Special Article

SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation

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Learning objectives:

1. To identify current knowledge gaps in the clinical management of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

2. To identify key research questions and gaps pertinent to SJS/TEN.

3. To discuss advances in knowledge of the genetic and mechanistic basis of SJS/TEN and their translational outputs such as pharmacogenomic screening.

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E. J. Phillips has received research support from the National Health and Medical Research Council Australia, the NIH, and ACH2 Australia; receives royalties from UpToDate; has received consultancy fees from Biocryst, Aicuris, Xcovery, and Medicines for Malaria (MMV); and is codirector of the company holding the patent for HLA-B*57:01 testing for abacavir hypersensitivity reaction. The rest of the authors declare that they have no relevant conflicts of interest. M. Schatz disclosed no relevant financial relationships.

This article is a summary of a meeting that was held on March 2, 2017. You may view the presentations from the meeting and earn additional CME credit at http://www.jaci-inpractice.org/sjs-ten-2017.

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a life-threatening, immunologically mediated, and usually drug-induced disease with a high burden to individuals, their families, and society with an annual incidence of 1 to 5 per 1,000,000. To effect significant reduction in short- and long-term morbidity and mortality, and advance clinical care and research, coordination of multiple medical, surgical, behavioral, and basic scientific disciplines is required. On March 2, 2017, an investigator-driven meeting was held immediately before the American Academy of Dermatology Annual meeting for the central purpose of assembling, for the first time in the United States, clinicians and scientists from multiple disciplines involved in SJS/TEN clinical care and basic science research. As a product of this meeting, this article summarizes the current state of knowledge and expert opinion related to SJS/TEN covering a broad spectrum of topics including epidemiology and

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Abbreviations used
ADR- Adverse drug reaction
AMT- Amniotic membrane transplantation
BSA- Body surface area
CPNDS- Canadian Pharmacogenomics Network for Drug Safety
DIHS- Drug-induced hypersensitivity syndrome
DRESS- Drug reaction with eosinophilia and systemic symptoms
DSC- Drug safety communication
EMM- Erythema multiforme majus
EHR- Electronic health record
FAERS- Food and Drug Administration Adverse Event Reporting System
FDA- Food and Drug Administration
GBFDE- Generalized bullous fixed drug eruption
HAS- Health Sciences Authority
HCP- Healthcare professional
HIV- Human immunodeficiency virus
HLA- Human leukocyte antigen
ICD- International Classification of Diseases
IM-ADR- Immunologically mediated adverse drug reaction
ITCH- International Consortium on Drug Hypersensitivity
IVIG- Intravenous immunoglobulin
MIRM- Mycoplasma-induced rash and mucositis
NATIENS- North American Therapeutics in Epidermal Necrolysis Syndrome
NK- Natural killer
NPV- Negative predictive value
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
PBMC- Peripheral blood mononuclear cells
PD-1- Programmed cell death protein 1
PMC- Postmarketing commitments
PMR- Postmarketing requirements
PMTCT- Prevention of mother-to-child HIV transmission
PPV- Positive predictive value
PTSD- Posttraumatic stress disorder
REMS- Risk evaluation and mitigation strategies
SCAR- Severe cutaneous adverse reaction
SCORTEN- Severity of illness score for TEN
SDH- Society of Dermatology Hospitalists
SJS/TEN- Stevens-Johnson syndrome/toxic epidermal necrolysis
TB- Tuberculosis
TCR- T-cell receptor
TEN- Toxic epidermal necrolysis
TNF- Tumor necrosis factor
Treg- Regulatory T

pharmacogenomic networks; clinical management and complications; special populations such as pediatrics, the elderly, and pregnant women; regulatory issues and the electronic health record; new agents that cause SJS/TEN; pharmacogenomics and immunopathogenesis; and the patient perspective. Goals include the maintenance of a durable and productive multidisciplinary network that will significantly further scientific progress and translation into prevention, early diagnosis, and management of SJS/TEN. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:38-69)

Key words: *Stevens-Johnson; Toxic epidermal necrolysis; HLA; Networks; Pharmacogenomics; Pharmacovigilance; Electronic health record; T cells; Granulysin*

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the severest in the spectrum of immunologically mediated adverse drug reactions (IM-ADRs) that are considered to be primarily T-cell—mediated. SJS/TEN is characterized by a painful blistering skin rash that is often associated with multiorgan involvement, commonly fever, hematologic abnormalities, and ophthalmologic and genitourinary involvement. Early dermatologic findings may include erythematous or dusky colored macules that evolve to become fluid-filled bullae and/or denuded skin. Involved nonblistered skin often sloughs with direct lateral pressure (Nikolsky sign) and demonstrates interface dermatitis with necrotic

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keratinocytes and epidermal separation on histopathologic examination (Table I). SJS and TEN are thought to be the same disease across a spectrum of severity defined by the percentage of skin detachment related to the body surface area (BSA) comprising SJS (<10%), SJS/TEN overlap (10%-30%), and TEN (>30%) (Table I). The mortality associated with TEN in the setting of aggressive supportive care at experienced centers is approximately 30%; however, in the elderly and immunocompromised populations this can exceed 50%. The short-term morbidity associated with SJS/TEN is well recognized and includes sepsis, respiratory complications, gastrointestinal and genital tract mucositis, and eye disease. However, long-term morbidity is also considerable and includes vision loss, urogynecological complications, chronic respiratory disease, depression and posttraumatic stress, disfigured painful skin, restricted therapeutic choices, and shortened life span. Over the last 10 to 15 years, there have been significant advances in our understanding of the immunogenomics of IM-ADRs.[2] For SJS/TEN this has included several strong associations from Southeast Asia between HLA class I alleles and drug-associated SJS/TEN including HLA-B*15:02 and carbamazepine SJS/TEN and HLA-B*58:01 and allopurinol SJS/TEN. This has led not only to successful HLA-B*15:02 screening programs in Taiwan, Singapore, and other parts of Southeast Asia that have almost eliminated carbamazepine-associated SJS/TEN, but also furthered our understanding of the immunopathogenesis of SJS/TEN. Despite this progress there are still a large number of clinical and research gaps. A few highlights of these gaps include the lack of (1) an evidence-based approach to guide therapeutic interventions above aggressive supportive care in acute SJS/TEN, (2) predictive biomarkers for early diagnosis and prognosis, (3) genetic predictors for most drugs that cause SJS/TEN, and (4) an explanation for why only a small proportion (<10%) of those carrying an HLA risk allele will develop SJS/TEN following drug exposure.[2]

To explore gaps and unmet needs for further research into the epidemiology, pathogenesis, treatment, and prevention of SJS/TEN, the National Human Genome Research Institute, along with the Food and Drug Administration and 5 other National Institutes of Health institutes and centers (the National Center for Advancing Translational Sciences, the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis, Musculoskeletal and Skin Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases), brought together 30 international experts in severe cutaneous adverse reactions, pharmacogenomics, and related fields for a 2015 workshop titled "Research directions in genetic predispositions to SJS/TEN.".[3,4] This 2-day workshop reviewed the current state of knowledge of surveillance, pathogenesis, and treatment of SJS/TEN, examined the role of genomics in the etiology, treatment, and eradication of preventable cases of SJS/TEN, and identified gaps, unmet needs, and priorities for future research to work toward the global elimination of genetically mediated SJS/TEN. A primary conclusion of this meeting was that although there have been great research strides in SJS/TEN with compelling examples of implementation of personalized medicine, there is continued need to broaden these discoveries for translation and implementation across diverse populations and causative drugs. Overarching and facilitative research goals were set and 3 high priority areas were identified and targeted: clinical care, pharmacovigilance and epidemiology, and basic research. An important outcome of the meeting was recognition of the need, because of the overall rarity and diverse epidemiology of SJS/TEN, to develop a large global collaborative network and a supportive funding infrastructure to further all aspects of SJS/TEN research.

An ongoing dialogue among an SJS/TEN working group comprising members from academia and government followed this meeting and has led to new initiatives that have included the establishment of an SJS/TEN phenotyping group that published a standardized case report form for SJS/TEN,[5] a subgroup evaluating SJS/TEN causality assessment tools, and a national survey of dermatologists, burn surgeons, and ophthalmologists who care for patients with SJS/TEN that identified knowledge gaps, priorities, unmet needs, and unresolved controversies in SJS/TEN clinical care and research. More than 50% of survey respondents were interested in the opportunity for further engagement in all aspects of SJS/TEN research.[6]

The fundamental clinical, epidemiological, and basic research questions identified in the 2015 National Institutes of Health workshop served as a catalyst for further efforts toward organized collaboration. To engage a broad constituency of stakeholders in this effort, a meeting "Stevens-Johnson-syndrome/Toxic epidermal necrolysis 2017: Building Multidisciplinary Networks to Drive Science and Translation" was held on March 2, 2017. This meeting had representation across allergy-immunology, dermatology, ophthalmology, burns surgery, gynecology, clinical pharmacology, basic science (immunobiology, genetics), epidemiology, informatics, regulatory science, patients and their families, and government and included 142 participants from 6 continents (Figure 1). A major goal of this meeting was to bring together established and new investigators to create a durable network of SJS/TEN clinicians and scientists to discuss and prioritize achievable short- and long-term research objectives. This meeting was charged with presentation of the most current and cutting-edge research relevant to SJS/TEN, provision of mentorship for new investigators of disparate backgrounds to become future leaders in SJS/TEN, and, importantly, to provide a multidisciplinary and interactive forum where the most controversial areas of SJS/TEN clinical care and research could be discussed. The meeting highlighted key areas amenable to network building and clinical translation. Representatives from 3 National Institutes of Health institutes—the National Human Genome Research Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Arthritis, Musculoskeletal and Skin Diseases—provided updates on funding mechanisms relevant to SJS/TEN with a focus on newer R01/R21 funding related to serious IM-ADRs.[7,8]

This article is a summary of the proceedings of the meeting that includes the new and evolving science, key controversies, outputs of the meeting, and proposed future directions.

GLOBAL EPIDEMIOLOGY AND PHARMACOGENOMICS NETWORKS*

Key Points:

- SJS/TEN is a life-threatening mainly drug-induced disease with considerable short- and long-term morbidity and

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TABLE I. Phenotypic characteristics of SJS/TEN and severe cutaneous syndromes

Characteristic	SJS/TEN	EMM	GBFDE
Target lesions	Flat, atypical target lesions present	Typical or raised atypical target lesions	No
Blisters and erosions	Yes <10%: SJS; 10%-30%: SJS/TEN overlap; >30%: TEN	Yes, in the center of targets	Yes
Distribution	Widespread	Mainly limbs or acral	Localized
Well-demarcated, erythematous patches (≥5 cm)	No	No	Yes
Erosions of mucosa (eye/lip/genital)	Yes	Yes	Yes or no
Recurrent history	Rare	Occasional	Common
Prognosis	Mortality depends on risk factors (SCORTEN[1])	Favorable	Generally favorable but associated with higher morality with >20% BSA involvement and in elderly
Etiology	Usually drug-induced	Suspected infection not drug	Usually drug-induced

EMM, Erythema multiforme majus; *GBFDE*, generalized bullous fixed drug eruption.
SCORTEN: Age < 40 y (0), >40 y (+1); Associated malignancy: no (0), yes (+1); Heart rate (beats/min): <120 (0), >120 (+1); serum blood urea nitrogen (mg/dL): <28 (0), >28 (+1); detached or compromised body surface: <10% (0), >10% (+1); Serum bicarbonate (mEq/L): >20 (0), <20 (+1); Serum glucose (mg/dL): <252 (0), >252 (+1).

FIGURE 1. Participants representing 14 countries from 6 medical subspecialties, SJS/TEN advocacy groups, the US government, and the SJS/TEN research community gathered in Orlando, Florida, on March 2, 2017, for the inaugural *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation meeting*. Thirty predoctoral and postdoctoral trainees attended and presented original research at this meeting. **A**, Subspeciality distribution of participants. **B**, Global distribution of participants. *PGx*, Pharmacogenomics.

mortality that poses a burden to health care systems and families disproportionate to its prevalence.
- The rarity of SJS/TEN has created challenges for the generation of evidence-based treatment.
- Collaborative pharmacogenomic studies have been successful in determining HLA associations in SJS/TEN and provide the promise for more associations to be delineated in the future.
- The development of networks that include an SJS/TEN phenotype adjudication committee as well as centralized biological sample collection and repositories would provide a platform to study pathogenesis and predictors.

A number of collaborative networks exist that study the epidemiology and pharmacogenomics of SJS/TEN across genetically diverse populations, seek to discover pathogenic mechanisms and other mediators of disease risk, and allow for the development of clinical trials to evaluate therapeutic interventions. Session one of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured representatives from some of these international collaborative networks. The strength of these networks lies in the rigorous definitions for clinical diagnosis, causality assessment at the individual case level, estimation of risk factors for each severe cutaneous adverse reaction (SCAR) entity, and centralized collection of samples to facilitate investigation of the mechanisms and search for new therapeutic options.

The Society of Dermatology Hospitalists SJS/TEN Study Group (United States)

The Society of Dermatology Hospitalists (SDH) is a US-based organization dedicated to the care of complex dermatological patients in the inpatient setting. In an effort to describe the SJS/TEN experience of dermatology hospitalists in the United States and explore ongoing management controversies in SJS/TEN, the SDH retrospectively collected information on the disease course, management, and outcomes of patients treated for SJS/TEN at member institutions. As a collaborative research effort of 18 tertiary care centers, the SDH has

compiled a database of 405 US SJS/TEN cases between 2000 and 2015, with most patients treated from 2010 onward. Medications were the most common cause of SJS/TEN in this cohort, accounting for 91.3% of cases and trimethoprim/sulfamethoxazole was most often implicated (26.0%). Sixty-six percent of patients met criteria for TEN (>30% BSA denuded) or SJS/TEN overlap (10%-30% BSA denuded) at the time of admission. The severity of illness score for TEN (SCORTEN)[1] predicted mortality for the cohort at the time of admission to be 20.0%. Sixty-seven percent of patients were managed in a specialized burn or intensive care unit and 70% received pharmacotherapeutic intervention in addition to supportive care, most commonly corticosteroids, intravenous immunoglobulin (IVIG), or both steroids and IVIG. Only 4 patients in this cohort received cyclosporine and 1 patient received the TNF-α inhibitor etanercept. Actual mortality of patients in the cohort was 13.7%, for a standardized mortality ratio of 0.69 (95% CI, 0.57-0.78). The improved survival of patients in this cohort compared with SCORTEN-predicted mortality is notable and likely multifactorial. Preliminary analyses showed an overall lack of consensus regarding the management of SJS/TEN and no clear evidence of benefit from any particular pharmacotherapeutic intervention compared with supportive care alone. Additional work to account for relevant confounding factors and choice of pharmacotherapy is ongoing. Future work of the SDH will include evaluation of the updated SCORTEN algorithm to predict SJS/TEN mortality, longitudinal analyses of SJS/TEN survivors to determine sequelae and quality of life following recovery, and a prospective SJS/TEN cohort study and, ultimately, randomized controlled trial.

The North American Therapeutics in Epidermal Necrolysis Syndrome Trial Network (North America)

Composed of 24 academic institutions and burn centers in the United States and Canada, the North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) Trial Network brings together expertise in burn surgery, dermatology, eye, and mucosal complications and leaders in immunogenetic science to create the feasibility for a multicenter, translational clinical trial comparing cyclosporine, etanercept, and supportive care.[6] The NATIENS Trial Network's mission is to enhance the quality and standardization of care for patients with SJS/TEN through accelerating scientific discovery. The NATIENS Trial Network also includes 3 scientific centers with expertise in immunogenetics, next-generation genomic sequencing, cellular immunology, and pharmacokinetics. A double-blind randomized controlled trial assessing standardized supportive care and immunomodulatory therapeutics in SJS/TEN is planned to begin in 2019 and will be the first to rigorously study SJS/TEN in a multicenter setting. Its members have developed tools for standardized assessment of skin involvement and reepithelialization to measure response to therapy, a comprehensive supportive care protocol, and immunogenetic and cellular analyses to study the underlying pathophysiology. Outcomes from the NATIENS Trial Network's clinical trial will include a rigorous and objective assessment of a standardized supportive care model and immunomodulatory therapies in acute SJS/TEN, longitudinal patient follow-up for standardized assessment of short- and long-term sequelae, systemic and tissue-specific genetic and immunologic analyses to define pathogenic mechanisms and provide mechanistic support for immunomodulatory therapies in acute disease, as well as the infrastructure and clinical and scientific partnerships for the future study of unexplored therapeutic targets and markers of SJS/TEN risk in North American populations.

The Canadian Pharmacogenomics Network for Drug Safety

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) consists of more than 65 multidisciplinary expert collaborators from 26 pediatric and adult academic health centers in Canada that recruit patients via active surveillance and collect genomic samples and clinical information on drug outcomes. Currently, the CPNDS active surveillance clinical database includes detailed clinical information for various drugs from more than 9,313 adverse drug reaction cases and 84,082 drug-exposure—matched controls. More patients are recruited networkwide each day. The CPNDS has used this methodology to study the pharmacogenomics of several severe adverse drug reactions (ADRs) and was the first to confirm the role of *HLA* markers for carbamazepine-related skin reactions in children.[9] The CPNDS is actively addressing the problem of these severe reactions by using diverse approaches such as (1) *discovery/replication through collaboration.* This approach is used to confirm previously identified pharmacogenomic biomarkers as well as identify novel genomic variation associated with these reactions, which, given the rarity of SJS/TEN, requires collaboration between international consortia. Further collaboration with the EpiPGX Consortium (Europe) has led to the identification of more than 80 cases of severe cutaneous ADRs associated with anticonvulsants. A genomewide assessment of these cases using both genotyping arrays and exome sequencing is in process. Collaborations with additional international consortia are underway. (2) *Knowledge translation and commercialization.* A key outcome is translation of pharmacogenomics into clinical practice. The CPNDS has published clinical practice guidelines for carbamazepine-related ADRs[10] and is currently working with the Clinical Pharmacogenetics Implementation Consortium to update relevant guidelines and develop commercial pediatric pharmacogenomic panels that will include ADR pharmacogenomic markers (for more information, please visit https://cpicpgx.org/).

The International Consortium on Drug Hypersensitivity network

The International Consortium on Drug Hypersensitivity (ITCH) network, coordinated in Liverpool, UK, and funded by the International Serious Adverse Event Consortium, was established for the recruitment of patients with SCAR and now includes 1,500 precisely phenotyped cases from 12 countries with associated genetic data.[11] Analyses using the ITCH cohort have concentrated on identifying drug-specific genetic predisposing factors and genetic factors predisposing to SJS/TEN irrespective of drug etiology. Genomewide association studies from 1,260 SCAR cases in the ITCH cohort rely on careful quality control procedures that include controlling for population stratification, imputation using the latest releases of genomic data, and validation of imputed genetic variants, where appropriate.

The ITCH database includes 177 SJS/TEN cases that are derived from Caucasian patients from 3 ethnic groups: Spanish, Italian, and Northern European. Analysis of all 177 SJS/TEN cases identified an HLA-B allele that is associated with SJS/TEN

irrespective of drug. This HLA-B allele is present at 0.02% of the general Caucasian population (n = 9,237 not exposed to drug) but is found at 100-fold higher frequency among SJS/TEN cases (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). Interestingly, this association seems to be largely limited to Italian patients. Replication in Italian patients will be challenging given the rarity of SJS/TEN and new patients will need to be recruited for this analysis.

Drug-specific analysis in the ITCH cohort has also led to replication of HLA allele associations that have been previously identified in other populations. For instance, in 13 European patients with allopurinol-induced SCAR of whom 9 had SJS, HLA-B*58:01 was identified at a genomewide significance level with an odds ratio of 36. Although the association of HLA-B*58:01 with SJS was just below genomewide significance in this population, the odds ratio was higher at 45 (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). This is consistent with previous data that suggest that HLA-B*58:01 is present in approximately 60% of allopurinol patients of European ancestry with SJS/TEN.

The ITCH network also includes African recruitment sites. Work in this cohort has identified the association of HLA-C*04:01 carriage and SJS/TEN secondary to the antiretroviral drug nevirapine. Further analysis of the interaction of HLA-C*04:01 with the *endoplasmic reticulum aminopeptidase* genes that influence peptide processing showed that *endoplasmic reticulum aminopeptidase 2* may have a potentially protective effect.[12]

The RegiSCAR Network and sample repository

The RegiSCAR project was born out of experience with multiple epidemiological studies on SCAR that have been undertaken in Europe during the past 3 decades. Early studies included large retrospective case compilations performed in the 1980s and published in the early 1990s, followed by a large case-control study that provided the best available evidence for drug causality at the time (SCAR study).[13-15] In parallel, a population-based registry on SJS/TEN was started in Germany to assess disease incidence and demography, using the same criteria for case validation and ascertaining medication history.[16] Later, a second case-control surveillance (EuroSCAR study, 1997-2001) was undertaken that could confirm results on drug risk of the previous study and provide new data on recently marketed drugs.[17-20] These studies were followed by a multinational registry (RegiSCAR study) that was founded to systematically collect biological samples of patients with SCAR and patients were followed longitudinally after hospital discharge.[20-23] These studies required that investigators establish and maintain a network of hospitals and departments likely to treat SCAR, determine precise definitions of clinical entities (phenotypes), and determine methods for systematic case ascertainment, standardized case validation, and data management and statistical analysis. Case ascertainment was done by trained investigators (health care professionals) using a standardized questionnaire in direct conversation with the patient and in cases of severe illness, the patient's relatives, treating physicians, family physician, and medical records.

The RegiSCAR project is a registry of SCAR cases in several European and non-European countries that combines a protocol for systematic blood sampling and centralized biobanking of PBMCs, plasma, and DNA and cohort studies investigating outcome, sequelae, and treatment.[20,21] Earlier studies focused on SJS/TEN, whereas RegiSCAR includes a broader spectrum of reactions including drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and generalized bullous fixed drug eruption (GBFDE). Continuous surveillance of SJS/TEN in this cohort shows that approximately 67% of strictly validated cases had a probable or very probable drug cause as determined by the algorithm for assessment of drug causality in epidermal necrolysis score (Table II ; M. Mockenhaupt, MD, unpublished data, March 2017), 20% were secondary to a possible drug cause, and 13% were unlikely or not at all drug-induced. Genetic studies of SJS/TEN in European cases in the RegiSCAR cohort have led to the identification of risk alleles differing from other ethnic groups and genomewide association study analysis demonstrated that the HLA region on chromosome 6 is of major importance.[22,23] A RegiSCAR cohort study of several hundred patients with SJS/TEN revealed that the vast majority of survivors are left with sequelae persisting over months and years.

Thai-SCAR and the Southeast Asian Pharmacogenomics Research Network

In Thailand and other parts of Southeast Asia drugs that commonly cause SCAR have been marketed since 1980, an era of less socioeconomic development and limited clinical research capacity in the region, and this resulted in a lack of pharmacovigilance and an increase in SCAR incidence during this time frame. In 1984, Thailand developed Thai VigiBase, a database and spontaneous reporting system for SJS/TEN and other serious ADRs administered by the Thailand Food and Drug Administration. Thai VigiBase receives approximately 50,000 reports each year of which approximately 20% are serious immune-mediated ADRs and 70.4% of these cases are SJS/TEN. Using this resource, multiple predictive genomic markers that may be used to identify patients at elevated risk for the most common drug-specific SJS/TEN in the Thai population were discovered by the international collaborative research team. For example, HLA-B*15:02 and HLA-B*58:01 are common alleles among Southeast Asian populations and are strongly associated with carbamazepine- and allopurinol-induced SJS/TEN, respectively.[26-30] In Thailand, the Ramathibodi Hospital in Bangkok has effectively incorporated pharmacogenomics practice into health care settings through the use of preprescription genetic testing that has been reimbursed by the Thai universal health coverage scheme since 2014 (cost per test equates to 985.7 Thai baht or ~US $30 per patient). As a result of the proactive approach, the incidence of SJS/TEN has decreased sharply and the country is now working to eradicate SJS/TEN and the associated morbidity and mortality (Figure 2). Thailand and other Southeast Asian countries have further organized a collaborative approach to overcoming genetically mediated SJS/TEN by forming the Southeast Asian Pharmacogenomic Network that includes 10 nations and approximately 560 million Southeast Asians. The mission of this network is for these countries to work together to collaborate on sustainable pharmacogenomic research among regions with similar genetic backgrounds that will lead to further discovery and clinical translation. There is a critical need to identify and determine the population frequencies of genetic variants and implement

TABLE II. The algorithm for assessment of drug causality in epidermal necrolysis score (ALDEN)

Criterion	Values	Rules to apply	Score
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 d	−3 to 3
	Compatible +2	From 29 to 56 d	
	Likely +1	From 1 to 4 d	
	Unlikely −1	>56 d	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 2 to 4 d Likely: +1: from 5 to 56 d	
Drug present in the body on the index day	Definite 0	Drug continued up to the index day or stopped at a time point less than 5 times the elimination half-life* before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point before the index day by more than 5 times the elimination half-life* but liver or kidney function alterations or suspected drug interactions† are present	
	Excluded −3	Drug stopped at a time point before the index day by more than 5 times the elimination half-life,* without liver or kidney function alterations or suspected drug interactions†	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar‡ drug or other reaction with the same drug	
	Positive unspecific: 1	Other reaction after use of similar‡ drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case-control studies§	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies§	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study with sufficient number of exposed controls‡	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest in intermediate score	−1
		If at least 1 has an intermediate score of >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

NSAID, Nonsteroidal anti-inflammatory drug.
<0, Very unlikely; 0-1, unlikely; 2-3, possible; 4-5, probable; >6, very probable.
This table is reprinted with permission from Sassolas et al.[24] The legend has been modified from the original text.
*Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks and in Sassolas et al[24]), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance.
†Suspected interaction was considered when more than 5 drugs were present in a patient's body at the same time.
‡Similar drug = same ATC (anatomical therapeutic chemical) code up to the fourth level (chemical subgroups[25]); see Sassolas et al[24] for methods.
§See Mockenhaupt et al[18] for definitions of "high risk," "lower risk," and "no evidence of association." "High-risk" drugs include sulfamethoxazole-trimethoprim, sulfonamide anti-infectives, allopurinol, carbamazepine, phenytoin, phenobarbital, oxicam-NSAIDs. "Lower risk" drugs include acetic acid NSAIDs, macrolides, quinolones, cephalosporins, tetracyclines, aminopenicillins. Drugs with "no evidence of association" with SJS/TEN include beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide diuretics, furosemide, propionic acid NSAIDs, sulfonylurea antidiabetics, insulin.

