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Drug hypersensitivity reactions in Asia: regional issues and challenges

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Bernard Yu-Hor Thong [1], **Michaela Lucas** [2], **Hye-Ryun Kang** [3],
Yoon-Seok Chang [4], **Philip Hei Li** [5], **Min Moon Tang** [6], **James Yun** [7],
Jie Shen Fok [8], **Byung-Keun Kim** [9], **Mizuho Nagao** [10], **Iris Rengganis** [11],
Yi-Giien Tsai [12], **Wen-Hung Chung** [13], **Masao Yamaguchi** [14],
Ticha Rerkpattanapipat [15], **Wasu Kamchaisatian** [16], **Ting Fan Leung** [17],
Ho Joo Yoon [18], **Luo Zhang** [19], **Amir Hamzah Abdul Latiff** [20], **Takao Fujisawa** [21],
Francis Thien [22], **Mariana C. Castells** [23], **Pascal Demoly** [24], **Jiu-Yao Wang** [25],
and Ruby Pawankar [26]

[1]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore
[2]Department of Immunology, Pathwest and Sir Charles Gairdner Hospital, Medical School, University of Western Australia, Perth, Australia
[3]Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Department of Internal Medicine, Seoul National University College of Medicine, Drug Safety Center, Seoul National University Hospital, Seoul, Korea
[4]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[5]Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
[6]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[7]Faculty of Medicine and Health, The University of Sydney, Division of Medicine, Nepean Hospital, Sydney, Australia
[8]Department of Respiratory Medicine, Box Hill Hospital, Eastern Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia
[9]Department of Internal Medicine, Korea University Medical Center Anam Hospital, Seoul, Korea
[10]Allergy Center of Mie National Hospital, Tsu, Japan
[11]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[12]School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[13]Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Keelung and Linkou Branches, College of Medicine, Chang Gung University, Taipei, Taiwan
[14]Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan
[15]Allergy, Immunology and Rheumatology Division, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[16]Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Ratchathewi, Bangkok, Thailand
[17]Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong
[18]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea
[19]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China
[20]Allergy & Immunology Centre, Pantai Hospital, Kuala Lumpur, Malaysia
[21]Allergy Center of Mie National Hospital, Tsu, Japan
[22]Eastern Health, Melbourne; Monash University, Melbourne, Australia
[23]Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Mastocytosis Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[24]Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, UPMC Univ Paris 06, UMRS 1136, Equipe - EPAR - IPLESP, Sorbonne Universités, Paris, France
[25]Graduate Institute of Medical Sciences, China Medical University, Taichung, Taiwan
[26]Department of Pediatrics, Nippon Medical School, Tokyo, Japan

*Correspondence to
Bernard Yu-Hor Thong
Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Tel: +65-63577822
Fax: +65-63572686
E-mail: bernard_thong@ttsh.com.sg

ORCID iDs
Bernard Yu-Hor Thong
https://orcid.org/0000-0002-6338-8482
Michaela Lucas
https://orcid.org/0000-0001-8881-9990
Hye-Ryun Kang
https://orcid.org/0000-0002-2317-4201
Yoon-Seok Chang
https://orcid.org/0000-0003-3157-0447
Philip Hei Li
https://orcid.org/0000-0002-9155-9162
Min Moon Tang
https://orcid.org/0000-0001-7760-3238
James Yun
https://orcid.org/0000-0002-3482-5663
Jie Shen Fok
https://orcid.org/0000-0002-3450-0877

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Byung-Keun Kim
https://orcid.org/0000-0001-5147-6306
Mizuho Nagao
https://orcid.org/0000-0003-3557-8761
Iris Rengganis
https://orcid.org/0000-0001-8748-8544
Yi-Giien Tsai
https://orcid.org/0000-0002-6744-1682
Wen-Hung Chung
https://orcid.org/0000-0003-1681-0959
Masao Yamaguchi
https://orcid.org/0000-0001-6167-0591
Ticha Rerkpattanapipat
https://orcid.org/0000-0002-6630-2795
Wasu Kamchaisatian
https://orcid.org/0000-0003-0839-7682
Ting Fan Leung
https://orcid.org/0000-0002-6469-1926
Ho Joo Yoon
https://orcid.org/0000-0002-4645-4863
Luo Zhang
https://orcid.org/0000-0002-0910-9884
Amir Hamzah Abdul Latiff
https://orcid.org/0000-0002-6304-0494
Takao Fujisawa
https://orcid.org/0000-0002-9196-9436
Francis Thien
https://orcid.org/0000-0003-0925-6566
Mariana C. Castells
https://orcid.org/0000-0001-6451-0163
Pascal Demoly
https://orcid.org/0000-0001-7827-7964
Jiu-Yao Wang
https://orcid.org/0000-0003-4540-9822
Ruby Pawankar
https://orcid.org/0000-0002-3091-7237

