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Epidemiology and risk factors for drug allergy

Bernard Y-H. Thong & Teck-Choon Tan

Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore

Correspondence
Dr Bernard Yu-Hor Thong MBBS MRCP (UK), Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433 Singapore.
Tel.: + 65 6357 7822
Fax: + 65 6357 2686
E-mail: bernard_thong@ttsh.com.sg

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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/ idiosyncratic 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 exanthematous 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% erythroderma 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

Year	Author	Type of study	Period of study	Types of reaction studied	Number studied	Patient type	Number with ADR	Number with severe ADR	Types of ADR	Implicated drugs
1983	Allain *et al*. [22]	• Prospective • Departmental	12 months	Cutaneous ADR	550	Inpatient	30 (5.6%)	1 death	Erythroderma Drug eruption	Cardiovascular drugs Anti-inflammatory drugs Antimicrobials
1986	Bigby *et al*. [23]	Boston Collaborative Drug Surveillance Programme BCDSP	3 years 8 months	Cutaneous ADR	15 438	Inpatient	347 (2.2%)	Unknown	95% morbilliform 5% urticaria	Amoxicillin (5.1%) Ampicillin (4.5%) Penicillins (4.5%) Cotrimoxazole (3.7%) Cephalosporins (1.5%) Gentamicin (1%)
1991	Classen *et al*. [24]	Prospective	1 year 6 months	ADR	36 653	Inpatient	731 (1.8%)	Unknown	32.7% allergic	Unknown
1995	Rademaker *et al*. [25]	• Prospective • Departmental • Case verification by dermatologist	6 months	Cutaneous ADR	60	Inpatient	27 allergy 4 allergic contact dermatitis	Unknown	Unknown	Penicillin Furosemide Prednisolone Allopurinol Carbamazepine
1997	Hunziker *et al*. [26]	• Comprehensive Hospital Drug Monitoring (CHDM) • Prospective • Multi-centre • Case verification by dermatologist	40 years	Cutaneous ADR	48 005	Inpatient	1308 allergy	Nil	91.2% maculopapular 5.9% urticaria 1.4% vasculitis 0.38% erythema multiforme 0.45% fixed drug eruption	Penicillins (8.0%) Cotrimoxazole (2.8%) Cephalosporin (1.9%)
2001	Sharma *et al*. [27]	Prospective	6 years	Cutaneous ADR	500	Inpatient	500	10 deaths from TEN	34.6% maculopapular 30.0% fixed drug eruption 14.0% urticaria	Antimicrobials (42.6%) Anticonvulsants (22.2%)
2002	Thong *et al*. [28]	• Prospective • Electronic, Inpatient Drug Allergy Reporting System • Drug allergy verified by allergist	2 years	Cutaneous and systemic drug allergies Incidence of allergic reactions = 4.2/1000 hospitalizations	366	Inpatient	210 allergy	11 (5.2%) - SJS (3.3%) - TEN (1.4%) - GED (0.5%) 4 deaths	95.7% cutaneous - 62.7% maculopapular - 17.9% urticaria 30.0% systemic - 52.4% hepatic - 44.4% fever - 27% haematological	Penicillins (25.2%) Cephalosporins (15.7%) Cotrimoxazole (9.0%) Phenytoin (8.1%) Carbamazepine (6.2%) Allopurinol (5.7%)
2003	Fiszenson-Albala *et al*. [29]	• Prospective • Drug allergy verified by dermatologist and pharmacologist	6 months	Cutaneous allergy Prevalence of cutaenous allergic reactions = 3.6/1000 hospitalizations	48	Inpatient	48 allergy	24% severe	57% exanthema 8% erythroderma 2% SJS/TEN.	21% betalactams
2006	Hernández-Salazar *et al*. [30]	Prospective	10 months	Cutaneous ADR	4785	Inpatient	35	AGEP 2.4% SJS 4.9% TEN 2.4% DiHS 2.4% 1 death	Morbilliform rash 51.2% Urticaria 12.2% Erythema multiforme 4.9%	Amoxicillin clavulanate (22.9%) Metamizole (11.4%) Amphotericin B (5.7%)
2008	Park *et al*. [31]	• Prospective • Electronic, Inpatient Drug Allergy Reporting System • Drug allergy verified by allergist	7 months	Cutaneous and systemic drug allergies Incidence of drug hypersensitivity = 1.8/1000 hospitalizations	532	Inpatient		16% severe SJS/TEN 1% Anaphylaxis 11%	70% cutaneous - Urticaria/ angioedema 26% - Maculopapular 33% 30% systemic - Respiratory 18% - Fever 3% - Hepatic 1% - Haematologic 1%	Antibiotics (32%), Radiocontrast media (26%) Antineoplastic drugs (17%).