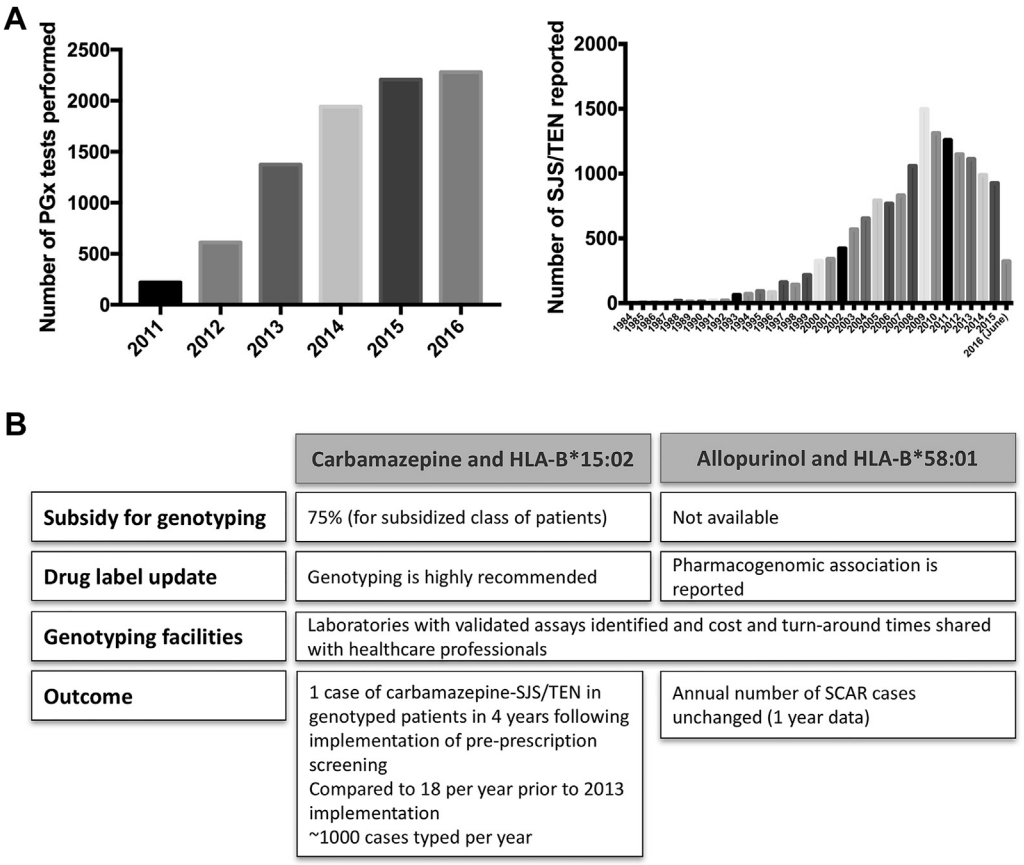

FIGURE 2. Pharmacogenomic testing to prevent SJS/TEN in Thailand and Singapore. **A**, Thai VigiBase and implementation. Following the incorporation of pharmacogenomics testing at Ramathibodi Hospital in Bangkok, Thailand, the number of pharmacogenomics tests performed rose from fewer than 500 in 2011 to more than 2,000 in 2015. Concurrently, with financial reimbursement supplied by the Thai universal health coverage scheme from 2014 onward, the number of reported cases of SJS/TEN collected through Thai-VigiBase fell, demonstrating the efficacy of genetic testing to prevent SJS/TEN in this population. **B**, Pharmacovigilance in Singapore. Carbamazepine and allopurinol are 2 of the most common causes of SCARs in Singapore and the risk alleles associated with carbamazepine- and allopurinol-SCARs (HLA-B*15:02 and HLA-B*58:01, respectively) occur at high frequency in the Singapore population. In 2013, the primary regulatory body in Singapore, the HSA, in conjunction with the Ministry of Health recommended HLA-B*15:02 genotyping before initiation of carbamazepine as standard of care for new patients of Asian ancestry. Following this recommendation, only 1 case of carbamazepine-associated SJS/TEN in 4 years has been reported, a marked reduction in incidence from the pretesting baseline of approximately 18 cases per year. For allopurinol, because of the low (2%) PPV of HLA-B*58:01 testing and lower efficacy or higher cost of alternative medications, genotyping was not recommended for routine standard of care for patients with chronic gout initiating drug therapy, although testing facilities were identified so that physicians have the option to conduct genotyping for high-risk patients such as those with renal impairment. *PGx*, Pharmacogenomics.

knowledge of genetic variation in pharmacogenomics in Thailand and other Southeast Asian populations to construct prescribing guidelines that will further facilitate SJS/TEN prevention.

The Japanese Research Committee on Severe Cutaneous Adverse Reactions

To date, no epidemiologic data of SJS/TEN have been reported in Japan, a population of 120 million. In Japan, drug-related adverse events are adjudicated by the Ministry of Health, Labor, and Welfare and patient medical costs are partially covered without revealing the localization of legal responsibility by the Japanese Post Marketing Adverse Event Relief System.[31] To investigate the epidemiology of SJS/TEN, the Japanese Research Committee on Severe Cutaneous Adverse Reactions collected a total of 370 cases (258 cases of SJS and 112 cases of TEN) using registration forms obtained from 2005 to 2007. The incidence of SJS/TEN per million per year is similar to that in other countries (3.1 for SJS, 1.3 for TEN, and 4.4 for SJS/TEN combined), with a relative SJS-to-TEN ratio of 2.3:1. Incidence was highest among Japanese individuals in the seventh decade of life (23.3% of all SJS cases, 19.8% of all TEN cases occurring among persons ages 60-69 years), and there was no obvious sex bias observed. The mortality rates for SJS and TEN were 3% and 19%, respectively. The rates of mortality and short- or long-term sequelae were significantly higher for TEN than for SJS (mortality $P = 4.39 \times 10^{-7}$; sequelae $P = 1.04 \times 10^{-8}$,

chi-square test). The most frequently suspected agents were antibiotics (16.3% for SJS and 19.5% for TEN), nonsteroidal anti-inflammatory drugs (14.6% for SJS and 16.8% for TEN), and anticonvulsants (14% for SJS and 9.9% for TEN). The period from the start of anticonvulsant treatment to the onset of the rash was significantly longer than that of antibiotics or nonsteroidal anti-inflammatory drugs (onset of 70%-80% of cases was 4 weeks for anticonvulsants and 2 weeks for antibiotics and nonsteroidal anti-inflammatory drugs). Eye involvement was documented in 26% of SJS cases and 77% of patients with TEN, and mucous membrane involvement was significantly more frequent in TEN than in SJS.[32]

Variants in pharmacogenes associated with carbamazepine and allopurinol SJS/TEN in the Japanese population were also examined in this study. HLA-B*15:02, the risk allele most commonly associated with carbamazepine-SCAR in South East Asians, was not identified among 61 patients with SCAR, whereas HLA-B*15:11, which, along with HLA-B*15:02, belongs to the B75 serotype, was recognized in 4 of 14 patients with carbamazepine-SCAR.[33] In contrast and in keeping with previously published data from Japanese and Europeans, HLA-A*31:01 was present in 45 of 77 patients with carbamazepine-induced SCAR, including 21 of 36 patients with drug reaction and eosinophilia and systemic symptoms and 5 of 6 patients with SJS/TEN, relative to 54 of 420 carbamazepine-tolerant controls (odds ratio [OR], 10.8; $P = 3.64 \times 10^{-15}$).[34] Regarding allopurinol, HLA-B*58:01 was found in 10 of 18 patients with SCAR (OR, 62.8; $P = 5.39 \times 10^{-12}$).

SPECIAL POPULATIONS AND CONSIDERATIONS*

Key Points:

- SJS/TEN survivors frequently suffer from psychological complications and decreased health-related quality of life. Prompt recognition and treatment is needed to address the psychological sequelae of SJS/TEN.
- Drugs that are commonly suspected to cause SJS/TEN in children are similar to causative drugs in adults although non−drug-related diseases that mimic SJS/TEN such as erythema multiforme majus (EMM) are common, making diagnosis challenging. SJS/TEN mortality is low in children compared with adults.
- The risk of developing SJS/TEN and particularly drug-related SJS/TEN is significantly higher among the elderly and short- and long-term morbidity and mortality are higher as compared with younger adults.
- Pregnant women and especially HIV and/or HIV-TB coinfected pregnant women are at risk to receive drugs that more commonly cause SJS/TEN. Available data demonstrate that maternal SJS/TEN does not transmit to the fetus. However, maternal SJS/TEN is associated with higher than expected intrauterine death and sequelae may affect future reproductive capacity.

Session 2 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* focused on SJS/TEN in special populations including survivors, the young, the elderly, pregnant females, and individuals with infectious comorbidities.

Psychological complications and quality of life in SJS/TEN

Long-term psychological sequelae, posttraumatic stress disorder (PTSD), and fear of taking drugs in the future are important morbidities associated with SJS/TEN.[35-37] Two studies that explored patients' perspectives of surviving SJS/TEN found that ADRs had a persisting impact on survivors' lives physically and psychologically long after the event.[38,39] Survivors of drug reaction with eosinophilia and systemic symptoms were found to suffer from psychological symptoms of anxiety, depression, and PTSD.[40]

A recent study characterized the psychological complications and health-related quality of life of SJS/TEN survivors treated at a tertiary care burn center.[37] The Toronto study was conducted between 1995 and 2015 and included 17 adults (≥18 years) with biopsy-proven SJS/TEN at a mean of 51.6 ± 74.7 months (median, 9 months; range, 1-228 months) following acute disease who were capable of participating in follow-up and answering questionnaires. Participants were assessed by validated emotional and health-related quality-of-life questionnaires.[41-46] Participants were also evaluated by a health-related quality-of-life questionnaire specially designed for this study and by a medical interview conducted with a structured detailed questionnaire. Eleven out of 17 (65%) were found to have symptoms of PTSD (Impact of Events Scale-Revised, mean = 22.4 ± 19.9) and 5 (29%) met the criteria for PTSD. Twelve (71%) had psychological distress (General Health Questionnaire, mean total score = 4.6 ± 4.2) and 11 (65%) had symptoms of a psychiatric clinical disorder (Hospital Anxiety and Depression Scale, mean total score = 14.5 ± 8.4). History of past psychiatric disorder was not significantly associated with scores in the psychological assessment questionnaires. The dermatology quality-of-life index indicated a moderate to extremely large effect on the lives of 9 (53%) participants (mean total score, 6.9 ± 7.6). Skindex-29 indicated a mild to severe effect on health-related quality of life in 10 (59%) participants (mean, 24.6 ± 21.5). Participants rated their general health at a mean of 66.2/100 ± 18.1 (EuroQol five-dimensional questionnaire Visual analogue scale).[37] Fourteen out of 17 (82%) participants reported that SJS/TEN decreased their current quality of life, 12 (71%) reported that SJS/TEN influenced their current emotional status, and only 29% were employed following SJS/TEN. Participants wrote statements in the open text area, expressing their perspectives: "I have difficulty coping with stress and anxiety," "My emotions are out of whack. It is so easy to be introverted but that makes me depressed, so I keep a journal to record my thoughts and emotions," "The first years of my recovery were very agonizing and very depressing." Despite most survivors having psychological complications, only 4 were assessed by a mental health professional during the period following SJS/TEN.[37]

The high burden of psychological sequelae and impact of SJS/TEN on health-related quality of life suggest that all patients and their families should be offered psychological support during hospitalization, before discharge, and throughout follow-up, and should be offered contact with a support group. Several

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support groups have been established in different countries (see Box I).

SJS/TEN in children

Estimating the true incidence of SJS/TEN is hampered by the fact that non−drug-related diseases such as EMM may be confused with SJS/TEN, particularly in children. The skin lesions in EMM are often targetoid in appearance with central dusky or blistering skin surrounded by erythematous inflammation and an outer ring of pale edematous skin (Table I).[47] In children a high percentage of SJS/TEN may be non−drug-related and infectious causes are associated in up to 30%. *Mycoplasma pneumoniae* and herpes simplex virus have been associated with EMM in children. In the case of *Mycoplasma pneumoniae*, a distinct syndrome called *Mycoplasma*-induced rash and mucositis (MIRM) has recently been defined.[48-50]MIRM, which may represent an atypical form of EMM, can result in severe mucosal involvement. MIRM differs from typical SJS/TEN because of sparse cutaneous involvement. In addition, Mycoplasma-associated disease tends to affect younger patients and is not commonly associated with long-term complications. However, recurrence of mucosal and skin lesions has been observed.

Drugs that are commonly suspected to cause SJS/TEN in children are similar to drugs in adults and include sulfa antimicrobials and aromatic anticonvulsants (phenobarbital, carbamazepine, phenytoin, and lamotrigine).[51,52] Overall mortality is lower in children with SJS/TEN compared with adults,[53] suggesting that algorithms used in adults to predict SJS/TEN mortality are not applicable to children and the existing models that predict outcomes need to be modified or redesigned for pediatric patients.[54]

Children with SJS/TEN require high-acuity hospital care, and up to 50% have long-term sequelae including blindness, which can occur many years after the initial acute SJS/TEN episode. Ophthalmologic disease may impact children less frequently and preferentially affect those children with more severe disease: 100% of children with TEN had evidence of ocular involvement.[55] Ophthalmologic conditions were more common among children with concurrent infectious diseases than among children with noninfectious diseases, with the highest proportion seen among those with MIRM.[56] Because both short- and long-term ophthalmologic complications can occur in children with SJS/TEN, involvement of a pediatric ophthalmologist should occur early upon diagnosis. In children, recurrence of SJS is well reported, occurring in up to 20% of cases.[51]

In summary, compared with adults, children have lower rates of mortality, but their survival comes with high rates of long-term complications. Further work is needed to define SJS/TEN in children and determine the most optimal treatment strategies.

SJS/TEN in the elderly

The incidence of drug-associated SJS/TEN in patients older than 64 years is twice as high when compared with that in patients aged 20 to 64 years (9.4 per 10^6 vs 4.6 per 10^6 person-years).[57] Whether this is due to polypharmacy or other age-associated factors is unclear. Older adults also appear to be at a greater risk of a cutaneous disease similar to SJS or TEN, referred to as GBFDE. The skin lesions seen in GBFDE appear very similar to those of SJS/TEN, consisting of large erythematous, often violaceous patches with overlying fluid-filled bullae, but GBFDE is typically considered less severe than SJS/TEN because constitutional symptoms are absent and lesions are well demarcated and usually limited to the skin without mucosal involvement (Table I).[58] Despite its more benign presentation, GBFDE when associated with BSA involvement of more than 20% can be associated with mortality rates of more than 20%, which highlights the significance of cutaneous reactions in older adults.[58]

Advanced age is also a predictor of SJS/TEN mortality. Age more than 40 years is an independent risk factor for death in adults with SJS/TEN and mortality rates as high as 70% have been described in those older than 65 years.[1] Underlying diseases (eg, severe kidney or liver disease and malignancy) are also associated with higher rates of mortality from 90 days to 1 year following the SJS/TEN presentation.[21] Complications such as multiorgan failure, nosocomial infections, and septicemia may lead to death, even following initial healing of skin lesions. Sekula et al[21] found that 25% of patients with a serious comorbidity or who were older than 70 years who survived the first 3 months following a SJS/TEN diagnosis died during the subsequent 9 months.

As the older population continues to grow globally, the number of geriatric patients who develop SJS/TEN will also likely continue to increase. Given the paucity of data on therapeutic approaches to treat SJS/TEN in the geriatric population and the high rate of associated mortality among this group, further studies are needed to determine optimal treatment strategies and decrease the risk of death in both the short-term and long-term following a SJS/TEN diagnosis.

SJS/TEN in pregnancy and in HIV-infected pregnant women

SJS/TEN during pregnancy has potential consequences for both the mother and the fetus. There is limited epidemiological data on SJS/TEN in pregnant women and existing evidence is derived mainly from case reports. A review of published literature up to 2010 identified only 36 cases of SJS/TEN in pregnant women. The authors concluded that SJS/TEN mortality in pregnant women is lower than expected and this finding was likely attributable to younger age and lower SCORTEN among pregnant patients compared with other SJS/TEN cohorts.[59] Certain antiretroviral drugs are strongly associated with SJS/TEN and other IM-ADRs in certain genetic backgrounds (ie, nevirapine/HLA-C*04:01 SJS/TEN and abacavir/HLA-B*57:01 hypersensitivity syndrome).[60-64]

In the developing world, nevirapine is used to treat HIV-infected pregnant women. Studies that have examined mother-to-child transmission of HIV have documented cases of maternal SJS/TEN[59,65,66] and nevirapine has been identified as a causative drug in multiple cases (Figure 3).[67-69] However, since 2012, nevirapine has been replaced with efavirenz as the nonnucleoside reverse transcriptase inhibitor of choice for the prevention of mother-to-child HIV transmission (PMTCT) in South Africa. Between January 2013 and December 2015, the incidence rate of SJS/TEN in the same population dropped to 0 cases per year compared with 3.4 cases per year for the preceding 7 years.[68,69] Although an earlier case-control study of antiretroviral-associated SCAR suggested that pregnancy was independently associated with SCAR after controlling for nevirapine exposure,[68] these new data suggest that nevirapine might be associated with a higher incidence of SJS/TEN in

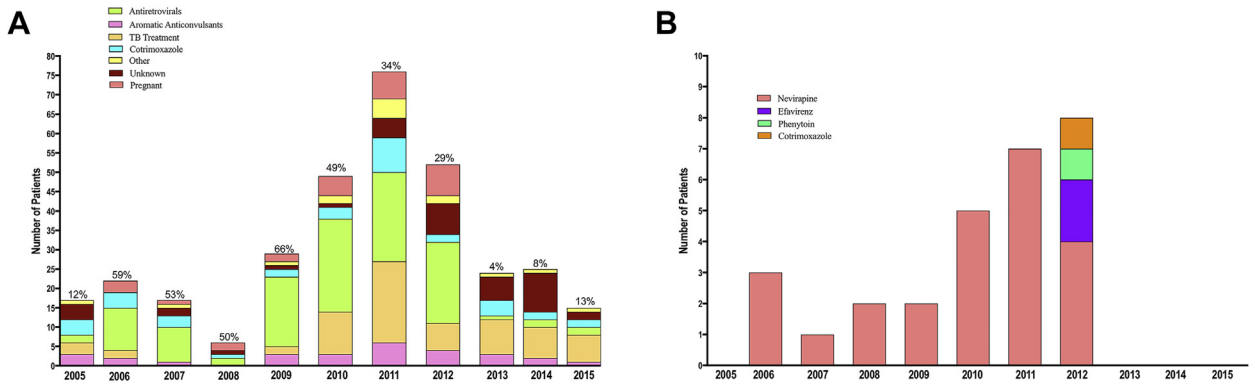

FIGURE 3. Epidemiology of SJS/TEN in special populations. **A**, All cases of SJS/TEN seen at Groote Schuur Hospital in South Africa between 2005 and 2015 showing the proportion of offending drugs. The proportion attributable to nevirapine for that year is shown as a percentage. **B**, All cases of pregnant women with SJS/TEN seen at Groote Schuur Hospital between 2005 and 2015 showing the proportion of offending drugs.

pregnancy but that pregnancy does not itself seem to predispose to SJS/TEN.[69] In a case series of HIV-infected women, no maternal deaths from SJS/TEN were seen during pregnancy, a finding that supports the findings by Struck et al that SJS/TEN mortality in pregnant women is lower than expected.[1,59,68-71]

Despite the observation that pregnant women with SJS/TEN have lower than expected mortality, fetal outcomes are worse, with higher than expected intrauterine death. Five of the 36 cases (14%) published by Struck et al delivered stillbirths and in a separate series of HIV-infected pregnant women this was 11%, higher than expected.[59,68,71] It remains uncertain whether maternal TEN, the more severe form of the disease, is associated with poorer fetal outcomes. Rarely, SJS/TEN can affect the fetus and there are 2 published cases of fetal SJS/TEN, one concurrently affecting the mother and the fetus and the other the fetus alone.[72,73] It may be difficult to differentiate between SJS/TEN and fetal maceration because maceration-associated desquamation starts within 6 hours of intrauterine death.[74] However, the finding of irregular purpuric macules in the case presented by Rodriguez et al[72] supported a diagnosis of SJS/TEN. The case published by Sweetnam et al[73] healed with keloidal scarring, an unusual feature in SJS/TEN in the absence of secondary infection, immobility, sustained pressure, or delayed reepithelialization.[75] Despite the extensive use of nevirapine in PMTCT, there are disproportionately few cases, if any, of neonatal SJS/TEN.[65] We can safely conclude that SJS/TEN rarely, if at all, affects newborns. In the context of PMTCT in HIV-infected mothers with SJS/TEN, concerns regarding the interruption of an antiretroviral causative drug and the potential risk of neonatal HIV infection have been evaluated in only a few instances. Most published reports on SJS/TEN in pregnant women, including those designed for PMTCT, do not address the risk of maternal HIV transmission to the fetus.[65,66] Reassuringly, in 12 children who had received PMTCT and were born to mothers with SJS/TEN during pregnancy, all were found to be HIV uninfected at 6 weeks following delivery.[68]

Consideration for the method of delivery in the current and subsequent pregnancies is important because long-term sequelae of genital mucositis in SJS/TEN, including structural changes secondary to adhesions, stenosis, hematocolpos, adenosis, and endometriosis, may impact future reproductive health and modes of delivery.[75] Both vaginal and cesarian section deliveries have been reported in the setting of past and current SJS/TEN.[59,68] The extent to which vaginal delivery is contraindicated is difficult to establish because of the rarity of SJS/TEN in pregnancy, the lack of a standardized case definition for genital disease, incomplete reporting of vaginal complications, and breadth and variability of indication for cesarian section based on hospital practice.[59,68] Awareness of sequelae and preventive strategies in acute SJS/TEN should reduce the incidence of vaginal fibrosis and consequently the number of cesarian sections performed.[68]

CLINICAL MANAGEMENT*

Key Points:

- Cessation of the implicated drug and intensive supportive care with early multidisciplinary involvement is key to the management of SJS/TEN.
- Up to 77% of patients with SJS/TEN have genitourinary involvement in the acute phase and of these up to 25% go on to have some form of chronic complications. Early genitourinary examination and acute management are likely to be key in avoiding chronic complications.
- Ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist if there is suspicion of SJS/TEN. Early interventions such as amniotic membrane transplantation (AMT) have been key to preventing long-term ocular morbidity. For patients who survive the acute phase, ocular complications are the most common and debilitating chronic sequelae and blindness can occur decades after the acute episode, which necessitates lifelong follow-up.

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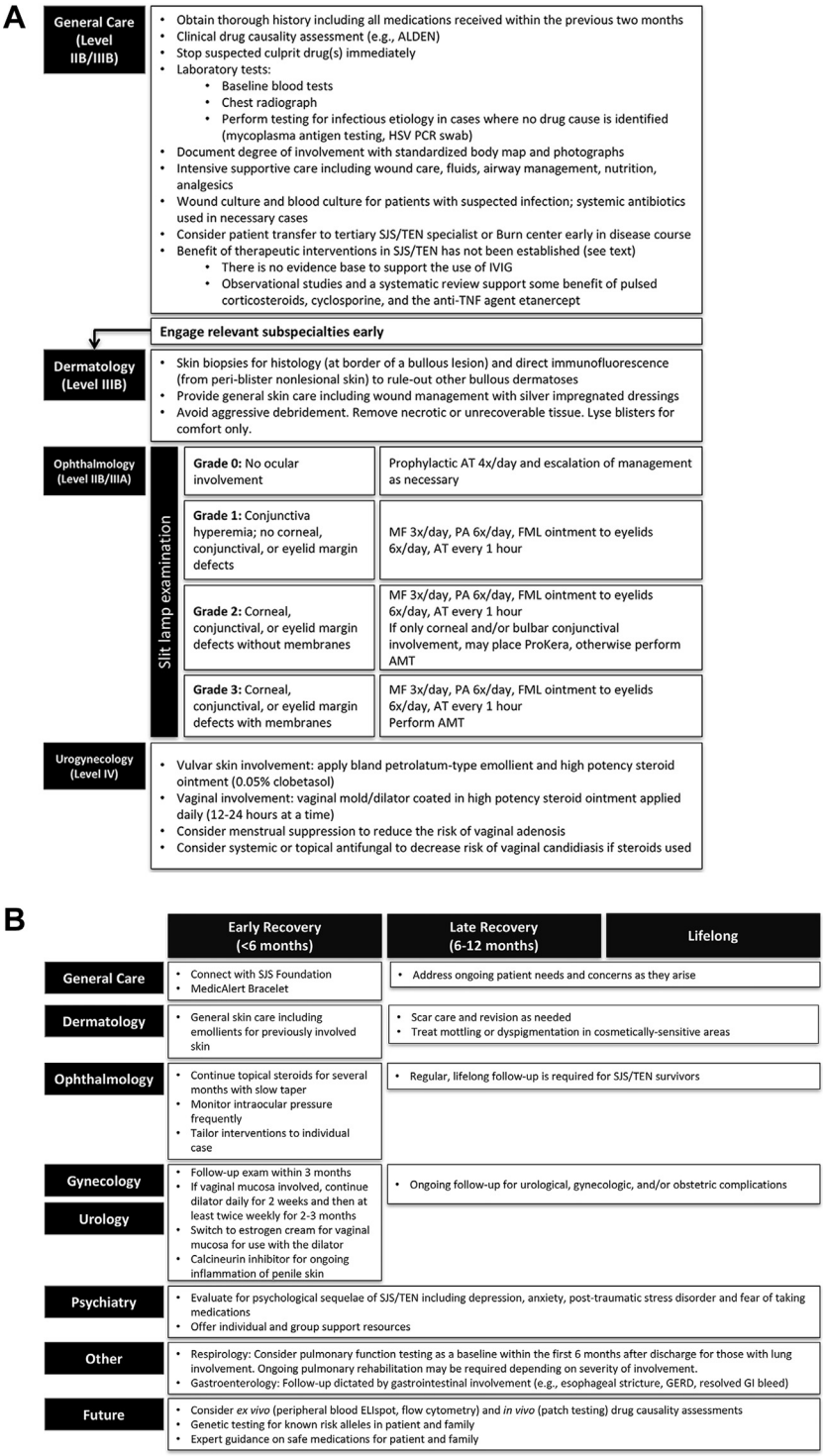

FIGURE 4. Suggested multidisciplinary approach to the management of (**A**) acute- and (**B**) recovery-phase SJS/TEN. Key points highlighted include the necessity to (1) recognize and stop the offending medication quickly, (2) provide care for SJS/TEN in a tertiary critical care center (most often a burn center), (3) consider all organ systems involved in SJS/TEN and consult relevant subspecialists early in the disease course, and (4) provide posthospital and long-term follow-up for patients to manage complications of SJS/TEN. *ALDEN*, Algorithm for assessment of drug causality in epidermal necrolysis; *AT*, artificial tears; *FML*, fluorometholone 0.1% ophthalmic ointment; *GERD*, gastroesophageal reflux disease; *GI*, gastrointestinal; *HSV*, herpes simplex virus; *MF*, moxifloxacin 0.5% ophthalmic solution; *PA*, prednisolone acetate 1% ophthalmic solution.

