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REVIEW

Changing patterns in the epidemiology of drug allergy

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Abstract

Drug allergy (DA) remains a complex and unaddressed problem worldwide that often deprives patients of optimal medication choices and places them at risk for life-threatening reactions. Underdiagnosis and overdiagnosis are common and due to the lack of standardized definitions and biomarkers. The true burden of DA is unknown, and recent efforts in data gathering through electronic medical records are starting to provide emerging patterns around the world. Ten percent of the general population engaged in health care claim to have a DA, and the most common label is penicillin allergy. Up to 20% of emergency room visits for anaphylaxis are due to DA and 15%–20% of hospitalized patients report DA. It is estimated that DA will increase based on the availability and use of new and targeted antibiotics, vaccines, chemotherapies, biologicals, and small molecules, which are aimed at improving patient's options and quality of life. Global and regional variations in the prevalence of diseases such as human immunodeficiency virus and mycobacterial diseases, and the drugs used to treat these infections have an impact on DA. The aim of this review is to provide an update on the global impact of DA by presenting emerging data on drug epidemiology in adult and pediatric populations.

KEYWORDS
anaphylaxis, drug allergy, drug-induced anaphylaxis, epidemiology, mortality, risk factors, trends

Abbreviations: AGEP, acute generalized exanthematous pustulosis; BL, beta-lactam antibiotics; COX, cyclooxygenase; CRR, cytokine release reaction; DA, drug allergy; DRESS, drug rash with eosinophilia and systemic symptoms syndrome; FDA, U.S. Food & Drug Administration; HIV, human immunodeficiency virus; HSR, hypersensitivity reaction; ICD, International Classification of Diseases; mAbs, monoclonal antibodies; NSAIDS, nonsteroidal anti-inflammatory drugs; RCM, radio contrast media; SCARS, severe cutaneous drug adverse reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

1 | INTRODUCTION

The life expectancy of the world population is increasing in part due to new and better medications,[1] and exposure to multiple drugs for repeated and prolonged periods increases the risk for sensitization and drug allergy (DA).

Over- and underdiagnosis of DA limits the use of first line medications, which affects the quality of life and survival of targeted adult and pediatric populations.[2–7]

Drug exposures are different across the globe due to costs and supply chain.[8] Patients with cystic fibrosis, cancer, and chronic inflammatory conditions have chronic and multiple drug exposure patterns as opposed to the general population, who is exposed to drugs intermittently.[8,9]

A DA label is typically acquired in childhood and never challenged until an urgent need arises in adulthood, when delabeling may have time constraints and be deemed unsafe. The lack of harmonized strategies to record DA hampers collection of comparable epidemiological data.[10] The paucity of specific International Classification of Diseases (ICD) codes until recently and the use of de-identified information and unconfirmed diagnoses have hampered an accurate description of worldwide DA.[11] More accurate definitions, classifications, and coding are expected to contribute to a better-quality morbidity and mortality data, providing reliable information on DA epidemiology.

1.1 | Drug allergy documentation, prevalence, and world differences

Epidemiologic studies of DA rely on electronic health record (EHR) data which are currently lagging behind standardization and specific ICD codes.[11–13] Most published studies deal with adverse drug reactions (ADRs) and do not specify the types of reactions, including allergy or HSRs. Additionally, in most studies the diagnosis of allergy is not confirmed and include self-reported DA labels. Therefore, the true incidence of drug allergy in general population remains largely unknown. Unfiltered data entry in EHR lead to overuse of DA allergy labels and unnecessary avoidance.[10] Mortality and hospital admission data underestimates the true rate of DA since most reactions occur outside the hospital settings and a minority of reactions result in hospitalization.[11–14] It is estimated that DA accounts for 1%–2% of hospital admissions[15–19] and 14% of emergency department visits of which 0.6% are drug-induced anaphylaxis and lead to hospitalizations in 15% of cases.[20]

The prevalence of self-reported DA is higher in adults, increases with age[21,22] and more adults than children are hospitalized due to DA.[23] Urticaria and maculopapular rashes are the main presentation[19] in children and adults[23] and the main causes of DA-related hospitalizations include anaphylaxis and delayed reactions such as severe cutaneous adverse reactions (SCARs).[16,17,19] Females over 55 years of age exposed to multiple medications are overrepresented.[9,18] The incidence of Stevens–Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) is 1.4 to 6 per million individuals per year,[24] drug rash with eosinophilia and systemic symptoms syndrome (DRESS) is 10 cases per million and acute generalized exanthematous pustulosis (AGEP) one to five cases per million per year with an overall SCAR mortality of 10%, which increases up to 50% or higher for SJS/TEN in the elderly and immunocompromised hosts.[25–29]

