Epidemiology and risk factors for drug allergy

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The aim of this review was to describe the current evidence-based knowledge of the epidemiology, prevalence, incidence, risk factors and genetic associations of drug allergy. Articles published between 1966 and 2010 were identified in MEDLINE using the key words adult, adverse drug reaction reporting systems, age factors, anaphylactoid, anaphylaxis, anaesthetics, antibiotics, child, drug allergy, drug eruptions, ethnic groups, hypersensitivity, neuromuscular depolarizing agents, neuromuscular nondepolarizing agents, sex factors, Stevens Johnson syndrome and toxic epidermal necrolysis. Additional studies were identified from article reference lists. Relevant, peer-reviewed original research articles, case series and reviews were considered for review. Current epidemiological studies on adverse drug reactions (ADRs) have used different definitions for ADR-related terminology, often do not differentiate immunologically and non-immunologically mediated drug hypersensitivity, study different study populations (different ethnicities, inpatients or outpatients, adults or children), utilize different methodologies (spontaneous vs. non-spontaneous reporting, cohort vs. case-control studies), different methods of assessing drug imputability and different methods of data analyses. Potentially life-threatening severe cutaneous adverse reactions (SCAR) are associated with a high risk of morbidity and mortality. HLA associations for SCAR associated with allopurinol, carbamazepine and abacavir have been reported with the potential for clinical use in screening prior to prescription. Identification of risk factors for drug allergy and appropriate genetic screening of at-risk ethnic groups may improve the outcomes of drug-specific SCAR. Research and collaboration are necessary for the generation of clinically-relevant, translational pharmacoepidemiological and pharmacogenomic knowledge, and success of health outcomes research and policies on drug allergies.

Introduction

Adverse drug reactions (ADRs) which account for 3 to 6% of all hospital admissions and occur in 10 to 15% of hospitalized patients, result in morbidity, prolonged hospitalization and risk of mortality. An ADR is defined by the World Health Organization (WHO) as ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’ [1]. Type A ADRs which are predictable and dose dependent, comprise up to 80% of all ADR, e.g. pharmacological side-effects like gastrointestinal bleeding following treatment with non-steroidal anti-inflammatory drugs (NSAID). Type B ADRs are unpredictable, dose independent and comprise 15–20% of all ADRs. These may include immunologically mediated drug hypersensitivity (drug allergy) or non-immune mediated/ idioyncratic reactions [2]. ADRs should be differentiated from adverse drug events (ADEs) [3] as ADEs extend beyond ADRs to include harm related to medication errors and drug/food interactions.

The World Allergy Organization (WAO) in 2003 defined ‘drug allergy’ as an immunologically mediated drug hypersensitivity reaction. The mechanism of drug allergy may be either IgE or non-IgE mediated, with T-cell mediated reactions largely represented in the latter [4].

Severe cutaneous adverse reactions (SCAR) include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) [5–9], drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) [10]. Acute generalized exanematous pustulosis (AGEP) [11, 12] has recently been added to the list comprising SCAR. Anaphylaxis is a severe, life-threatening,
generalized or systemic hypersensitivity reaction [3, 13] for which drugs are a common cause [14].

The true incidence of drug allergy is not known. The majority of currently available epidemiologic studies have been on ADRs rather than drug allergy specifically [15]. Most studies focus only on select population groups, e.g. inpatients or outpatients at the emergency departments, general practice clinics or specialist allergy centres; children or adults; cutaneous or severe cutaneous adverse reactions (SCAR) [16], or all causes of anaphylaxis alone. Diagnosis of ADRs and drug imputability in the majority of these studies used the WHO ADR terms. Definitions of different types of SCAR were different in the earlier studies from the 1980s and early 1990s, compared with later studies. In addition, the majority of studies that addressed drug allergy per se relied heavily on a clinical history of the temporal relationship between drug use and disease onset, and suggestive clinical features for the diagnosis of drug allergy, with few studies/datasets [17] using standardized clinical questionnaires [18] and validated in vivo or in vitro tests to confirm the diagnosis of drug allergy [19–21].

Studies on hospital-based inpatient populations

To date, there have only been a few studies that have attempted to evaluate the prevalence and incidence of drug allergy in hospital-based populations. Most studies (summarized in Table 1), including the Boston Collaborative Drug Surveillance Programme, only monitored cutaneous reactions [22–27]. Others reported on only single classes of drugs. The incidence and prevalence of drug allergy were either unknown or estimated in most studies. Case-verification in most studies was based on chart review and not formal patient examination during the episode of reaction, although case-verification was conducted by dermatologists in two reports [25, 26]. The reported cases were diagnosed based on probability, without firm evidence of drug allergy being the main mechanism using the WAO definition of allergy and/or validated allergological tests.

To date, only two prospective studies on cutaneous ADRs have attempted to study the incidence or prevalence of cutaneous ADRs or cutaneous drug allergy. In France in 2003, a 6 month prospective study on the incidence of cutaneous allergic reactions from systemic drugs in a French hospital was carried out [29]. Each reported case was physically examined by a dermatologist and reviewed with a pharmacologist. Among 48 inpatients with cutaneous drug allergy, the prevalence of cutaneous allergic reactions was 3.6 per 1000 hospitalized patients. Among these patients, 57% had exanthematous reactions, 8% erythoderma and 2% SJS/TEN. Beta-lactam antibiotics were implicated in 21% of cutaneous allergic reactions studied. The most frequently associated disorders were human immunodeficiency virus (HIV) infection (19%), connective tissue disease (10%) and viral or autoimmune hepatitis (12%). A third of the cases had a previous history of drug allergy.