- Although IVIG has been widely applied, there is no evidence base to support its use.
- Improved evidence-based data to support specific clinical management and therapeutic intervention remains a priority need for SJS/TEN.

Although characterized by predominant epidermal and mucous membrane involvement, SJS/TEN is a multisystem disease. Session 3 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured discussion and expert recommendations from clinicians in dermatology, burn surgery and critical care medicine, ophthalmology, and gynecology. The state of current practices in the clinical management of SJS/TEN, unmet clinical research needs, and future directions were discussed (Figure 4).

Management and clinical guidelines

SJS/TEN causes both acute and chronic complications across a diverse group of patient populations.[76] Although early intervention is considered key to minimizing short- and long-term sequelae, international consensus and treatment guidelines for the management of SJS/TEN are lacking. A comprehensive, systematic review of the management of SJS/TEN in adults was undertaken in the United Kingdom in 2016 and included accreditation from the British Association of Dermatologists, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, and the National Institutes for Health and Care Excellence.[77,78] The most important initial step in the management of SJS/TEN is to immediately discontinue any potential culprit drug (Figure 4). In many cases, the culprit drug is obvious from the exposure timeline, but in some cases, several or no culprits may be apparent. Where many possible culprits exist, all suspected drugs need to be stopped and, if needed, a structurally disparate alternative therapy with low risk for cross-reactivity with the culprit drug should be initiated. Any drug that has been tolerated for more than 3 months can safely be continued. The algorithm for assessment of drug causality in epidermal necrolysis causality score (Table II), particularly designed and validated for SJS/TEN, is an important tool to help aid in the causality assessment of potential culprit drugs.[24] Other drug causality assessments have also recently been developed.[79] In the cases where no drug is suspected, then infection may be implicated and screening tests are indicated (eg, Mycoplasma PCR, Herpes simplex swab PCR, and Enterovirus PCR). Furthermore, it is important to consider that other dermatoses such as linear IgA disease, staphylococcal scalded skin syndrome, GBFDE, pemphigus vulgaris and other autoimmune bullous diseases, and graft-versus-host disease can sometimes be difficult to distinguish from SJS/TEN by clinical appearance. Therefore, skin biopsy for routine histology and direct immunofluorescence is an important tool. Despite the urgency of the acute care for SJS/TEN, immediate consideration of postrecovery morbidities such as those involving the eyes and genitourinary mucosa is critical. This requires early input from the relevant specialties (Figure 4).

Optimal therapeutic intervention in SJS/TEN is controversial. Since the first report of a small case series showing response to IVIG, interest in the role of this therapy has been maintained. Recent surveys confirm that many physicians who treat SJS/TEN continue to support its use.[6,80,81] One systematic analysis of the published literature of IVIG in SJS/TEN included 17 case series from different countries where comparison with supportive care alone could be made. Although the number of publications showing benefit was greater than those showing no benefit, comparison of the total number of patients reported demonstrated no benefit of IVIG.[19,80,82-96] In addition, methodological concerns exist because of evidence of duplicated cases, variable dosing, and combined treatment with corticosteroids in many of the published case series. Thus, the benefit of treatment of SJS/TEN with IVIG is uncertain. Although review of the literature shows no evidence of harm, overall, there is no convincing evidence of benefit.[77,78]

Treatment of SJS/TEN with corticosteroids (eg, prednisolone, methylprednisolone, and dexamethasone) versus supportive care was also examined systematically. Only 3 studies out of 10 showed benefit of this treatment and the number of cases treated in studies where no benefit was seen was again higher than in those showing benefit (273 vs 78).[19,89,97-104] One small case series not included in this review suggested that pulsed dexamethasone given at a dose of 1.5 mg/kg for 3 days was helpful when given near the time of disease onset.[100] The weight of this evidence is small in comparison to the larger systematic review. However, methodological criticisms highlighting poor case validation and variable dosing suggest that some caution in data interpretation is required. A separate recent meta-analysis of observational studies for immunomodulating therapies of SJS/TEN (including IVIG, pulsed dose corticosteroids, and cyclosporine) showed that corticosteroids were associated with a survival benefit in 3 different analyses (aggregated study data: OR, 0.5; 95% CI, 0.3-1.01; individual patient data unstratified: OR, 0.7; 95% CI, 0.5-0.97; individual patient data stratified: OR, 0.8; 95% CI, 0.4-1.3). Despite low patient numbers, cyclosporine was associated with a promising significant result in the feasible unstratified individual patient data analysis (OR, 0.1; 95% CI, 0.0-0.4). IVIG was not beneficial in this meta-analysis.[105]

The published evidence of cyclosporine treatment of SJS/TEN showed evidence of a therapeutic benefit in case series and an open-label phase II trial.[106-111] No deaths were reported in the trial and the arrest of disease progression as well as reepithelialization was hastened. The meta-analysis above[105] also showed both study and patient-level benefit. However, the overall sample sizes reported are low, represent single-center experiences, or lack control groups. Lack of case validation in the reported case series should create caution against overinterpreting the data. G-CSF and anti-TNF receptor antagonists also have some reasonable evidence to suggest further examination of these therapies for SJS/TEN but as yet, experience remains limited with these treatments.[112-115] A recent phase II randomized controlled trial showed benefit in mortality of the anti-TNF agent etanercept over steroids (relative risk reduction, 50% vs 20%) and reduction of time to reepithelialization in the etanercept group.[115] Thalidomide, which was trialed in the late-1990s because of its anti-TNF activity, is the only treatment to have undergone a placebo-controlled randomized controlled trial. This study, however, was stopped early because thalidomide was associated with higher day 2 plasma TNF concentrations and increased mortality.[116]

For all therapeutic interventions to date, the inevitable delay between the onset of the rash and interventional treatment caused by the time taken for transfer to specialist centers means

that early intervention has yet to be thoroughly examined. Cyclosporine and etanercept have shown benefit in their respective trials when initiated up to approximately 5 days after the onset of skin signs of disease.

Ocular involvement and management

Acute ocular involvement in SJS/TEN occurs in up to 100% of patients and ranges from conjunctival hyperemia to near-total sloughing of the ocular surface and eyelid margins.[117-120] Acute pathology can result in chronic complications including corneal epithelial stem cell deficiency and eyelid margin keratinization, which, in turn, lead to corneal neovascularization and opacity, persistent corneal epithelial defects, severe dry eye, and ultimately blindness. Blindness can also occur in the acute phase as a result of corneal perforation, largely a result of inadequate care. There is incomplete correlation between the severity of SJS/TEN illness and ocular complications and the degree of ocular involvement in SJS/TEN is highly variable.[118,119,121-123] Furthermore, the immunopathogenesis of how SJS/TEN affects the eye, which is an immune-privileged site, is also largely unknown. Literature from specific populations has supported potential associations between specific HLA class I alleles and ocular involvement.[124-128]

The single best predictor of chronic corneal complications is acute eyelid margin involvement. Acute eyelid margin deepithelialization and ulceration leads to eventual eyelid margin keratinization, which causes corneal disease through various mechanisms and a window of opportunity exists in the acute phase to mitigate the severity of eyelid margin disease through the use of AMT.[129-132] Early treatment is the key to management and this reduces the risk of blindness. Dissemination of this message is urgently needed because in the United States alone, only 66% of burn intensive care units routinely consult ophthalmology on patients with SJS/TEN during their hospital stay.[6]

The critical period for ophthalmological care is within 7 days of disease onset, beyond which a crucial window of opportunity for ocular intervention is lost, and irreversible damage can occur. Further challenges and constraints on this time window exist because of delays in diagnosis and hence delayed transfer of patients to an appropriate care environment. Further delays may be incurred by aspects of clinical management such as waiting for skin biopsy results or for clinical signs to fully manifest. Importantly, ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist even if there is any suspicion of SJS/TEN, while awaiting confirmation.

The ocular examination consists of examining the eyelid skin, eyelid margin, conjunctiva, and cornea, assessing for epithelial sloughing, defects, ulceration, and inflammation. The acute care involves the use of lubrication with artificial tears and ointments, topical antibiotics for infection prophylaxis, topical corticosteroids to control inflammation, and AMT in moderate to severe ocular disease to decrease inflammation, speed healing, and prevent keratinization.[120] The exact mechanism by which AMT improves outcomes is unknown. Treatment regimens depend on the severity of disease and can be found in Figure 4, *A*. Adjunct therapies are used on a case-by-case basis and include the use of bandage and scleral contact lenses for persistent epithelial defects of the cornea. Follow-up in the acute phase depends on the severity of ocular involvement, but at the very least, patients should be seen 24 to 48 hours after initial ophthalmologic examination because ocular involvement can progress quickly over time. Once acute disease has stabilized, follow-up can be tailored to the individual.

There is no defined protocol for the management of chronic ocular disease after hospital discharge, with few prospective studies and no randomized clinical studies. The consensus from experts in the field is that patients should be maintained on topical corticosteroids for several months, tapering slowly while monitoring the intraocular pressure. Close follow-up by an ophthalmologist is essential because new ocular signs can manifest over time, which also have limited windows during which interventions can be sight saving. These interventions include punctal occlusion, retinoic acid ointment to the eyelid margin, specialized scleral contact lenses, and oral mucous membrane grafting to the eyelids. End-stage disease may require a keratoprosthesis/artificial cornea for visual rehabilitation. A role for topical cyclosporine for the treatment of chronic dry eye following SJS/TEN may be limited by patient intolerance for the drug formulation.[133] Patients with SJS/TEN should be followed by an ophthalmologist for life because worsening symptoms and vision loss can occur decades after disease onset.

Genitourinary disease

The acute genitourinary manifestations of SJS/TEN in females include erosions and ulcerations of the vulva and vagina. These acute manifestations occur in up to 77% of patients and can lead to chronic complications in the form of vulvar adhesions and vaginal stenosis, resulting in hematocolpos, dyspareunia, chronic pain and bleeding, and difficulty conceiving.[68,134] Data are limited, but it is thought that urogynecological complications are common, and that they occur in up to 77% of female patients with SJS/TEN of which 9% to 25% of survivors go on to have chronic complications.[135,136] An additional complication is vaginal adenosis, where stratified squamous epithelium is replaced with columnar glandular epithelium.[137] Adenosis can increase the risk of vaginal malignancy. To prevent the complications above, all female patients should have a gynecologic examination at the time of admission for suspected SJS/TEN and should be followed closely in the early stages of SJS/TEN because mucosal disease can develop and spread rapidly. Any vulvar pathology should prompt an evaluation by a gynecologist for possible vaginal involvement.

Special patient categories in this respect include pediatric and pregnant patients. For the former, cooperation with examinations and treatments can be difficult and they may be deemed invasive. For the latter, decisions about mode and timing of delivery can be complicated by the presence of vaginal or vulvar erosions, abdominal skin pathology, or vaginal stenosis. In younger patients, evaluation may need to be done under sedation or anesthesia. General anesthesia may be difficult to accomplish in the acute phase when the patient is too unstable to be taken to the operating room. These determinations should be made on a case-by-case basis, taking patient cooperation and hospital resources into account. The goal of treatment in the acute phase is to decrease inflammation and prevent the development of adhesions. The following treatment recommendations are not all-inclusive and have not been proven through clinical trials but serve as a foundation for treatment as our understanding and study of gynecologic pathology in SJS/TEN grows.

Vulvar skin involvement can be treated with a bland petrolatum-type emollient. A high-potency steroid ointment, such as 0.05% clobetasol, can also be used to decrease inflammation and discomfort. If increased irritation occurs with such products, emollients alone should be used. Consider decreasing the frequency of steroid use after initial treatment.[138] Vaginal disease should be treated with twice-daily use of a soft, small vaginal mold/dilator or a tampon/roll of gauze covered with a nonlubricated condom. The device should be coated in high-potency steroid ointment before it is applied. This intervention is to provide anti-inflammatory treatment to the mucosa and to physically separate the mucosa to prevent adhesions, rather than to dilate the vagina, and the device should just be large enough to accomplish these ends. The vaginal mold can be left in place for 12 to 24 hours at a time, but should be removed at least once daily for cleaning of the device with soap and water and for application of additional anti-inflammatory medication. Even for those patients without visible disease, prophylactic treatment as above should be considered for several hours a day.

Patients uncomfortable with using a vaginal dilator/mold, particularly pediatric patients, can apply medication twice daily with a vaginal applicator. Even for virginal and/or pediatric patients, use of a small mold or a condom-covered tampon should be encouraged if the patient is emotionally and physically comfortable with the regimen. Other general considerations include menstrual suppression to reduce discomfort and to possibly decrease the risk of vaginal adenosis. Systemic and/or topical antifungal medication may be considered to decrease the risk of vaginal candidiasis in the setting of vaginal steroid use. The medication on the dilator can be changed to, or alternated with, estrogen cream to help promote healing of the vaginal mucosa. Lidocaine 5% ointment can also be used at the vaginal introitus, once open sores have healed, to reduce discomfort with the use of vaginal dilators. In pregnant women, usual obstetric care should continue and decisions about delivery made in consultation with the obstetrical team.

As with complications associated with SJS/TEN, outpatient follow-up after discharge from the hospital is essential. All patients should be scheduled for follow-up with a gynecologist within 3 months of discharge. Patients who had active vaginal disease in the acute phase should continue to use a dilator at least 2 times a week for 2 to 3 months after discharge.

Additional acute and recovery management of respiratory and gastrointestinal complications in SJS/TEN may be required as outlined in Figure 4. Although limited data suggest that urologic manifestations are common in SJS/TEN, aside from acute supportive measures and catheterization, there is limited research in this area and currently no clear guidelines or expert consensus on the management of acute urethral involvement or long-term urethral complications.[139] This represents an important area of future work in the field.

Clinical management summary

Rapid withdrawal of the culprit drug and intensive supportive care from a multidisciplinary team is the central priority in the management of acute SJS/TEN. There is no conclusive evidence that IVIG or corticosteroids are harmful or beneficial in the context of SJS/TEN. Smaller studies have shown some benefit, but the weight of evidence does not currently support their use. It may be that initiation of therapy close to the time of skin signs is needed with loss of efficacy within a few days. Although accumulating evidence exists for the use of cyclosporine and other immunomodulatory therapies such as etanercept from small studies and now phase II trials, sufficient experience with these treatments to recommend their use is lacking. In addition, it is currently unknown whether patients would present early enough at most centers for these treatments to be beneficial. Regardless of therapeutic intervention, there should be efforts to move toward a harmonized strategy of aggressive supportive care. Multidisciplinary collaboration is required in the acute care setting and in follow-up to identify and manage potential chronic sequelae early.

PHARMACOVIGILANCE AND THE ELECTRONIC HEALTH RECORD*

Key Points:

- The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a database of spontaneous adverse event reports, is the primary tool used by the FDA to detect safety signals of SJS/TEN in the postmarketing setting.
- The Singapore Health Sciences Authority (HSA) has evaluated 2 common (~15%-20% carriage) HLA allele-drug pairs associated with SJS/TEN:
  - Genotyping for HLA-B*15:02 for new users of carbamazepine in patients of Southeast Asian descent/ethnicity became a diagnostic standard in 2013 and widespread screening has reduced the number of associated cases of SJS/TEN from approximately 18 per year to 1 case in the 4 years since implementation.
  - Genotyping for HLA-B*58:01 for new users of allopurinol was not mandated because of lower efficacy or higher costs of alternative gout medications. However, clinicians were notified of a laboratory where testing was available.
- Mining electronic health records (EHRs) can reliably identify common disease phenotypes for genomic studies. Rare drug adverse events have also been successfully studied using this technique.
  - 12% of general medicine patients in a large EHR were exposed to 1 of 5 SJS/TEN-associated drugs. Combining this information with genetic data could be used to prevent SJS/TEN in persons at high risk.

Session 4 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* centered on pharmacosurveillance mechanisms and sources of large data sets and bioinformatic methods for the detection and validation of SJS/TEN cases and predictors of risk.

Regulatory science and pharmacosurveillance: US Food and Drug Administration

The FDA's Division of Pharmacovigilance uses a number of tools and processes for the detection and evaluation of safety signals for SJS/TEN.[140] The FAERS is the primary tool used in the postmarketing setting (Figure 5). FAERS is a database of spontaneous adverse event reports that supports FDA's postmarketing surveillance program for drugs and therapeutic

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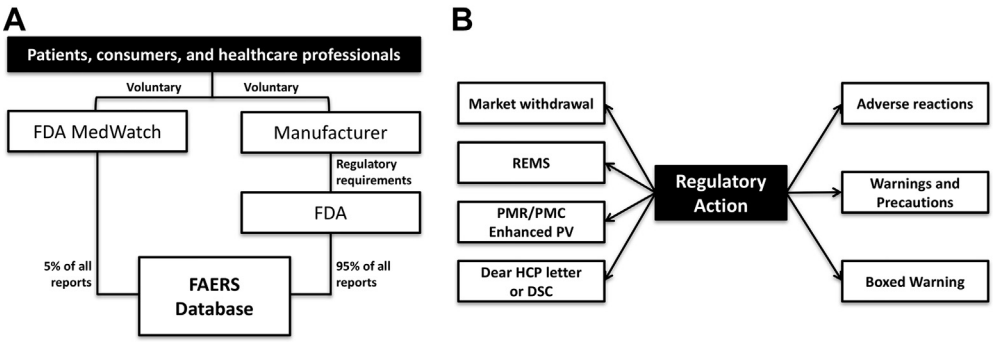

FIGURE 5. Regulatory mechanisms in the United States. **A**, The FAERS is a spontaneous adverse event reporting database that is the primary tool used for the detection of safety signals by the FDA. Reports are generated on a voluntary basis by patients, consumers, and health care providers. Reports may be submitted to the FAERS either directly by the consumer through the FDA MedWatch event reporting system or by drug manufacturers as determined by regulatory requirements. **B**, When a safety signal is identified, there are a number of possible regulatory actions that may be issued by the FDA. Regulatory actions highlighted in blue represent options for drug label modifications to reflect the adverse event. Drug-associated SJS/TEN is most often reported in the *Warnings and Precautions* section but may also appear as a *Boxed Warning* or in the *Postmarketing Experience* section of the drug label. Other potential regulatory actions are highlighted in green. These include (1) manufacturer issuance of a Dear Healthcare Professional (HCP) letter or a Drug Safety Communication (DSC), (2) use of postmarketing requirements (PMRs) or postmarketing commitments (PMCs) to further evaluate the event, (3) use of risk evaluation and mitigation strategies (REMS) to manage risk while enabling continued access to the drug, and (4) drug withdrawal. *DSC*, Drug safety communication; *FAERS*, Food and Drug Administration adverse event reporting system; *HCP*, healthcare professional; *PMC*, postmarketing commitments; *PMR*, postmarketing requirements; *PV*, pharmacovigilance; *REMS*, risk evaluation and mitigation strategies.

biologics. The data files, which are updated quarterly, can be downloaded from the FDA's Web site,[141] and individual case safety reports can be requested by submitting a Freedom of Information Act request. Adverse event reports can be submitted to the FDA from the Web site, or through MedWatcher, a free mobile application. Case reports for SJS/TEN should include patient characteristics such as age, sex, medical history, and all descriptors of the event including diagnostic information and the time to onset of symptoms from initiation of drug therapy to onset of disease should also be included. A comprehensive list of drugs including concomitant and recently discontinued products, including over-the-counter products and supplements, and time of initiation should also be included. The specific action taken for the suspect and concomitant products (continuation, discontinuation) should be reported. The reporter contact information should be included and if significant additional information becomes available after a report has been submitted, a follow-up report should be considered.

Adverse events that are reported to a drug manufacturer are required to be submitted to the FDA within 15 days of receipt if they are serious and unexpected by regulatory definition. Relevant to SJS/TEN, serious adverse events are defined as those that result in death, are life-threatening, result in initial or prolonged hospitalization, are associated with persistent or significant disability or incapacity, congenital anomalies, or other serious events. Expectedness is based on what currently appears in the FDA-approved labeling for that product. Events that are serious and expected as well as nonserious events can be submitted to the FDA on a quarterly basis for the first 3 years after product approval, and then annually.

Health care professionals review incoming FAERS reports. These safety reviewers receive a list of incoming reports for SJS, TEN, and other selected serious adverse events to ensure that those reports are prioritized. They use case definitions and causality assessment tailored to spontaneous reports to evaluate potential safety signals. Examples of regulatory actions that may be taken when a safety signal is identified include (1) updating the product labeling, (2) issuing a Drug Safety Communication, (3) postmarketing requirements or commitments to evaluate the event, (4) implementing risk evaluation and mitigation strategies to manage serious risks while enabling patients to have continued access to the product, or (5) market withdrawal (Figure 5).

In addition to FAERS, safety reviewers use VigiBase, a global database of adverse event reports maintained by the World Health Organization-Uppsala Monitoring Centre. Data mining in FAERS and VigiBase can be used to identify events that are disproportionately reported for a drug. Reports for the event are then reviewed to determine whether there is a potential safety signal. The medical literature is another important data stream because some published cases may not have been previously reported to regulatory authorities or manufacturers. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance database is another useful resource. It uses trained abstractors to collect data on adverse drug events diagnosed and treated in a nationally representative sample of emergency departments.

Postmarketing pharmacoepidemiology studies using prospective data collection, such as registries, can be useful in providing specific patient information, such as genetic information and ethnicity. Important limitations include underascertainment of cases and the need for large numbers of enrolled patients to identify rare events. Pharmacoepidemiology studies involving retrospective data collection, for example, from large administrative databases, have the advantage of providing large numbers of patients with

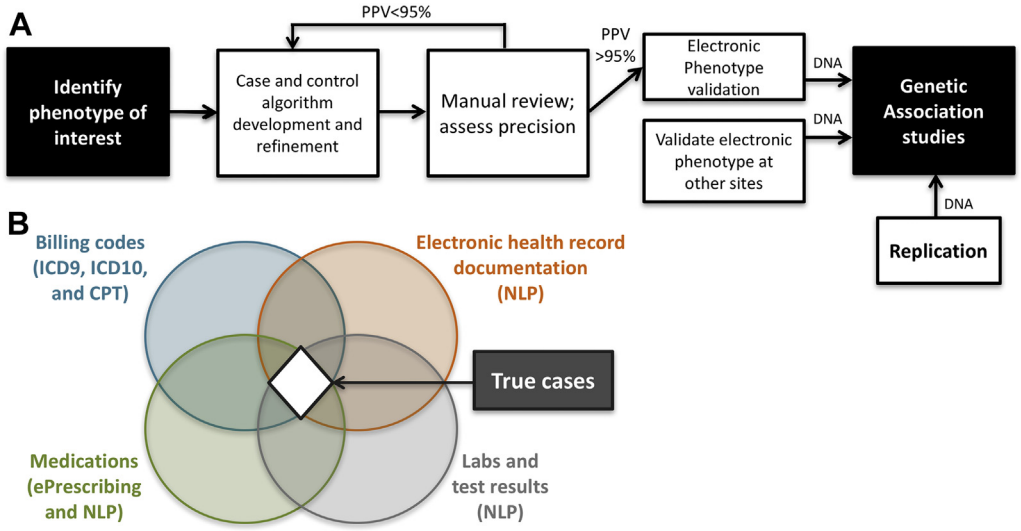

FIGURE 6. Use of EHR data to identify rare disease cases and for the discovery of genetic associations. **A**, For a phenotype of interest, an iterative algorithm incorporating multiple aspects of patient data is developed and validated to identify cases in the medical record. The predictive algorithm is deployed at the test site and replicated across additional sites. Identification of allelic variants associated with the phenotype of interest is achieved using genetic analysis of biobanked DNA linked to the research EHR. **B**, A predictive algorithm with high PPV relies on the incorporation of multiple forms of patient data including billing codes, medication history, clinic notes, and laboratory and test results. *CPT*, Current Procedural Terminology; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *NLP*, Natural language processing.

longitudinal follow-up in "real-world" settings, but cases may not be captured by billing codes alone and there may be incomplete capture of certain information such as ethnicity.

Finally, Sentinel is an active surveillance system sponsored by the FDA that uses administrative and claims data. The Active Risk Identification and Analysis System is a component of Sentinel comprising predefined analytic tools that enable rapid querying of the database.[142] Although evaluating SJS/TEN in Sentinel would be challenging at this time, research is ongoing.

In summary, FAERS is the primary tool used by the Division of Pharmacovigilance for the detection of safety signals for SJS/TEN and submission of high-quality reports by health care providers is essential. Supplementary tools include VigiBase, data mining, the medical literature, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance, pharmacoepidemiologic studies, and Sentinel/Active Risk Identification and Analysis.

Finding rare diseases such as SJS/TEN in the EHR

EHR data have proven to be an effective and efficient resource for studying common diseases and drug response phenotypes (eg, drug efficacy or adverse drug responses). The genetic basis for hundreds of diseases has been uncovered, including replicating many known, expected genetic associations.[143,144] However, finding these diseases in the EHR is not a trivial effort. EHRs represent a longitudinal record of diseases with records generated for various purposes along the course of illness.[145,146] Thus, they can contain inaccurate data.[147] Accurate disease phenotypes typically require some combination of multiple types of EHR data including billing codes, laboratory data, medications prescribed to the patient, and narrative data such as in clinical reports (Figure 6).[145] Algorithms leveraging scores, Boolean logic, natural language processing, and machine learning approaches typically produce reliable algorithms.[148] These algorithms typically are usually developed with clinical experts working in concert with biomedical informaticians. Several example algorithms were presented, including autoimmune hypothyroidism[149] (as an example of one of many disease phenotypes) and 2 drug adverse events phenotypes, angiotensin-converting enzyme inhibitor—associated cough[150] and heparin-induced thrombocytopenia,[151] for which significant novel genetic associations were discovered using EHR data. The latter example demonstrates the potential for using EHRs for rare drug adverse events, such as SJS/TEN.