Antibiotics represent 14.8% of all anaphylactic reactions reported to FDA (U.S. Food & Drug Administration) from 1999 to 2019 and monoclonal antibodies (mAbs) hypersensitivity reaction (HSR) rate has increased from 2% in 1999 to 17.4% in 2019.[30] The most frequent non-beta-lactam (BL) antibiotic involved in DA includes sulfonamides in USA and Australia[19–22,26] and quinolones in Europe.[20,31–33] Dipyrone is the main cause of anaphylaxis related to nonsteroidal anti-inflammatory drugs (NSAIDs) in South America[34] while it is not available in all European countries or North America where ibuprofen and diclofenac are the most prevalent NSAIDS implicated in DA.[35] Anaphylaxis to neuromuscular blocking agents (NMBAs), although rare, represents one of the leading causes of perioperative anaphylaxis and has also been found to have a geographic distribution, being reported a high frequency in France, Australia, New Zealand, United Kingdom, Norway, Belgium, South Korea, and Spain.[36–38] Allergic sensitization induced by environmental exposure to other quaternary ammonium-containing compounds, such as pholcodine, a cough suppressant opioid, 12 months prior to NMBA usage, has been implicated. Consequently, drug regulatory agencies have been recommending withdrawing over the counter medications containing pholcodine since there are not effective biomarkers to identify the population at risk.[39] Anaphylaxis during pregnancy is estimated to be 1.5 to 3.8 per 100,000 women, with 49 to 74% of the cases during caesarean section, and 75% associated to BL antibiotics and anesthetic agents[40] (Table 1).

1.2 | Presentation of drug allergy: Phenotypes, endotypes, and biomarkers

Recent classification of DA involves the identification of the symptoms (phenotypes), and mechanisms (endotypes), timing, and severity of reactions[4,52,53] (Figure 1).

Immediate reactions are IgE,[54,55] and non IgE-mediated, which include complement receptors activation, MRGPRX2[56] induced, COX-1 inhibition,[57] cytokine release reactions (CRR) and mixed reactions (Type I/CRR).[58] Most immediate reactions are amenable to desensitization,[59,60] a ground breaking immunotherapy procedure allowing safe reintroduction of culprit drugs. Delayed reactions[61] can be skin-limited benign reactions associated with long lasting T-cell memory, single organ toxicity due to nonimmune cell-receptor interactions, immune complex-mediate serum sickness-like reactions, cytotoxic IgG-mediated reactions, and SCARS such as (DRESS), SJS and TEN, AGEP some of which have been shown to be human leukocyte antigen (HLA) class I alleles restricted[62,63] (Figure 1; Tables 1 and 2) and not amenable to desensitization. In vivo biomarkers[64] include skin testing by skin prick and intradermal methods, patch

TABLE 1 Published data on DA epidemiology.

Reference	*N*	Study period/ Country	Inclusion criteria	Study design	Data source	Aim of study	Incidence	Age (years)	Sex ratio F:M	Drug involved in HS
Leone, Drug Safety 2005[41]	744/27512	1990–2003 Italy	ADR	Retrospective	Spontaneous reporting database	DIA	2.6%	49 ± 21.2	1.3:1	Antibiotics 35.5% -BL 56.88% Penicillins 36.21% Ceph. 20.57% Other 1.23% -Quinolones26.62% -Macrolides 5.76% -Glycopeptides 2.88% -Aminoglycosides 2.05% -Tetracyclines 0.41% -Others 1.23% NSAIDs 14% RCM 13.4% Vaccines 6.7% Analgesics 5.4% Blood substitutes and perfusion solutions 4.4%
Liew, J Allergy Clin Immunol. 2009;123:434–43[42]		1997–2005 Australia	Death	Retrospective	Australian Institute of Health and Welfare	DIA fatalities	All subjects included are fatal DIA			Anaphylaxis fatalities were causes by drugs in 20% and probably by drugs in 38%, The paper does not describe the culprit drugs
Renaudin, Allergy 2013[43]	333	2002–2010 France	Anaphylaxis	Prospective?	Allergy Vigilance network	Severe DIA	All subjects included are severe DIA	42.7 ± 18	1.62:1	Antibiotics 49.6% NMBA 10.8% NSAIDs 9.9% RCM 4.2% Acetaminophen 3.9%
Ribeiro-Vaz, Eur J Clin Pharmacol 2013[44]	918/16157	2000–2010 Portugal	ADR	Retrospective	Portuguese Pharmacovigilance System (Spontaneous reporting database)	DIA	5.7%	48 ± 21	1.2:1	Antibiotics 16.7% NSAIDs/acetaminophen 13.4% Cytotoxic drugs 12.3% Immune modulator 9% Vaccines 6.5% RCM 4.4% Others 37.7%

Continues)

TABLE 1 (Continued)