In Mexico in 2006, a 10 month prospective cohort study of all hospitalized patients with cutaneous adverse drug reactions (CADR) [30] showed a prevalence of 35/4765 (0.7% or 7 per 1000 hospitalized patients), and mortality rate of 16.6% among six patients with SCAR. Risk factors for CADR included systemic lupus erythematosus (SLE) (14.6%), human immunodeficiency (HIV) infection (7.3%) and non-Hodgkin’s lymphoma (7.3%).

To our knowledge, two prospective studies from Singapore and Korea published are the only to date that specifically described both cutaneous and systemic manifestation of drug allergy, where all cases were allergist-verified, and reporting was electronic.

In Singapore in 2002, an inpatient network-based electronic drug allergy notification system in a general hospital [28] showed that of 366 cases reported from a total of 90 910 admissions during the study period, 210 cases were verified by an allergist to have drug allergy. Cutaneous eruptions were the most common clinical presentation (95.7%), systemic manifestations occurred in 30% and serious adverse reactions such as SJS/TEN and generalized exfoliative dermatitis occurred in 11 (5.2%) patients. The most common (75%) causative drugs among those with drug allergies were antimicrobials and anti-epileptic drugs. The estimated incidence of drug allergy was 4.2 per 1000 hospitalizations (95% confidence interval [CI] 2.93, 5.46), and the estimated mortality attributable to drug allergy was 0.09 per 1000 hospitalizations (95% CI 0.06, 0.12).

In Korea, a mandatory reporting system for immunologically-mediated drug hypersensitivity reactions monitored by an inpatient team of allergists in a university hospital was described [31]. There were 2682 reported cases of ADE (4.84%) among 55 432 admissions. Following allergists’ review, 532 were identified as significant drug hypersensitivity reactions, of which 100 were new events. There were 70% of new drug hypersensitivity reactions presenting with cutaneous manifestations, of which 2% developed exfoliative dermatitis and 1% developed SJS/TEN. Anaphylaxis occurred in 11% of all new drug hypersensitivity reactions. The most common culprit drugs among new drug hypersensitivity reactions were antibiotics (32%), radiocontrast media (26%) and antineoplastic drugs (17%). The estimated incidence of drug hypersensitivity reactions was 0.18 per 100 hospital admissions.

Studies in children and adolescents

The overall incidence of ADRs, based on prospective studies in children and adolescents, was 10.9% in hospitalized children, 1.5% in outpatient children, and rate of hospital admission due to ADRs 2.1% [32, 33]. Community-based studies [34] have shown that there is generally an
## Table 1
Summary of prospective studies on adverse drug reactions with differentiation into non-allergy and allergy