In a recent study of 12 research units and managed care organizations in the United States covering almost 60 million lives, electronic medical record databases were used to identify potential cases of SJS/TEN using *International Classification of Diseases* (*ICD*), *Ninth Revision* codes. Medical records were abstracted and standardized criteria applied by board-certified dermatologists to adjudicate diagnoses. Multivariate models were developed to identify factors independently associated with validated SJS/TEN case status. The likelihood of case status increased with the length of hospitalization and with the use of new *ICD* codes specific to SJS/TEN. The positive predictive value (PPV) of *International Classification of Diseases, Ninth Revision* codes 695.12 to 695.15 was 50% among hospitalized cases. Among patients hospitalized for 3 or more days, the PPV of these codes was even higher, and ranged from 57% to 92%. These results suggest that case finding using EHR data can be carried out using a combination of search codes and search terms.[152]

At Vanderbilt, manual chart reviews were used to investigate the potential identification of SJS/TEN in the EHR (Figure 6) including before 2008 when specific SJS/TEN billing codes, an important part of most algorithms, did not exist. Preliminary data suggest that SJS/TEN-specific *ICD* codes have a PPV of around 29%. Use of drug-specific *ICD* codes in combination with SJS/TEN or the more general erythema multiforme codes improve performance, increasing

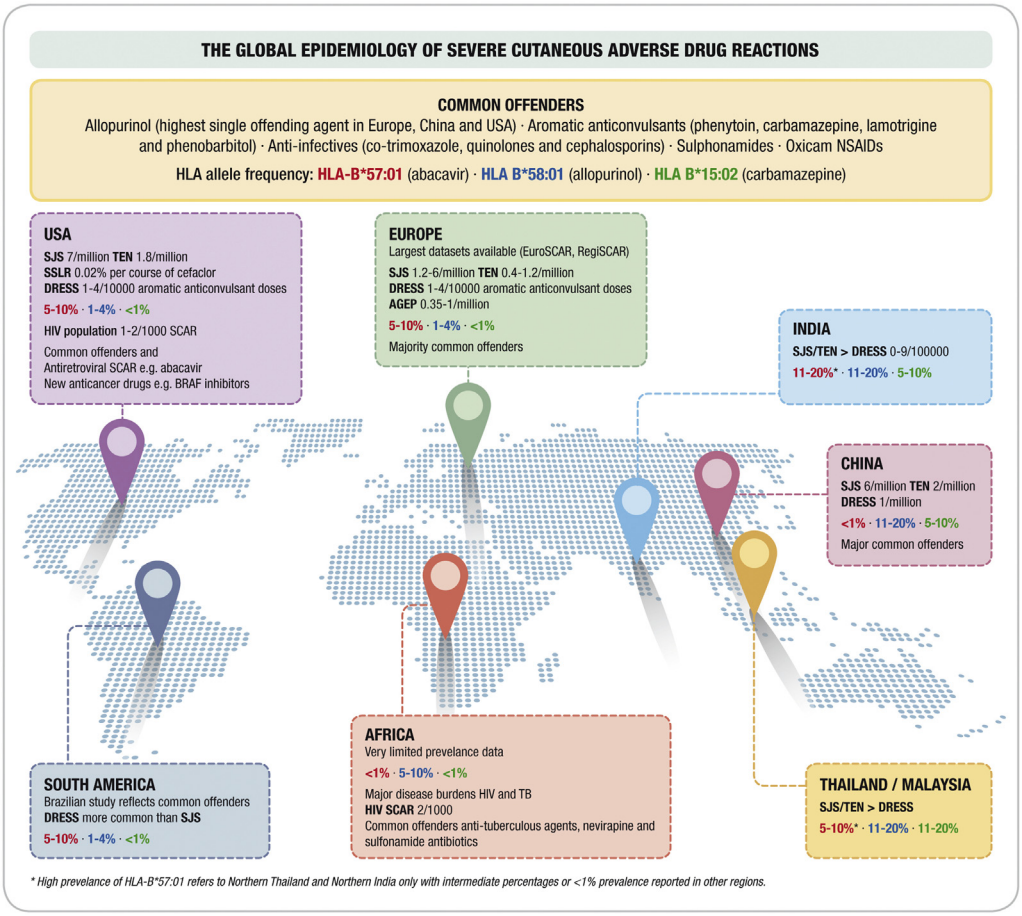

FIGURE 7. Global epidemiology of SJS/TEN and frequency of known risk HLA alleles. Incidence of SJS/TEN and other SCARs is represented for populations around the globe. Known common HLA risk allele frequencies are shown and color-coded to match the associated drug. *AGEP*, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SSLR*, serum-sickness like reaction. Reproduced with permission from Peter et al.[166]

the PPV to 38% and maintaining a 99.8% negative predictive value for phenytoin-related SJS/TEN. Given the rarity and severity of SJS/TEN, EHR-based algorithms designed to find SJS should focus on being able to identify most cases (ie, with a high senisitivity and high negative predictive value) with reasonable PPV. Another challenge in finding SJS/TEN cases in the EHR is confirming the phenotype because it can be difficult to verify the true diagnosis and clinical details of the cases if clinical details such as BSA involved, presence of mucosal involvement, pathology results, pictures, and other materials that are faxed into the EHR in a PDF format are not accessible by automated search methods. Many cases called "SJS" or "TEN" by treating physicians may not be SJS/TEN. The presence of a high-risk drug given in the appropriate time frame significantly increases the probability of a case identified through the EHR being SJS/TEN. In addition to difficulties finding true cases of SJS/TEN in the EHR, it is challenging to ascertain drug causality particularly if multiple drugs were started in a short time frame.

To estimate the potential number of individuals at risk, prescribing records of nearly one hundred thousand individuals at Vanderbilt University Medical Center "medical home" patients were analyzed for exposure to 5 drugs associated with severe delayed hypersensitivity syndromes including but not limited to SJS/TEN with known genomic predictors (allopurinol, lamotrigine, phenytoin, carbamazepine, and abacavir). Twelve percent of patients took at least 1 of these 5 medications, all of which except abacavir are known to be associated with SJS/TEN, and 6% took more than 1 drug. These numbers demonstrate the potential for prospective genotyping programs to potentially avert SJS/TEN events for these medications.

Regulatory perspective on pharmacogenomic screening for SJS/TEN in Singapore: Experience with implementation and cost-effectiveness

The experience of the drug regulatory authority of Singapore, the HSA, illustrates some of the benefits and challenges of implementing genetic screening to reduce the incidence of SJS/TEN. Two genetic associations with drug-induced SJS/TEN are relevant to this experience: HLA-B*15:02 with carbamazepine and HLA-B*58:01 with allopurinol. DNA collection of SJS/TEN cases and drug-tolerant controls confirmed strong genetic associations in the Singapore population (for carbamazepine: OR, 181; 95% CI, 8.7-3785; for allopurinol: OR, 100; 95% CI, 3.5-2820). Given the population frequency of these alleles

TABLE III. Adverse drug reactions with well-defined HLA associations

Drug ADR	HLA Allele	Allele frequency and carriage rate*	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
Abacavir Hypersensitivity syndrome[27,61-64]	B*57:01	*Allele frequency (%):* 1.6-7.1 European Caucasoid <3 Sub-Sahara African <3 Southeast Asian 0.3-2.4 African American 1-4 Thai	8% (3% true HSR and 2%-7% false-positive diagnosis)	960	100% for patch test confirmed	55%	13	Yes
		Carriage rate (%): 1.4-11.2 European Caucasoid* <1 Sub-Sahara African 0-2 Southeast Asian 0-2 African American						
Allopurinol SJS/TEN and DRESS/ DIHS[23,27,28,164,167,168]	B*58:01	*Allele frequency (%):* 0.5-6 European Caucasoid 2-8 Sub-Sahara African 0.5-17 Southeast Asian 2.6-6.4 African American 6-8.4 Thai	1/250-1/1,000	580	100% (Han Chinese)	3% (Han Chinese)†	250	Not in wide use (see section " Regulatory Perspective on Pharmacogenomic Screening for SJS/TEN in Singapore: Experience With Implementation and Cost-effectiveness")
		Carriage rate (%): 0-6.7 European Caucasoid 5.5-14 Sub-Sahara African 2-22 Southeast Asian >5.3 African American						
Carbamazepine SJS/TEN[27,163,165,169-171]	B*15:02	*Allele frequency (%):* <1 European Caucasoid <3 Sub-Sahara African 1-36 Southeast Asia <0.2 African American 8 Thai	<1-6/1,000	>1000	100% in Southeast Asian (with other B75 serotype)	2%-8%†	1,000	Yes
		Carriage rate (%): <1.2 European Caucasoid Up to 34 Southeast Asia						
Oxcarbazepine SJS/TEN[172]	B*15:02	*As above*		27.9	99.9% (Han Chinese)	0.73% (Han Chinese)		No
Carbamazepine DRESS/DIHS[173,174]	A*31:01	*Allele frequency (%):* 1-6 European Caucasoid <2 Sub-Sahara African 0.5-6 Southeast Asian <1 African American 7%-12% Japanese Up to 9.2% European Caucasoid* 5.5% Korean	0.05%	57.6	99.9%	0.89%	3,334	Not in wide use

(continued)

TABLE III. *(Continued)*

Drug ADR	HLA Allele	Allele frequency and carriage rate*	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
		Carriage rate (%): Up to 6 European Caucasoid <1 Sub-Sahara African	0.05%	23	99.9%	0.59%	5,000	Not in wide use
Dapsone DRESS/DIHS[175]	B*13:01	*Allele frequency (%):* <2 European Caucasoid 1-28 Southeast Asian 0 African American 28 Papuans/Australian Aboriginals 1.5 Japanese 2-4 Thai	1%–4% (Han Chinese)	20	99.8%	7.8%	84	Not in wide use
		Carriage rate (%): Up to 3.8 European Caucasoid 2-52 Southeast Asian						
Flucloxacillin DILI[176]	B*57:01	*As above*	8.5/100,000	81	99.99%	0.12%	13,819	No

DIHS, Drug-induced hypersensitivity syndrome; *DILI*, drug-induced liver injury; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *HSR*, hypersensitivity reaction; *NNT*, number needed to treat; *NPV*, negative predictive value.
*Allele frequencies and carriage rates were obtained from allelefrequencies.net.[177] Allele frequency describes the total number of copies of the allele in the relevant population. Allele carriage rate refers to the percentage of individuals who have the allele in the population including both homozygous and heterozygous carriers. For carbamazepine-induced SJS/TEN and abacavir hypersensitivity, there is no current evidence to suggest a gene-dose effect (ie, homozygosity or heterozygosity for an HLA risk allele) appear equally associated with risk of SJS/TEN.
†Although the NPV has been 100% for both HLA-B*15:02 and carbamazepine and HLA-B*58:01 and allopurinol SJS/TEN across Southeast Asian population, there has been variability in the PPV (2%-8% for Southeast Asians for carbamazepine and 2% for allopurinol SJS/TEN in Singapore).

(14.9% for HLA-B*15:02 and 18.5% for HLA-B*58:01), specificity and sensitivity of the tests,[153,154] and incidence of the reaction, the PPV of the genetic tests in Singapore is approximately 6% for HLA-B*15:02 and approximately 2% for HLA-B*58:01. Both tests have nearly a 100% negative predictive value across Southeast Asian populations.

Patients testing positive for HLA-B*15:02 have a number of alternative drugs to treat epilepsy or neuropathic pain. Cost-effectiveness analyses conducted from a health-systems perspective showed that genotyping for HLA-B*15:02 for new users of carbamazepine falls below a commonly used incremental cost-effectiveness ratio of US $50,000 per quality-adjusted life-year.[155] Before implementation, discussion sessions with clinicians and stakeholders highlighted 2 key concerns: genotyping test costs and turnaround time. Centralization of testing achieved a 40% to 50% cost reduction to US $146 and a turnaround time of 3 days. In April 2013, the Singapore Ministry of Health and the HSA issued a joint Dear Health Care Professional Letter stating that genotyping for HLA-B*15:02 would be the standard of care before prescribing carbamazepine to new users with a 75% subsidy to low-income patients for the HLA-B*15:02 test.[156] Orders for the HLA-B*15:02 test have since reached a steady rate of 250 tests per quarter. In the 3 years after the Dear Health Care Professional Letter, there were no reported cases of carbamazepine-induced SJS/TEN in genotyped patients in Singapore. In the fourth year, HSA received 1 report of SJS in a HLA-B*15:02−negative patient. Overall, genotyping has led to a significant reduction of carbamazepine-SJS/TEN from the historical incidence of 18 cases per year obtained from voluntary reporting. Similar national health policy programs for genotype reimbursement have been in place in Taiwan since 2010 and in Hong Kong since 2008 and have successfully reduced HLA-B*15:02−associated carbamazepine SJS/TEN in both settings.[157,158]

The case for HLA-B*58:01 genotyping for allopurinol has been more challenging because of limited options for the treatment of chronic gout. At 2% PPV, many HLA-B*58:01−positive patients would be given second-line or more expensive gout drugs. A similar cost-effectiveness analysis as done for carbamazepine was done for HLA-B*58:01 in the setting of new users of allopurinol and included an option for an enhanced safety monitoring program. At a test cost below US $90, genotyping would become cost-effective if test-positive patients are given probenecid and nonresponders are switched to allopurinol with an enhanced safety program. An enhanced safety program for all patients with gout without genotyping would become cost-effective at a program cost of less than US $39 per patient.[159] In March 2016, the Singapore Ministry of Health and the HSA issued another Dear Health Care Professional Letter stating that routine genotyping for HLA-B*58:01 was not required as standard of care but could be considered for patients who have other preexisting risk factors such as renal impairment.[160] Information on the availability of an HLA-B*58:01 genotyping test at a similar price as the HLA-B*15:02 test was communicated. Additional measures to mitigate the risk are publication of clinician and consumer guides for earlier recognition of different types of severe cutaneous adverse reactions, design of a low-cost safety program, and targeted genotyping for a higher risk subgroup of patients with gout.[160,161]

In summary, systems-wide implementation of genotyping requires weighing a multiplicity of factors: from the strength of

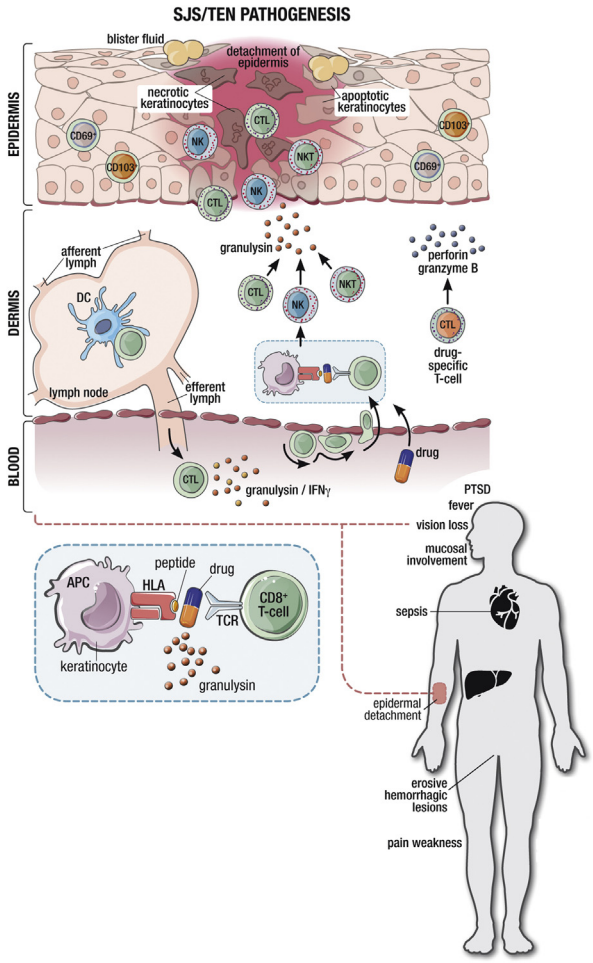

FIGURE 8. Proposed model of SJS/TEN immunopathogenesis. SJS/TEN affects the epidermis following interaction of pathogenic immune effector cells with drug-modified epitopes presented by HLA on the surface of keratinocytes. Cytotoxic CD8+ T cells, NK cells, and NK T cells that recognize HLA-drug epitopes produce cytolytic proteins such as granulysin and other mediators of inflammation. The result is widespread keratinocyte death, the formation of fluid-filled bullae containing immune cells, and, ultimately, epidermal necrosis and sloughing.

the genetic association and prevalence of the allele in the population to the PPV and availability of alternative drugs or treatment plans for test-positive patients.[161]

SJS/TEN PREVENTION, PREDICTION, AND PATHOGENESIS: WHAT'S NEW AND WHAT'S NEXT*

Key Points:

- HLA-associated SCARs including SJS/TEN have provided models for T-cell–mediated ADRs and a roadmap for assessment and implementation of pharmacogenomic screening that can be applied in clinical use for the prevention of drug hypersensitivity. Despite strong HLA associations, PPVs remain relatively low and many other factors contribute to the development of disease and present opportunities for further research into mechanism and pathogenesis.
- SJS/TEN and other cutaneous reactions secondary to immune checkpoint inhibitors of cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 during treatment of cancer are increasing as the use of these agents rises. The severity of adverse cutaneous reactions to immunotherapies correlates with improved cancer outcomes and survival, suggesting that patients most likely to benefit are also those most likely to develop toxicity. This provides potentially important clues to the immunopathogenesis of these reactions and underscores the need to manage these toxicities so that patients can benefit from anticancer therapies. In addition, gene expression analyses have shown similarities between lichenoid rash associated with immune checkpoint inhibitors and SJS/TEN to noncancer agents.
- In SJS/TEN there is currently much focus on effector memory $CD8^+$ T-cell responses. However, suppressor immune responses, such as those conferred by regulatory T (Treg) cells, play a key role in the maintenance of immune homeostasis in the skin and are notably diminished early in the course of SJS/TEN. Augmenting regulatory immune responses might provide alternative or complementary treatment modalities for SJS/TEN.
- Blister fluid cells from the skin lesions in patients with SJS/TEN are characterized by the infiltration of $CD8^+$ T cells, natural

TABLE IV. Frequencies of immune subsets in blister fluid obtained from patients with acute SJS/TEN

Surface CD expression	Case 1	Case 2	Case 3	Case 4	Case 5
CD3+	46%	70%	33%	68%	61%
CD4+	4%	0%	0%	9%	0%
CD8+	42%	70%	33%	59%	61%
CD20+	0%	0%	0%	0%	0%
CD56+	48%	70%	100%	100%	72%
CD3+, CD56− (T cells)	42%	30%	0%	0%	30%
CD3−, CD56+ (NK cells)	44%	30%	66%	32%	41%
CD3+, CD56+ (NK T cells)	4%	44%	33%	68%	31%
CD4+, CD56+	0%	0%	0%	9%	0%
CD8+, CD56+ (NKT cells)	4%	44%	33%	59%	31%

Unpublished data (Hung S.-I., PhD, March 2017), and Chung et al.[180]

TABLE V. Rapid immunochromographic test for granulysin

Syndrome	Blister fluid granulysin concentration
SJS/TEN	High: 100 ng/mL
Bullous fixed drug eruption	High: 100 ng/mL
Bullous erythema multiforme	Moderate: 50 ng/mL
Hand-foot-and-mouth disease bullae	Low: 10-20 ng/mL
Chemotherapy hemorrhagic bullae	Low: 10-20 ng/mL
Pemphigus	Negative: <5 ng/mL
Bullous pemphigoid	Negative: <5 ng/mL
Acute generalized exanthematous pustulosis	Negative: <5 ng/mL

Chung et al,[180] Su et al,[186] and unpublished data (Chung W.-H., MD, PhD, March 2017).

* Riichiro Abe, MD, PhD; Wen-Hung Chung, MD, PhD; Shuen-Iu Hung, PhD; Mario E. Lacouture, MD; David A. Ostrov, PhD; Rebecca Pavlos, PhD; Alec Redwood, PhD; Michael D. Rosenblum, MD, PhD; Katie D. White, MD, PhD

TABLE VI. Cutaneous adverse events and SJS/TEN associated with immune checkpoint inhibitors

Drug name	Target	Indication	Severe rash (%)	SJS/TEN reported[194,195]
Ipilimumab	CTLA-4	Melanoma	2.4	Yes
Nivolumab	PD-1	Melanoma, NSCLC, RCC, HL, HNSCC, UC, CRC	1.2	Yes
Ipilimumab + nivolumab	CTLA-4+ PD-1	Melanoma	5.0%	Yes
Pembrolizumab	PD-1	Melanoma, NSCLC, HNSCC, HL, dMMR tumors	1.7%	Yes
Atezolizumab	PD-L1	Bladder cancer, NSCLC	1.3%	No
Avelumab	PD-L1	Merkel cell carcinoma	0%	Yes

CRC, Colorectal cancer; *dMMR*, defective mismatch repair; *CTLA-4*, cytotoxic T-lymphocyte–associated protein 4; *HL*, Hodgkin lymphoma; *HNSCC*, head and neck squamous cell carcinoma; *PD-L1*, programmed cell death protein ligand 1; *NSCLC*, non–small cell lung cancer; *RCC*, renal cell carcinoma; *UC*, urothelial carcinoma.

killer (NK) cells, and NK T cells. A public T-cell receptor (TCR) αβ clonotype has been found in blister fluid and PBMCs from Taiwanese patients with HLA-B*15:02–restricted carbamazepine SJS/TEN. Binding assays with this TCR recombinant protein support a pharmacological interaction with immune proteins model for carbamazepine SJS/TEN. The applicability of this model to other class I HLA-restricted drug-induced SJS/TEN is currently being explored.

- Virtual modeling predicts that carbamazepine binds to HLA-B*15:02 at a higher affinity in the absence of peptide and contacts both HLA and TCR.
- T-cell, NK cell, and NK T-cell–derived granulysin is a key mediator of tissue damage and disease in SJS/TEN. Serum granulysin levels, as well as IL-15, may prove useful as prognostic markers during acute SJS/TEN. Targeting granulysin as well as pathogenic T cells may provide additional therapeutic interventional strategies to join other biologics such as anti-TNF (etanercept) therapy.
- In some patients, a generalized exanthema develops following antibiotic treatment for gastrointestinal infection. It is hypothesized that the risk for cutaneous ADRs may be influenced by the gut microbiome or potentially other bacterial pathogens.

Understanding the immunopathogenesis of SJS/TEN is central to the development of pretherapy screening strategies and effective SJS/TEN treatment regimens. Critical to this is deciphering and linking the influences of host genetics and structural, biochemical, and functional interactions between drugs and/or pathogens and the immune system. Session 5 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* reviewed seminal advances in our understanding of the pharmacogenomics and immunology of SJS/TEN and other T-cell–mediated severe ADRs and ongoing basic and translational science research in this field.

SJS/TEN is an IM-ADR influenced by genes that affect pharmacokinetics, pharmacodynamics, and immune responses. Additional influences include comorbid disease such as renal impairment and external factors such as environmental exposures and viral infection.[162] Class I associations that have also provided key insights to IM-ADR pathogenesis include carbamazepine and HLA-B*15:02 in SJS/TEN and allopurinol and HLA-B*58:01 in SCARs.[163-165] Many other HLA associations with drugs that cause SCARs including SJS/TEN are documented and incidence varies across ADR phenotypes and across populations, reflecting risk allele carriage (Figure 7). However, for most drugs

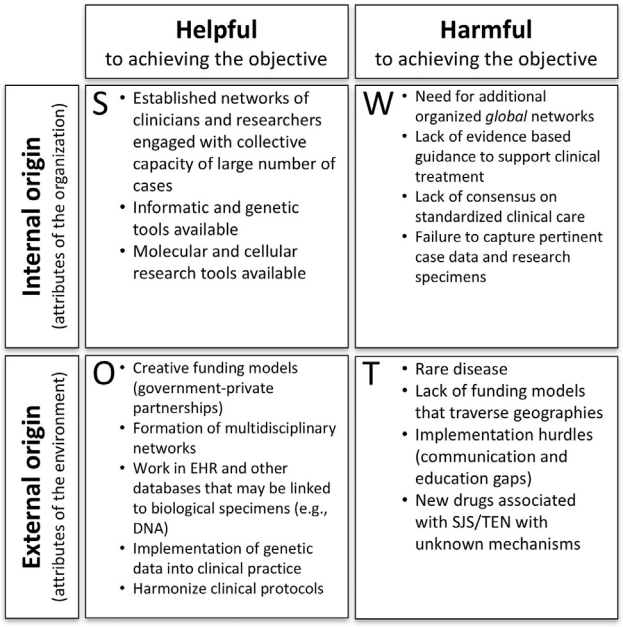

FIGURE 9. Strengths, weaknesses, opportunities, and threats (SWOT) analysis for SJS/TEN clinical management and research. Participants at *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* contributed to a SWOT analysis to define unmet needs in SJS/TEN clinical care and research and to identify approaches to address these needs.

that are implicated in SJS/TEN there remains no known HLA association, and for up to 20% of SJS/TEN cases no causative drug is identified.