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 $\leq$ 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

shock or anaphylactoid reaction; cutaneous or systemic reactions (involving at least two organs/systems involvement), with time to onset (not defined) suggesting an allergic reaction. Each case was reviewed by an *ad hoc* panel comprising toxicologists, clinical pharmacologists and pharmacists. A total of 27 175 ADRs were analysed, of which 3143 (11.6%) were deemed to be due to drug allergy. The causative drug classes with significant reported odds ratio (ROR) were antibiotics (2.92, 95% CI 2.71, 3.15) and NSAIDs (1.65, 95% CI 1.51, 1.81). The study showed that among antibiotics, cinoxacin (6.88, 95% CI 4.19, 11.29) and moxifloxacin (4.20, 95% CI 3.19, 5.55) were related with the highest ROR values, while propionic acid derivatives (2.75, 95% CI 2.30, 3.28) and, in particular, ibuprofen (4.2, 95% CI 3.13, 5.63) showed the highest ROR values among NSAIDs.

The French Pharmacovigilance database was established in 1985 to register spontaneous reporting of ADRs. By law, every prescriber in France must report 'serious' or 'unexpected' ADRs to their French Regional Pharmacovigilance Centre. A recent study on allergic drug reactions to local anaesthetic agents using the French Pharmacovigilance database and the GERAP (Groupe d'Etudes des Re'actions Anaphylactoïdes Peranesthe'siques: study group of peranaesthetic anaphylactoid reactions) database over a 12 year period (1995–2006), identified 16 reports (seven from the Pharmacovigilance database and nine from the GERAP database) [45]. Local anaesthetic allergic reactions occurred mostly in young females (female : male sex ratio 14:2). An immediate-type allergic reaction was encountered in 11/16 cases. Lidocaine was found to be the local anaesthetic most often involved (11/16). Skin prick, intradermal and drug provocation tests were used to confirm the diagnosis. Cross-reactivity between the different amide type local anaesthetics was found in six cases (lidocaine-mepivacaine in all cases).

Collaborations similar to this and the Galenda project [17], comprising allergologists, toxicologists, pharmacologists and pharmacists working through such pharmacovigilance databases, are very useful sources of information in defining the true incidence, prevalence and patterns of allergic drug hypersensitivity.

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 peri-operative period) were a common cause of IgE-mediated allergic anaphylaxis. NSAIDs and radiocontrast 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 oxicam-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