Reference	N	Study period/ Country	Inclusion criteria	Study design	Data source	Aim of study	Incidence	Age (years)	Sex ratio F:M	Drug involved in HS
Faria, J Investig Allergol Clin Immunol 2014[45]	313	2007–2010 Portugal	DIA	Prospective?	National anaphylaxis notification system	DIA	All subjects included are DIA	43.8 ± 17.4	2:01	NSAIDs 47.9% Antibiotics 35.5% Anesthetic agents 6.1% Cytostatics 2.9% Corticosteroids 1.6% Analgesics 1.6% PPI 1.3% Vitamins 1.3% RCM 0.93% Vaccines 0.6% Others 3.2%
Jares, J Allergy Clin Immunol Pract 2015[46]	264/1005	2011–2014 Latin America	Hypersensitivity	Cross-sectional	Database	DIA	26.3%	38.2	2.3:1	NSAIDs 57.8% BL 14.3% Non-BL antibiotics 5.2%
Nguyen, Drug Saf 2018[47]	4873	2010–2016 Vietnam	ADR	Retrospective	Spontaneous reporting database (National Pharmacovigilance Database of Vietnam)	DIA	13.2%	42 (23–61)	1.1:1	Antibiotics 68% -Beta-lactam 3rd gen ceph. 59.1% Penicillins 14.16% 1st gen ceph. 6.29% 2nd gen ceph. 6.02% 4th gen ceph. 2.47% Carbapenems 0.93% -Quinolones 6.84% -Aminoglycosides 2.68% -Sulfonamides 1.41% -Macrolides 0.96% -Others 3.85% NSAIDs 4.6% Blood substitutes and perfusion solutions 4.1% RCM 3.9% Anesthetic drugs 3.3% Antipyretics and drugs containing paracetamol 2.6% Antineoplastic agents 2.1% Others 19.6%
Mota, Eur Ann Allergy Clin Immunol 2018[48]	125	2010–2016 Portugal	Systematic review of patients with history of DIA referred to the allergy unit	Retrospective		DIA	All subjects included are DIA	41.1 ± 16.7	Not shown	NSAID 43.2% Antibiotics 41.6% PPI 4.8% NMBA 4% Carboplatin 2.4% Corticosteroids 1.6% Local anesthetics 1.6% Ranitidine 0.8% Midazolam 0.8% Patent blue 0.8%

TABLE 1 (Continued)

Reference	N	Study period/ Country	Inclusion criteria	Study design	Data source	Aim of study	Incidence	Age (years)	Sex ratio F:M	Drug involved in HS
Zhao, Int J Clin Pharm 2018[49]	1189	2004–2014 China	ADR	Retrospective	Beijing Pharmacovigilance Database	DIA	12.61%	47.6 ± 20.1	1.11:1	Antibiotics 39.3% -Beta-lactam 23.1% -Quinolones 11.6% -Macrolides 2.4% -Other 2.2% Traditional Chinese medicines 11.9% RCM 11.9% Antineoplastic agents 10.3% Vaccines 1.9% Immunomodulators 1.8% mAb 1% NMBAs 1% NSAIDs 1% Opioids 0.4% Others 19.5%
Jares, J Allergy Clin Immunol Pract 2019[50]	286	2017–2018 Latin America	DIA	Prospective?	On line survey	DIA	All subjects included are DIA	37 (24–52)	1.8:1	NSAIDs 54.6% BL 16.6% Non-BL antibiotics 6.4%
Dhopeshwarkar, J Allergy Clin Immunol Pract 2019[51]	19,836/1756,481	1995–2013 USA	Patients attending hospital	Retrospective	Electronic health records	DIA	1.1%	Not shown	2.8:1	Antibiotics 77.5% -Penicillins 45.9% -AX 2% -Ceph. 6.1% -Sulfonamides 15.1% -Macrolides 3.8% -Quinolones 3.7% -Tetracyclines 2% -Vancomycin 0.9% NSAIDS 13% Opioids 9.8% Antineoplastics 1.5% mAb 1.2% Other 20.8%
Yu, J Allergy Clin Immunol Pract 2021[30]	47,496/ 17,506,002	1999–2019 USA, France, UK, Canada, Japan	ADR	Retrospective	Spontaneous reporting (FDA Adverse Event Reporting System Database)	DIA	0.27%	52 (interquartile rage 28)	1.7:1	Antibiotics 14.87% mAb 13.06% NSAID and acetaminophen 8.3% Intraoperatory agents 8.95% Chemotherapy agents 5.56% DMARDS 4.01% Anti-anaphylaxis agents 3.91% RCM 2.52% Other 3.94%

Abbreviations: ADR, adverse drug reactions; AX, amoxicillin; BL, beta-lactams antibiotics; Ceph., cephalosporin; DA, drug allergy; DIA, drug-induced anaphylaxis; DMARDS, disease-modifying antirheumatic drugs; Gen., generation; mAb, monoclonal antibody; NMBA, neuromuscular blockin agent; NSAIDS, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RCM, radio contrast media.