ABSTRACT

There are geographical, regional, and ethnic differences in the phenotypes and endotypes of patients with drug hypersensitivity reactions (DHRs) in different parts of the world. In Asia, aspects of drug hypersensitivity of regional importance include IgE-mediated allergies and T-cell-mediated reactions, including severe cutaneous adverse reactions (SCARs), to beta-lactam antibiotics, antituberculous drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and radiocontrast agents. Delabeling of low-risk penicillin allergy using direct oral provocation tests without skin tests have been found to be useful where the drug plausibility of the index reaction is low. Genetic risk associations of relevance to Asia include human leucocyte antigen (HLA)-B*1502 with carbamazepine SCAR, and HLA-B*5801 with allopurinol SCAR in some Asian ethnic groups. There remains a lack of safe and accurate diagnostic tests for antituberculous drug allergy, other than relatively high-risk desensitization regimes to first-line antituberculous therapy. NSAID hypersensitivity is common among both adults and children in Asia, with regional differences in phenotype especially among adults. Low dose aspirin desensitization is an important therapeutic modality in individuals with cross-reactive NSAID hypersensitivity and coronary artery disease following percutaneous coronary intervention. Skin testing allows patients with radiocontrast media hypersensitivity to confirm the suspected agent and test for alternatives, especially when contrasted scans are needed for future monitoring of disease relapse or progression, especially cancers.

Keywords: Anaphylaxis; Asthma; Drugs; Hypersensitivity, Pharmacogenetics

INTRODUCTION

Drug hypersensitivity reactions (DHRs) are a major cause of morbidity among adults [1] and children [2] in inpatient and outpatient settings. The World Allergy Organization (WAO) [3] and International Consensus [4] define drug allergies as DHRs for which a definite immunological mechanism (either through drug-specific antibody or T cell) is demonstrated. DHR may also be classified based on the following mechanisms of action [5]:

- allergic immune mechanisms (IgE, IgG, or T cells);
- direct pharmacological interaction with T-cell receptors or human leucocyte antigen (HLA)-receptors for certain T-cell-mediated reactions including maculopapular exanthema (MPE), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP);
- pseudoallergic reactions (nonallergic DHR) mediated by drugs binding to receptors and enzymes e.g., Mas-related G-protein coupled receptor member X2 stimulation of mast cells, inhibition of cyclooxygenase in nonsteroidal anti-inflammatory drugs (NSAID) DHR, and of bradykinin metabolism in angiotensin-converting enzyme inhibitor therapy.

There are geographical, regional, and ethnic differences in the patterns, phenotypes, and endotypes of patients with DHR in different parts of the world. Prescribing patterns in different age groups e.g., antimicrobials [6] and NSAIDs [7] in children and adults, availability of different drug formulations in different markets, drug and host factors e.g., genetic and ethnic predisposition for antiepileptic and allopurinol severe cutaneous adverse reactions (SCARs) (comprising SJS/TEN/DRESS/AGEP) in Asians [8] contribute to some of these differences.

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In this review, we will focus on 5 aspects of DHR where much research has originated from the Asia-Pacific region, and review the published literature:
- beta-lactam allergy;
- SCAR;
- antituberculous drug allergy;
- NSAID hypersensitivity;
- radiocontrast media (RCM) hypersensitivity.

BETA-LACTAM ALLERGY

The overdiagnosis of penicillin allergy is a worldwide problem [9], resulting in the overuse of non-beta-lactam alternatives, antimicrobial resistance (e.g., methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*), and the risk of developing *Clostridiodes difficile* infection from the overuse of broad-spectrum antimicrobial agents. Global self-reported penicillin allergy rates are probably much higher than the true incidence of clinically significant DHR of <5% in both adults and children [10]. In a Hong Kong study based on 3,641 patients, the prevalence of beta-lactam allergy labels in hospitalized Chinese patients was 5%, but only 14% of suspected beta-lactam allergics were found to be genuine after testing [6]. There was also a high rate of confirmed piperacillin-tazobactam allergy, which may be related to the different prescribing practices in South-East Asia. Differences in beta-lactam sensitization profiles across different populations will require further study.