Year	Author	Type of study	Period of study	Country	Number of cases	Age (range)	Sex F : M	Causes	Outcome measures
1994	Yocum *et al.* [47]	Retrospective allergy clinic	3 years 6 months	United States	179	Mean 36 years	1.9:1	Food (33%) Idiopathic (19%) Insect venom (14%) Drugs (13%) Exercise (7%)	Nil
1995	Kemp *et al.* [48]	Retrospective allergy clinic	14 years	United States	266	Paediatric and adult Mean 38 years (12–75)	1.4:1	Idiopathic (37%) Food (34%): Drugs (20%): NSAID Exercise (7%) Latex (0.8%)	Nil
1996	Pumphrey *et al.* [49]	Retrospective allergy clinic	Unknown	United Kingdom	172	Paediatric and adult 5 months – 69 years	1:1	Peanut (42) Tree nut (23) Other food (20) FDEIA (5) Venom (6 bee, 22 wasp) NMRB (7) NRL (6) Idiopathic (20)	Nil
1998	International Collaborative Study of Severe Anaphylaxis [50]	Prospective, multicentre	3 years	Hungary, Spain, India, Sweden	123	Unknown	Unknown	Unknown	Mortality 2%
1998	Novembre *et al.* [51]	Retrospective paediatric allergy clinic	2 years	Italy	76	Unknown	0.5:1	Food (57%) Venom (12%) Drugs (11%) Exercise (9%) Idiopathic (6%) Vaccines (2%) Additives (1%) Specific immunotherapy (1%) NRL (1%)	Nil
2000	Pumphrey & Roberts [52]	Retrospective fatal anaphylaxis registry	8 years	United Kingdom	56	Paediatric and adult Median 52 years (7–85)	1.5:1	Drugs (38%) Venom (34%) Food (28%)	Nil
2001	Pastorello *et al.* [53]	Retrospective emergency room attendances	2 years	Italy	140	Unknown	Female	Food (39%) Drugs (36%) Idiopathic (21%) Venom (2%) Others (2%)	Incidence 4%
2001	Cianferoni *et al.* [54]	Retrospective inpatient hospitalizations	11 years	Italy	107	Adult Mean 48 ± 18 years	0.8:1	Drugs (49%) Venom (29%) Food (8%) Specific immunotherapy (6%) Idiopathic (6%) Exercise (2%)	Nil

Table 2

Continued

Year	Author	Type of study	Period of study	Country	Number of cases	Age (range)	Sex F : M	Causes	Outcome measures
2001	Brown *et al.* [55]	Retrospective emergency room attendances	1 year	Australia	142	Paediatric and adult ≥ 13 years Mean 37.3 ± 15.8 years (14–86)	1.5:1	Drugs] Venom] 73% Food] Idiopathic (27%)	Incidence 1:439 Mortality 0.7%
2004	Helbling *et al.* [56]	Retrospective case review from hospitals/allergy clinics	3 years	Switzerland	226	Paediatric and adult Mean 41 years (5–74)	0.9:1	Venom (59%) Drugs (18%) Food (10%) Idiopathic (5.3%)	Annual incidence 7.9–9.6/100 000 inhabitants Mortality 1.3%
2004	Peng & Jick [57]	Observational follow-up (UK General Practice Research Database)	6 years	United Kingdom	675	Unknown	Unknown	Venom Drugs	Incidence 8.4/100 000 person-years Mortality 0.1%
2004	Bohlke *et al.* [58]	Retrospective study from health maintenance organization diagnosis codes	6 years	United States	67	Paediatric Median age 12 years (7 month–17 years)	0.7:1	Unknown	Incidence 10.5/100 000 person-years
2004	Cianferoni *et al.* [59]	Prospective follow-up study	7 years	Italy	76	Paediatric	Unknown	Unknown	Nil
2005	Thong *et al.* [60]	Retrospective allergy clinic	3 years 8 months	Singapore	67	Adult	0.5:1	Food (44.8%) Insect stings (32.8%) Idiopathic (22.4%)	Nil
2006	Webb *et al.* [61]	Retrospective medical record review from private university-affiliated allergy-immunology practice	25 years	United States	601	Adult and paediatric Mean 37 years (1–79)	1.6:1	Food (22%) Drugs (11%) Exercise (5%)	Nil
2006	Braganza *et al.* [62]	Retrospective, case based study of paediatric ED visits	3 years	Australia	57	Paediatric Median age 4.1 years (0.2–14.1)	Unknown	Food (56%) Idiopathic (31.8%) Drug (5.3%) Insect venom (5.3%)	Incidence 1:1000