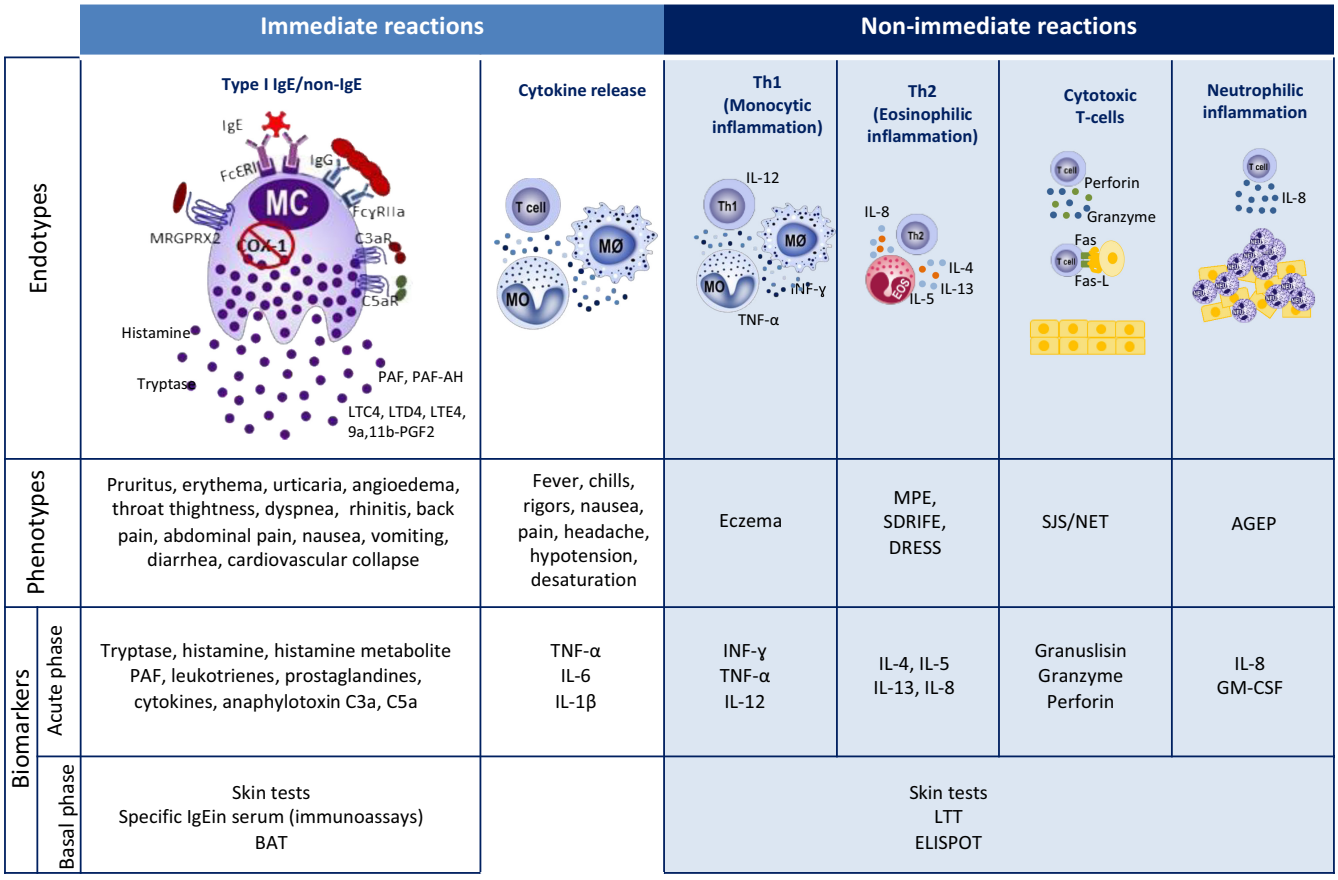

FIGURE 1 Phenotypes, endotypes, and biomarkers in drug hypersensitivity. AGEP: acute generalized exanthematous pustulosis. BAT, basophil activation test; DRESS, drug rash with eosinophilia and systemic symptoms syndrome; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; INF, interferon; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; PAF, platelet-activating factor; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor.

testing and drug challenges[7,65–67] and in vitro tests include tryptase, interleukin (IL)-6, basophil activation test (BAT), mast cell activation test (MAT), nanoparticles and genotyping[58,68–75] (Figure 1).