Cross-reactivity between penicillin and cephalosporin drugs occurs in about 2% of cases, less than the 8% reported historically. Cross-reactivity is particularly low with 3rd and 4th generation cephalosporins which have distinct R1 and R2 side chains as the antigenic determinants [11]. Risk stratification of the likelihood of penicillin allergy based on history and non–IgE-mediated type of clinical manifestations of the index adverse drug reaction form the basis of safe direct oral amoxicillin/penicillin challenge for low-risk patients without the need for skin tests [12]. For example, an absence of anaphylactic severity, unknown name of the index drug and a reaction occurring more than 1 year before testing has a negative predictive value of 98.4% [13]. Further validation in large scale settings is needed. Penicillin skin testing, which carries a negative predictive value that approaches 100% when combined with amoxicillin challenge can then be reserved for moderate to high-risk patients, reducing logistic and financial constraints of preparing/diluting skin test reagents. Delabeling [14, 15] and de-escalation encourage appropriate narrow-spectrum antimicrobial use which is especially important in immunocompromised [16] and cancer patients [17] who tend to require empirical broad-spectrum antimicrobials during episodes of neutropenic sepsis. Antibiotic stewardship programs have gradually evolved from allergist-led to pharmacist-led or nurse-led antibiotic delabeling programs with collaborative definitions of clinical algorithms, workflows and training in some centers [18].

In a multicenter Australian study [19] of 447 adult patients, among low-risk patients (54.6%) defined by a history of penicillin-associated rash (without angioedema, mucosal ulceration, or systemic involvement) more than 1 year before, 97.1% tolerated a direct 1- or 2-dose oral penicillin challenge without prior skin tests or drug provocation tests (DPTs). This simple risk-based delabeling strategy could potentially be used by nonallergists, leading to more efficient penicillin allergy delabeling service provision. In another study from Sydney, New South Wales [20], penicillin allergy evaluation with DPT without skin prick test was shown to

be feasible for similarly low-risk adult patients with a reported history of suspected penicillin DHR without history of anaphylaxis within the last 10 years, or a Gell and Coomb's type 2, 3, or 4 (severe) hypersensitivity reaction. Direct DPT has also been shown to be useful and safe in children from Perth, Western Australia [21] with low-risk histories to avoid painful skin testing, in particular the intradermal test (IDT).

SEVERE CUTANEOUS ADVERSE REACTIONS

SCAR is associated with high risk of morbidity and mortality. The most commonly implicated drugs in most series are antiepileptic drugs (carbamazepine, phenytoin, lamotrigine), allopurinol and antimicrobials [22]. Erythema multiforme (EM) is distinct from SJS/TEN, most commonly due to viral aetiologies, especially in children, and is not considered a spectrum of SCAR disorders [23, 24].

The Asian SCAR consortium's [8] analysis of registration databases from multiple Asian countries during the period 1998–2017 identified a total 1,028 SJS/TEN cases. Oxcarbazepine, sulfasalazine, cyclooxygenase II (COX-II) inhibitors, and strontium ranelate were identified as new potential causes of SJS/TEN. In addition to sulphonamide-based drugs and beta-lactam antibiotics, quinolones were also a common cause.

The China National Knowledge Infrastructure and Wanfang database and the First Affiliated Hospital of Fujian Medical University cohort from 2006–2016 [25] comprised 166 patients, of which TEN was the most common (56.6%) followed by SJS (42.2%), and SJS/TEN overlap (1.2%). The most common causative drug classes were antibiotics (29.5%) and anticonvulsants (24.1%). Carbamazepine (17.5%), allopurinol (9.6%), and penicillins (7.2%) were the most frequent causative drugs. Seventy-six patients (45.8%) received systemic corticosteroid and intravenous immunoglobulins (IVIGs) in combination therapy, especially for TEN (80.3%). In another study from Beijing [26], the prevalence rates were 0.32 per 1,000 hospitalizations for overall SCAR, 0.15 per 1,000 for SJS, 0.10 per 1,000 for exfoliative dermatitis, 0.04 per 1,000 for TEN, and 0.07 per 1,000 for DRESS. The reported incidence of SCAR in Haidian district was not less than 1.8 per million person-years; and for erythroderma, SJS, TEN, and DRESS not less than 0.6, 0.8, 0.05, and 0.4 per million person-years, respectively. Antibiotics were the most common offending drugs followed by anticonvulsants and traditional Chinese medicines.