Carriage of a given risk HLA allele is permissive but insufficient for the development of drug hypersensitivity as evidenced by the small percentage of individuals carrying the risk alleles who develop an ADR when exposed to the drug (Table III). Identifying additional factors that contribute to the development of ADRs will be important in understanding mechanisms of pathogenesis and also help guide pharmacogenomic screening in the future. Drug dose, metabolism, and clearance rate are known to be independent pharmacological factors in the development of SJS in some settings and may account for part of the PPV gap. For example, variants in the allele coding for the metabolic enzyme *CYP2C9*3* are significantly associated with phenytoin SCAR in Taiwan, Japan, Malaysia, and Thailand.[178,179] In

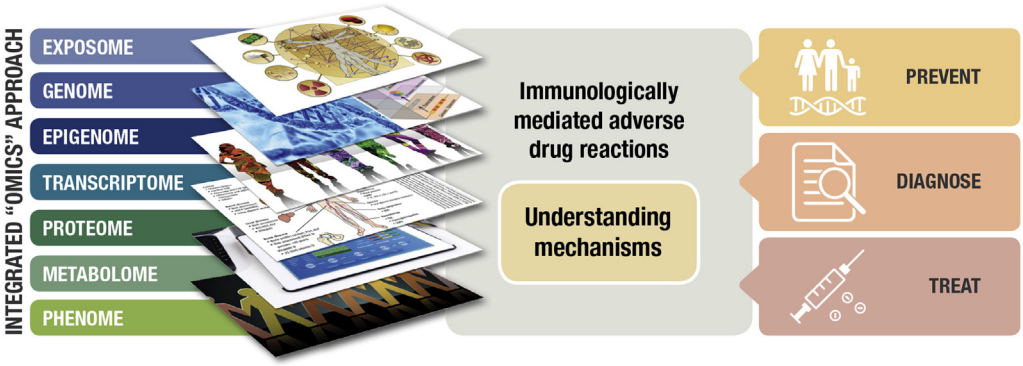

FIGURE 10. Integrated—omics approaches as part of personalized medicine in SJS/TEN. There exist multiple opportunities to apply personalized medicine approaches for the prevention and treatment of SJS/TEN. Part of these approaches will include integrated—omics platforms that link genetic, immunologic, ecologic, and other data within an individual patient to estimate risk of disease, facilitate precise and rapid diagnosis, inform prognosis and response to therapy, and predict which medications are safe for future use. Aggregation of these data may allow us to define the general principals of immunopathogenesis and genetics that may be applied more broadly to larger populations.

addition to HLA and metabolic-based genetic factors, potential roles for risk-enhancing TCR clonotypes, tissue-specific memory T-cell subsets, NK cells, and NK T cells are under investigation. Finally, the nature of HLA and peptide alterations following drug exposure as determined by genetic factors within the proteasome pathway and peptide processing machinery may potentially contribute to disease pathogenesis and are under study.

Studies showing a strong association between HLA class I alleles and drug-induced SJS/TEN disease support the concept that class I—restricted antigen-driven $CD8^+$ T cells are of fundamental importance in immunopathogenesis (Figure 8).[164,165] Hung et al have shown that cells recruited to the blisters in SJS/TEN are predominantly T cells, NK cells, and NK T cells, and that the percentage of each cell subset varies between patients (Table IV). Using blister fluid as a source of potentially pathogenic effector cells, T cells identified in blister fluid from individuals with SJS/TEN are characterized by a dominant clonotype(s), defined as a population of $CD8^+$ T cells that express the same TCR sequence. This suggests that T cells bearing this TCR are able to bind and be stimulated by peptides from the eliciting drug. These T cells also express granulysin and granzyme-B consistent with a cytotoxic T lymphocyte phenotype. Similar shared TCRs were not found in patients with allopurinol SCAR, although some evidence of clonal expansion within individual patients was seen in blister fluid.[181]

Surface plasmon resonance experiments have demonstrated that carbamazepine (and carbamazepine metabolites) are capable of binding directly to HLA-B*15:02 and residues important in the HLA-carbamazepine interaction have been mapped to the HLA peptide-binding groove using site-directed mutagenesis studies.[182,183] Ostrov et al[184] and Illing et al[185] previously solved the crystal structure of abacavir bound to HLA-B*57:01 that defined the altered peptide repertoire model for drug-HLA interaction. More recent work by Ostrov et al has focused on determining whether known HLA and drug structures can be used to predict which drug will bind a particular HLA protein. Modeling algorithms of drug-binding affinities predicted that abacavir would bind to HLA-B*57:01 with higher affinity in the presence of a self-peptide. This is consistent with known crystallagraphy data and represents proof-of-concept for this type of *in silico* approach to predicting drug-HLA interactions. Using this approach, carbamazepine binding was not predicted to bind a site within the antigen-binding cleft (under the peptide, as abacavir interacted with the F pocket of HLA-B*57:01). Based on the crystal structures of HLA-B*15:02, TCR complexes with HLA-B molecules and atomic models of HLA-B*15:02 complexed with peptides corresponding to HLA-B*15:02 elution studies and TCRαβ sequences of the shared TCR discovered in Taiwanese patients mentioned above, carbamazepine was predicted to bind complexes of peptide and HLA-B*15:02 in a TCR contact site located at the interface of the trimolecular HLA-B*15:02-peptide-TCR complex (D. Ostrov, PhD, unpublished data, March 2017).

Cytotoxic protein and cytokine mediators are important in SJS/TEN pathogenesis and have potentially important applications as diagnostic and predictive markers and therapeutic targets. Chung et al[180] discovered that the cytolytic protein granulysin, produced by $CD8^+$ T cells, NK cells, and NK T cells, is a primary mediator of keratinocyte cell death in SJS/TEN. Granulysin is found at high concentration in serum and blister fluid from patients with SJS/TEN and plasma levels correlate with disease severity and prognosis.[180,186] Chung et al have developed a rapid immunochromographic test to measure blister fluid granulysin concentration and this assay measured over multiple time points appears to distinguish SJS/TEN and bullous fixed drug eruption from other blistering skin diseases such as bullous erythema multiforme, bullous pemphigus, and viral infection (Table V). His group has also identified that systemic IL-15, a cytokine that activates NK cells and cytotoxic T cells, is also correlated with SJS/TEN severity and both IL-15 and granulysin may be used as prognostic markers during acute SJS/TEN.[186]

Chung et al have also conducted an open, prospective, randomized trial evaluating the efficacy of immunomodulatory therapies for the treatment of SJS/TEN. This study included 48 patients randomized to receive the TNF-α inhibitor etanercept and 45 patients to receive corticosteroid therapy. This study demonstrated that etanercept reduced time to reepithelialization

Box I. The SJS Foundation and Patient Perspectives

FIGURE 11A. Julie McCawley.

Julie McCawley. Jean and Julie McCawley, Katie Niemeyer, and the family of Angela Anderson attended *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* on behalf of patients and families around the world who have been affected by SJS/TEN.

Julie McCawley, now aged 23 years, developed SJS/TEN at age 11 months and as a result suffers from severe sight impairment (Figure 11, *A*). In March of 1995, her mother, Jean, founded the Stevens-Johnson Syndrome Foundation (http://sjsupport.org), a grassroots nonprofit patient support and advocacy group that aims to bring public awareness to this devastating and life-threatening illness. In 1997, the SJS Foundation launched its first Web site that included an online chat room for patients and families affected by SJS. Their network quickly brought together numerous patients and families affected by SJS/TEN from around the world. In 1999, the SJS Foundation collaborated with physicians at Johns-Hopkins to create an SJS fact sheet that has now been distributed to more than 100,000 hospitals and pharmacies and to the general public through awareness campaigns. The SJS Foundation now supports a voluntary case registry, has championed the establishment of August as SJS Awareness month, actively supports SJS/TEN research, and maintains a Facebook page with more than 5,000 followers. Julie McCawley is now an elementary school teacher and creator of SJS Kids Support (www.freewebs.com/sjskidssupport), a Web site for children affected by SJS/TEN that explains the disease and its complications in accessible terminology with content focused on the concerns of young victims and of children with loved ones affected by SJS/TEN.

FIGURE 11B. Angela Anderson.

"Angela was unique. She was a trendsetter … one in a million. The disease that took her was one in a million. Even in death, she stood out from the crowd." —Eulogy for Angela Anderson (Figure 11, *B*). Paul Anderson shared the story of his daughter Angela's vibrant 22-year life and tragic 4-day hospitalization with SJS/TEN that ended in her death on December 28, 2015. In memory of Angela, he and his wife, Wanpen, and son, Tim, established the Angela Anderson SJS Research Fund to promote SJS/TEN research. The Anderson family recruited support from family, friends, and the general public through awareness events, media communications, and a GoFundMe campaign to raise $22,000 for SJS/TEN research. This is an especially significant contribution because it represents $1000 in research funding for each year of Angela's life. Angela's story has been reported in numerous media outlets, further raising community awareness of SJS/TEN. The Angela Anderson SJS Research Fund continues to receive donations to further research efforts and her family and friends continue to work tirelessly to disseminate her story as education for the public and medical communities.

and reduced mortality. This work and other early studies suggest the potential efficacy of etanercept as a therapeutic option for SJS/TEN and provide a mechanism to explain therapeutic responses with this drug.[112,115,187,188] Future work that may translate into targeted therapy is focused on developing and testing novel inhibitors to pathogenic mediators in SJS/TEN including an mAb targeting granulysin and an mAb targeting the TCR$\alpha\beta$ subunits to disrupt TCR signaling.[189,190] Another insight into the immunopathogenesis of SJS/TEN has come from studies demonstrating that interaction of annexin A1 with the formyl peptide receptor 1, expressed on the surface of keratinocytes obtained from patients with SJS/TEN but not present on control keratinocytes, is a key mediator of keratinocyte necroptosis in SJS/TEN.[191]

More recently Abe et al (R. Abe, MD, PhD, unpublished data, March 2017) have examined the role of the microbiome in the development of severe cutaneous ADRs. Using PBMCs obtained from patients who developed a generalized exanthema within 1 to 3 days after completing treatment for gastrointestinal bacterial infection, they have shown that $CD4^+$ cells express the activation marker CD154 following exposure to whole, killed bacteria. Cell culture supernatants from these experiments contain elevated levels of inflammatory cytokines compared with cultures derived from PBMCs obtained from normal donors. Abe et al are investigating the hypothesis that treatment of bacterial gastrointestinal infection generates bacterial products that stimulate an immune response. This raises the interesting possibility that the risk for cutaneous ADRs may be influenced by the microbiome and in particular bacterial pathogens in the gut.

FIGURE 11C. Katie Neimeyer with SJS/TEN survivor and PGA champion Gene Sauers.

Katie Niemeyer is a survivor of SJS/TEN as a teenager and now works as a certified nurse anesthetist, entrepreneur, mother, and philanthropist to promote SJS/TEN awareness and research (Figure 11, *C*). Left with chronic eye irritation that hindered her training as a distance runner, Katie created a high-performance wristband, Handana, to keep sweat from burning her already sensitive eyes. Handana was the first runner up in the 2015 Under Armour Future Show. Katie has donated proceeds from her business endeavors to supporting research in the treatment of acute and chronic SJS/TEN eye disease and established the Katie Niemeyer Research Fund at the Massachusetts Eye and Ear clinic. Katie is also the founding member of the SJ Syndrome of Texas (www.sjsyndrome.com) and frequently shares her story with health care and general audiences around the country to educate and inspire hope within and outside the SJS/TEN community.

These stories underscore major threats associated with SJS/TEN, a disease that (1) affects previously healthy individuals in an unpredictable manner in the absence of validated screening mechanisms, (2) is characterized by sequelae that are numerous, severe, and lifelong, (3) lacks highly specific diagnostic modalities that often results in delayed recognition of acute disease, and (4) in its severest form, moves quickly and with high mortality.

Severe cutaneous syndromes associated with novel cancer immunotherapeutics have provided significant insights into the potential immunopathogenesis of SJS/TEN. First approved for clinical use in 2011, the immune checkpoint inhibitors are a class of drugs that block inhibitory receptors such as PD-1 (nivolumab) and cytotoxic T-lymphocyte–associated protein 4 (ipilimumab) on the surface of T cells promoting T-cell activation and effector functions.[192] This class of therapy has shown tremendous efficacy in the treatment of certain cancers including stage IV melanoma, lymphoma, and cancers of the head and neck, lung, bladder, and kidney.[193] Cutaneous eruptions occur in approximately one-third of patients treated with checkpoint blockade (Table VI). Most often these eruptions are clinically benign, do not limit treatment, and respond to topical corticosteroids. A small proportion of patients receiving checkpoint inhibitor blockade develop SJS/TEN.[196-198] Importantly, the severity of the cutaneous ADR related to checkpoint inhibitor therapy correlates with improved tumor response and patient survival.[199,200] Similarities in gene expression profiling among the various phenotypes of cutaneous reactions associated with anti–PD-1/programmed cell death protein ligand 1 therapy that resemble those associated with SJS/TEN suggest that PD-1 may be important in specifically regulating epidermal integrity.[201] Lacouture et al[195] have shown that serum IL-6 is elevated in patients with early maculopapular rash secondary to checkpoint inhibitor therapy. Furthermore, they are investigating whether therapeutics that target T-cell activation pathways and inflammation, such as Janus kinase inhibitors and/or IL-6 inhibition, might provide benefit for the treatment of checkpoint inhibitor blockade-associated cutaneous reactions.

Another key in the immunopathogenesis of many immunologically mediated diseases including SJS/TEN is thought to be an imbalance of effector/autoreactive and regulatory immune responses. Extensive research supports the scientific premise that autoimmune disease reflects a disruption of this balance. Treg cells are defined as $CD4^+$ T cells that express the transcription factor FoxP3 that drives the suppressor phenotype. Tissue-resident Treg cells are highly abundant in the skin and gut tissues of mice and humans. Individuals who lack functional Treg-cell responses succumb at an early age to fulminant systemic autoimmune disease, highlighting the critical role these cells play in immune regulation.[202,203] Treg-cell suppressor function is mediated via various mechanisms including IL-10 secretion, surface expression of the inhibitory receptor cytotoxic T-lymphocyte–associated protein 4, and through IL-2 consumption by the high-affinity IL-2 receptor CD25. Rosenblum et al[204] have developed a murine model of cutaneous autoimmune disease that demonstrated that mice spontaneously suppress skin inflammatory responses over time despite ongoing antigen exposure but that depletion of Treg cells in these mice leads to prolonged disease and death. These data support a mechanistic role for Treg cells in maintaining immune homeostasis in the skin. Furthermore, it has been shown that (1) Treg cells are less abundant in skin from patients with SJS/TEN compared with erythema multiforme,[205] (2) that circulating Treg cells obtained from patients with SJS/TEN display impaired suppressor function,[206] (3) that Treg cells can prevent epidermal injury in animal TEN model systems,[207] and (4) that Treg-cell–mediated suppression decreases cytotoxic T-cell responses to drugs in *in vitro* systems.[208] Data from human trials have shown that therapies that augment Treg-cell function (including adoptive transfer of expanded autologous Treg cells and low-dose systemic IL-2) ameliorate alopecia areata, chronic graft-versus-host disease, and systemic lupus erythematosus.[209-212] As noted above, immunohistochemistry experiments have shown that Treg cells are present at significantly reduced numbers in skin from

patients with SJS/TEN compared with EMM and this can be used to differentiate these 2 disease phenotypes.[205] The use of strategies to boost regulatory immune responses in acute SJS/TEN is intriguing and warrants further study.

DISCUSSION AND FUTURE DIRECTIONS

SJS/TEN is a life-threatening disease that in adults is usually drug related and in children in particular, both SJS/TEN and its mimickers (Table I) can create unique diagnostic challenges in the absence of an apparent causative agent. The low incidence of SJS/TEN of 1 to 5 per 1,000,000 and high mortality rate have highlighted the need for research and clinical networks to drive research, translation, consensus guidelines, and evidence-based approaches. This 1-day meeting highlighted that there has been significant progress to strengthen SJS/TEN research efforts over the last decade. Harnessing strengths and opportunities and proactively addressing weaknesses and threats will be crucial to these research efforts moving forward (Figure 9). Key strengths have included the establishment of epidemiological and pharmacogenomic networks, the ability to use informatics tools to find SJS/TEN cases in the EHR, and access to genetic tools to analyze the data. With these research strengths has come the opportunity to establish and access DNA and cellular biobanks to facilitate further genetic and mechanistic discovery science. The preexisting networks also create a unique platform for the establishment of larger multidisciplinary networks where clinical protocols can be harmonized and therapeutic approaches studied. Addressing weaknesses and threats will be equally important. Lack of evidence-based treatment guidelines and consensus on standardized clinical care has been a hurdle to the creation of very large global networks to study treatment interventions. In addition, many studies have been strictly epidemiologically based and have not had the resources or infrastructure to collect and cryopreserve valuable research samples. Ultimately creative strategies will be needed to maximize and coordinate research efforts and may require creative funding mechanisms from multiple governments and other sources. It is also predicted that the patient-centered integrated -omics approaches that are part of the personalized medicine of the future will be key to not only understanding the mechanistic basis of SJS/TEN but also furthering preventive efforts and facilitating earlier diagnosis and treatment (Figure 10).

You may view the Abstracts presented at this meeting at: https://medsites.mc.vanderbilt.edu/sjsmeeting/home.

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REFERENCES

1. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Investig Dermatol 2000;115:149-53.
2. White KD, Chung WH, Hung SI, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. J Allergy Clin Immunol 2015;136:219-34. quiz 35.
3. Manolio TA, Hutter CM, Avigan M, Cibotti R, Davis RL, Denny JC, et al. Research Directions in Genetically-Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Available from: https://www.genome.gov/27560487/research-directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/. Accessed December 7, 2017.
4. Manolio TA, Hutter CM, Avigan M, Cibotti R, Davis RL, Denny JC, et al. Research directions in genetic predispositions to Stevens-Johnson syndrome/toxic epidermal necrolysis [published online ahead of print November 6, 2017]. Clin Pharmacol Therapeut. https://doi.org/10.1002/cpt.890.
5. Maverakis E, Wang EA, Shinkai K, Mahasirimongkol S, Margolis DJ, Avigan M, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis standard reporting and evaluation guidelines: results of a National Institutes of Health Working Group. JAMA Dermatol 2017;153:587-92.
6. Ergen EN, Holmes JH, Ye F, Luo L, Phillips EJ. Foundations of a North American SJS/TEN Research Network: results of a web-based survey of dermatologists and surgeons. Presented at: American Burn Association (ABA) 49th Annual Meeting; March 20-24, 2017; Boston, MA.
7. Department of Health and Human Services. Serious Adverse Drug Reaction Research (R21). Available from: https://grants.nih.gov/grants/guide/pa-files/PAR-16-274.html. Accessed December 7, 2017.
8. Department of Health and Human Services. Serious Adverse Drug Reaction Research (R01). Available from: https://grants.nih.gov/grants/guide/pa-files/PAR-16-275.html. Accessed December 7, 2017.
9. Amstutz U, Ross CJ, Castro-Pastrana LI, Rieder MJ, Shear NH, Hayden MR, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Therapeut 2013;94:142-9.
10. Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia 2014;55:496-506.
11. Pirmohamed M, Friedmann PS, Molokhia M, Loke YK, Smith C, Phillips E, et al. Phenotype standardization for immune-mediated drug-induced skin injury. Clin Pharmacol Therapeut 2011;89:896-901.
12. Carr DF, Bourgeois S, Chaponda M, Takeshita LY, Morris AP, Castro EM, et al. Genome-wide association study of nevirapine hypersensitivity in a sub-Saharan African HIV-infected population. J Antimicrob Chemother 2017;72:1152-62.
13. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Flechet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981-1985. Arch Dermatol 1990;126:37-42.
14. Schopf E, Stuhmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. Arch Dermatol 1991;127:839-42.
15. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.
16. Rzany B, Mockenhaupt M, Baur S, Schroder W, Stocker U, Mueller J, et al. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. J Clin Epidemiol 1996;49:769-73.
17. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, Naldi L, Viboud C, Roujeau JC, et al. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. Aids 2001;15:1843-8.
18. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Investig Dermatol 2008;128:35-44.
19. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol 2008;58:33-40.
20. Lee HY, Dunant A, Sekula P, Mockenhaupt M, Wolkenstein P, Valeyrie-Allanore L, et al. The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. Br J Dermatol 2012;167:555-62.

21. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Investig Dermatol 2013;133:1197-204.
22. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, et al. A marker for Stevens-Johnson syndrome…: ethnicity matters. Pharmacogenomics J 2006;6:265-8.
23. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al, RegiSCAR study group. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18:99-107.
24. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Therapeut 2010;88:60-8.
25. World Health Organization (WHO) Collaborating Centre for Drug Statistic Methodology, Norwegian Institute of Public Health. ATC/DDD Index. Available from: http://www.whocc.no/atcddd. Accessed December 7, 2017.
26. Sukasem C, Puangpetch A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. Asian Pac J Allergy Immunol 2014;32:111-23.
27. Puangpetch A, Koomdee N, Chamnanphol M, Jantararoungtong T, Santon S, Prommas S, et al. HLA-B allele and haplotype diversity among Thai patients identified by PCR-SSOP: evidence for high risk of drug-induced hypersensitivity. Front Genet 2014;5:478.
28. Sukasem C, Jantararoungtong T, Kuntawong P, Puangpetch A, Koomdee N, Satapornpong P, et al. HLA-B (*) 58:01 for allopurinol-induced cutaneous adverse drug reactions: implication for clinical interpretation in Thailand. Front Pharmacol 2016;7:186.
29. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 2010;51:926-30.
30. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704-9.
31. Tominaga T, Miyazaki S, Oniyama Y, Weber AD, Kondo T. The Japanese Postmarketing Adverse Event Relief System: a confluence of regulatory science, the legal system, and clinical pharmacology. Clin Pharmacol Therapeut 2017;102:277-82.
32. Kitami A, Watanabe H, Sueki H, Iijima M, Aihara M, Ikezawa Z, et al. Japanese Research Committee on Severe Adverse Reaction (J-SCAR). Epidemiological survey of Stevens-Johnson syndrome and toxic epidermal necrolysis throughout Japan: supported by the Japanese Research Committee on Severe Adverse Reactions (J-SCAR) and partially by Health and Labor Sciences research grants (Research on Intractable Diseases) from the Ministry of Health, Labor and Welfare of Japan and the Japanese Dermatological Association [in Japanese]. Jpn J Dermatol 2011;121:2467-82.
33. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia 2010;51:2461-5.
34. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet 2011;20:1034-41.
35. Dodiuk-Gad RP, Laws PM, Shear NH. Epidemiology of severe drug hypersensitivity. Semin Cutan Med Surg 2014;33:2-9.
36. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson syndrome and toxic epidermal necrolysis: an update. Am J Clin Dermatol 2015;16:475-93.
37. Dodiuk-Gad RP, Olteanu C, Feinstein A, Hashimoto R, Alhusayen R, Whyte-Croasdaile S, et al. Major psychological complications and decreased health-related quality of life among survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2016;175:422-4.
38. Butt TF, Cox AR, Lewis H, Ferner RE. Patient experiences of serious adverse drug reactions and their attitudes to medicines: a qualitative study of survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. Drug Saf 2011;34:319-28.
39. Butt TF, Cox AR, Oyebode JR, Ferner RE. Internet accounts of serious adverse drug reactions: a study of experiences of Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug Saf 2012;35:1159-70.
40. Lew TT, Creamer D, Mackenzie J, Walsh SA. Post-traumatic stress disorder following drug reaction with eosinophilia and systemic symptoms. Br J Dermatol 2015;172:836-7.
41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
42. Sanchez-Lopez Mdel P, Dresch V. The 12-Item General Health Questionnaire (GHQ-12): reliability, external validity and factor structure in the Spanish population. Psicothema 2008;20:839-43.
43. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. Behav Res Ther 2003;41:1489-96.
44. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
45. Prinsen CA, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. J Investig Dermatol 2011;131:1945-7.
46. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
47. Schroder W, Mockenhaupt M, Schlingmann J, Schneck B, Hering O, Schopf E. Clinical re-classification of severe skin reactions and evaluation of their etiology in a population-based registry. Presented at: Medical informatics, biostatistics and epidemiology for efficient health care and medical research: contributions from the 44th annual conference of the GMDS, Urban and Vogel, Heidelburg; 1999:S107-10.
48. Watkins LKF, Olson D, Diaz MH, Lin X, Demirjian A, Benitez AJ, et al. Epidemiology and molecular characteristics of *Mycoplasma pneumoniae* during an outbreak of *M. pneumoniae*-associated Stevens-Johnson syndrome. Pediatr Infect Dis J 2017;36:564-71.
49. Olson D, Watkins LK, Demirjian A, Lin X, Robinson CC, Pretty K, et al. Outbreak of *Mycoplasma pneumoniae*-associated Stevens-Johnson syndrome. Pediatrics 2015;136:e386-94.
50. Olson D, Abbott J, Lin C, Prok L, Dominguez SR. Characterization of children with recurrent episodes of Stevens Johnson syndrome. J Pediatr Infect Dis Soc 2017;6:e140-3.
51. Finkelstein Y, Soon GS, Acuna P, George M, Pope E, Ito S, et al. Recurrence and outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Pediatrics 2011;128:723-8.
52. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, Flahault A, Kelly JP, et al. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics 2009;123:e297-304.
53. Hsu DY, Brieva J, Silverberg NB, Paller AS, Silverberg JI. Pediatric Stevens-Johnson syndrome and toxic epidermal necrolysis in the United States. J Am Acad Dermatol 2017;76:811-817.e4.
54. Beck A, Quirke KP, Gamelli RL, Mosier MJ. Pediatric toxic epidermal necrolysis: using SCORTEN and predictive models to predict morbidity when a focus on mortality is not enough. J Burn Care Res 2015;36:167-77.
55. Catt CJ, Hamilton GM, Fish J, Mireskandari K, Ali A. Ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Am J Ophthalmol 2016;166:68-75.
56. Moreau JF, Watson RS, Hartman ME, Linde-Zwirble WT, Ferris LK. Epidemiology of ophthalmologic disease associated with erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis in hospitalized children in the United States. Pediatr Dermatol 2014;31:163-8.
57. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990;126:43-7.
58. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2013;168:726-32.
59. Struck MF, Illert T, Liss Y, Bosbach ID, Reichelt B, Steen M. Toxic epidermal necrolysis in pregnancy: case report and review of the literature. J Burn Care Res 2010;31:816-21.
60. Carr DF, Chaponda M, Jorgensen AL, Castro EC, van Oosterhout JJ, Khoo SH, et al. Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a Malawian HIV-infected population. Clin Infect Dis 2013;56:1330-9.
61. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-2.
62. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002;359:727-32.

63. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008; 358:568-79.
64. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46:1111-8.
65. Chasela CS, Hudgens MG, Jamieson DJ, Kayira D, Hosseinipour MC, Kourtis AP, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med 2010;362:2271-81.
66. Marazzi MC, Germano P, Liotta G, Guidotti G, Loureiro S, da Cruz Gomes A, et al. Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women. HIV Med 2006;7:338-44.
67. Dube N, Adewusi E, Summers R. Risk of nevirapine-associated Stevens-Johnson syndrome among HIV-infected pregnant women: the Medunsa National Pharmacovigilance Centre, 2007-2012. South African Med J 2013;103:322-5.
68. Knight L, Todd G, Muloiwa R, Matjila M, Lehloenya RJ. Stevens Johnson syndrome and toxic epidermal necrolysis: maternal and foetal outcomes in twenty-two consecutive pregnant HIV infected women. PloS One 2015;10: e0135501.
69. Stewart A, Lehloenya R, Boulle A, de Waal R, Maartens G, Cohen K. Severe antiretroviral-associated skin reactions in South African patients: a case series and case-control analysis. Pharmacoepidemiol Drug Saf 2016;25:1313-9.
70. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, Roujeau JC, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Investig Dermatol 2006;126:272-6.
71. Pattinson R, Rhoda N. Saving Babies 2012-2013: Ninth report on perinatal care in South Africa. Available from: https://www.ppip.co.za/wp-content/uploads/Saving-Babies-2012-2013.pdf. Accessed January 14, 2016.
72. Rodriguez G, Trent JT, Mirzabeigi M, Zaulyanov L, Bruce J, Vincek V. Toxic epidermal necrolysis in a mother and fetus. J Am Acad Dermatol 2006;55:S96-8.
73. Sweetnam WP, Barlow AJ, Denniss RG. Intrapartum toxic epidermal necrolysis. Arch Dis Childhood 1964;39:517-8.
74. Gold KJ, Abdul-Mumin AR, Boggs ME, Opare-Addo HS, Lieberman RW. Assessment of "fresh" versus "macerated" as accurate markers of time since intrauterine fetal demise in low-income countries. Int J Gynaecol Obstetr 2014; 125:223-7.
75. Lee HY, Walsh SA, Creamer D. Long term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis: the spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multi-disciplinary follow up. Br J Dermatol 2017;177:924-35.
76. Olteanu C, Shear NH, Chew HF, Hashimoto R, Alhusayen R, Whyte-Croasdaile S, et al. Severe physical complications among survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis [published online ahead of print October 19, 2017]. Drug Saf. https://doi.org/10.1007/s40264-017-0608-0.
77. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK, et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. J Plast Reconstr Aesthet Surg 2016;69:e119-53.
78. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK, et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016 (print summary - Full guidelines available at https://doi.org/10.1016/j.bjps.2016.01.034). J Plast Reconstruct Aesthet Surg 2016; 69:736-41.
79. Goldman JL, Chung W-H, Lee B, Hoetzenecker W, Micheletti RG, Yasuda S, et al. Adverse drug reaction causality assessment tools for drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: room for improvement. Clin Pharmacol Therapeut 2017;101:S30.
80. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490-3.
81. Dodiuk-Gad RP, Olteanu C, Jeschke MG, Cartotto R, Fish J, Shear NH. Treatment of toxic epidermal necrolysis in North America. J Am Acad Dermatol 2015;73:876-877.e2.
82. Stella M, Cassano P, Bollero D, Clemente A, Giorio G. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. Dermatology 2001;203:45-9.
83. Aihara M, Kano Y, Fujita H, Kambara T, Matsukura S, Katayama I, et al. Efficacy of additional i.v. immunoglobulin to steroid therapy in Stevens-Johnson syndrome and toxic epidermal necrolysis. J Dermatol 2015;42:768-77.
84. Lee HY, Lim YL, Thirumoorthy T, Pang SM. The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre. Br J Dermatol 2013;169: 1304-9.
85. Firoz BF, Henning JS, Zarzabal LA, Pollock BH. Toxic epidermal necrolysis: five years of treatment experience from a burn unit. J Am Acad Dermatol 2012; 67:630-5.
86. Stella M, Clemente A, Bollero D, Risso D, Dalmasso P. Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS): experience with high-dose intravenous immunoglobulins and topical conservative approach. A retrospective analysis. Burns 2007;33:452-9.
87. Gravante G, Delogu D, Marianetti M, Trombetta M, Esposito G, Montone A. Toxic epidermal necrolysis and Steven Johnson syndrome: 11-years experience and outcome. Eur Rev Med Pharmacol Sci 2007;11: 119-27.
88. Tan AW, Thong BY, Yip LW, Chng HH, Ng SK. High-dose intravenous immunoglobulins in the treatment of toxic epidermal necrolysis: an Asian series. J Dermatol 2005;32:1-6.
89. Kim KJ, Lee DP, Suh HS, Lee MW, Choi JH, Moon KC, et al. Toxic epidermal necrolysis: analysis of clinical course and SCORTEN-based comparison of mortality rate and treatment modalities in Korean patients. Acta Derm Venereol 2005;85:497-502.
90. Shortt R, Gomez M, Mittman N, Cartotto R. Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis. J Burn Care Rehabil 2004; 25:246-55.
91. Brown KM, Silver GM, Halerz M, Walaszek P, Sandroni A, Gamelli RL. Toxic epidermal necrolysis: does immunoglobulin make a difference? J Burn Care Rehabil 2004;25:81-8.
92. Al-Mutairi N, Arun J, Osama NE, Amr Z, Mazen AS, Ibtesam el A, et al. Prospective, noncomparative open study from Kuwait of the role of intravenous immunoglobulin in the treatment of toxic epidermal necrolysis. Int J Dermatol 2004;43:847-51.
93. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami Experience. Arch Dermatol 2003;139: 39-43.
94. Prins C, Kerdel FA, Padilla RS, Hunziker T, Chimenti S, Viard I, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol 2003;139:26-32.
95. Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. Acta Derm Venereol 2003; 83:430-2.
96. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol 2003;139:33-6.
97. Hirahara K, Kano Y, Sato Y, Horie C, Okazaki A, Ishida T, et al. Methylprednisolone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis: clinical evaluation and analysis of biomarkers. J Am Acad Dermatol 2013;69:496-8.
98. Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. Eur J Dermatol 2010;20: 743-7.
99. Yang Y, Xu J, Li F, Zhu X. Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China. Int J Dermatol 2009;48:1122-8.
100. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol 2007; 87:144-8.
101. Ducic I, Shalom A, Rising W, Nagamoto K, Munster AM. Outcome of patients with toxic epidermal necrolysis syndrome revisited. Plast Reconstruct Surg 2002;110:768-73.
102. Tripathi A, Ditto AM, Grammer LC, Greenberger PA, McGrath KG, Zeiss CR, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. Allergy Asthma Proc 2000; 21:101-5.
103. Schulz JT, Sheridan RL, Ryan CM, MacKool B, Tompkins RG. A 10-year experience with toxic epidermal necrolysis. J Burn Care Rehabil 2000;21: 199-204.
104. Murphy JT, Purdue GF, Hunt JL. Toxic epidermal necrolysis. J Burn Care Rehabil 1997;18:417-20.

105. Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol 2017;153:514-22.
106. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol 2014;71:941-7.
107. Singh GK, Chatterjee M, Verma R. Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid. Ind J Dermatol Venereol Leprol 2013;79:686-92.
108. Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maitre B, Revuz J, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2010;163:847-53.
109. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. J Trauma 2000;48:473-8.
110. Gonzalez-Herrada C, Rodriguez-Martin S, Cachafeiro L, Lerma V, Gonzalez O, Lorente JA, et al, PIELenRed Therapeutic Management Working Group. Ciclosporin use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. J Investig Dermatol 2017;137:2092-100.
111. Roujeau JC, Mockenhaupt M, Guillaume JC, Revuz J. New evidence supporting cyclosporine efficacy in epidermal necrolysis. J Investig Dermatol 2017;137:2047-9.
112. Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol 2014;71:278-83.
113. Hunger RE, Hunziker T, Buettiker U, Braathen LR, Yawalkar N. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. J Allergy Clin Immunol 2005;116:923-4.
114. de Sica-Chapman A, Williams G, Soni N, Bunker CB. Granulocyte colony-stimulating factor in toxic epidermal necrolysis (TEN) and Chelsea & Westminster TEN management protocol [corrected]. Br J Dermatol 2010;162:860-5.
115. Wang C-W, Su S-C, Hung S-I, Ho H-C, Yang C-H, Chung W-H. Efficacy of tumor necrosis factor—α antagonists in Stevens−Johnson syndrome and toxic epidermal necrolysis: a randomized controlled trial and immunosuppressive effects evaluation. Clin Transl Allergy 2016;6:S32.
116. Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet 1998;352:1586-9.
117. Morales ME, Purdue GF, Verity SM, Arnoldo BD, Blomquist PH. Ophthalmic manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis and relation to SCORTEN. Am J Ophthalmol 2010;150:505-510.e1.
118. Yip LW, Thong BY, Lim J, Tan AW, Wong HB, Handa S, et al. Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. Allergy 2007;62:527-31.
119. Gueudry J, Roujeau JC, Binaghi M, Soubrane G, Muraine M. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. Arch Dermatol 2009;145:157-62.
120. Kohanim S, Palioura S, Saeed HN, Akpek EK, Amescua G, Basu S, et al. Acute and chronic ophthalmic involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis—a comprehensive review and guide to therapy, II: ophthalmic disease. Ocul Surf 2016;14:168-88.
121. Power WJ, Ghoraishi M, Merayo-Lloves J, Neves RA, Foster CS. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. Ophthalmology 1995;102:1669-76.
122. Chang YS, Huang FC, Tseng SH, Hsu CK, Ho CL, Sheu HM. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. Cornea 2007;26:123-9.
123. Lopez-Garcia JS, Rivas Jara L, Garcia-Lozano CI, Conesa E, de Juan IE, Murube del Castillo J. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. Ophthalmology 2011;118:265-71.
124. Ueta M, Kannabiran C, Wakamatsu TH, Kim MK, Yoon KC, Seo KY, et al. Trans-ethnic study confirmed independent associations of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe ocular surface complications. Sci Rep 2014;4:5981.
125. Ueta M, Kaniwa N, Sotozono C, Tokunaga K, Saito Y, Sawai H, et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. Sci Rep 2014;4:4862.
126. Nakaji S, Ueta M, Sotozono C, Inatomi T, Kinoshita S. HLA-class I gene polymorphisms in Japanese Stevens-Johnson syndrome patients with ocular surface complications [in Japanese]. Nippon Ganka Gakkai Zasshi 2012;116:581-7.
127. Ueta M, Tokunaga K, Sotozono C, Inatomi T, Yabe T, Matsushita M, et al. HLA class I and II gene polymorphisms in Stevens-Johnson syndrome with ocular complications in Japanese. Mol Vision 2008;14:550-5.
128. Ueta M, Tokunaga K, Sotozono C, Sawai H, Tamiya G, Inatomi T, et al. HLA-A*0206 with TLR3 polymorphisms exerts more than additive effects in Stevens-Johnson syndrome with severe ocular surface complications. PloS One 2012;7:e43650.
129. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. Ophthalmology 2011;118:908-14.
130. Hsu M, Jayaram A, Verner R, Lin A, Bouchard C. Indications and outcomes of amniotic membrane transplantation in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control study. Cornea 2012;31:1394-402.
131. Ciralsky JB, Sippel KC. Prompt versus delayed amniotic membrane application in a patient with acute Stevens-Johnson syndrome. Clin Ophthalmol 2013;7:1031-4.
132. Gregory DG. New grading system and treatment guidelines for the acute ocular manifestations of Stevens-Johnson syndrome. Ophthalmology 2016;123:1653-8.
133. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. J Ocul Pharmacol Therapeut 2013;29:372-7.
134. Meneux E, Wolkenstein P, Haddad B, Roujeau JC, Revuz J, Paniel BJ. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. Obstetr Gynecol 1998;91:283-7.
135. Oplatek A, Brown K, Sen S, Halerz M, Supple K, Gamelli RL. Long-term follow-up of patients treated for toxic epidermal necrolysis. J Burn Care Res 2006;27:26-33.
136. Saeed H, Mantagos IS, Chodosh J. Complications of Stevens-Johnson syndrome beyond the eye and skin. Burns 2016;42:20-7.
137. Emberger M, Lanschuetzer CM, Laimer M, Hawranek T, Staudach A, Hintner H. Vaginal adenosis induced by Stevens-Johnson syndrome. J Eur Acad Dermatol Venereol 2006;20:896-8.
138. Kaser DJ, Reichman DE, Laufer MR. Prevention of vulvovaginal sequelae in Stevens-Johnson syndrome and toxic epidermal necrolysis. Rev Obstetr Gynecol 2011;4:81-5.
139. Van Batavia JP, Chu DI, Long CJ, Jen M, Canning DA, Weiss DA. Genitourinary involvement and management in children with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Pediatr Urol 2017;13:490.e1-7.
140. Woodcock J, Behrman RE, Dal Pan GJ. Role of postmarketing surveillance in contemporary medicine. Annu Rev Med 2011;62:1-10.
141. US Food and Drug Administration. FDA Adverse Event Reporting System (FAERS). Available from: https://www.fda.gov/drugs/informationondrugs/ucm135151.htm. Accessed December 7, 2017.
142. Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's Sentinel initiative—a comprehensive approach to medical product surveillance. Clin Pharmacol Therapeut 2016;99:265-8.
143. Denny JC, Bastarache L, Ritchie MD, Carroll RJ, Zink R, Mosley JD, et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. Nat Biotechnol 2013;31:1102-10.
144. Crawford DC, Crosslin DR, Tromp G, Kullo IJ, Kuivaniemi H, Hayes MG, et al. eMERGEing progress in genomics—the first seven years. Front Genet 2014;5:184.
145. Denny JC. Chapter 13: mining electronic health records in the genomics era. PLoS Comput Biol 2012;8:e1002823.
146. Kho AN, Pacheco JA, Peissig PL, Rasmussen L, Newton KM, Weston N, et al. Electronic medical records for genetic research: results of the eMERGE consortium. Sci Transl Med 2011;3:79re1.
147. Wei WQ, Denny JC. Extracting research-quality phenotypes from electronic health records to support precision medicine. Genome Med 2015;7:41.
148. Kirby JC, Speltz P, Rasmussen LV, Basford M, Gottesman O, Peissig PL, et al. PheKB: a catalog and workflow for creating electronic phenotype algorithms for transportability. J Am Med Inform Assoc 2016;23:1046-52.
149. Denny JC, Crawford DC, Ritchie MD, Bielinski SJ, Basford MA, Bradford Y, et al. Variants near FOXE1 are associated with hypothyroidism and other thyroid conditions: using electronic medical records for genome- and phenome-wide studies. Am J Hum Genet 2011;89:529-42.
150. Mosley JD, Shaffer CM, Van Driest SL, Weeke PE, Wells QS, Karnes JH, et al. A genome-wide association study identifies variants in KCNIP4 associated with ACE inhibitor-induced cough. Pharmacogenomics J 2016;16:231-7.

151. Karnes JH, Cronin RM, Rollin J, Teumer A, Pouplard C, Shaffer CM, et al. A genome-wide association study of heparin-induced thrombocytopenia using an electronic medical record. Thromb Haemost 2015;113:772-81.
152. Davis RL, Gallagher MA, Asgari MM, Eide MJ, Margolis DJ, Macy E, et al. Identification of Stevens-Johnson syndrome and toxic epidermal necrolysis in electronic health record databases. Pharmacoepidemiol Drug Saf 2015;24:684-92.
153. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126-33.
154. Ko TM, Tsai CY, Chen SY, Chen KS, Yu KH, Chu CS, et al. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ 2015; 351:h4848.
155. Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;79:1259-67.
156. Toh DS, Tan LL, Aw DC, Pang SM, Lim SH, Thirumoorthy T, et al. Building pharmacogenetics into a pharmacovigilance program in Singapore: using serious skin rash as a pilot study. Pharmacogenomics J 2014;14: 316-21.
157. Pan RY, Dao RL, Hung SI, Chung W H. Pharmacogenomic advances in the prediction and prevention of cutaneous idiosyncratic drug reactions. Clin Pharmacol Therapeut 2017;102:86-97.
158. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology 2014;83: 2077-84.
159. Dong D, Tan-Koi WC, Teng GG, Finkelstein E, Sung C. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. Pharmacogenomics 2015;16: 1781-93.
160. Tan-Koi WC, Sung C, Chong YY, Lateef A, Pang SM, Vasudevan A, et al. Tailoring of recommendations to reduce serious cutaneous adverse drug reactions: a pharmacogenomics approach. Pharmacogenomics 2017;18:881-90.
161. Ng CY, Yeh YT, Wang CW, Hung SI, Yang CH, Chang YC, et al. Impact of the HLA-B(*)58:01 allele and renal impairment on allopurinol-induced cutaneous adverse reactions. J Investig Dermatol 2016;136:1373-81.
162. Chung WH, Chang WC, Stocker SL, Juo CG, Graham GG, Lee MH, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Ann Rheum Dis 2015;74:2157-64.
163. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
164. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134-9.
165. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006;16:297-306.
166. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. J Allergy Clin Immunol Pract 2017; 5:547-63.
167. Chan SH, Tan T. HLA and allopurinol drug eruption. Dermatologica 1989; 179:32-3.
168. Genin E, Schumacher M, Roujeau JC, Naldi L, Liss Y, Kazma R, et al. Genome-wide association study of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe. Orphanet J Rare Dis 2011;6:52.
169. Wu XT, Hu FY, An DM, Yan B, Jiang X, Kwan P, et al. Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. Epilepsy Behav 2010;19: 405-8.
170. Wang Q, Zhou JQ, Zhou LM, Chen ZY, Fang ZY, Chen SD, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. Seizure 2011;20:446-8.
171. Zhang Y, Wang J, Zhao LM, Peng W, Shen GQ, Xue L, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. Eur J Clin Pharmacol 2011;67:885-7.
172. Chen CB, Hsiao YH, Wu T, Hsih MS, Tassaneeyakul W, Jorns TP, et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology 2017;88:78-86.
173. Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, Chang PY, et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J 2014;14:281-8.
174. Yip VL, Pirmohamed M. The HLA-A*31:01 allele: influence on carbamazepine treatment. Pharmacogenomics Pers Med 2017;10:29-38.
175. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B*13:01 and the dapsone hypersensitivity syndrome. N Engl J Med 2013;369:1620-8.
176. Daly AK, Day CP. Genetic association studies in drug-induced liver injury. Semin Liver Dis 2009;29:400-11.
177. The Allele Frequency Net Database. Allele, haplotype and genotype frequencies in world populations. Available from: allelefrequencies.net. Accessed December 7, 2017.
178. Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA 2014;312:525-34.
179. Tassaneeyakul W, Prabmeechai N, Sukasem C, Kongpan T, Konyoung P, Chumworathayi P, et al. Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population. Pharmacogenet Genomics 2016;26: 225-34.
180. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14:1343-50.
181. Chung WH, Pan RY, Chu MT, Chin SW, Huang YL, Wang WC, et al. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. J Investig Dermatol 2015;135:2237-48.
182. Yang CW, Hung SI, Juo CG, Lin YP, Fang WH, Lu IH, et al. HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol 2007;120:870-7.
183. Wei CY, Chung WH, Huang HW, Chen YT, Hung SI. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. J Allergy Clin Immunol 2012;129:1562-1569.e5.
184. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci U S A 2012;109:9959-64.
185. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature 2012;486:554-8.
186. Su SC, Mockenhaupt M, Wolkenstein P, Dunant A, Le Gouvello S, Chen CB, et al. Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. J Investig Dermatol 2017;137: 1065-73.
187. Famularo G, Di Dona B, Canzona F, Girardelli CR, Cruciani G. Etanercept for toxic epidermal necrolysis. Ann Pharmacother 2007;41:1083-4.
188. Gubinelli E, Canzona F, Tonanzi T, Raskovic D, Didona B. Toxic epidermal necrolysis successfully treated with etanercept. J Dermatol 2009;36:150-3.
189. Flechner SM, Mulgoankar S, Melton LB, Waid TH, Agarwal A, Miller SD, et al. First-in-human study of the safety and efficacy of TOL101 induction to prevent kidney transplant rejection. Am J Transpl 2014;14:1346-55.
190. Wang CW, Chung WH, Cheng YF, Ying NW, Peck K, Chen YT, et al. A new nucleic acid-based agent inhibits cytotoxic T lymphocyte-mediated immune disorders. J Allergy Clin Immunol 2013;132:713-722.e11.
191. Saito N, Qiao H, Yanagi T, Shinkuma S, Nishimura K, Suto A, et al. An annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions. Sci Transl Med 2014;6:245ra95.
192. Sharma P, Wagner K, Wolchok JD, Allison JP. Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. Nat Rev Cancer 2011;11:805-12.
193. MediPaper Medical Communications Ltd. List of U.S. FDA Approved ImmuneCheckpoint Inhibitors. Available from: https://medi-paper.com/approved-immunotherapies/. Accessed December 7, 2017.
194. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016;60:12-25.
195. Lacouture ME, Wolchok JD, Yosipovitch G, Kahler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol 2014;71:161-9.
196. Harding JJ, Pulitzer M, Chapman PB. Vemurafenib sensitivity skin reaction after ipilimumab. N Engl J Med 2012;366:866-8.
197. Nayar N, Briscoe K, Fernandez Penas P. Toxic epidermal necrolysis-like reaction with severe satellite cell necrosis associated with nivolumab in a patient with ipilimumab refractory metastatic melanoma. J Immunother 2016;39: 149-52.

198. Vivar KL, Deschaine M, Messina J, Divine JM, Rabionet A, Patel N, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. J Cutan Pathol 2017;44:381-4.
199. Sanlorenzo M, Vujic I, Daud A, Algazi A, Gubens M, Luna SA, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. JAMA Dermatol 2015;151:1206-12.
200. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016;22:886-94.
201. Goldinger SM, Stieger P, Meier B, Micaletto S, Contassot E, French LE, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. Clin Cancer Res 2016;22:4023-9.
202. Sanchez Rodriguez R, Pauli ML, Neuhaus IM, Yu SS, Arron ST, Harris HW, et al. Memory regulatory T cells reside in human skin. J Clin Investigat 2014; 124:1027-36.
203. Scharschmidt TC, Vasquez KS, Truong HA, Gearty SV, Pauli ML, Nosbaum A, et al. A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 2015;43:1011-21.
204. Rosenblum MD, Gratz IK, Paw JS, Lee K, Marshak-Rothstein A, Abbas AK. Response to self antigen imprints regulatory memory in tissues. Nature 2011; 480:538-42.
205. Iwai S, Sueki H, Watanabe H, Sasaki Y, Suzuki T, Iijima M. Distinguishing between erythema multiforme major and Stevens-Johnson syndrome/toxic epidermal necrolysis immunopathologically. J Dermatol 2012;39:781-6.
206. Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. J Immunol 2009;182:8071-9.
207. Azukizawa H, Sano S, Kosaka H, Sumikawa Y, Itami S. Prevention of toxic epidermal necrolysis by regulatory T cells. Eur J Immunol 2005;35: 1722-30.
208. Gibson A, Faulkner L, Lichtenfels M, Ogese M, Al-Attar Z, Alfirevic A, et al. The effect of inhibitory signals on the priming of drug hapten-specific T cells that express distinct Vbeta receptors. J Immunol 2017;199:1223-37.
209. Koreth J, Matsuoka K, Kim HT, McDonough SM, Bindra B, Alyea EP III, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med 2011;365:2055-66.
210. Castela E, Le Duff F, Butori C, Ticchioni M, Hofman P, Bahadoran P, et al. Effects of low-dose recombinant interleukin 2 to promote T-regulatory cells in alopecia areata. JAMA Dermatol 2014;150:748-51.
211. He J, Zhang X, Wei Y, Sun X, Chen Y, Deng J, et al. Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. Nat Med 2016;22:991-3.
212. Koreth J, Kim HT, Jones KT, Lange PB, Reynolds CG, Chammas MJ, et al. Efficacy, durability, and response predictors of low-dose interleukin-2 therapy for chronic graft-versus-host disease. Blood 2016;128:130-7.

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Review Article

An Updated Review of the Molecular Mechanisms in Drug Hypersensitivity

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Drug hypersensitivity may manifest ranging from milder skin reactions (e.g., maculopapular exanthema and urticaria) to severe systemic reactions, such as anaphylaxis, drug reactions with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), or Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Current pharmacogenomic studies have made important strides in the prevention of some drug hypersensitivity through the identification of relevant genetic variants, particularly for genes encoding drug-metabolizing enzymes and human leukocyte antigens (HLAs). The associations identified by these studies are usually drug, phenotype, and ethnic specific. The drug presentation models that explain how small drug antigens might interact with HLA and T cell receptor (TCR) molecules in drug hypersensitivity include the hapten theory, the p-i concept, the altered peptide repertoire model, and the altered TCR repertoire model. The broad spectrum of clinical manifestations of drug hypersensitivity involving different drugs, as well as the various pathomechanisms involved, makes the diagnosis and management of it more challenging. This review highlights recent advances in our understanding of the predisposing factors, immune mechanisms, pathogenesis, diagnostic tools, and therapeutic approaches for drug hypersensitivity.

1. Introduction

Drug hypersensitivity reactions are an important public health problem due to their potential to cause life-threatening anaphylaxis and rare severe cutaneous adverse reactions (SCAR). Drug hypersensitivity can be induced by immunologically mediated reactions (referred as drug allergies) as well as nonallergic direct mast cell-mediated drug reactions. Immunologic reactions have been divided into four categories according to the classical Gell and Coombs system: type I reactions, which are immediate in onset and mediated by IgE and mast cells and/or basophils;

type II reactions, which are delayed in onset and caused by antibody- (usually IgG) mediated cell destruction; type III reactions, which are delayed in onset and caused by IgG drug immune complex deposition and complement activation; and type IV reactions, which are delayed in onset and are T cell mediated [1]. According to the World Allergy Organization (WAO), drug hypersensitivity reactions can also be categorized into immediate reactions and delayed reactions based upon the timing of the appearance of symptoms [2].

Immediate-type reactions usually occur within minutes or hours of drug exposure. The clinical manifestations range from pruritus, urticaria, angioedema, and bronchospasm to anaphylaxis. Type I reactions require the presence of drug-specific IgE or the portion of the drug that forms a hapten complex. Drug-specific IgE is produced upon the first exposure to the drug antigen, and then, it binds to basophils or mast cells with the high-affinity Fc receptor. Upon the next exposure to the same drug, two or more IgE molecules on the basophil or mast cell surface may then bind to one multivalent antigen molecule, initiating a series of cellular activation events. This activation causes the extracellular release of granules with preformed inflammatory mediators, including histamine, leukotrienes, prostaglandins, heparin, and other cytokines [3]. IgE-mediated immunologic drug allergy represents a smaller fraction of drug hypersensitivity compared with nonimmunologic drug hypersensitivity [4]. According to the WAO classification system, immunologic anaphylaxis can be caused by an IgE-mediated or non-IgE-mediated mechanism, whereas nonimmunologic anaphylaxis involves direct mast cell activation [2]. Regardless of the underlying mechanism, however, the clinical symptoms of both types of anaphylaxis are similar and often indistinguishable. The mechanism of immediate-type reactions is explained more fully later in this article. In this review, the terminology used to categorize "immediate" or "delayed" drug hypersensitivity is in accordance with the WAO classification system. At the same time, the immediate-type reactions discussed herein are composed of both IgE-mediated reactions as defined by the Gell and Coombs system, as well as non-IgE-mediated and nonimmunologic anaphylactic reactions.