Epidemiological data from official statistics based on hospitalization and emergency department information cover both immediate and delayed reactions. However, most data are based on severe spectrum since non-severe reactions can be auto-limited, with no need to admissions. Considering the severe spectrum of the reactions, immediate reactions are more frequently than delayed and most of data related to SCARs come from specialized registries. Underlying mechanisms are complex and have been recently reviewed.[76]

1.3 | Risk factors For drug allergy

The use of high doses, repeated administrations with frequent intervals, and intravenous or subcutaneous routes are associated with increased rates of DA, as they are likely to influence the recognition by antigen present in cells and T cells.[58] Large molecules such as mAbs which contain nonhuman epitopes such as rituximab or glycosylation sites such as cetuximab have increased allergenic potential and can induce specific IgG and IgE. Women and the elderly are targeted populations for DA, which is promoted by polypharmacy. Atopy has been found to be a risk factor for BL and radio contrast media (RCM) and elevated IgE has been associated with carboplatin allergy[77] (Tables 3 and 4). A relationship between atopy and NSAIDs hypersensitivity has been shown in children.[79,80]

During viral infections including Epstein–Barr virus, children and adults with skin reactions temporally associated with aminopenicillins may be labeled as penicillin-allergic. Patients with HIV infection with low $CD4^+$ T cell counts and high viral load have increased rate of skin reactions to sulfonamides and other drugs.[81–86] In one study up to 60% of patients tolerated cotrimoxazole when the viral load decreased. Abacavir hypersensitivity has largely disappeared due to screening for HLA-B*57:01. Recently, it has been identified that HLA-A*32:01 is strongly associated with vancomycin-induced DRESS,[87,88] so testing this variation in the HLA region could improve antibiotic safety (Table 2). HLA-A*32:01 has also been associated with vancomycin DRESS in Asian populations; however, it is potentially not the only association with this allele less commonly represented. In addition, since vancomycin DRESS has a median latency of 3 weeks countries that step-down earlier to oral therapy experience less vancomycin DRESS in their populations.[89]

TABLE 2 Genetic HLA associations with certain drug hypersensitivities.

Drug	HLA allele	Hypersensitivity reactions	Population
Abacavir	B*57:01	DHIS/DRESS	Australian
			African American
			Brazilian
			British
			Indian
			Iranian
Carbamazepine	B*15:02	SJS/TEN	Taiwanese
			Han Chinese
			Thai
			Malaysian
			Asian
	A*31:01	SJS/TEN MPE, DHIS/DRESS	Han Chinese
			Caucasian
			Japanese
	B*15:11	SJS/TEN	Japanese
Allopurinol	B*58:01	SJS/TEN DHIS/DRESS (possibly)	Han Chinese
			Caucasian
			Thai
		SCARS	Taiwanese
Lamotrigine	A*31:01	DHIS/DRESS	British
	B*15:02	SJS/TEN	Han Chinese
Vancomycin	A*32:01	DRESS	American and Australian with European ancestry

Abbreviations: DHIS/DRESS, hypersensitivity syndrome drug reaction with eosinophilia and systemic symptoms; MPE, maculopapular exanthema; SCARs, severe cutaneous adverse reactions; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis; TNF, tumor necrosis factor.

TABLE 3 Risk factors associated with chemotherapy DA.

	Taxanes	Platinum compounds	Asparaginase
Elevated IgE	No	Yes	No
History of HSR to other drugs	Yes	Yes	No
Age	<70 years	<60 years	No
Gender	No	Female	No
Most frequent drugs	Paclitaxel, Docetaxel	Carboplatin, Oxaliplatin	*E. coli*-asparaginase preparation
Increased severity in previous reactions	Yes	Yes	Yes

Source: Modified from Pagani et al.[78]

Cystic fibrosis patients have higher rates of DA potentially due to higher exposures of large doses of oral and intravenous antibiotics, which leads to changes in microbiome.[90–92] NSAIDs exacerbated respiratory disease (N-ERD) is associated with nasal polyps and severe asthma and is more frequent in females. NSAIDs can exacerbate urticaria in patients with chronic spontaneous urticaria as well.[93–98] Reactions to opioids, fluoroquinolones, general anesthetics, vancomycin, and basic and tetrahydroisoquinolines-motif containing medications are linked to mast cell activation through the MRGPRX2 receptor.

Chronic kidney and liver disorders, cardiovascular diseases, and malignancies increase the risk of DA due to altered metabolism and increased inflammation, with an increase in mortality rates due to DA.[99] Patients with mastocytosis present increased prevalence of NSAIDs, opioids, fluoroquinolones and RCM hypersensitivity.[100,101] Recently a genetic trait related to the duplication of tryptase genes TPSAB1 has been uncovered and due to its familial and autosomal dominant expression named hereditary alpha-tryptasemia (HaT). It is present in 4%–6% of the general population and is associated to an increased anaphylaxis risk.[102] Studies are ongoing to evaluate if

TABLE 4 Potential risk factors for hypersensitivity reactions to RCM.