The Korean Adverse Event Reporting System (1988–2013) [27] reported 755 SCAR cases comprising 508 SJS/TEN (67.3%) and 247 DRESS (32.7%). The number of SCAR cases increased up to 100 cases/yr from 2010. Allopurinol was the most common causative drug (DRESS, 11.3%; SJS/TEN, 10.2%), followed by carbamazepine (DRESS, 9.7%; SJS/TEN, 8.7%). There were 20 SCAR-related deaths (2.6%), most commonly from antimicrobials (8 cases) and antiepileptics (5 cases).

In a SCAR study from Vietnam (2010–2015) [28], majority were in adults (mean age, 42.5±22.9 years). Up to 91.8% of drugs induced SJS/TEN within 1–28 days, and 45% SJS/TEN cases were evaluated as life-threatening. Carbamazepine and allopurinol were the most common causes of SCAR.

Clinical audits published by a few dermatology centers in Malaysia [29-32] showed that SJS/TEN was the most common type of SCAR phenotype encountered (53.3%–84.8%) followed

by DRESS (12.7%–26.7%) and AGEP (4.8%–17.7%). The most frequently reported causative drugs for SJS/TEN included allopurinol (20.1%–41.7%), carbamazepine (21.8%) and cotrimoxazole (12.7%). The main causative drugs for DRESS were allopurinol (16.7%–60%) and dapsone (17.6%–25%). The in-hospital mortality reported was 0%–6.2% for SJS, 13.3%–66.7% for TEN and 5.9%–41.7% for DRESS.

In a retrospective study of 42 inpatients from a public hospital in Singapore who developed SCAR between 2007–2011 [33], the mean age was 51.8 years, in whom 69% had underlying comorbidities. SJS (54.8%) was the most common, followed by AGEP (24%), TEN (11.9%), and DRESS (2%). Antibiotics was the most common culprit drug group. Sixteen patients (38.1%) had complications, and there was one reported death. These findings were similar to an earlier retrospective study of SJS/TEN from a general hospital from 2004–2010 [34] comprising 18 SJS, 3 TEN, and 7 SJS/TEN overlap. The mean age of 50.6 years, with a range of 13–85 years was similar; with anticonvulsants (35.7%), antibiotics (28.5%), NSAIDs (14.3%), allopurinol (7.1%), and traditional Chinese medication (7.1%) being the common causes. Most SJS cases (88%) were treated with corticosteroids, of which 61% were given high-dose systemic corticosteroids. Six out of the 7 SJS/TEN (85.7%) overlap syndrome and all 3 TEN cases (100.0%) were given IVIG. One patient with TEN died. An earlier prospective study of 210 cases of allergist-verified, inpatient drug allergy from 1997–1999 [35] reported a SCAR incidence of 5.2% and mortality attributable to drug allergy of 0.09 per 1,000 (95% confidence interval, 0.06–0.12) hospitalizations.

A retrospective study of 57 patients with SCAR from Bandung, Indonesia [36] over 5 years from 2009–2013 comprised 68.4% SJS, 19.3% TEN and 12.3% SJS/TEN overlap. The common causative drugs were paracetamol (16.56%), carbamazepine (7%), amoxicillin (5.73%), ibuprofen (4.46%), rifampicin (RIF) (3.18%), and trihexyphenidyl (3.18%). All cases were treated with systemic corticosteroid alone. Seven patients (12.28%) died, of whom 5 were from sepsis and 2 cases from respiratory failure. The mortality rate was 36.36% in TEN, 7.69% in SJS, and 0% in SJS/TEN overlap. In another study from eastern India [37], an observational study over a 1-year period from a tertiary care teaching hospital showed that SJS/TEN comprised 24.5% of all cutaneous adverse drug reaction (ADR) reported. Drugs implicated were sulfonamides (17%), fixed-dose combinations of fluoroquinolones with nitroimidazoles (11.3%), analgesics (11.3%), antiepileptics (11.3%), beta-lactam antibiotics (9.4%), fluoroquinolones alone (7.5%), allopurinol (7.5%), and azithromycin (5.7%). The different patterns of causative drugs are likely a reflection of different prescribing patterns, genetic and/or ethnic risk factors.