<table>
<thead>
<tr>
<th>Year</th>
<th>Author et al.</th>
<th>Type of study</th>
<th>Period of study</th>
<th>Types of reaction studied</th>
<th>Number studied</th>
<th>Patient type</th>
<th>Number with ADR</th>
<th>Number with severe ADR</th>
<th>Types of ADR</th>
<th>Implicated drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Allain et al. [22]</td>
<td>Prospective, Departmental</td>
<td>12 months</td>
<td>Cutaneous ADR</td>
<td>550</td>
<td>Inpatient</td>
<td>30 (5.6%)</td>
<td>1 death</td>
<td>Erythroderma, Drug eruption</td>
<td>Cardiovascular drugs, Anti-inflammatory drugs, Antimicrobials</td>
</tr>
<tr>
<td>1986</td>
<td>Bigby et al. [23]</td>
<td>Boston Collaborative Drug Surveillance Programme BCDSP</td>
<td>3 years 8 months</td>
<td>Cutaneous ADR</td>
<td>15 438</td>
<td>Inpatient</td>
<td>347 (2.2%)</td>
<td>Unknown</td>
<td>95% morbilliform, 5% urticaria</td>
<td>Amoxicillin (5.1%), Ampicillin (4.5%), Penicillin (4.5%), Cotrimoxazole (3.7%), Cephalosporins (1.5%), Gentamicin (1%)</td>
</tr>
<tr>
<td>1991</td>
<td>Classen et al. [24]</td>
<td>Prospective</td>
<td>1 year 6 months</td>
<td>ADR</td>
<td>36 653</td>
<td>Inpatient</td>
<td>731 (1.8%)</td>
<td>Unknown</td>
<td>32.7% allergic</td>
<td>Unknown</td>
</tr>
<tr>
<td>1995</td>
<td>Rademaker et al. [25]</td>
<td>Prospective, Departmental, Case verification by dermatologist</td>
<td>6 months</td>
<td>Cutaneous ADR</td>
<td>60</td>
<td>Inpatient</td>
<td>27 allergy, 4 allergic contact dermatitis</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>1997</td>
<td>Hunziker et al. [26]</td>
<td>Comprehensive Hospital Drug Monitoring (CHDM)</td>
<td>40 years</td>
<td>Cutaneous ADR</td>
<td>48 005</td>
<td>Inpatient</td>
<td>1308 allergy</td>
<td>Nil</td>
<td>91.2% maculopapular, 5.9% urticaria, 1.4% vasculitis, 0.38% erythema multiforme, 0.45% fixed drug eruption</td>
<td>Penicillin, Furosemide, Prednisolone, Allopurinol, Carbamazepine, Cephalosporin (1.9%)</td>
</tr>
<tr>
<td>2001</td>
<td>Sharma et al. [27]</td>
<td>Prospective</td>
<td>6 years</td>
<td>Cutaneous ADR</td>
<td>500</td>
<td>Inpatient</td>
<td>500</td>
<td>10 deaths from TEN</td>
<td>34.6% maculopapular, 30.0% fixed drug eruption, 14.0% urticaria</td>
<td>Antimicrobials (42.6%), Anticonvulsants (22.2%)</td>
</tr>
<tr>
<td>2002</td>
<td>Thong et al. [28]</td>
<td>Prospective, Electronic, Inpatient Drug Allergy Reporting System</td>
<td>2 years</td>
<td>Cutaneous and systemic drug allergies, Incidence of allergic reactions = 4.2/1000 hospitalizations</td>
<td>366</td>
<td>Inpatient</td>
<td>210 allergy</td>
<td>11 (5.2%), - SJS (3.3%), - TEN (1.4%), - GED (0.5%), 4 deaths</td>
<td>95.7% cutaneous, - 62.7% maculopapular, - 17.9% urticaria, - 30.0% systemic, - 52.4% hepatic, - 44.4% fever, - 27% haematological</td>
<td>Penicillin (25.2%), Cefalosporine (15.7%), Cotrimoxazole (9.0%), Phenytoin (8.1%), Carbamazepine (6.2%), Allopurinol (5.7%)</td>
</tr>
<tr>
<td>2003</td>
<td>Fiszensson-Albala et al. [29]</td>
<td>Prospective, Drug allergy verified by dermatologist and pharmacologist</td>
<td>6 months</td>
<td>Cutaneous allergy, Prevalence of cutaneous allergic reactions = 3.6/1000 hospitalizations</td>
<td>48</td>
<td>Inpatient</td>
<td>48 allergy</td>
<td>24% severe</td>
<td>57% exanthema, 8% erythroderma, 2% SJS/TEN</td>
<td>21% betalactams</td>
</tr>
<tr>
<td>2006</td>
<td>Hernández-Salazar et al. [30]</td>
<td>Prospective</td>
<td>10 months</td>
<td>Cutaneous ADR</td>
<td>4785</td>
<td>Inpatient</td>
<td>35</td>
<td>AGEP 2.4%, SJS 4.9%, TEN 2.4%, DiHS 2.4%, 1 death</td>
<td>Mobilliform rash 51.2%, Urticaria 12.2%, Erythema multiforme 4.9%</td>
<td>Amoxicillin clavulinate (22.9%), Metamizole (11.4%), Amphotericin B (5.7%)</td>
</tr>
<tr>
<td>2008</td>
<td>Park et al. [31]</td>
<td>Prospective, Electronic, Inpatient Drug Allergy Reporting System</td>
<td>7 months</td>
<td>Cutaneous and systemic drug allergies, Incidence of drug hypersensitivity = 1.8/1000 hospitalizations</td>
<td>532</td>
<td>Inpatient</td>
<td>16% severe SJS/TEN 1%, Anaphylaxis 11%</td>
<td>70% cutaneous, - Urticaria/angioedema 26%, - Maculopapula 33%, - 30% systemic, - Respiratory 18%, - Fever 3%, - Hepatic 1%, - Haematologic 1%</td>
<td>Antibiotics (32%), Radiocontrast media (26%), Antineoplastic drugs (17%).</td>
<td></td>
</tr>
</tbody>
</table>
overestimation of the rates of ADRs/drug allergy among children and adolescents, with parental self-reporting of ADRs of 2.5–10.2% compared with confirmed drug allergy of 6% following allergological tests. The majority of paediatric studies on ADRs looked at overall prevalence or incidence of ADRs without categorizing these into allergic and non-allergic drug hypersensitivity. There has only been one 10 year retrospective cohort study of paediatric patients who experienced an ADR (pharmacist reviewed) at a community-based, tertiary care, children’s teaching hospital in the United States [35] which showed that 51% were deemed to be allergic/idiosyncratic in nature, and 24% of all ADRs were attributed to drug hypersensitivity reactions/SJS predominantly from phenytoin and carbamazepine. Antibiotics were the most common cause of ADRs (33%), followed by narcotic analgesics (12%) and anticonvulsants (11%). There were two deaths, neither of which was definitively due to drug allergy. Apart from this study, there are no other studies in children or adolescents looking specifically at the types and causes of paediatric drug allergy.

Studies from outpatients

Most of the studies from allergy centres and clinics involve either inpatients alone, outpatients or both and involve adults and/or children. These studies may not be reflective of the true incidence/prevalence of drug allergy in the community in view of referral bias. It is likely that only the more severe and/or complex cases would be referred to an allergy clinic. The comparator in these studies was often the number of all cases referred to the allergy clinic/centre during the study period.

The Spanish Alergológica 2005 study was a descriptive, cross sectional, prospective observational epidemiologic study in Spain, involving 332 allergists across the country. Gamboa [36] reported 4991 adult patients consulting allergology services for the first time. There were 732 patient consultations for possible drug allergies. Among these, 26.6% of cases were diagnosed to have drug allergies, 75% reported only cutaneous symptoms, 0.75% SJS and 10% anaphylaxis. Antibiotic allergy accounted for 47% of drug allergies, of which 73% were due to amoxicillin, 29% were caused by NSAIDs and 10% by pyrazolones. The most common diagnostic tests used were skin tests and oral drug provocation tests. Ibanez & Garde [37] analysed the data from patients younger than 14 years from the Alergológica 2005 study. A sub-group analysis of 69 patients (7.5% of total patient consults) younger than 14 years who consulted the allergology service for the first time for suspected drug allergy, showed a 3% prevalence of drug hypersensitivity with the majority of cases attributed to antibiotics and NSAIDs.

England et al. [38] reviewed a total of 1284 inpatient allergy/immunology consults from 1987 to 2001 from the United States, where 36% of consults were for evaluation of ADRs. Dietrich et al. [39] followed up with a review of allergy/immunology consults in the same US centre from January to December 2006. A total of 1412 outpatient paediatric and adult consults were requested of which 4.7% were for suspected drug allergy.