Patient related risk factors	Procedure related risk factors
Previous reaction	First administration
Advanced age (>65 years old)	Repeat administration
Atopy	High dose
Female gender	Use of ionic contrast media
Asthma	Fast administration I
Allergies to other drugs	
Oncological diseases	
Cardiovascular diseases	

Source: Modified from Bilo et al.[53]

the population of patients with DA and proven drug-induced anaphylaxis is enriched with HaT. Although different haplotypes have been identified with penicillin allergy,[103–105] there is no evidence that penicillin allergy has a familial expression pattern. Similarly, family history of drug hypersensitivity has not been identified as a risk factor for allergy to most drugs.

2 | PREVALENCE AND RISK FACTORS OF DA: SPECIFIC DRUGS

2.1 | Antibiotics

A penicillin allergy label is more common in adult females and the elderly[106,107] and based on epidemiological studies it is a risk factor for a label of drug allergy to related or unrelated antibiotics DA.[108,109] The prevalence of reported BL allergy has increased from 1%–2% in 1980 to 5%–13%[27,106,107,110–118] in the last decade.

Benzylpenicillin was the first DA to BL and amoxicillin is currently the most frequently reported BL DA[44,46,119] in Europe[43,119–121] and cephalosporins in the USA[2,10,21,122] and Vietnam.[47] Clavulanic acid[123–125] and in particular cefazolin, have been recently identified as prevalent triggers in perioperative anaphylaxis in the USA, Australia, Spain, UK, France, and South America,[46,126–128] while cefuroxime is the most common drug inducing anaphylaxis in Germany.[30] These changes may relate to availability, costs and prescription habits. Fluoroquinolones, which cause mast cell degranulation through MRGPRX2, are the most common non-BL antibiotic involved in DA in Spain,[129] Italy,[32] Vietnam[47] and China[49] and drug-induced anaphylaxis in the USA[15] due to moxifloxacin.[31,129–131] Ciprofloxacin has been associated with an increased risk for SCARs.[131] Patients with mastocytosis have an increased risk for fluoroquinolones reactions.[132]

2.2 | Chemotherapeutics

Chemotherapy drugs are the third leading cause of fatal DA in USA.[122] In Japan platinum-based drugs are in the top 10 drugs inducing anaphylaxis.[133] Reactions to taxanes and some mAbs occur typically at first or second exposure, while reactions to platins require several exposures and are typically IgE-mediated with positive skin tests.[134] Reactions to paclitaxel occur in up to 40% of patients without anti-histamine and steroids premedication and in 1.5% of pre-medicated patients.[133] The rate of reactions after multiple exposures is 10.7%–18.9% for oxaliplatin, 12%–44% for carboplatin, and 5%–20% to cisplatin.[133,135–138] The rate of carboplatin HSR increases from 1% during the first six cycles to 27% after >6 cycles and sooner for BRCA mutations carriers.[51,136,139]

2.3 | Biological agents

Anaphylaxis to mAbs has increased from 2% in 1999 to 17.4% in 2019, placing mAbs as the most frequent drugs involved in anaphylaxis.[30] In countries such as Germany, mAbs contributes to the top 10 drugs inducing anaphylaxis,[140] which may be related to drug usage patterns and genetic effects. The rate of reactions has been reported as 5%–10% for rituximab; 2%–3% for infliximab; 3%–22% for cetuximab; and 0.6%–5% for trastuzumab.[133,135–138] Risk factors for HSRs to biological agents include the underlying disease, the patient's immune status, degree of humanization, glycosylation pattern, type of sourcing cells, dosing interval, and excipients. Patients with anti-drug antibodies are more likely to develop DA.[59,141,142]

2.4 | NSAIDs

The overall prevalence of NSAID hypersensitivity in Europe has increased from 1.9% in 1990 to 3.5% in 2013.[110,111,143,144] NSAIDS are the second most frequent drug inducing DA after opioids[110,145] in Europe[32,33,111] and the third in USA and Australia. They are the main class of drugs inducing DIA in Latin America,[46,146] and Portugal,[45,48] the second in Italy[41] and Vietnam.[47] Ibuprofen is the most frequently implicated NSAID in HSRs,[30,43,47,51,110,147–149] parallel to the high consumption of this drug in the last two decades.[8]

2.5 | Radio contrast media

RCM can be classified according to number of particles generated in solution into high, low and isosmolar; and into ionic or nonionic if it transforms into ions or charged particles in aqueous solution or not, respectively.[150] In the past, the high osmolarity of ionic RCM was related to a high incidence of immediate reactions, reaching up to 15% of treated individuals due to the nonspecific release of vasoactive mediators, while following the introduction of nonionic low-osmolarity RCM the incidence decreased to less than 0.1%.[151–154] Recently, an increase in the rate of non-immediate reactions has been observed with nonionic RCM.[155–157] In Japan, RCM are the most common drugs implicated in drug-induced anaphylaxis[30] and in China the third one.[49] In Spain, non-immediate HSRs have

TABLE 5 Risk factors related to DA.