2006	Low & Stables [63]	Review of coronial autopsies	20 years	New Zealand	18	Adult Mean 52 years (33–76)	1:1	Drugs (55.5%) (anaesthetic agents, antibiotic) Insect venom (22.2%) Food (11.1%) Idiopathic (11.1%)	Nil
2007	Jirapongsananu-ruk *et al.* [64]	Retrospective review of hospitalized inpatients	6 years	Thailand	101	Paediatric and adult Mean 24 ± 22 years	Paed: more males Adult: more females	Drugs (50%) Food (24%) Idiopathic (15%) Insect venom (11%)	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.
2007	Yang *et al.* [65]	Retrospective review inpatients, outpatients and emergency department attendances	6 years 6 months	South Korea	138	Unknown	Unknown	Drugs (35.3%): RCM most common Food (21.3%): buckwheat most common FDEIA (13.2%) Insect stings (11.8%), Exercise induced (2.9%) Blood products (1.5%) NRL (0.7%).	Prevalence 0.014% Mortality rate 0.0001%.
2008	Decker *et al.* [66]	Population-based incidence study	10 years	United States	211	Paediatric and adult Mean age 29 ± 18 years (0.8–78.2)	1.3:1	Food (33.2%) Insect venom (18.5%) Drugs (13.7%) Idiopathic (25.1%)	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.
2008	De Silva *et al.* [67]	Retrospective, paediatric emergency department	5 years	Australia	123 episodes in 117 patients	Paediatric Median 2.4 years (IQR 1.4–6.6)	Unknown	Food (85%) Idiopathic (7%) Drugs (6%) Insect venom (3%)	Mortality 1%
2009	Liew *et al.* [68]	Retrospective study all anaphylaxis fatalities from National Mortality Database	9 years	Australia	112	Adult and paediatric	Unknown	Probable drug (38%) Drug (22%) Insect venom (18%) Indeterminate (13%) Food (6%) Others (5%)	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.

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)

Year	Author	Type of study	Period of study	Country	Number of cases	Age (range)	Sex F : M	Systemic manifestations	Causes	Outcome measures
1986	Guillaume *et al.* [6]	Prospective, TEN	13 years	France	87	Unknown	Unknown	Unknown	Sulfonamides (20.7%) – sulfamethoxazole/trimethoprim (67%) Anticonvulsants (8%) – barbiturates and carbamazepine only NSAIDs (33.3%) -phenylbutazone, oxicam derivatives Allopurinol (3.4%) Chlormezanone (3.4%)	Unknown
1990	Chan *et al.* [79]	Retrospective, EM/SJS/TEN	14 years	United States	37 EM/SJS /TEN	Unknown	Unknown	Unknown	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).	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.
1990	Schopf *et al.* [81]	Retrospective, SJS/TEN	5 years	Germany	259 TEN 315 SJS	Mean age 63 years (TEN); 25 years (SJS)	TEN: 2:1; SJS: 1:2	Unknown	Antibiotics (TEN, 40%; SJS, 34%) Analgesics (TEN, 23%; SJS, 33%)	TEN: Annual risk of 0.93 per million, mortality 34% SJS: Annual risk 1.1 per million, mortality 1%
1990	Roujeau *et al.* [82]	Retrospective, TEN	5 years	France	399 TEN	Unknown	Unknown	Unknown	Sulfadiazine Isoxicam Oxyphenbutazone Phenytoin Fenbufen Cotrimoxazole	Incidence 1.2 cases per million per year
1993	Leenutaphong *et al.* [84]	Retrospective, SJS and TEN	9 years	Thailand	Total = 78 58 SJS, 20 TEN	Unknown	Unknown	Unknown	Antibiotics (41%) – penicillin, sulfonamides, tetracycline, erythromycin Anticonvulsants (11.5%) – phenytoin, carbamazepine barbiturates Antitubercular drugs (10.3%) – thiacetazone	Mortality rate 14%; 40% TEN, 5% SJS
1995	Roujeau *et al.* [85]	Retrospective, Case-control study	4 years	France, Germany, Italy, and Portugal	Total = 245 SJS 89 SJS-TEN overlap 76 TEN 80	Unknown	Unknown	Unknown	Sulfonamides, trimethoprim-sulfamethoxazole Carbamazepine Oxicam NSAIDs Chlormezanone Phenytoin Allopurinol	Unknown