Studies from emergency department (ED) attendances

Emergency room attendances are often used to study the incidence and prevalence of severe types of allergic reactions requiring urgent attention, in particular anaphylactic reactions. In the United States National Electronic Injury Surveillance System: Co-operative Adverse Drug Events Surveillance System (NEISS-CADES) [40], the estimated incidence for ADRs between 2004–05 was 2.4 ED visits per 1000 population (95% CI 1.7, 3.0 per 1000 persons). Drug allergies comprised 33.5% of all ADR-related ED visits, with 11.3% requiring hospitalization. Cohen et al. [41] subsequently conducted a prospective cohort study on a paediatric population using data from the NEISS-CADES project where the annual estimated population incidence for ADRs in children ≤ 18 years old was 2 per 1000 persons (95% CI 1.5, 2.6 per 1000 persons). Of these cases, 35% were attributed to drug allergy (based on history alone) with the most common putative drug class being antimicrobial agents (60.8%). No deaths were reported.

The majority of the other studies on the prevalence of drug allergy in emergency departments were retrospective. In Italy, a retrospective study over a 6 year period on the incidence of allergic diseases in a Novaran hospital emergency department showed that out of 6107 of 165 120 visit records for suspected allergic reactions, drug allergy was reported in 7.5% of adult patients and 6.1% of paediatric patients [42]. The other studies on ED attendances among adults and children, predominantly on all causes of anaphylaxis, will be discussed in a later section.

Studies from pharmacovigilance databases

Pharmacovigilance databases may take the form of ADRs collated from spontaneous reporting or intensive monitoring of prescriptions via electronic prescribing or dispensing systems, each with its inherent limitations [43]. Several attempts have been made to obtain epidemiological data on drug allergies from such databases of ADRs. From a retrospective case control study using an ADR database of the Italian Interregional Group of Pharmacovigilance (GIF) which collected spontaneous ADR reports from seven regions in Italy, Salvo et al. investigated drug allergy associated with oral drug usage from the period 1988 to 2006 [44]. Drug allergy was defined as anaphylactic
Serious drug allergies

Drug-induced anaphylaxis

The epidemiology of all causes of anaphylaxis in the United States, United Kingdom, Europe, Australia, New Zealand, Korea, Singapore and Thailand has been described in several studies involving both adults and children [46–68] and are summarized in Table 2. The population prevalence or incidence of anaphylaxis has been difficult to quantify because of a lack of consensus on the definition of anaphylaxis, analysis of different sample populations, and the use of varying methodologies for data collection. The estimated incidence or prevalence of anaphylaxis in western countries is in the range of 8–50 per 100 000 person-years, with a lifetime prevalence of 0.05–2.0% [69]. However, the true incidence/prevalence and mortality due to drug-induced anaphylaxis is unknown. In these studies, drugs (penicillin, anaesthetic agents given during the perioperative period) were a common cause of IgE-mediated allergic anaphylaxis. NSAIDs and radiograph contrast media were common causes of non-allergic anaphylaxis. Drug-induced anaphylaxis was highest in the 55–84 year age group (3.8/100 000 population) with a predominance of males in the less than 15 year age group in Australia [68], and were the most common cause of fatalities in the United Kingdom [52], New Zealand [63] and Australia [55].

Among all causes of drug-induced anaphylaxis, penicillin in the 1960s and 1970s was purported to be the most common cause of drug-induced anaphylaxis in the United States [70, 71]. Subsequently there has been little epidemiological evidence to show this to be true [72]. Drugs used during the peri-operative period are another important cause of anaphylaxis in several studies worldwide. The estimated incidence of all immune- and non-immune-mediated immediate anaesthetic hypersensitivity reactions was 1 in 5000 to 1 in 13 000 in Australia [73], 1 in 4600 in France [74], 1 in 5000 in Thailand [75], 1 in 1250 to 1 in 5000 in New Zealand and 1 in 3500 in England [76]. The estimated incidence of immune-mediated reactions was 1 in 10 000 to 1 in 20 000 in Australia [73], 1 in 13 000 in France [74], 1 in 10 263 in Spain, 1 in 5500 in Thailand [75] and 1 in 1700 to 1 in 20 000 in Norway [77]. The most common causes were neuromuscular blocking agents (NMBA) and antibiotics [78].

Severe cutaneous adverse reactions (SCAR)

The reported incidence for SJS/TEN is between 1.4 and 6 per million person-years [79–81]. The estimated mortality from SJS is 10%, SJS/TEN overlap 30% and TEN almost 50% [9]. Various cohorts on SCAR have been described since the 1990s [79–93] from Europe, United States, South Asia and the Asia Pacific (Table 3). Most of these described cohorts included both adult and paediatric inpatients, with only a limited number describing organ and systemic manifestations of SCAR. Antibiotics and anticonvulsants were the classes of drugs most commonly implicated in most series.

Large multicentre collaborative European SCAR registries include the population-based registry of SCAR in Germany [86], the prospectively-ascertained study of community cases in the SCAR and case-control EuroSCAR studies [92], and the RegisSCAR study comprising both community- and hospital-onset SCAR with clear definitions of SCAR comprising SJS, TEN and overlap syndromes [5]. These studies have shown that the time to onset of SCAR was within 4 weeks, although this varies among different drugs; certain drugs were ‘high risk’ for SCAR (e.g. cotrimoxazole, allopurinol, carbamazepine, phenytoin, phenobarbital and oximans-NSAIDs), and no significant risk persisted beyond 8 weeks of use [92]. AGEP was recently
Table 2
Summary of epidemiological studies on anaphylaxis including drugs as a cause