Variable	Risk factors
Drug related factors	Large molecules High doses Prolonged use Frequent administration Intravenous or subcutaneous routes Multiple drug use
Individual factors	Advanced age Atopy (not true for the majority of drugs) Family history of drug hypersensitivity (not true for the majority of drugs) Female gender History of drug hypersensitivity
Comorbidities	Asthma Mastocytosis Cystic fibrosis Chronic urticaria Chronic disorders (Kidney failure, malignancies, cardiovascular diseases)

increased in the last decade, with one third of patients being allergic to more than one RCM.[158] Risk factors for hypersensitivity to RCM include a previous reaction, female gender, kidney disease, a history of asthma, DA, and food allergy as well as repeated exposures to RCM (Table 5). A multicentered study with near two hundred thousand patients identified a family history of RCM reactions as a risk factor.[53]

3 | SCARS AND GLOBAL EPIDEMIOLOGY IN RELATION TO GENETIC RISK

Current rates of SCAR reactions including DRESS (1/1000–1/10,000 treatment courses), SJS/TEN (1-5/million persons per year) and AGEP (1/million persons per year) are based on information from the developed world where SCAR reactions are less common.[159,160] This is in contrast to mild to moderate morbilliform drug eruptions that occur in 2%–5% or more treatment courses. Data collected from pharmacovigilance databases suggest that the specific prevalent small molecule causes SCARs, which include in the case of DRESS/SJS/TEN sulfonamide antibiotics, aromatic antiepileptic drugs, and allopurinol. Vancomycin is a prevalent cause of DRESS globally, which rarely causes SJS/TEN. In addition to carriage of the HLA-A*32:01 allele risk factors have included age lower than 50 and higher vancomycin through level.[87,161] The top causes of both DRESS and SJS/TEN have remained stable over the last 15 years.[162,163] Increasing recognition of drugs used in immunotherapy of cancers particularly in the developed world have highlighted that drugs such as immune checkpoint inhibitors and other immunotherapies can cause SJS/TEN like illness and autoimmune bullous diseases, DRESS, and AGEP. Lichenoid bulloid eruptions can mimic SJS/TEN clinically; however, they tend to evolve more slowly and are distinct on histopathology. In addition, these reactions commonly do not consistently recur on immune checkpoint inhibitors (ICI) rechallenge.[164–166] One such case series studied 13 patients with ICI associated DRESS where 5/13 were on dual ICI therapy and all 5 had viral reactivation. Rechallenge with an alternative PD-1 inhibitor under steroid coverage was tolerated in 4/5.[165] A previous cohort study looked at immune-related adverse events (irAE) associated with anti-PD-1 or anti-PD-L1 rechallenge and approximately 55% developed the same or different irAE that occurred at a shorter time interval however rechallenge irAEs were not more severe than the first one.[164]

ICI also appear to increase the risk of a drug hypersensitivity to a small molecule drug dosed after the onset of immunotherapy[167] and it is important to differentiate this from a reaction that could be directly triggered by ICI in the absence of another drug. In the developing world, SCARs and drug-induced liver injury associated with first line antituberculous drugs such isoniazid, rifampin, ethambutol, and pyrazinamide are prevalent and the number of cases seen annually is several folds higher than the developed world with estimates of 2/1000 treatment courses for HIV and HIV-tuberculosis co-infected individuals.[159] Aside from differences in drug usage patterns related to drug availability and treatment of prevalent global infectious diseases a primary driver and risk of the geographic variation in prevalence of SCAR relates to the fact that many of these are Class I HLA restricted and the prevalence of the primary HLA risk alleles differs across different geographies (Table 2). With abacavir hypersensitivity early clues to genetic risk was the early observation that the highest risk was in White populations with underrepresentation in Black populations in the developed world.[168] Subsequently it was determined that the main risk factor for abacavir hypersensitivity was carriage of HLA-B*57:01 which is one of the most prevalent alleles carried in 5%–10% of European populations. The same followed for the associations between HLA-B*15:02 and carbamazepine SJS/TEN, HLA-B*58:01 and DRESS and SJS/TEN and HLA-B*13:01 and dapsone and sulfonamide antibiotic SCARs (Table 2). The negative predictive value of these HLA alleles is highest in Southeast Asian populations where allele carriage rates are high and lowest in Europe, North America and Africa. Carbamazepine SCARs in European and Japanese populations has been associated with HLA-A*31:01 which is not a prevalent cause of SJS/TEN in other parts of Southeast Asia[169]; however, it is associated with carbamazepine

