allergy Clin Immunol* 2004; 113:764–770.  
• This shows that hypersensitivity reactions to penicillin in outpatients are not so frequent and, when they happen, are largely ignored by prescribing physicians.
- 32 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.
- 33 Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol* 2000; 136:849–854.
- 34 Burke P, Burne SR. Allergy associated with ciprofloxacin. *Br Med J* 2000; 320:679.
- 35 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.  
• An innovative methodology was applied for the study of drug hypersensitivity in a general population.
- 36 Falcao H, Lunet N, Gomes E, *et al.* Drug allergy in university students from Porto, Portugal. *Allergy* 2003; 58:1210.
- 37 Juntti Patinen L, Neuvonen PJ. Drug-related death in a university central hospital. *Eur J Clin Pharmacol* 2002; 58:479–482.
- 38 Moore N, Lecoindre 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.
- 39 Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med* 1995; 155:1749–1754.
- 40 Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into epidemiology. *Arch Intern Med* 2001; 161:15–21.
- 41 Matasar MJ, Neugut AI. Epidemiology of anaphylaxis in the United States. *Curr Allergy Asthma Rep* 2003; 3:30–35.
- 42 Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *Br Med J* 2000; 320:1441.
- 43 Pumphrey R. Anaphylaxis: Can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol* 2004; 4:285–290.
- 44 Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144–1150.
- 45 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.  
• This was a large observational follow-up study on epidemiological aspects of anaphylaxis in a general population, showing the important role of oral medicines.
- 46 Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940000 inhabitants of the Swiss canton Bern. *Clin Exp Allergy* 2004; 34:285–290.  
• This study on a large screened population gave important epidemiological data on anaphylaxis.
- 47 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.
- 48 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.
- 49 Lenler-Petersen P, Hansen D, Andersen M, *et al.* 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.
- 50 Roujeau JC, Stern RS. Severe cutaneous adverse reactions to drugs. *N Engl J Med* 1994; 331:1272–1285.
- 51 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.
- 52 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.
- 53 Blanca Gomez M, Torres MJ, Mayorga C, *et al.* Immediate allergic reactions to betalactams: facts and controversies. *Curr Opin Allergy Clin Immunol* 2004; 4:261–266.
- 54 De Weck AL. Pharmacologic and immunochemical mechanisms of drug hypersensitivity. *Immunol Allergy Clin North Am* 1991; 11:461–474.
- 55 Cetinkaya F, Cag Y. Penicillin sensitivity among children without a positive history for penicillin allergy. *Pediatr Allergy Immunol* 2004; 15:278–280.  
• This paper highlights the high prevalence of penicillin sensitization among children following several courses of oral penicillin therapy.
- 56 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.
- 57 Juan WH, Yang LC, Hong HS. Acute generalized exanthematous pustulosis induced by topical lindane. *Dermatology* 2004; 209:239–240.
- 58 McIlwain M, Primosh R, Bimstein E. Allergic reaction to intranasal midazolam HCL: a case report. *Pediatr Dent* 2004; 26:359–361.
- 59 Barranco P, Lopez-Serrano MC. General epidemiological aspects of allergic drug reactions. *Clin Exp Allergy* 1998; 28 (Suppl 4):S61–S62.
- 60 Haddi E, Charpin D, Tafforeau M, *et al.* Atopy and systemic reactions to drugs. *Allergy* 1990; 45:236–239.
- 61 Asero R. Detection of patients with multiple drug allergy syndrome by elective tolerance tests. *Ann Allergy Asthma Immunol* 1998; 80:185–188.
- 62 Demoly P, Bousquet J. Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol* 2001; 1:305–310.
- 63 Temple ME, Robinson RF, Miller JC, *et al.* Frequency and preventability of adverse drug reactions in paediatric patients. *Drug Saf* 2004; 27:819–829.  
• This interesting paper highlights several important epidemiological aspects on ADRs in pediatric patients.
- 64 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.
- 65 Ponvert C, Le Clainche L, de Blic J, *et al.* Allergy to  $\beta$ -lactam antibiotics in children. *Pediatrics* 1999; 104:45.
- 66 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.
- 67 Easterbrook PJ, Waters A, Murad S, *et al.* Epidemiological risk factors for hypersensitivity reactions to abacavir. *HIV Med* 2003; 4:321–324.
- 68 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 Prac* 2004; 10:499–509.
- 69 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.
- 70 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.
- 71 Molinaro G, Cugno M, Perez M, *et al.* Angiotensin-converting enzyme inhibitor-associated angioedema is characterized by a slower degradation of des-arginine(9)-bradykinin. *J Pharmacol Exp Ther* 2002; 303:232–237.
- 72 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 U S A* 2004; 101:4180–4185.
- 73 Pimohamed M, Lin K, Chadwick D, Park BK. TNF $\alpha$  promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 2001; 56:890–896.
- 74 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.
- 75 Martinez C, Blanco G, Ladero JM, *et al.* Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. *Br J Pharmacol* 2004; 141:205–208.
- 76 Sanak M, Simon HU, Szczeklik A. Leukotriene C4 synthase (LTC4s) promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997; 350:1599–1600.

- 77 Fahrrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 2003; 24:113–124.
- 78 Ventura MT, Muratore L, Calogiuri GF, *et al.* Allergic and pseudoallergic reactions induced by glucocorticoids: a review. *Curr Pharm Des* 2003; 9:1956–1964.
- 79 Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993; 328:1670–1674.
- 80 Temesgen Z, Beri G. HIV and drug allergy. *Immunol Allergy Clin N Am* 2004; 24:521–531.
- 81 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.
- 82 Moneret-Vautrin DA, Morisset M. Adult food allergy. *Curr Allergy Asthma Rep* 2005; 5:80–85.
- 83 Backstrom M, Mjorndal T, Dahlqvist R. Under-reporting of serious adverse drug reactions in Sweden. *Pharmacoepidemiol Drug Saf* 2004; 13:483–487.  
This study involving five hospitals confirmed the problem of underreporting of ADRs. It showed that 86% of the reactions are not reported.
- 84 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.  
The authors describe concerning numbers showing that only 4–10% of serious cutaneous reactions are reported.
- 85 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.  
This interesting paper based on drug provocation tests results done in 898 patients shows that more than three-quarters of drug allergy diagnoses could not be confirmed.