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Type of study</th>
<th>Period of study</th>
<th>Country</th>
<th>Number of cases</th>
<th>Age (range)</th>
<th>Sex F : M</th>
<th>Causes</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Yocum et al. [47]</td>
<td>Retrospective allergy clinic</td>
<td>3 years 6 months</td>
<td>United States</td>
<td>179</td>
<td>Mean 36 years</td>
<td>1.9:1</td>
<td>Food (33%)</td>
<td>Nil</td>
</tr>
<tr>
<td>1995</td>
<td>Kemp et al. [48]</td>
<td>Retrospective allergy clinic</td>
<td>14 years</td>
<td>United States</td>
<td>266</td>
<td>Paediatric and adult Mean 38 years (12–75)</td>
<td>1.4:1</td>
<td>Idiopathic (37%)</td>
<td>Nil</td>
</tr>
<tr>
<td>1996</td>
<td>Pumphrey et al. [49]</td>
<td>Retrospective allergy clinic</td>
<td>Unknown</td>
<td>United Kingdom</td>
<td>172</td>
<td>Paediatric and adult 5 months – 69 years</td>
<td>1:1</td>
<td>Peanut (42)</td>
<td>Nil</td>
</tr>
<tr>
<td>1998</td>
<td>International Collaborative Study of Severe Anaphylaxis [50]</td>
<td>Prospective, multicentre</td>
<td>3 years</td>
<td>Hungary, Spain, India, Sweden</td>
<td>123</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Peanut (42)</td>
<td>Mortality 2%</td>
</tr>
<tr>
<td>1998</td>
<td>Novembre et al. [51]</td>
<td>Retrospective paediatric allergy clinic</td>
<td>2 years</td>
<td>Italy</td>
<td>76</td>
<td>Unknown</td>
<td>0.5:1</td>
<td>Food (57%)</td>
<td>Nil</td>
</tr>
<tr>
<td>2000</td>
<td>Pumphrey &amp; Roberts [52]</td>
<td>Retrospective fatal anaphylaxis registry</td>
<td>8 years</td>
<td>United Kingdom</td>
<td>56</td>
<td>Paediatric and adult Median 52 years (7–85)</td>
<td>1.5:1</td>
<td>Drugs (38%)</td>
<td>Nil</td>
</tr>
<tr>
<td>2001</td>
<td>Pastorello et al. [53]</td>
<td>Retrospective emergency room attendances</td>
<td>2 years</td>
<td>Italy</td>
<td>140</td>
<td>Unknown</td>
<td>Female</td>
<td>Food (39%)</td>
<td>Incidence 4%</td>
</tr>
<tr>
<td>2001</td>
<td>Gianferoni et al. [54]</td>
<td>Retrospective inpatient hospitalizations</td>
<td>11 years</td>
<td>Italy</td>
<td>107</td>
<td>Adult Mean 48 ± 18 years</td>
<td>0.8:1</td>
<td>Drugs (49%)</td>
<td>Nil</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Type of study</td>
<td>Period of study</td>
<td>Country</td>
<td>Number of cases</td>
<td>Age (range)</td>
<td>Sex F : M</td>
<td>Causes</td>
<td>Outcome measures</td>
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<tr>
<td>2001</td>
<td>Brown et al. [55]</td>
<td>Retrospective emergency room attendances</td>
<td>1 year</td>
<td>Australia</td>
<td>142</td>
<td>Paediatric and adult 13 years Mean 37.3 ± 15.8 years (14–86)</td>
<td>1.5:1</td>
<td>Drugs</td>
<td>Venom (73%) Food (27%)</td>
</tr>
<tr>
<td>2004</td>
<td>Helbling et al. [56]</td>
<td>Retrospective case review from hospitals/allergy clinics</td>
<td>3 years</td>
<td>Switzerland</td>
<td>226</td>
<td>Paediatric and adult Mean 41 years (5–74)</td>
<td>0.9:1</td>
<td>Venom (59%) Drugs (18%) Food (10%) Idiopathic (5.3%)</td>
<td>Annual incidence 7.9–9.6/100 000 inhabitants Mortality 1.3%</td>
</tr>
<tr>
<td>2004</td>
<td>Peng &amp; Jick [57]</td>
<td>Observational follow-up (UK General Practice Research Database)</td>
<td>6 years</td>
<td>United Kingdom</td>
<td>675</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Venom Drugs</td>
<td>Incidence 8.4/100 000 person-years Mortality 0.1%</td>
</tr>
<tr>
<td>2004</td>
<td>Bohlke et al. [58]</td>
<td>Retrospective study from health maintenance organization diagnosis codes</td>
<td>6 years</td>
<td>United States</td>
<td>67</td>
<td>Paediatric Median age 12 years (7 month–17 years)</td>
<td>0.7:1</td>
<td>Unknown</td>
<td>Incidence 10.5/100 000 person-years</td>
</tr>
<tr>
<td>2004</td>
<td>Cianferoni et al. [59]</td>
<td>Prospective follow-up study</td>
<td>7 years</td>
<td>Italy</td>
<td>76</td>
<td>Paediatric</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Nil</td>
</tr>
<tr>
<td>2005</td>
<td>Thong et al. [60]</td>
<td>Retrospective allergy clinic</td>
<td>3 years 8 months</td>
<td>Singapore</td>
<td>67</td>
<td>Adult</td>
<td>0.5:1</td>