DRESS globally. Screening for HLA-B*15:02 which is associated with carbamazepine SJS/TEN but not DRESS will hence reduce the risk of carbamazepine SJS/TEN in countries such as South Asia where carriage is prevalent but not DRESS. In addition, other B75 serotypes such as HLA-B*15:21 have been associated with carbamazepine SJS/TEN in many Southeast Asian countries which will not be picked up on HLA-B*15:02 screening. This "negative predictive value gap" of HLA for specific drug hypersensitivities will be narrowed in the future with discovery of new HLA associations across more diverse populations. The positive predictive value of an HLA allele for a specific SCAR reaction varies between 2% and 20% for most SCAR.[63] It was as high as 55% for abacavir hypersensitivity.[170] Although there are positive and negative predictive value gaps for HLA associations and SCAR and HLA is thought to be necessary but not sufficient for the development of SCAR if a risk allele is present in an individual, the risk implications are thought to be the same regardless of race and ethnicity.[63] Race and ethnicity targeted pre-prescription HLA testing is now discouraged.[160,171]

4 | DRUG ALLERGY IN CHILDREN

Limited studies describing the true incidence of DA in children are available and recent efforts have been directed at delabeling low risk patients with direct ingestion challenge.[23] A systematic review of 17 prospective studies shows that drug reactions in children were responsible for 2.09% of emergency visits, 1.46% of outpatient visits, and 9.53% of inpatient admissions.[23,172]

The frequency of reported DA increases with age and risk factors include infants, male gender, and receiving ≥4 medications. Children who had undergone general anesthesia have more than six times the risk of developing an adverse drug reaction, with general anesthetics and opioids as the main triggers. BLs are the most frequent cause of drug hypersensitivity reactions in childhood with amoxicillin the most reported drug.[23,172] In a large study in USA evaluating 411,543 adult and pediatric medical records found that the overall incidence of self-reported antibiotic allergy was as high as 15.3% in children. Another study found that of 10,096 questionnaires, in 792 (7.87%), parents reported a history of DA in their child, and 117 (1.1%) were consistent with an IgE–mediated reaction by history and of the 101 children who had allergy workup only 7 (0.11%) had positive testing results.[34,35,173] Children labeled as penicillin-allergic have higher rates of broad-spectrum and second-line antibiotic usage, increased adverse events, and unnecessary healthcare utilization.[21]

DA to quinolones, vancomycin, aminoglycosides, and tetracyclines are rare except in children with cystic fibrosis and chronic diseases with repeated antibiotic exposures.[23,172] Less than 20% of children with a reported history of NSAIDs hypersensitivity had the diagnosis confirmed through challenge.[23,100,172,174–177]

General anesthesia agents and opioid analgesics are a significant cause of DA in hospitalized children and children who had undergone a general anesthesia had more than six times the risk of developing an adverse drug reaction.[100,177]

5 | CONCLUSIONS

A global effort is necessary to comprehensively assess DA epidemiology and what factors shape its expression including age, sex, race, socioeconomic status, exposures, genetics, epigenetics and other ecological factors. More accurate definitions, classification and coding of DA will contribute to improved and reliable data worldwide. New perspectives are expected with the worldwide implementation of the new ICD-11 coding. Standardization of DA phenotypes, endotypes, and biomarkers is necessary for database harmonization. Genotyping with appropriate patient counselling to account for risk benefit ratio and negative and positive predictive gaps can be a useful preventive tool for SCAR such as DRESS and SJS/TEN. Artificial intelligence algorithms should be generated for big DA data collection and to guide improved outcomes. Basic research is needed to identify new biomarkers and visual data repositories should be generated to aid machine learning. Worldwide guidelines are needed since all medical specialities are touched by DA. This will allow all DA patients to benefit from sound and standardized approaches in prevention, early diagnosis, management, and treatment options.

AUTHOR CONTRIBUTIONS

Immaculada Doña, Maria Jose Torres and Mariana Castells designed the review and coordinated the work. Authors contributed to different sections: Mariana Castells "Introduction" and "Conclusions", Immaculada Doña and Luciana Kase Tanno "Drug allergy documentation, prevalence and world differences", Immaculada Doña and Maria Jose Torres "Presentation of drug allergy: phenotypes, endotypes and biomarkers", Gulfem Celik "Risk factors for drug allergy", Immaculada Doña, Gulfem Celik, Luciana Kase Tanno "Prevalence and risk factors of DA: specific drugs", Elizabeth Phillips "SCARS and global epidemiology in relation to genetic risk", Gulfem Celik "Drug allergy in children". All authors reviewed and accepted the manuscript.

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The authors declare that they do not have conflict of interests related to the contents of this article.

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