Delayed-type reactions consist primarily of type IV reactions, which are T cell-mediated delayed-type drug hypersensitivity reactions. These reactions usually take several days or even weeks to manifest following drug exposure. These manifestations range from mild maculopapular exanthema (MPE), contact dermatitis, chronic allergic rhinitis, chronic asthma, nephritis, hepatitis, and fixed drug eruptions (FDEs) to life-threatening SCAR. SCAR includes drug reactions with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) [5]. The MPE phenotype consists of self-limited diffuse erythematous macules and papules without systemic involvement [6]. DRESS syndrome, meanwhile, is characterized by cutaneous involvement with typical skin eruptions (e.g., exfoliative dermatitis and generalized maculopapular exanthema), fever, atypical lymphocytosis, eosinophilia, lymphadenopathy, and systemic involvement (e.g., liver involvement and kidney involvement). This hypersensitivity syndrome was first named after many different terms had already been used to describe the syndrome, with those terms, such as "anticonvulsant hypersensitivity syndrome," "allopurinol hypersensitivity syndrome," and "sulfone syndrome," primarily depending on the culprit drug involved [7, 8]. The term "DRESS" was initially proposed by Bocquet et al. in 1996 in order to provide a more concise description of the syndrome and decrease the ambiguity resulting from the various terms previously used to refer to it [9]. That said, it should be noted that DRESS is also termed "DIHS" by Japanese experts, with the criteria of DRESS as defined by the RegiSCAR group and the criteria of DIHS as defined by Japanese experts being similar, except that HHV-6 reactivation is included in the diagnostic criteria for DIHS [10]. This nosology is somewhat confusing; however, there is a consensus that DRESS and DIHS are likely within the same disease spectrum. Specifically, patients with typical DIHS may represent a severe form of DRESS syndrome [11]. SJS and TEN (SJS/TEN) are characterized as a rapidly progressing blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment. SJS is defined as involving less than 10% body surface area skin detachment, SJS-TEN overlap as involving 10–29%, and TEN as involving more than 30% [12]. AGEP, meanwhile, typically presents as a sudden eruption of small nonfollicular pustules on a background of erythema with systemic involvement along with fever and neutrophilia [13].

Most forms of drug hypersensitivity involve T cell-mediated immune responses against specific drug/peptide antigens, leading to various clinical phenotypes. T cell receptor (TCR), $CD4^+$, and $CD8^+$ T cells are involved in the different delayed-type drug hypersensitivity reactions [14]. The molecular mechanisms and checkpoints for drug hypersensitivity include T cell activation and immune responses, cytotoxic proteins and cytokine/chemokine secretion, specific TCR clonotypes, impaired drug metabolism or clearance (e.g., the strong association of cytochrome P450 family 2 subfamily C member 9*3 *(CYP2C9*3)* with phenytoin-induced SCAR), and the cell death mechanisms (e.g., miR-18a-5p-induced apoptosis and annexin A1 and formyl peptide receptor 1-induced necroptosis in keratinocytes). In addition, genetic polymorphisms and specific *HLA* loci also play an important role (e.g., *HLA-B*15:02* for carbamazepine- (CBZ-) induced SJS/TEN, *HLA-B*58:01* for allopurinol-induced SCAR, and *HLA-B*57:01* for abacavir-induced hypersensitivity reactions). Moreover, environmental factors, autoimmune disorders, and patients with a prior medical history of viral infection have also been reported to be implicated in susceptibility to drug hypersensitivity.

2. Clinical Perspectives and Variabilities in Severe Drug Hypersensitivity

2.1. Immediate-Type Hypersensitivity. Immediate-type hypersensitivity reactions may range from urticaria and

angioedema to severe fatal reactions, such as bronchospasm and anaphylaxis. Anaphylaxis is a life-threatening systemic hypersensitivity reaction mainly mediated by mast cells and basophil activation via IgE-mediated, non-IgE-mediated, or nonimmunologic mechanisms. Drugs are the most common anaphylaxis triggers in adults, while foods are the most common triggers in children and teenagers [15]. The incidence of drug-induced anaphylaxis has been reported to range from 0.04 to 3.1%, with a mortality rate of around 0.65% [2]. NSAIDs are the main culprits, followed by beta-lactam antibiotics [16, 17]. Perioperative anaphylaxis also remains an issue due to the administration of various combinations of neuromuscular blocking agents (NMBAs), induction agents (e.g., propofol, etomidate, midazolam, and ketamine), and antibiotics [18, 19]. Nonsteroidal anti-inflammatory drugs (NSAIDs) (with the exception of pyrazolones) are believed to rarely be among the causes of IgE-mediated anaphylaxis, but such anaphylaxis is more commonly related to an aberrant arachidonic acid metabolism [20–22]. The non-IgE-mediated immunologic mechanisms can be mediated by IgG antibodies, as well as by complement or contact system activation, but non-IgE-mediated anaphylaxis is clinically indistinguishable from IgE-mediated anaphylaxis [23, 24]. The causes of non-IgE-mediated immunologic anaphylaxis include biologics, lipid incipients, and dextran [2]. In contrast, nonimmunologic anaphylaxis, previously regarded as a form of pseudoallergic drug reaction, involves the direct stimulation of mast cell degranulation. These reactions are limited to certain groups of drugs, including NSAIDs, such as aspirin, as well as opiates, vancomycin, quinolones, and NMBAs [24, 25]. For radiocontrast media-induced anaphylaxis, the mechanisms are not entirely clear and several mechanisms may be involved, including IgE-mediated or direct stimulating histamine release or the activation of the complement cascades [24, 26, 27].

Due to the complexity of NSAID-induced drug hypersensitivity, a panel of experts from the European Academy of Allergy and Clinical Immunology (EAACI) has proposed a classification and practical approach to cases of drug hypersensitivity caused by NSAIDs [28]. The most frequently occurring type of these cases is cross-reactive hypersensitivity, for which the mechanism is not immunological but, rather, is primarily linked to cycloxygenase-1 inhibition. This immunological type of NSAID-induced hypersensitivity includes NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/angioedema (NIUA) [28]. NSAIDs can also induce immunological (noncross-reactive) hypersensitivity reactions, including IgE-mediated single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), and T cell-mediated single-NSAID-induced delayed hypersensitivity reactions (SNIDHR). Both cross-reactive reactions and SNIUAA are immediate-type reactions [28].

2.2. Delayed-Type Hypersensitivity

2.2.1. Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Syndrome (DIHS). There have been no large epidemiologic studies of DRESS/DIHS, a shortcoming which could be due to the fact that the term "hypersensitivity syndrome" was instead used before [5]. It could also be explained by the difficulty of diagnosing DRESS/DIHS, which presents with a complex natural course, a wide diversity of manifestations, and various laboratory abnormalities, and also because there is no specific code for this condition [29]. The incidence of anticonvulsant-related DRESS/DIHS is about one per 1000 to one per 10,000 new users [30]. DRESS/DIHS can occur in pediatric patients, but is more common in adults [31]. Antiepileptic agents and allopurinol are the most commonly reported offending medications [32]. The symptoms often begin 2 to 6 weeks after drug incubation [9]. Damage to multiple systemic organs may occur during the course of DRESS/DIHS syndrome. The liver is most commonly involved among the organs, with liver involvement having been found in 51–84% of patients [33, 34]. Renal involvement also occurs frequently, having been reported in 10–57% of patients [33, 34]. Lung involvement is the third most common type of systemic involvement and may present in various forms ranging from nonspecific symptoms to interstitial pneumonitis, pleuritis, and acute respiratory distress syndrome [35, 36]. Cardiac involvement, meanwhile, has been reported in 4–27% of patients with DRESS/DIHS [37]. This complication is likely associated with the fatal outcomes of the condition, especially when acute necrotizing eosinophilic myocarditis occurs [38]. Several other systemic organs can also be involved in DRESS/DIHS, including the gastrointestinal tract, pancreas, central nervous system, and thyroid, while multiple organ failure associated with disseminated intravascular coagulation or hemophagocytic syndrome may also occur [31, 39]. The overall mortality rate of DRESS/DIHS is around 10% [32]. The likelihood of mortality in cases of DRESS/DIHS is primarily determined by the degree of systemic involvement [35]. Tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome (SIRS) have also been found to be associated with poor outcomes in DRESS/DIHS patients [33].

2.2.2. Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN). Large epidemiologic investigations of SCAR, especially SJS/TEN, have been performed in Europe beginning 30 years [40, 41]. The reported incidence rates of SJS/TEN for various countries and ethnicities have included 0.93–1.89 cases (Germany), 1.2 cases (France (TEN)), 1.4 cases (Italy), 5.76 cases (United Kingdom), 8.0 cases (Han Chinese), and 12.7 cases (United States) per million people per year [5, 40–45]. The large variation among these rates of incidence might be due to differences in the studies reporting them, including differences in the populations studied, generational differences, differing diagnostic criteria, and differing methodologies (such as the use of registration databases or electronic nationwide healthcare databases). SJS/TEN can occur in different age groups, but the incidences of SJS, SJS-TEN, and TEN appear to be lower in US children than in adults [46]. Racial disparities in SJS/TEN incidence were first reported by a large population-based study, which found that SJS/TEN is more strongly associated

with people of nonwhite ethnicities, particularly Asians and blacks [42]. Pharmacogenetic studies, meanwhile, have pointed out that the strength of genetic associations is related to the prevalence with which susceptibility alleles are carried in different ethnic populations, such as *HLA-B*15:02* and *HLA-B*58:01* in Asians [47, 48]. Although the above classical examples partially explain the phenomenon of specific drug hypersensitivity in specific ethnicities with specific genetic factors, not all cases of drug hypersensitivity can be fully elucidated using this approach.

Cases of SJS/TEN are primarily induced by medications, but *Mycoplasma pneumonia* infection, viral infection, and collagen vascular diseases have also been found to account for a small portion of such cases [49–52]. The European ongoing case-control surveillance of the SCAR (EuroSCAR) group used a case-control study to identify the drugs carrying a high risk of such reactions and found that they included sulfonamides, aromatic convulsants, allopurinol, oxicam nonsteroidal anti-inflammatory drugs, and nevirapine [53]. Newly developed drugs, such as anticancer target therapies, also have the potential to induce SJS/TEN [54]. SJS/TEN induced by monoclonal antibodies targeting the coinhibitory immune checkpoint with antiprogrammed death-1 (PD-1) (nivolumab) and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab) has likewise been reported [55, 56]. Proton pump inhibitors, meanwhile, have been known to induce type I hypersensitivity reactions, but they carry some risk of inducing life-threatening type IV hypersensitivity reactions as well [57]. That risk, however, is mostly confined to the first 8 weeks drug exposure, after which the onset of SCAR is much less likely [53]. Meanwhile, the ALDEN (ALgorithm for Drug causality in Epidermal Necrolysis) has been used to provide structured assistance for the assessment of culprit drugs in SJS/TEN patients [58].

The mortality rates of the various forms of SJS/TEN are high, at approximately 10% for SJS, 30% for overlapping SJS/TEN, and 50% for TEN, for an overall rate of about 25% [34, 59]. Indeed, the mortality rate for cases of TEN has remained high, with reported rates of 15.8%–49.0%, even with the overall improvements to health care in recent decades [42, 44, 60]. A disease severity scoring system called SCORTEN (SCORe of Toxic Epidermal Necrolysis) built on seven independent variables (age > 40 years; presence of malignancy; body surface area involved > 10%; serum urea nitrogen level > 28 mg/dL; glucose level > 252 mg/dL; bicarbonate [HCO_3] level < 20 mEq/L; and heart rate > 120 beats per minute) can be used to help predict mortality in individual cases of SJS/TEN [61, 62]. Modified versions of this scoring system may be needed for specific populations, like pediatric patients [63].

2.2.3. Acute Generalized Exanthematous Pustulosis (AGEP). The annual incidence of AGEP is estimated to be one to five per million [64]. The EuroSCAR group conducted a large case cohort study of 97 validated cases of AGEP [13]. The mean age of the patients was 56 years (range: 4–91 years) [13]. The list of drugs reported to have been involved is extensive, but certain medications such as aminopenicillins, pristinamycin, quinolones, terbinafine, diltiazem, antimalarials, and Chinese herbs are known to be associated with higher risks of AGEP [13, 65]. The mortality rate of AGEP has been reported to be about 4%, a relatively low rate compared to those of SJS/TEN and DRESS/DIHS [13].

3. Genetic Factors in Drug Hypersensitivity

3.1. Genetic Factors in Immediate-Type Drug Hypersensitivity. Genetic predisposing factors have been reported in cases of immediate-type drug hypersensitivity resulting from the use of beta-lactams, aspirin, and other NSAIDs. Interestingly, HLA class II genes (*HLA-DRA* and the *HLA-DRA*|*HLA-DRB5* interregion) have been linked to immediate reactions to beta-lactams (Table 1) [66]. The genetic variants of proinflammatory cytokines (*IL4*, *IL13*, *IL10*, *IL18*, *TNF*, and *IFNGR1*), the cytokine receptor (*IL4R*), the genes involved in the IgE/FceRI pathway (the galectin-3 gene (*LGALS3*)), and nucleotide-binding oligomerization domain (*NOD*) gene polymorphisms are also strongly associated with beta-lactam-induced immediate reactions (Table 2) [67–73].

The involvements of *HLA-DRA*, *ILR4*, *NOD2*, and *LGALS3* have also been further validated by a replication study [72]. *HLA-DRB1*13:02* and *HLA-DRB1*06:09* are associated, meanwhile, with aspirin-induced urticaria/angioedema [74]. In addition, *HLA-B44* and *HLA-Cw5* have also been reported to be associated with chronic idiopathic urticaria associated with aspirin- and/or NSAID-induced hypersensitivity [75]. Several genetic predisposing factors have been reported to be associated with immediate-type aspirin hypersensitivity, with those factors involving cytokines (TGFB1, TNF, and IL18) and the production and release of mediators (LTC4S, TBXA2R, PTGER4, FCER1A, MS4A2, FCER1G, and HNMT) [76, 77]. Immediate-type hypersensitivity to NSAIDs has also been reported to be associated with genes belonging to the arachidonic acid pathway (*ALOX5*, *ALOX5AP*, *ALOX15*, *TBXAS1*, *PTGDR*, and *CYSLTR1*) [72, 78]. However, the association of common genetic variations in histamine receptor genes was not found in patients with hypersensitivity to NSAIDs [79].

3.2. Genetic Factors in Delayed-Type Drug Hypersensitivity. Recently, the number of pharmacogenetic studies of HLA-associated drug hypersensitivity and related drug-induced syndromes, such as fixed drug reaction, delayed rash, lupus erythematosus, drug-induced liver disease, DRESS/DIHS, SJS, and TEN, has been increasing. These associations are usually drug and ethnic specific (Table 1), which implies that specific HLA molecules may have higher binding affinities for specific drug antigens and present the drug antigens to specific TCRs, causing a series of T cell activations and adverse immune responses.

3.2.1. Aromatic Anticonvulsants. Aromatic anticonvulsants, such as carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC), and lamotrigine (LTG), are known to carry higher risks of inducing SCAR. A strong genetic association between *HLA-B*15:02* and CBZ-induced SJS/TEN was found in 2004 in Han Chinese (corrected P value $= 3.1 \times 10^{-27}$, odds ratio (OR) = 2504, and 95% confidence interval

Table 1: HLA association with various phenotypes of drug hypersensitivity in different populations.

Associated drug	HLA allele	Hypersensitivity reactions	Ethnicity	Reference
Aromatic anticonvulsants				
Carbamazepine	*B*15:02*	SJS/TEN	Han Chinese, Thai, Indian, Malaysian, Vietnamese, Singaporean, Hong Kongese	[45, 82, 83, 226–230]
	*A*31:01*	DRESS	Han Chinese, European, Spanish	[86, 87, 231]
	*A*31:01*	DRESS/SJS/TEN	Northern European, Japanese, Korean	[88–90]
	*B*15:11*	SJS/TEN	Han Chinese, Japanese, Korean	[89, 232, 233]
	*B*59:01*	SJS/TEN	Japanese	[234]
	*B*38:01*	SJS/TEN	Spanish	[231]
	*B*15:02*	SJS/TEN	Han Chinese, Thai	[81, 84]
	*B*15:02*	SJS/TEN	Han Chinese, Thai	[81, 83]
Oxcarbazepine Phenytoin	*B*15:02*, *B*13:01*, *B*51:01*	SJS/TEN	Han Chinese, Japanese, Malaysian	[91]
	*A*33:03*, *B*38:02*, *B*51:01*, *B*56:02*, *B*58:01*, *C*14:02*	SJS/TEN	Thai	[235]
	*B*51:01*	DRESS	Thai	[235]
	*B*15:13*	DRESS/SJS/TEN	Malaysian	[236]
	*CYP2C9*3*	DRESS/SJS/TEN	Han Chinese, Japanese, Malaysian	[91]
	*CYP2C9*3*	SJS/TEN	Thai	[235]
Phenobarbital Lamotrigine	*B*15:02*	SJS/TEN	Han Chinese	[81, 85, 237]
	*B*38; B*58:01*, *A*68:01*, *Cw*07:18*	SJS/TEN	European	[93, 238]
	*B*38:01*	SJS/TEN	Spanish	[231]
	*A*31:01*	SJS/TEN	Korean	[239]
	*A*24:02*	DRESS/SJS/TEN	Spanish	[231]
Allopurinol	*B*58:01*	DRESS/SJS/TEN	Han Chinese, Thai, Japanese, Korean, European	[92–96]
Antiretroviral drugs				
Abacavir	*B*57:01*	HSS	European, African	[98, 99]
Nevirapine	*DRB1*01:01*	DRESS	Australian	[240]
	*B*35:05*	DRESS	Thai	[101]
	*B*14:02*, *Cw*08:01*, *Cw*08:02*	HSS	Sardinian, Japanese	[102, 241]
	*C*04:01*	DRESS/SJS/TEN	Malawian	[242]
Antibiotics				
Beta-lactam	*DR9*, *DR14.1*, *DR17*, *DR4*	Immediate-type drug hypersensitivity	Chinese	[243]
	DRA rs7192, *DRA* rs8084	Immediate-type drug hypersensitivity	Spanish, Italian	[66]
Cotrimoxazole	*B*15:02*, *C*06:02*, *C*08:01*	SJS/TEN	Thai	[244]
Dapsone	*B*13:01*	HSS	Han Chinese	[105]
Sulfamethoxazole	*B*38:02*	SJS/TEN	European	[93]
Sulfonamide	*A*29*, *B*12*, *DR*7*	TEN	European	[245]
NSAIDs				
Aspirin	*DRB1*13:02*, *DRB1*06:09*	Urticaria/angioedema	Korean	[74]
Aspirin and other NSAIDs	*DRB1*11*	Urticaria/angioedema and hypotension/laryngeal edema	Spanish	[246]
Aspirin and other NSAIDs	*B*44*, *Cw*5*	Chronic idiopathic urticaria	Italian	[75]

Table 1: Continued.

Associated drug	HLA allele	Hypersensitivity reactions	Ethnicity	Reference
Oxicam NSAIDs	*B*73:01*	SJS/TEN	European	[93]
Other drugs				
Methazolamide	*B*59:01*, *CW*01:02*	SJS/TEN	Korean, Japanese	[108]

DRESS: drug reaction with eosinophilia and systemic symptoms; HSS: hypersensitivity syndrome; MPE: maculopapular exanthema; NSAIDs: nonsteroidal anti-inflammatory drugs; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

Table 2: Genetic association with pathogenetic pathways in immediate-type drug hypersensitivity.

Associated drug	Ethnicity	Cytokines/chemokines	Production and release of mediators	Drug metabolism	Others	Reference
Beta-lactam antibiotics	Korean	—	*MS4A2*	—	—	[247, 248]
	Chinese	*IL4R*, *IL4*, *IL10*, *IL13*, *IFNGR1*, *STAT6*	—	—	—	[69, 70, 249–252]
	Italian	*IL4R*, *IL13*, *NOD2*	*LGALS3*	—	—	[66, 68, 73]
	French	*IL4R*, *IL10*	—	—	—	[253]
	American	*IL4R*, *IL4*	—	*LACTB*	—	[67]
	Spanish	*IL4R*, *TNF*, *NOD2*	*LGALS3*	—	—	[66, 73, 254, 255]
Aspirin	Korean	*IL18*, *TGFB1*, *TNF*	*ALOX5*, *FCER1A*, *FCER1G*, *HNMT*, *TBXA2R*, *PTGER4*	—	—	[76, 256–263]
	Poles	—	*LTC4S*	—	*GSTM1*	[264]
	Venezuelan	—	*LTC4S*	—	—	[265]
NSAIDs	Spanish	—	*ALOX5*, *ALOX5AP*, *ALOX15*, *CTSLTR1*, *DAO*, *PPARG*, *PTGDR*, *TBXAS1*	—	*CEP68*	[78, 266, 267]
	French	—	*ALOX5*, *PTGER1*	—	—	[268]
	Brazilian	*IL4R*, *IL10*	*DAO*	—	*CTLA4*	[269]

(CI) = 126–49,522) and has further been validated in cohorts of various other Asian populations including Thai, Indian, Malaysian, Vietnamese, Singaporean, and Hong Kongese cohorts [45, 80]. The *HLA-B*15:02* allele has also been identified as the common risk factor for SJS/TEN caused by other aromatic antiepileptic drugs [81], such as PHT [82, 83], OXC [84], and LTG [85]. The association between *HLA* alleles and CBZ-induced SCAR is phenotype and ethnic specific. The *HLA-A*31:01* allele is as specific predictor of CBZ-induced DRESS but not CBZ-induced SJS/TEN in Europeans and Han Chinese [86, 87]. In contrast, a strong association with *HLA-A*31:01* was found in CBZ-induced cutaneous adverse drug reactions (cADR) but not only in DRESS/DIHS in Northern Europeans, Japanese, and Koreans [88–90]. In addition to HLA alleles, a genome-wide association study showed a strong association of CYP2C9*3 with PHT-induced SCAR in patients from Taiwan, Japan, and Malaysia and this finding was further supported by evidence indicating the delayed clearance of plasma PHT levels in PHT-induced SCAR [91].

3.2.2. Allopurinol. Allopurinol is a first-line drug used to treat gouty arthritis and urate nephropathy. In 2005, Hung et al. reported that *HLA-B*58:01* was the genetic risk marker for allopurinol-induced hypersensitivity in Han Chinese (corrected P value $= 4.7 \times 10^{-24}$, OR = 580.3, and 95% CI = 34.4–9780.9) [92]. This correlation was subsequently validated among different populations, including various Asian and European populations [93–96]. The gene dosage effect of *HLA-B*58:01* also influences the development of allopurinol-induced hypersensitivity (OR = 15.3 for *HLA-B*58:01* heterozygotes and OR = 72.5 for homozygotes), and the strength of the *HLA-B*58:01* association has been found to be correlated with the disease severity of allopurinol-induced hypersensitivity (OR = 8.5 for MPE, OR = 44.0 for SCAR) [97].

3.2.3. Antiretroviral Drugs, Antibiotics, and Other Drugs. The antiretroviral drugs, such as abacavir and nevirapine, are also known to cause hypersensitivity reactions. The association with abacavir was first found in 2002 due to the significant association between the *HLA-B*57:01* and abacavir-induced hypersensitivity reactions (corrected P value < 0.0001, OR = 117, and 95% CI = 29–481). The positive predictive value of *HLA-B*57:01* for abacavir hypersensitivity reactions has been reported to be 55% in Caucasians [98, 99]. Nevirapine, meanwhile, has been associated with nevirapine-induced hypersensitivity or DRESS in patients with *HLA-DRB1*01:01* in Western Australia [100], *HLA-B*35:05* in Thailand [101], and *HLA-Cw8* in Japan [102]. In addition, several antibiotic-induced hypersensitivity reactions and pharmacogenomic associations have also been reported,

such as sulfonamide-induced allergic reactions [103], penicillin-induced SCAR [104], *HLA-B*13:01* and dapsone-induced hypersensitivity syndrome in Chinese [105], *HLA-B*57:01* and flucloxacillin-induced liver injury [106], and *HLA-A*02:01* and *HLA-DQB1*06:02* and amoxicillin-clavulanate hepatitis [107]. Other pharmacogenomic associations include *HLA-B*59:01* and methazolamide-induced SJS/TEN in Koreans and Japanese [108], *HLA-B*73:01* and oxicam-induced SJS/TEN in Europeans [93], and *ABCB11*, *C-24T*, *UGT2B7*2*, and *IL-4 C-590-A* and diclofenac-induced liver disease in Europeans [109, 110].

4. Cellular Immunology and Immune Mechanisms in Drug Hypersensitivity

4.1. Antigen Presentation and Processing. Drugs are considered to be foreign antigens and bind to the HLA/peptide/TCR complex to trigger immune and hypersensitivity reactions. There are four hypotheses regarding drug presentation mechanisms that have been proposed to explain how small drug antigens might interact with HLA and TCR in drug hypersensitivity: (1) the hapten theory, (2) the pharmacological interaction with immune receptors (p-i) concept, (3) the altered peptide repertoire model, and (4) the altered TCR repertoire model [111–115].

First, the hapten theory states that the culprit drugs or their reactive metabolites are too small to be immunogenic on their own, whereas they covalently bind to the endogenous peptides to form an antigenic hapten-carrier complex. The hapten-carrier complex is presented to the HLA molecule and then recognized by TCR, resulting in the induction of drug-specific cellular or humoral immune responses. The hapten theory has been shown to be valid in cases of penicillin-induced cADR [111, 116]. Second, the pharmacological interaction with immune receptor (p-i) concept postulates that drugs may directly, reversibly, and noncovalently bind to the HLA and/or TCR protein and bypass the classic antigen-processing pathway in antigen-presenting cells. Wei et al. previously found that CBZ/aromatic antiepileptic drugs can directly interact with *HLA-B*15:02* protein. No intracellular antigen processing or drug metabolism was involved in the *HLA-B*15:02* presentation of CBZ [112]. Oxypurinol, the reactive metabolite of allopurinol, provides another example of the p-i concept in that it can directly and immediately activate drug-specific T cells via the preferential use of *HLA-B*58:01* without intracellular processing [113]. Third, the altered peptide repertoire model states that the culprit drugs occupy the position in the peptide-binding groove of the HLA protein, changing the binding cleft and the peptide specificity of HLA binding. Abacavir-induced hypersensitivity has been found to belong to this model, as the crystal structure of *HLA-B*57:01* has been found to form complexes with abacavir and peptides [114, 115]. These studies showed that abacavir binds to the F-pocket of *HLA-B*57:01* and alters the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and resulting in polyclonal T cell activation and autoimmune-like systemic reaction manifestations. Finally, the altered TCR repertoire model suggests that some drugs, such as sulfamethoxazole, directly interact with TCR, but not with the peptides or HLA molecules. The drug antigens bind to specific TCRs and alter the conformation of those TCRs, giving them the potential to bind to HLA-self peptide complexes to elicit immune reactions [117]. In this model, TCR is regarded as an initial drug interaction molecule, suggesting that TCR is as crucial as HLA molecules and contributes to the occurrence of drug hypersensitivity. Furthermore, viruses have also been proposed to participate in HLA/drug/TCR interactions, in that they may provide exogenous peptides for drug presentation and play important roles in cADR [116].