<td>Food (44.8%) Insect stings (32.8%) Idiopathic (22.4%)</td>
<td>Nil</td>
</tr>
<tr>
<td>2006</td>
<td>Webb et al. [61]</td>
<td>Retrospective medical record review from private university-affiliated allergy-immunology practice</td>
<td>25 years</td>
<td>United States</td>
<td>601</td>
<td>Adult and paediatric Mean 37 years (1–79)</td>
<td>1.6:1</td>
<td>Food (23%) Drugs (11%) Exercise (5%)</td>
<td>Nil</td>
</tr>
<tr>
<td>2006</td>
<td>Braganca et al. [62]</td>
<td>Retrospective, case based study of paediatric ED visits</td>
<td>3 years</td>
<td>Australia</td>
<td>57</td>
<td>Paediatric Median age 4.1 years (0.2–14.1)</td>
<td>Unknown</td>
<td>Food (56%) Idiopathic (31.8%) Drug (5.3%) Insect venom (5.3%)</td>
<td>Incidence 1:1000</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Study Type</td>
<td>Country</td>
<td>Population</td>
<td>Age</td>
<td>Sex Ratio</td>
<td>Etiology</td>
<td>Prevalence</td>
<td>Mortality</td>
</tr>
<tr>
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</tr>
<tr>
<td>2006</td>
<td>Low &amp; Stables [63]</td>
<td>Review of coronial autopsies</td>
<td>New Zealand</td>
<td>Adult</td>
<td>Mean 52 years (33–76)</td>
<td>1:1</td>
<td>Drugs (55.5%) (anaesthetic agents, antibiotic)</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 years</td>
<td></td>
<td></td>
<td>Insect venom (22.2%)</td>
<td>Food (11.1%)</td>
<td>Idiopathic (11.1%)</td>
</tr>
<tr>
<td>2007</td>
<td>Jirapongpananukul et al. [64]</td>
<td>Retrospective review of hospitalized inpatients</td>
<td>Thailand</td>
<td>Paediatric and adult</td>
<td>Mean 24 ± 22 years</td>
<td>Paed: more males</td>
<td>Adult: more females</td>
<td>Drugs (50%)</td>
<td>Food (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 years</td>
<td></td>
<td></td>
<td>Annual occurrence of anaphylaxis increased from 9.16 per 100 000 admitted persons in 1999 to 55.45 per 100 000 admitted persons in 2004. Case fatality rate was 0.19 per 100 000 admitted persons.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Yang et al. [65]</td>
<td>Retrospective review of inpatients, outpatients and emergency department attendances</td>
<td>South Korea</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Drugs (35.3%): RCM most common</td>
<td>Food (21.3%): buckwheat most common</td>
<td>FDEIA (13.2%)</td>
<td>Insect stings (11.8%), Exercise induced (2.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 years 6 months</td>
<td></td>
<td></td>
<td>Prevalence 0.014%</td>
<td>Mortality rate 0.0001%</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Decker et al. [66]</td>
<td>Population-based incidence study</td>
<td>United States</td>
<td>Paediatric and adult</td>
<td>Mean age 29 ± 18 years (0.8–78.2)</td>
<td>1:3:1</td>
<td>Food (33.2%)</td>
<td>Insect venom (18.5%)</td>
<td>Drugs (13.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 years</td>
<td></td>
<td></td>
<td>Overall age- and sex-adjusted incidence rate was 49.8 (95% CI 45.0, 54.5) per 100 000 person-years. Age-specific rates were highest for ages 0 to 19 years (70 per 100 000 person-years). Overall incidence rate 49.8 per 100 000 person-years.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>De Silva et al. [67]</td>
<td>Retrospective, paediatric emergency department</td>
<td>Australia</td>
<td>123 episodes in 117 patients</td>
<td>Paediatric Median 2.4 years (IQR 1.4–6.6)</td>
<td>Unknown</td>
<td>Food (85%)</td>
<td>Idiopathic (7%)</td>
<td>Drugs (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 years</td>
<td></td>
<td></td>
<td>Relative number of deaths to admissions was 1:1000 for food-induced anaphylaxis and 11:1000 for non-food-induced anaphylaxis. Rate of anaphylaxis fatality in Australia 0.64 deaths per million population per year.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Liew et al. [68]</td>
<td>Retrospective study all anaphylaxis fatalities from National Mortality Database</td>
<td>Australia</td>
<td>Adult and paediatric</td>
<td>Unknown</td>
<td>Probable drug (38%)</td>
<td>Drug (22%)</td>
<td>Insect venom (18%)</td>
<td>Indeterminate (13%)</td>
</tr>
</tbody>
</table>