GENETICS OF SCAR IN ASIA

Since the early 2000s, the Asia-Pacific region has led the way in international studies on the genetic basis of SCAR. This in turn has transformed clinical practice by introducing the value of pharmacogenomic screening prior to the use of drugs at high risk of SCAR. Initial evidence on the role of HLA in the predisposition to SCAR in ethnic Asians originated from Taiwan with findings of the association of HLA-B*1502 and carbamazepine SCAR in 2004 [38], followed by HLA-B*5801 and allopurinol SCAR [39] in 2005. In 2008, Australia was the first to publish in a double-blind prospective randomized trial, the use of a pharmacogenetic test in preventing abacavir hypersensitivity among human immunodeficiency virus (HIV) patients [40]. In 2011, the association of HLA-B*1502 with carbamazepine SCAR and the effectiveness

of prospective pharmacogenetic screening [41] led to regulatory initiatives to mandate pre-testing prior to the use of carbamazepine in individuals of Asian ethnicity, labeling of product inserts and public subsidies for pre-testing as part of personalized medicine initiatives.

HLA risk-associations with specific drug-related SCAR among Asians to date include:
- Abacavir hypersensitivity: HLA-B*57:01 (white Caucasians, Perth, Australia) [40]
- Allopurinol SJS/TEN: HLA-B*58:01 (Han Chinese, Taiwan [39, 42, 43]; Hong Kong [44])
- Carbamazepine SCAR: HLA-B*15:02 (Han Chinese, southern mainland China and Taiwan [41], Hong Kong [44]; Chinese (adults and children [45], Singapore), Vietnam [46], Indians (India) [47]; Malaysian Malay and Chinese [48, 49]
- Carbamazepine DRESS: HLA-A*31:01 (Taiwan, Japan [50], Korean [51], Han Chinese)
- Carbamazepine SJS/TEN and HLA-B*1511 (Japan, Korea) [51]
- Dapsone: SCAR: HLA-B*13:01 Taiwan [52]; DRESS and SCAR: Thailand [53]
- Oxcarbazepine SJS: HLA-B*15:02 (Chinese, Thai) [54]
- Phenytoin SCAR: HLA-B*15:13 and HLA-B*15:02 (Malays, Malaysia [55]; Han Chinese, Hong Kong [43])
- Phenytoin hypersensitivity: HLA-B*13:01 and HLA-B*5101 in Taiwan, Japan, Thailand [56]
- Phenytoin SCAR: CYP2C9*3, known to reduce drug clearance (Taiwan, Japan, Malaysia) [56, 57]
- Phenobarbital SCAR: CYP2C19*2 (Thailand, children) [58].

In addition, for HLA-genotype screening to be cost-effective for high-risk drugs, HLA-gene frequency should not be low, the screening test should not be expensive, and alternative therapies which are not too expensive should be available. In Korea and Japan, the allele frequency of HLA-B*1511 is less than 1%, thus making pre-screening for carbamazepine SJS/TEN not cost-effective. In Singapore, although HLA-B*1502 screening has been found to be cost-effective prior to initiating carbamazepine [59], HLA-B*5801 screening for allopurinol SCAR has not. This is due to the low positive predictive value of the test, presence of nongenetic risk factors like chronic kidney disease reducing oxypurinol renal clearance, and high cost of febuxostat as an alternative urate lowering therapy. Thus local guidelines from the Ministry of Health's Agency for Care Effectiveness have proposed starting low (dose) and going slow (dose escalation) (http://www.ace-hta.gov.sg/our-guidance/gout-achieving-the-management-goal.html). A recent Cochrane review found no eligible evidence on genetic testing for severe drug-induced skin rash in relation to different drugs and classes of drugs [60].

In the immunopathogenesis of DRESS, the finding of human herpes virus reactivations in DRESS, the possible role of regulatory T cells and development of autoimmune diseases as sequelae originated from studies in Japan [61]. The Asian Research Committee on Severe Cutaneous Adverse Reactions [62], comprising doctors from Japan and Taiwan, analyzed 145 survivors of DRESS which showed that long-term sequelae in the form of autoimmune thyroid disorders (Graves' disease [n = 2], Hashimoto disease [n = 3]), painless thyroiditis (n = 2), and type 1 diabetes mellitus (n = 5) were the most common.