1996	Rzany *et al*. [86]	Retrospective, dZh German population-based registry for severe skin reactions.	2 years 8 months	Germany	SJS 139 SJS-TEN overlap 95 TEN 56	Unknown	Unknown	Unknown	Unknown	Incidence of SJS/TEN Up to 1.89 per 1 million inhabitants per year
1998	Kamaliah *et al*. [87]	Retrospective, EM/SJS/TEN (EM excluded in this table)	8 years	East Malaysia	Total = 25 22 SJS, 3 TEN	19 adult and 6 paediatric Paed: 10 month–12 years Adult: 15–65 years	0.73:1	Fever (62.1%) Leukocytosis (34.5%) Hepatitis (31%)	Antibiotics (36%) Cotrimoxazole Ampicillin/amoxicillin Anticonvulsants (32%) Allopurinol (4%)	Mortality: TEN 37.3%, SJS 4.5%
1999	Wong *et al*. [87]	Retrospective, SJS/TEN	12 years	Australia	Total = 17 10 SJS, 7 TEN	Mean age 61.5 years	0.5:1	Unknown	Betalactam antibiotics (52.9%)	Mortality: 28.6% TEN 10% SJS
2007	Gerdts *et al*. [89]	Retrospective	15 years	The Netherlands	19	Adult and paediatric Mean age 45.6 ± 23.9 years (5–70)	1.6:1	Unknown	Anticonvulsants – phenytoin/ carbamazepine (36.8%) Amoxicillin (10.5%)	Mortality (15.8%)
2007	Yamane *et al*. [90]	Retrospective, all cases published from Japan	6 years	Japan	Total = 117 52 SJS, 65 TEN	SJS: mean 45.2 years TEN: mean 45.7 years	SJS 1.7:1 TEN	Hepatitis (55.6%) Respiratory (25.6%) Renal dysfunction (19.7%)	Anticonvulsants (17.9%) Antibiotics (17.1%) NSAIDs (12.8%)	Mortality: SJS 1.9% TEN 6.2%
2008	Sharma *et al*. [91]	Retrospective	3 years	India	Total = 30 15 TEN, 9 SJS-TEN overlap and 6 SJS	Paediatric and adult Mean age 22.3 ± 15.4 years (4–65)	1.2:1	Haematological (86.7%) Hepatitis (36.7%) Renal (13.3%) Pnemonitis (10%)	Anticonvulsants (35.1%) – phenytoin 45%, carbamazepine 30% Antibiotics (33.3%) – cephalosporins 26% NSAIDS (24.6%).	Mortality 16.7% 13.3% TEN, 3.3% SJS-TEN overlap
2008	Mockenhaupt *et al*. [92]	Retrospective, case-control (EuroSCAR)	Unknown	Europe	Total = 379 134 SJS, 136 SJS/TEN-overlap, 109 TEN	Paediatric and adult Median 50 years (IQR 28–68) (1–95)	1.6:1	Unknown	Nevirapine Lamotrigine Carbamazepine Phenytoin Phenobarbital Cotrimoxazole and other anti-infective sulfonamides Sulfasalazine Allopurinol Oxicam-NSAIDs	Unknown
2010	Wetter *et al*. [93]	Retrospective	8 years	United States	27 SJS	Paediatric and adult Mean 28.1 ± 22.3 years	0.7:1	Fever (70%) Hepatitis (37%) Leukocytosis (22%)	74% drug related Antibiotics (35%) – cotrimoxazole Anticonvulsants (35%) – phenytoin, lamotrigine NSAID (10%)	Mortality 5%

included as one of the SCAR in the EuroSCAR studies [94]. Medications associated with AGEP (aminopenicillins, pristinamycin, quinolones, hydroxychloroquine, diltiazem) were different from those associated with SJS/TEN. Different latent periods from drug intake to reaction onset were observed for different drugs (e.g. median treatment duration of 1 day for antibiotics *vs.* 11 days for non-antibiotics), shorter than the overall time to onset for most SJS/TEN reactions.