FDEIA, food dependent exercise induced anaphylaxis; NMRB, neuromuscular receptor blockers; NRL, natural rubber latex.
# Table 3
Summary of epidemiological studies on severe cutaneous adverse reactions (SCAR)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Type of study</th>
<th>Period of study</th>
<th>Country</th>
<th>Number of cases</th>
<th>Age (range)</th>
<th>Sex F : M</th>
<th>Systemic manifestations</th>
<th>Causes</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Guillaume et al. [6]</td>
<td>Prospective, TEN</td>
<td>13 years</td>
<td>France</td>
<td>87</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Sulfonamides (20.7%) – sulfamethoxazole/trimethoprim (67%) Anticonvulsants (8%) – barbiturates and carbamazepine only NSAIDs (33.3%) – phenylbutazone, oxicam derivatives Allopurinol (3.4%) Chlormezanone (3.4%)</td>
<td>Unknown</td>
</tr>
<tr>
<td>1990</td>
<td>Chan et al. [79]</td>
<td>Retrospective, EM/SJS/TEN</td>
<td>14 years</td>
<td>United States</td>
<td>37 EM/SJS/TEN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>43% attributed to drugs Drug therapies with reaction rates in excess of 1 per 100 000 exposed individuals include phenobarbital (20 per 100 000), nitrofurantoin (7 per 100 000), sulfamethoxazole and trimethoprim, and ampicillin (both 3 per 100 000), and amoxicillin (2 per 100 000).</td>
<td>Incidence of TEN alone due to all causes was 0.5 per 106 person-years. Incidence of EM, SJS, or TEN associated with drug use were 7.0, 1.8, and 9.0 per 106 person-years, respectively, for persons younger than 20 years of age, 20 to 64 years of age, and 65 years of age and older.</td>
</tr>
<tr>
<td>1990</td>
<td>Schopf et al. [81]</td>
<td>Retrospective, SJS/TEN</td>
<td>5 years</td>
<td>Germany</td>
<td>259 TEN 315 SJS</td>
<td>Mean age 63 years (TEN); 25 years (SJS)</td>
<td>TEN: 2.1; SJS: 1.2</td>
<td>Unknown</td>
<td>Antibiotics (TEN, 40%; SJS, 34%) Analgesics (TEN, 23%; SJS, 33%)</td>
<td>TEN: Annual risk of 0.93 per million, mortality 34% SJS: Annual risk 1.1 per million, mortality 1%</td>
</tr>
<tr>
<td>1990</td>
<td>Roujeau et al. [82]</td>
<td>Retrospective, TEN</td>
<td>5 years</td>
<td>France</td>
<td>399 TEN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Sulfadiazine Oxicam Isoxsuphensbutazone Phenytoin Fenbufen Cotrimoxazole</td>
<td>Incidence 1.2 cases per million per year</td>
</tr>
<tr>
<td>1993</td>
<td>Leenutaphong et al. [84]</td>
<td>Retrospective, SJS and TEN</td>
<td>9 years</td>
<td>Thailand</td>
<td>Total = 78 58 SJS, 20 TEN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Antibiotics (41%) – penicillin, sulfonamides, tetracycline, erythromycin Anticonvulsants (11.5%) – phenytoin, carbamazepine barbiturates Antitubercular drugs (10.3%) – thiacetazone</td>
<td>Mortality rate 14%; 40% TEN, 5% SJS</td>
</tr>
<tr>
<td>1995</td>
<td>Roujeau et al. [85]</td>
<td>Retrospective, Case-control study</td>
<td>4 years</td>
<td>France, Germany, Italy, and Portugal</td>
<td>Total = 245 SJS 89 SJS-TEN overlap 76 TEN 80</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Sulfonamides, trimethoprim-sulfamethoxazole Carbamazepine Oxicam NSAIDs Chlormezanone Phenytoin Allopurinol</td>
<td>Unknown</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Study Design</td>
<td>Duration</td>
<td>Country</td>
<td>Total</td>
<td>SJS</td>
<td>TEN</td>
<td>SJS-TEN Overlap</td>
<td>Age</td>
<td>Diagnosis</td>
</tr>
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</tr>
<tr>
<td>1996</td>
<td>Rzany et al. [86]</td>
<td>Retrospective, d27</td>
<td>2 years 8 months</td>
<td>Germany</td>
<td>SJS 139</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Incidence of SJS/TEN Up to 1.89 per 1 million inhabitants per year</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Kamaliah et al. [87]</td>
<td>Retrospective, EMIS/TEN (EM excluded in this table)</td>
<td>8 years</td>
<td>East Malaysia</td>
<td>Total = 25</td>
<td>19 adult and 6 paediatric</td>
<td>0.73:1</td>
<td>Fever (62.1%)</td>
<td>Retrospectively, EMIS/TEN (EM excluded in this table)</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Wong et al. [87]</td>
<td>Retrospective, SJS/TEN</td>
<td>12 years</td>
<td>Australia</td>
<td>Total = 17</td>
<td>Mean age 61.5 years</td>
<td>0.5:1</td>
<td>Unknown</td>
<td>Mortality: TEN 37.3%, SJS 4.5%</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Gerdts et al. [89]</td>
<td>Retrospective</td>
<td>15 years</td>
<td>The Netherlands</td>
<td>19</td>
<td>Adult and paediatric Mean age 45.6 ± 23.9 years (5–70)</td>
<td>1.6:1</td>
<td>Unknown</td>
<td>Mortality (15.8%)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Yamane et al. [90]</td>
<td>Retrospective, all cases published from Japan</td>
<td>6 years</td>
<td>Japan</td>
<td>Total = 117</td>
<td>SJS: mean 45.2 years, TEN: mean 45.7 years</td>
<td>1.7:1</td>
<td>Haematological (86.7%), Respiratory (25.6%), Renal dysfunction (19.7%)</td>
<td>Mortality: SJS 1.9% TEN 6.2%</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Sharma et al. [91]</td>
<td>Retrospective</td>
<td>3 years</td>
<td>India</td>
<td>Total = 30</td>
<td>Paediatric and adult Mean age 22.3 ± 15.4 years (4–69)</td>
<td>1.2:1</td>
<td>Haematological (86.7%), Respiratory (25.6%), Renal dysfunction (19.7%)</td>
<td>Mortality 16.7% TEN 13.3% SJS-TEN overlap</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Mockenhaupt et al. [92]</td>
<td>Retrospective, case-control (EuroSCAR)</td>
<td>Unknown</td>
<td>Europe</td>
<td>Total = 379</td>
<td>Paediatric and adult Median 50 years (IQR 28–68)</td>
<td>1.6:1</td>
<td>Unknown</td>
<td>Nevirapine Lamotrigine Carbamazepine Phenytoin Phenobarbital Cotrimoxazole and other anti-infective sulfonamides Sulphasalazine Allopurinol Oxicam-NSAIDs</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Wetter et al. [93]</td>
<td>Retrospective</td>
<td>8 years</td>
<td>United States</td>
<td>27 SJS</td>
<td>Paediatric and adult Mean 28.1 ± 22.3 years</td>
<td>0.7:1</td>
<td>Fever (70%), Leukocytosis (22%)</td>
<td>74% drug related</td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology and risk factors for drug allergy