ANTITUBERCULOUS DRUG ALLERGY

Tuberculosis (TB) remains endemic within various parts of Asia, especially east and southeast Asia. At-risk individuals include patients with HIV infection, poorly controlled

type 2 diabetes mellitus and rheumatology patients treated with anti-tumor necrosis factor biologics for inflammatory arthritis. Multidrug first-line regimes comprising induction isoniazid (INH), RIF, ethambutol (EMB), and pyrazinamide (PZA) not infrequently result in SCAR, of which DRESS is relatively more common [63]. Discerning the putative drug is a challenge in view of the lack of commercially available, reliable, standardized *in vitro* tests (e.g., lymphocyte transformation tests, Elispot tests) [64, 65]. As such, various "desensitization-rechallenge" protocols have been developed [64, 66], many published from centers in Asia. The reason why these have been described as "desensitization-rechallenge" rather than just desensitization is because the identification of the suspected drug within the combination of 3–4 drugs during induction treatment is often presumptive. In certain centers where research-based *in vitro* tests or *in vivo* tests are used to facilitate identity of the culprit drug, then are the regimens considered truly "desensitizations" i.e., initiation and increment protocols for temporary tolerance induction [67, 68]. In most centers where these diagnostic tests are not available, TB drugs may be reintroduced sequentially using drug provocation regimes as a diagnostic test [69] for the 1–2 less likely drugs, followed by desensitization regimens for the remaining 1–2 more likely drugs (usually RIF or INH) for tolerance induction. The risks of such procedures need to be balanced against the alternatives of second-line TB treatments [70] which also have attendant toxicities, and for which a longer treatment course is needed. As many TB DHR are SCARs, desensitization or any re-exposure is of much higher risk.

A Korean prospective, observational cohort study [71] on subjects who experienced hypersensitivity reactions, including MPE and DRESS to first-line antituberculosis medications was carried out. Patch, intradermal, lymphocyte transformation, and oral provocation tests were performed to determine culprit drugs, which were desensitized with rapid and graded challenge protocols. Breakthrough reactions (BTR) during or after desensitization were assessed. In total, 31 desensitization treatments (INH, 8; EMB, 8; RFP, 11; PZA, 4) in 12 patients (8 with MPE and 4 with DRESS) were performed. The overall success rate of desensitization was 80.7%. All the study subjects except one completed the full course of antituberculosis treatment. The overall BTR free rate was 64.5%. Sixteen treatments (80%) for MPE and 4 (36.4%) for DRESS were BTR free ($p = 0.023$). Drugs that were positive on any 2 of 3 immunologic studies showed significantly high BTR rates ($p = 0.014$), although this was not correlated with desensitization failure rate.

In a retrospective Thai study comprising adults age>18 years old with positive DPT to the culprit drug, patients with severe index reactions comprising erythema multiforme (3), SJS (4), DRESS (1) were included [72]. A total of 19 desensitization procedures, starting at 1:100,000 of the therapeutic dose over 14 days, were performed (INH, 7; RIF, 6; EMB, 6). The median duration of desensitization was 18 days, with a success rate of 78.9%. Those who failed desensitization developed mild maculopapular rashes but not SCAR.

In a retrospective Singapore cohort of adult patients [73], a tailored desensitization-rechallenge regimen according to the severity of the initial reaction was used. In cases of severe cutaneous ADR, a multistep protocol starting at 1: 6,000 of the therapeutic dose was used, and in mild-to-moderate cutaneous ADR, a single daily step increase starting at 1:3 of therapeutic dose. Eleven patients completed 25 desensitization procedures of whom 23 of 25 (92%) desensitizations were tolerated. Two patients developed mild skin reactions to INH on day 3 including one where the original reaction was DRESS.

NSAID HYPERSENSITIVITY

NSAIDs are a common cause of DHR in the Asia-Pacific region among adults and children [7]. The European Network on Drug Allergy/Global Allergy and Asthma European Network (ENDA/GA²LEN) classification of NSAID DHRs comprises cross-reactive and selective NSAID DHR. Nonallergic drug hypersensitivity i.e., NSAIDs exacerbated respiratory disease (NERD), NSAIDs exacerbated cutaneous disease (NECD) and NSAIDs induced urticaria-angioedema (NIUA); is more common than NSAID allergy [74]. Diagnostic and management algorithms have been well-described [75]. In children and adolescents, the NSAID DHR phenotype tends to have overlapping features, with a much lower prevalence of NERD compared to adults [76].