Hospital-based studies from a district in China [95] showed an overall prevalence of 0.32 per 1000 hospitalizations, 0.15 per 1000 hospitalizations for SJS, 0.04 per 1000 for TEN, and 0.07 per 1000 for DRESS. Antibiotics were the most common putative drug followed by anti-epileptic drugs and traditional Chinese medicines. The risk of SCAR from systemic drugs among hospitalized patients was 0.03/1000 (0.02/1000 for SJS, and 0.01/1000 for ED and DRESS). The reported incidence of SCAR 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.

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 was also generally higher in females than in males [98]. Other studies have also shown that overall women appear to be more affected than men [99, 100]. In our registry of hospitalized patients with drug allergy, hospitalized females 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 [101].

With regards to age groups, it is unclear at this point if the incidence of drug allergy is indeed lower in children [33, 102]. Although children are less likely to be exposed repeatedly to drugs necessary for sensitization to occur, widespread prescribing of certain drugs may theoretically increase the risk for sensitization in certain groups of children, for instance antibiotic sensitization in children with chronic diseases. The incidence of ADRs and ADR-associated hospitalization increases with age, but the association of age with drug allergy is less well studied [102]. Manifestations and outcome of drug allergy in elderly hospitalized patients appear to be similar to the non-elderly, but serious reactions (anaphylaxis, SJS, TEN, DiHS) are less common [103].

Concomitant disease states may predispose to the development of allergic drug reactions by altering metabolic pathways and inducing variations in the immunologic responses to drugs. The apparent increased risk for drug allergy in patients with SLE has not been consistently confirmed [104]. Drug allergies are frequently encountered in patients with HIV infection, particularly to certain drugs including cotrimoxazole, abacavir and nevirapine. It is likely that a complex interaction between the underlying state of immune-reconstitution and genetic host factors predisposes to these allergic drug reactions [105]. Similarly, reactivation of herpes virus [Ebstein-Barr virus, human herpes virus (HHV) 6 and 7, cytomegalovirus] appears to be associated with the pathogenesis of DiHS [106]. Atopy does not appear to be a major risk factor for most drug allergies [100].

Ethnicity and genetics appear to be increasingly important in the predisposition to certain types of drug allergy with specific examples discussed below.

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

association seen with maculopapular exanthema (MPE) in Han Chinese from Hong Kong and Thais.
- HLA B*1502 associated with phenytoin induced SJS in Han Chinese in Hong Kong (OR 71.9) [107] and Thais [OR 18.5 (95% CI 1.82, 188.4)] [108], but not with MPE among Han Chinese from Hong Kong.
- HLA B*5801 and allopurinol induced SJS/TEN in Han Chinese from Taiwan [OR 580.3 (95% CI 34.4, 9780.9)] [112], Thais [OR 348.3 (95%CI 19.2, 6336.9)] [113], Japanese [110] and Europeans [111];
- HLA B*5701 and abacavir drug hypersensitivity in Caucasians [OR 117 (95% CI 29, 481)] [114, 115], but not among Blacks [116]. This haplotype has been found to be uncommon in Taiwanese Chinese [117] and Korean populations [118].

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: Il-13 (R130Q and −1055C > T variants) and IL-4RA (150V, S478P, and Q551R variants) polymorphisms in Italians [125]; Ile75Val variant of IL-4Rα gene two linked Il-10 promotor gene polymorphisms (-819C > T and −592C > A) in Causasians [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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