Br J Clin Pharmacol / 715 / 693
Risk factors for drug allergy

Drug related factors

Drug related factors that affect its immunogenicity include its ability to act as a hapten, a prohapten or to bind covalently to immune receptors (Pi concept) [96]. Thus, certain classes of drugs tend to be associated with a higher frequency of drug allergies compared with others [97]. Although it is believed that intermittent and repeated administrations appear to be more sensitizing than uninterrupted treatment, and parenteral administration appears to be more sensitizing than the oral route, rigorous studies to support these are lacking.

Host related factors

Females appear more likely to develop drug allergies than males, but this may be attributable to the overall female predominance in ADRs. In the Alergológica 2005 study [36], the female : male ratio of first time consults for drug allergy was approximately 2:1. The incidence of self reported drug allergy in the Haidian district was not less than 1.8 per million person-years. The reported incidence of erythema multiforme, SJS, TEN and DRESS in the Haidian district was not less than 0.6, 0.8, 0.05 and 0.4 per million person-years, respectively. The most common underlying disorders were infection, pain-related diseases and epilepsy.

Genetics of drug allergy

The study of medical genetics in recent years has focused on the area of HLA genotypes and their association with severe drug hypersensitivity. To generate an immune reaction, HLA molecules function as antigen presenters to immune T-cells via the T cell receptor (TCR). HLA class I (HLA A, HLA B, HLA C) molecules are ubiquitous and are found on all nucleated cell surfaces. They present intracellular antigens to CD8+ cytotoxic T-cells. HLA class II (HLA DP, HLA DQ, HLA DR) molecules are found on the immune cells and they present extracellular antigens to CD4+ helper T-cells. It has been suggested that MHC presentation of drug derived antigen plays a key role in the development of drug hypersensitivity.

HLA associations that have been described in severe cutaneous adverse reactions include:

- HLA B*1502 associated with carbamazepine induced SJS/TEN in Han Chinese in Taiwan [odds ratio, OR 1357 (95% CI 193, 8838) – 2504 (95% CI 126, 49 522)] [106] and Hong Kong (OR 71.9) [107], Thais [OR 25.5 (95% CI 2.68, 242.61)] [108] and Indians [109] but neither in Japanese [110] nor Europeans of non-Asian ancestry [111]. There was no
A multi-national double-blind prospective randomized study has shown that HLA B*5701 screening prior to the use of abacavir in White populations is useful in preventing abacavir hypersensitivity reactions [119]. Although the United States Food and Drug Administration and Health Canada have also recommended testing for the HLA B*1502 allele in at-risk populations (e.g. South-east Asian ancestry) prior to the prescription of carbamazepine, most regulatory authorities in Asia have not made this mandatory at the moment. Given the strong association of HLA-B*5801 with hypersensitivity to allopurinol across different ethnic populations (i.e. Southeast Asian, Japanese, European), screening all patients before initiating allopurinol may also appear to be prudent in future. However, several factors need to be considered before such screening procedures can be considered cost-effective in the population at risk including: the population prevalence of that specific HLA allele, the prevalence of the condition for which the drug is used, the utilization rate of that particular drug, and lastly, rapid methods of detection, as for HLA-B*5701 and HLA-B*1502, need to be readily available [120, 121].

Apart from HLA associations with serious drug allergies, various other genetic associations have also been reported for:

- IgE mediated penicillin allergy: E237G variant of FcεR1β (high affinity IgE receptor β chain) gene, IL-4RαQ576R polymorphism, IL-4 Il-13-SNP polymorphisms in Chinese [122, 123, 124];
- Immediate allergic reactions to beta-lactams:II-13 (R130Q and −1055C > T variants) and IL-4RA (150V, S478P, and Q551R variants) polymorphisms in Italians [125]; Ile75Val variant of IL-4Ra gene two linked II-10 promoter gene polymorphisms (−819C > T and −592C > A) in Caucasians [126];
- Antituberculous drug induced hepatitis: CYP2E1 in the Chinese [127] (but not in Korean and British), NAT2 (N-acetyltransferase) in Koreans [128] and GST (glutathione-S-transferase) genotypes in Caucasians [129].

A recent update on genetic and ethnic associations with drug hypersensitivity to different drugs has been reviewed in detail elsewhere [130].

**Conclusion**

Epidemiologists study the factors affecting the health and illness of populations, enabling interventions to be made in the interest of public health and preventive medicine. Pharmacoepidemiology is the study of the use and effects (outcomes) of drugs (exposure) in large populations of people. Current epidemiological data on ADRs often do not differentiate immunologically and non-immunologically mediated drug hypersensitivity, study different study populations (different ethnicities, inpatients or outpatients, adults or children), utilize different methodologies (spontaneous vs. non-spontaneous reporting), different methods of assessing drug imputability and different methods of data analyses.

Standardization of definitions of terminology used in drug allergy will ensure better comparability among studies, facilitate the validation of in vivo and in vitro allergological tests, and improve our understanding of the immunological mechanisms underlying different types of drug allergies. Identification of risk factors for drug allergy and appropriate genetic screening of at-risk ethnic groups may improve the outcomes of drug-specific SCAR.

Research and collaboration among epidemiologists, allergists, pharmacologists, pharmacists, toxicologists, geneticists and immunologists, should be advocated as such partnerships will contribute significantly to the generation of clinically-relevant, translational pharmacoepidemiological and pharmacogenomic knowledge, and hence the success of health outcomes research and policies on drug allergies.

**Competing interests**

There are no competing interests to declare.

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123 Qiao HL, Yang J, Zhang YW. Relationships between specific serum IgE, cytokines and polymorphisms in the IL-4, IL-4Ralpha in patients with penicillin allergy. Allergy 2005; 60: 1053–9.