There are regional differences in the NSAID DHR phenotype within Asia. NERD appears to be more prevalent in East Asia (Korea, Japan, China) than in Southeast Asia. NSAID DHR among adults in chronic rhinosinusitis (CRS) cohorts from China was reported to be low (0.28%–1.46%), [77] with a predominance of the noneosinophilic (non-Th2) endotype of CRSwNP (CRS with nasal polyposis) from Guangdong [78]. Within COREA (COhort for Reality and Evolution of Adult Asthma in Korea), a prospective cohort study of patients aged 19 years or older with asthma involving 11 centers in Korea, aspirin intolerant asthma was associated with younger age, higher prevalence of rhinosinusitis and atopic dermatitis, and more frequent exacerbations [79]. In Korea, NERD may be associated with or without CRS, and with or without atopy or urticaria [80]. In Singapore, NERD is not as common [81] as NIUA among adults, in whom periorbital and facial edema is the most common manifestation. Majority (95%) of adults with NIUA are able to tolerate up to 120-mg Etoricoxib during DPT [82]. A similar pattern of NSAID DHR is seen among Malaysian adults where NIUA (63.9%) and NECD (9.8%) are much more common compared to NERD (1.6%), with overlapping features in 19.7% [83]. The most common causative NSAIDs are Diclofenac, Mefenamic acid or Paracetamol. Among Singaporean children, the same NSAID DHR phenotype has been observed [84], with a proportion cross intolerant to both NSAID and Paracetamol [85], but tolerant of selective cyclooxygenase-2 inhibitors [86]. It is likely that geographical differences in NSAID DHR phenotypes are related to genotypic differences as demonstrated by genome-wide association and case-control studies on NSAID DHR from Korea, Japan and [87] Malaysia [88].

What is likely to be more clinically relevant is the role of low-dose aspirin desensitization (up to 100 mg/day) for coronary artery disease. In individuals with cross-reactive NSAID DHR, this is an option following percutaneous coronary intervention to induce tolerance as part of dual anti-platelet therapy with clopidogrel [89]. The only published study from Asia is a retrospective case series from Hong Kong (N = 24), where the mean age of patients was 64 ± 13 years, majority male (67%), where the index reaction was NIUA in 92%. The acute cardiac event comprised 54% acute coronary syndrome, where 83% were successfully desensitized at the initial attempt. This was using a 5-step protocol up to 155-mg cumulative dose of aspirin. Among the 8 (33%) who developed DHR during desensitization, 4 of 8 (50%) were limited cutaneous reactions, and all patients completed desensitization [90]. High dose desensitization up to 650 mg/day for CRS does not appear to be common in Asia, possibly because of gastrointestinal intolerance and risks of upper gastrointestinal bleeding.

RADIOCONTRAST MEDIA HYPERSENSITIVITY

RCM DHR may be allergic or nonallergic, immediate or nonimmediate (delayed); with skin tests found to be increasingly useful in the management of patients with DHR, especially

those who may require repeat contrasted imaging [91, 92]. Nonionic and hyperosmolar agents are associated with higher risks of DHR.

Studies on the prevalence of immediate reactions in the Asia-Pacific region have been reported from Korea, Japan, Australia, India, Thailand, Turkey, and Qatar; delayed reactions have been reported from Japan, Korea, Thailand, and Turkey [93]. Much of the work in Asia on RCM DHR come from Korea where epidemiological studies have revealed no difference in the rate of RCM DHR among various RCMs [93-95]. A recent publication from the KAERS (Korea Adverse Event Reporting System) where immediate reactions were more commonly reported was based on spontaneous reports from hospitals where it is possible that delayed reactions were missed and hence not reported [96]. The use of low/iso-osmolar ionic reagents e.g., iodixanol has reduced the prevalence of RCM hypersensitivity to iodinated contrast media used in contrasted computed tomographic scans. In another Korean study, the incidence of delayed hypersensitivity during intra-arterial injection of contrast media during coronary angiography was found to be higher at 15.1% than 3.6% for immediate reactions, with iodixanol a significant risk factor compared to ioversol [97]. Other than using negative IDT to select alternative RCM to prevent recurrent DHR [98], other authors have proposed intravenous DPT using agents that are skin test negative to confirm tolerance prior to the next imaging [99]. International guidelines suggest changing RCM within the same class of low-osmolar RCM based on studies from Japan and Korea [100-102].

Rapid desensitization for immediate reactions for urgent coronary angiography has been reported using a combination of intravenous desensitization preceded by oral prednisolone/intravenous methylprednisolone and oral/intravenous diphenhydramine premedication [103-105]. Although an alternative for patients with moderate to severe RCM DHR could be the use of magnetic resonance imaging, the incidence of DHR to gadolinium-based contrast agents (GBCA) is also increasing. Meta-analyses have demonstrated the lowest rate of immediate allergic adverse events with the use of the nonionic linear GBCA gadodiamide in comparison with those of ionic linear or nonionic macrocyclic GBCAs. A higher rate of immediate allergic adverse events was associated with ionicity, protein binding, and macrocyclic structure [106]. Challenges in parts of Asia remain the lack of availability of a range of alternative agents in certain countries with small markets, and the noninterchangeability of different agents with different organ imaging specificities, which precludes skin testing to find an alternative agent with no skin test reactivity. Premedication after previous reactions remains an option in this instance if the benefits outweigh the risk of a systemic reaction.

CONCLUSION

Many clinical guidelines exist for the diagnostic evaluation and management of drug allergy/ hypersensitivity from regional and international allergy/immunology professional societies [4]. Drug allergy/hypersensitivity interest groups of regional societies like the Asia Pacific Association of Allergy Asthma and Clinical Immunology (APAAACI) can contribute to the evidence base by supplementing the guidelines with recommendations pertinent for certain Asian geographical sites and ethnicities. Possible areas for further collaboration and in-depth study could include the following:
- delabeling beta-lactam (penicillin) allergy in low-risk adults and children using direct oral challenges;
- pharmacogenomic testing, pre-emptive monitoring, and immunomodulation of SCARs;
- enhanced *in vitro* diagnostics for antituberculous drug allergy and NSAID hypersensitivity

to avoid high-risk challenges/desensitizations;
- coordinated registries for SCARs and anaphylaxis;
- joint management algorithms on RCM HSR among radiologists, oncologists, and allergists.

An APAAACI survey on diagnostic procedures and therapies in DHR similar to the WAO international survey carried out a decade ago [107] would be useful in developing regional guidelines on DHR.

Summary Table

Beta-lactam allergy
- Risk stratification of the likelihood of penicillin allergy based on history and non–IgE-mediated type of clinical manifestations of the index adverse drug reaction, form the basis of safe direct oral amoxicillin/penicillin challenge for low-risk patients without the need for skin tests.
- Delabeling and de-escalation encourage appropriate narrow-spectrum antimicrobial use, preventing the increasing incidence of antimicrobial resistance.

Severe cutaneous adverse reactions
- The most commonly implicated drugs in Asia are antiepileptic drugs (carbamazepine, phenytoin, lamotrigine), allopurinol and antimicrobials.
- Although HLA-B*1502 (carbamazepine), HLA-B*5801 (allopurinol) and HLA-B*5701 (abacavir) testing prior to drug initiation may reduce the risk of severe cutaneous adverse reaction (SCAR), a recent Cochrane review found no eligible evidence on genetic testing for severe drug-induced skin rash in relation to different drugs and classes of drugs.

Antituberculous drug allergy
- Many antituberculous drug hypersensivity reactions are SCARs.
- Desensitization or any re-exposure is of much higher risk. Desensitization protocols involving sequential re-introduction of antituberculous drugs are commonly used given the paucity of well-validated *in vitro* and *in vivo* tests to identify the causative drug to restart during induction combination therapy.

Nonsteroidal anti-inflammatory drug hypersensitivity
- The phenotype in children and adolescents tends to have overlapping features, with a much lower prevalence of nonsteroidal anti-inflammatory (NSAID) exacerbated respiratory disease compared to adults.
- Low-dose aspirin desensitization (up to 100 mg/day) for coronary artery disease has been found to be effective and safe in patients with NSAID hypersensitivity.

Radiocontrast media hypersensitivity
- Radiocontrast media (RCM) drug hypersensitivity reactions (DHR) may be allergic or nonallergic, immediate or non-immediate (delayed); nonionic and hyperosmolar agents are associated with higher risks of DHR.
- Skin tests are increasingly useful in the management of patients with RCM DHR, especially those who may require repeat contrasted imaging.
- Negative intradermal tests are used to select alternative RCM to prevent recurrent DHR. International guidelines suggest changing RCM within the same class of low-osmolar RCM.

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