4.2. Cellular Immunology and Immune Molecules Involved in Drug Hypersensitivity

4.2.1. Immediate-Type Drug Hypersensitivity. Immediate-type drug hypersensitivity can be mediated by IgE-mediated or non-IgE-mediated mechanisms [118]. IgE-mediated mechanisms are mediated by drug-specific IgE via an immune response to a hapten/carrier complex. In the primary drug sensitization, drug-specific IgE is formed when plasma cells are transformed from activated B cells and interact with T cells. In an allergic reaction, drug allergens bind to mast cells or basophils with high-affinity Fc receptors, to which drug-specific IgE is bound, causing degranulation of the mast cells or basophils that results in the release of various mediators, such as histamine, leukotrienes, prostaglandins, and cytokines [3]. Degranulation has recently been proposed to occur in two main forms that are related to reaction severity and progression: piecemeal degranulation and anaphylactic degranulation [2, 119]. Piecemeal degranulation is mediated through the upregulation of CD203c on basophils via the formation of small vesicles from the histamine-containing granules quickly shuttling to the plasma membrane to cause more severe and rapid reactions [120]. Anaphylactic degranulation results in the fusion of the main histamine-containing granules with the plasma membrane, releasing the entire contents of granules to the extracellular space and exposing CD63 on the surface of basophils [120].

The non-IgE-mediated immunologic mechanisms are mediated by IgG antibodies or by complement activation [23, 24]. IgG-mediated anaphylaxis has been established in mouse models, wherein the use of drugs with specific IgG bound to FcγRIII stimulates the release of platelet-activating factor (PAF) by basophils, macrophages, or neutrophils [24]. Although the IgG-mediated anaphylaxis mechanism has not been fully demonstrated in humans, some studies have shown that PAF is an essential mediator in such anaphylaxis [121]. In addition, a novel gain-of-function splice variant of FcγR FcγRIIA has been identified with the presence of IgG anti-IgA antibodies in patients with common variable immunodeficiency who developed anaphylaxis after intravenous immunoglobulin infusion [122]. Moreover, biological agents with IgA and infliximab have been shown to induce anaphylaxis in the absence of specific IgE but with high levels of specific IgG [123–125]. These observations also provide some additional evidence

for IgG-mediated anaphylaxis. Furthermore, complement activation can be induced through the absence of agent-specific IgE or IgG antibody immunocomplexes [24]. This condition can be observed in patients undergoing hemodialysis with a new dialysis membrane, protamine neutralization of heparin, and polyethylene glycol infusion [23, 126]. Drugs solubilized in therapeutic liposomes and lipid-based excipients (such as Cremophor EL used as the diluent for older preparations of propofol and paclitaxel) can form large micelles with serum lipids and cholesterol to stimulate the complement system [23, 126]. This activation of complement mechanisms further causes the release of C3a, C5a, and C5b-9, which trigger, in turn, the activation of mast cells, basophils, and other cells via their specific receptors, resulting in degranulation and mediator release [24].

The nonimmunologic-type hypersensitivity reaction directly activates mast cell degranulation without involving the activation of the immune system. There are several specific agents that induce different mechanisms beyond the direct immunoglobulin-mediated activation or complement activation. Oversulfated chondroitin sulfate-contaminated heparin was found to have caused various cases of anaphylaxis around 2007-2008 via the direct activation of the kinin system with increased production of bradykinin, C3a, and C5a [127]. The triggering of factor XII-driven contact system activation-mediated bradykinin formation also plays a key role in anaphylaxis [24]. NSAIDs, including aspirin, can result in anaphylactic reactions via the inhibition of cyclooxygenase with a decrease in the production of prostaglandins and the increased generation of cysteinyl leukotrienes [23]. Vancomycin can directly activate mast cells and/or basophils, leading to the release of histamine [128]. This mechanism was suggested to be mediated via the calcium-dependent activation of phospholipase-C and phospholipase-A2 pathways [128]. Opiates (e.g., meperidine, codeine, and morphine) also cause histamine release via direct mast cell degranulation [129]. Recently, it was proposed that nonimmunologic hypersensitivity reactions may also be mediated through the MAS-related G protein-coupled receptor-X2 (MRGPRX2) in cases involving specific drugs, such as icatibant, neuromuscular blocking drugs, and quinolone antibiotics [25]. The interaction of certain drugs with this mast cell receptor can stimulate degranulation and the release of TNF-α and prostaglandin D2 (PGD2), among other molecules, leading to nonimmunologic anaphylactic reactions [25]. The mouse counterpart of MRGPRX2 that participates in peptidergic drug-induced pseudoallergic reactions has been newly identified and could potentially be applied in preclinical screening models [25, 130].

4.2.2. Delayed-Type Drug Hypersensitivity. The main concept used to explain the pathomechanisms of delayed-type drug hypersensitivity consists of the view that specific T lymphocytes or natural killer (NK) cells are activated upon antigen recognition or Fas/FasL interaction and that various cytotoxic proteins, including perforin/granzyme B, and granulysin, are then released to attack keratinocytes or other cells, inducing skin rash or epidermal necrosis. In addition, several other cytokines/chemokines, including TNF-α, IFN-γ, GM-CSF, TARC/CCL17, IL-6, IL-8/CXCL8, IL-15, and IL-36, are also known to participate in the immune reactions of drug hypersensitivity. These cytokines/chemokines have been found to be highly expressed in the skin lesions, blister fluids, blister cells, peripheral blood mononuclear cells (PBMC), or plasma of patients. These immune mediators are responsible for the trafficking, proliferation, regulation, or activation of T lymphocytes and other leukocytes, thereby affecting the clinical presentations of drug hypersensitivity in various ways (Table 3).

(1) Fas-FasL Interaction. Fas ligand (FasL) belongs to the tumor necrosis factor (TNF) family. The binding of Fas and FasL plays an important role in regulating the immune system and is involved in the apoptosis of epidermal cells in patients with drug hypersensitivity. Briefly, upon Fas–FasL interaction, the Fas-associated death domain protein (FADD) is recruited and binds to the Fas–FasL complex. The FADD then recruits procaspase 8, bringing multiple copies of procaspase 8 together, which in turn autoactivate to become caspase 8, triggering the caspase cascade and resulting in intracellular DNA degradation [131]. Viard et al. proposed that a suicidal interaction between Fas and FasL, which are both expressed by keratinocytes, leads to the extensive necrosis of epidermal cells in individuals with SJS/TEN [132].

(2) Perforin/Granzyme B. A controversial hypothesis suggests that perforin and granzyme B play more important roles in the keratinocyte death in SJS/TEN than does the Fas–FasL interaction [133]. Granzymes are serine proteases that are released by cytoplasmic granules and can induce programmed cell death in the target cells. Upon activation, drug-specific cytotoxic T lymphocytes (CTL) and NK cells produce perforin, which can bind to and punch a channel through the cell membrane, promoting the entry of granzyme B into the target cells to activate the caspase cascade and the succeeding apoptosis [134]. Delayed reactions to drugs have shown that increasing levels of perforin and granzyme B are related to the disease severity of drug hypersensitivity [131].

(3) Granulysin. Granulysin is a cytolytic protein mainly released by CTL and NK cells. It functions to create holes in the cell membranes and thereby destroy target cells. In 2008, Chung et al. reported that 15 kDa secretory granulysin serves as a key mediator for the disseminated keratinocyte apoptosis seen in SJS/TEN [135]. In that study, the increased level of granulysin in blister fluids from the skin lesions of SJS/TEN patients was much higher than the levels of other cytotoxic proteins, such as perforin, granzyme B, and FasL, and depleting the granulysin reduced the cytotoxicity [135]. Further studies demonstrated that granulysin is strongly expressed in patients with drug-induced FDE, DRESS/DIHS, and SJS/TEN but not MPE [136–138].

(4) TNF-α, IFN-γ, TARC, IL-15, and Other Cytokines/Chemokines in SJS/TEN, DRESS/DIHS, and AGEP. TNF-α is a major proinflammatory cytokine and is produced by

Table 3: Delayed-type drug hypersensitivity-related cytokines and chemokines.

Phenotype	Cytokines/chemokines	Skin or blister	Plasma	PBMC	References
DRESS/DIHS	TNF-α		+		[160]
	IFN-γ	+	+	+	[270–272]
	IL-2			+	[270]
	IL-4			+	[270]
	IL-5			+	[270]
	IL-6		+		[160]
	IL-13			+	[270]
	IL-15		+		[138]
	TARC/CCL17		+		[273]
SJS/TEN	TNF-α	+	+	+	[131, 138, 141–143, 274, 275]
	IFN-γ	+		+	[131, 142, 143, 274]
	IL-2	+		+	[131, 143]
	IL-5	+			[143]
	IL-6	+	+	+	[143, 153, 154, 138]
	IL-8/CXCL8		+		[138]
	IL-10	+	+	+	[142, 153]
	IL-12	NS			[142]
	IL-13	+			[143]
	IL-15	NS	+		[142, 138]
	IL-18	+			[142]
	CCR3	+			[143]
	CXCR3	+			[143]
	CXCR4	NS			[143]
	CCR10			+	[152]
AGEP	IL-8/CXCL8	+			[145, 146]
	IL-36	+			[147, 148]
	GM-CSF			+	[145]

AGEP: acute generalized exanthematous pustulosis; CCR: C–C chemokine receptor; CXCR: CX chemokine receptor; DIHS: drug-induced hypersensitivity syndrome; DRESS: drug reactions with eosinophilia and systemic symptoms; IFN-γ: interferon-γ; IL: interleukin; NS: not significant; SJS/TEN: Stevens–Johnson syndrome and toxic epidermal necrolysis; TNF-α: tumor necrosis factor-α.

macrophages, T lymphocytes, NK cells, neutrophils, mast cells, and eosinophils. It regulates immune responses through the induction of cell apoptosis, activation, differentiation, and inflammation [139]. TNF-α was highly expressed and suggested to be responsible for the extensive necrosis of skin lesions of SCAR patients [140, 141]. IFN-γ is critical for both innate and adaptive immunity against viral and bacterial infection, and it is predominantly produced by $CD4^+$ T helper cells, $CD8^+$ CTL, and NK cells. IFN-γ was found to be increased in the skin tissue, blister cells, and plasma of patients with erythema multiforme, SJS, TEN, and DRESS/DIHS [131, 142, 143]. The immune mechanism of AGEP is not yet well understood. However, high levels of IL-8/CXCL8 production and the recruitment of neutrophils have been observed in the skin lesions of AGEP patients [144–146]. Mutations in the *IL36RN* gene encoding the IL-36 receptor antagonist (IL-36Ra) have also been identified in AGEP patients [147, 148]. DRESS/DIHS is characterized by leukocytosis with atypical lymphocytosis or eosinophilia [149]. Serum thymus and activation-regulated chemokine (TARC) was identified as a potential biomarker for early indication of the disease and a predictor of disease activity in DRESS/DIHS [150, 151]. Compared to patients with MPE and SJS/TEN, the TARC levels in patients with DRESS/DIHS are significantly higher during the acute phase and are correlated with skin eruptions [151]. Interleukin-15 (IL-15) is a cytokine that can induce the proliferation of NK cells and other leukocytes, and it has been found to be associated with the disease severity and mortality of SJS/TEN [138]. IL-15 has also been shown to enhance the cytotoxicity of cultured NK cells and blister cells from TEN patients [138]. In addition, other cytokines and chemokine receptors, including IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-18, CCR3, CXCR3, CXCR4, and CCR10, have been found to be upregulated in the skin lesions, blister fluids, PBMC, or plasma of drug hypersensitivity patients and to participate in the immune regulation of drug hypersensitivity [131, 138, 142, 143, 152–154].

(5) Syndrome-Specific Effector Cells. SJS/TEN is characterized by profound necrosis localized to the epidermis. Cytotoxic CD8 T cells, natural killer cells, and natural killer T cells

producing the cytotoxic molecules, especially granulysin, which causes extensive keratinocyte death, are enriched in blister fluid samples from the skin lesions of patients with SJS/TEN. Granulysin serum levels are correlated with the severity of acute disease and mortality [135, 155]. These cytotoxic cells mediate the disease pathogenesis. It is shown that the function of regulatory T cells (Tregs) in SJS/TEN is inadequate, although present in normal frequency [156]. Immunological changes of DRESS/DIHS are characterized by the increase of atypical lymphocytes or eosinophils [149, 157]. Eosinophilia can be observed in 60–95% of DRESS/DIHS patients at the early stage of the illness [32, 157]. Most of DRESS patients had increased numbers of $CD4^+$ T cells in the acute stage, which was associated with the severity of clinical symptoms, such as the extent of skin rash and reactivations of virus [158]. In addition, Tregs play important roles in DRESS/DIHS pathogenesis. Dramatic expansions of functional Tregs are found in the acute stage of DRESS/DIHS [156]. It is hypothesized that $CD4^+FoxP3^+$ T cells that are home to skin serve to limit the severity of acute disease by regulating the cytotoxic effector T cell responses. However, Treg responses eventually exhaust and this might contribute to ongoing viral replication and intermittent recurrence of clinical symptoms [156, 159]. In patients with AGEP, it is shown that the increased neutrophilic inflammatory processes are regulated by T lymphocytes, which is important in the pathogenesis. The recruitment of neutrophils was observed in the skin lesions of the patients with the late phase of disease development [144, 145].

5. Environmental Factors and Viral Infections in Drug Hypersensitivity

In addition to drug antigens, hypersensitivity reactions may be induced by other pathogens, such as *Mycoplasma pneumonia*, or viral infections. Virus-drug interactions associated with viral reactivation may also exist. For example, it is well known that human herpesvirus-6 (HHV-6) plays an important role in DRESS/DIHS. HHV-6 reactivation in patients with DRESS/DIHS may increase T cell activity after the initiation of the drug eruption and induce the synthesis of proinflammatory cytokines, including TNF-α and IL-6, which may in turn modulate the T cell-mediated responses [160]. Shiohara et al. reviewed the associations between viral infections and drug rashes, as well as the mechanisms by which viral infections induce drug rashes. The sequential reactivations of several herpes viruses (HHV-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)) were found to be coincident with the clinical symptoms of drug hypersensitivity reactions [161]. Chung et al. reported that a new variant of coxsackievirus A6 (CVA6) acting as the causative agent may induce widespread mucocutaneous blistering reactions mimicking the features of erythema multiforme major or SCAR [52]. In addition, the virus may also provide exogenous peptides for drug presentation and participate in HLA/drug/TCR interactions. White et al. recently proposed that some patients may acquire primary infection via HHVs or other pathogens that in turn induce drug hypersensitivity [116]. The presence of HHV peptides in patients with high-risk HLA alleles may trigger the activation of cytotoxic T cells, thereby resulting in the development of SCAR. The pathogenic factors underlying the unusual presentations of drug hypersensitivity related to viral infections need to be further investigated.

6. Diagnostic Tools for Drug Hypersensitivity

6.1. Diagnostic Tools for Immediate-Type Drug Hypersensitivity. The most commonly used laboratory test for confirming a diagnosis of anaphylaxis consists of determining the patient's total serum tryptase level [162]. Serial measurements of tryptase levels can be taken during an anaphylactic episode, although measurements of the baseline level are considered to be most useful. In fact, while serial measurements of tryptase levels taken during an anaphylactic episode can serve as useful markers for evaluating these reactions, this approach is not used so widely in clinical practice due to the limitations involved in measuring tryptase during the acute phase of an episode. Elevated levels of histamine, the first mediator released by mast cells, in plasma or urine are also consistent with anaphylaxis [2]. However, plasma histamine levels are only transiently elevated, making them of little utility if the patient is evaluated more than 1 hour after onset of the episode [163]. At the same time, normal levels of tryptase or histamine do not preclude a diagnosis of drug hypersensitivity [15]. Other newly identified biomarkers, such as PAF and carboxypeptidase A3, bring hope for enhancing diagnostic accuracy, although their use remains experimental [15, 164].

For IgE-mediated hypersensitivity reactions, serum drug-specific IgE (sIgE) quantification and the basophil activation test (BAT) are frequently used to assess the culprit drug. The tests used to conduct sIgE immunoassays consist of radioallergosorbent testing (RAST), enzyme-linked immunosorbent assays (ELISAs), and fluoroenzyme immunoassays (FEIAs) [165]. While RAST or ELISAs are usually conducted using in-house techniques, FEIAs can be performed using commercial products, such as the ImmunoCAP-FEIA system [166–168]. Only a few products are available, meanwhile, for some drugs, particularly beta-lactam antibiotics [167, 169]. The sensitivity of the various immunoassays used has been found to average 62.9%, while the average specificity, PPV, and NPV are 89.2%, 83.3%, and 77.8%, respectively [168]. The average NPV is also relatively low in order to exclude allergic reactions and determine whether to perform a provocation test [170]. In comparison, the BAT test provides a higher average specificity (94.6%) and PPV (93.4%) than immunoassays [168]. The test uses flow cytometry after drug stimulation to determine the levels of basophil activation or degranulation markers; the upregulation of CD63 and CD203c is also usually measured [171]. Of note, the results of the BAT for aspirin/NSAID-induced hypersensitivity remain inconclusive due to the fact that they encompass both IgE-mediated allergic reactions and nonimmunological intolerances, limiting the use of the BAT in assessing non-IgE-mediated reactions [172]. Mediator release assays, meanwhile, measure the mediator released (histamine or leukotriene 4) in a supernatant upon cell activation after

drug stimulation, but these assays have exhibited sensitivity and specificity levels too low for them to be recommended for the purposes of diagnosis [169, 173].

6.2. Diagnostic Tools for Delayed-Type Drug Hypersensitivity. The discovery of biomarkers for drug hypersensitivity is crucial for clinical purposes, including the early diagnosis and better prediction of this disease in order to prevent complications. We previously found granulysin to be a key cytotoxic molecule responsible for disseminated keratinocyte necrosis through the action of cytotoxic lymphocytes or NK-cell-mediated cytotoxicity with no direct cellular contact [135]. A significant correlation between the granulysin levels in blister fluids and clinical severity was also found [135]. In addition, the serum granulysin levels in patients with SJS/TEN have also been found to be significantly elevated before the development of skin detachment or mucosal lesions but then to drop rapidly within 5 days of disease onset [136]. As a potential marker for the early phase of SJS/TEN, a simple rapid immunochromatographic test for elevated serum granulysin was developed for immediate clinical use. Additionally, prolonged elevation of serum granulysin has also been found in DIHS patients, indicating that such elevation could possibly be used for the purposes of early diagnosis and predicting disease prognosis [174]. Furthermore, the levels of IL-15 were correlated with the disease progression and mortality of SJS/TEN at early stage [138]. Serum IL-15 levels can be further utilized as a marker for early diagnosis and prognosis monitoring [138]. For DRESS/DIHS, serum TARC levels in patients with DRESS/DIHS have been reported to be significantly higher than those in patients with SJS/TEN and MPE during the acute phase and to be correlated with skin eruptions [151]. TARC was thus identified as a potential biomarker for the early indication and disease activity of DRESS/DIHS and also for determining the prognosis of systemic severity of inflammation in drug eruptions other than SJS/TEN [150, 151]. For AGEP, meanwhile, no specific markers for diagnosing or predicting the disease have been identified at present [175].

Drug rechallenge is considered the gold standard for confirming a potential offending drug; however, its use is not practical due to the possible life-threatening consequences. As such, there is still no standard method for the confirmation of drug causality. Nonetheless, since HLA genotyping has been useful in screening for populations at risk for SCAR, HLA genotyping might be helpful for identifying culprit drugs via specific HLA alleles in at-risk populations [48, 176]. Several *in vitro* tests can be used to assist in the confirmation of drug causality, but the exact sensitivity and specificity of such tests are not well known [177, 178]. There are several tests currently available: the lymphocyte transformation test (LTT), ELISpot (Enzyme-linked immunospot assay) intracellular cytokine staining, and the enzyme-linked immunosorbent assay (ELISA) for the secretion of cytotoxic mediators including inflammatory cytokines, chemokine–chemokine receptors, IFN-γ, Fas–Fas ligand, perforin, granzyme B, and granulysin [179]. The LTT is a reproducible test for measuring the enhanced proliferative response of PBMC after the sensitization of T cells to a drug [180]. However, the sensitivity of the test has reportedly varied among various studies involving various drugs and clinical phenotypes and different timings for use of the test [181, 182]. The relevance of using the LTT in testing for SJS/TEN was relatively lower those using than DRESS/DIHS and AGEP [182]. Several modifications can help to increase the sensitivity of the LTT or ELISPOT, including stimulation with anti-CD-3/CD28 antibody-coated microbeads with IL-2, depletion of Treg/CD25hi cells, or the combined addition of anti-CTLA4 and anti-programmed cell death ligand 1 (PD-L1) antibodies to PBMC cultures [183–185]. IFN-γ-ELISpot showed a similar sensitivity (67%) and specificity in DRESS, but a higher sensitivity (71%) in SJS/TEN [179]. The data for an ELISA-based test used to detect granulysin showed better sensitivity (86%) in SJS/TEN, but the evidence was limited due to the small number of cases in the study [186]. Further larger studies will thus be needed to confirm both the sensitivity and specificity.

In vivo patch tests provide a low-risk method for reproducing delayed hypersensitivity with moderate reexposure of patients to suspected offending drugs [187]. The value of patch testing depends on the phenotypes and drugs involved. The sensitivity of such testing is generally <70%, but higher sensitivities have been reported for AGEP and for some selected populations such as abacavir-hypersensitivity, carbamazepine-induced SJS/DRESS, and fixed drug eruption patients [178, 187, 188]. The skin tests involving a prick or intradermal testing are considered to be crucial tools for evaluating drug hypersensitivity reactions, including IgE-mediated or delayed-type hypersensitivity, in both the European and American guidelines [22, 189–191]. However, these skin tests are usually not suggested for SCAR patients due to the risk of relapse, although late-reading intradermal tests are of value for AGEP patients and negative patch tests are of value for SCAR patients [187, 192].

7. Therapeutic Approaches in Drug Hypersensitivity

7.1. Therapeutic Approaches in Immediate-Type Drug Hypersensitivity. Anaphylaxis is a medical emergency and epinephrine is the treatment of choice for anaphylaxis to prevent its progression to a life-threatening condition [15, 193]. Epinephrine should be administered as soon as possible without delay to avoid mortality [194]. The intramuscular injection of epinephrine into the middle of the outer thigh is recommended to treat anaphylaxis in most settings and in patients of all ages [195]. Glucagon is indicated for patients receiving beta-blockers with refractory symptoms [196]. The use of corticosteroids was previously believed to decrease the risk of biphasic and protracted reactions; however, a systematic review of the literature failed to retrieve any randomized controlled trials to confirm their effectiveness [197]. An emergency department-based study also failed to find a decrease in the rates of return visits or biphasic reactions among patients treated with glucocorticoids [198]. These adjunctive therapies, including corticosteroids, antihistamines, and bronchodilators, could help to relieve symptoms,

but should not be substituted for epinephrine or delay the use of epinephrine [199, 200].

7.2. Therapeutic Approaches in Delayed-Type Drug Hypersensitivity. For the treatment of severe delayed-type drug hypersensitivity, such as SJS/TEN, there are no optimal treatment guidelines. Thus far, in fact, only a few randomized trials that could be regarded as references to guide treatment have been conducted. The efficacy of systemic immunosuppressants or immunomodulatory treatments (e.g., corticosteroids, cyclosporine, intravenous immunoglobulins (IVIg), and plasmapheresis) still remains controversial. Systemic corticosteroids could be the most common treatment option, but the prior use of corticosteroids was found to prolong disease progression with no definite benefit in terms of survival [60, 201–203]. IVIg is one of the most commonly utilized therapies for SJS/TEN and is frequently the adjunctive therapy used for severe cases or pediatric patients [204]. In a meta-analysis, however, IVIg, even high doses of IVIg, failed to achieve statistically significant results supporting the conclusion that it is clinically beneficial [204, 205]. IVIg has been found to yield better outcomes in pediatric patients, but children with TEN usually have lower rates of mortality and better prognoses than adult patients [204, 206]. Cyclosporine, has been found to decrease the mortality rate and the progression of detachment in adults in an open-label phase II trial [207]. However, one recent cohort study revealed a statistically insignificant survival benefit for cyclosporine therapy compared to supportive care [208]. In contrast, the first meta-analysis of 7 studies regarding the effect on mortality of cyclosporine in the treatment of SJS/TEN showed a beneficial effect [209]. A trend identified in the same study also indicated that cyclosporine demonstrated better survival than IVIg [209]. There have also been an increasing number of case reports regarding the benefit of treatment with anti-TNF-α biologic agents for patients with TEN [210–215]. One recent systemic review showed that glucocorticosteroids and cyclosporine are the most promising therapies in terms of survival benefit, but no such benefits were observed for IVIg, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, or granulocyte colony-stimulating factor [216]. Meanwhile, IL-15 was demonstrated to be a major cytokine orchestrating SJS/TEN, indicating that further novel therapeutics including IL-15 blockers, the mammalian target of rapamycin (mTOR) inhibitors, and Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors hold promise for impacting various therapeutic targets [138, 217]. That said, further prospective, randomized controlled studies are needed to provide more definitive conclusions regarding treatment in patients with SJS/TEN.

Systemic corticosteroids have been considered the treatment of choice for patients with DRESS/DIHS, but they may be associated with an increased risk of complications such as opportunistic infections [218]. CMV and HHV-6 viral loads were also reported to be increased in patients receiving systemic corticosteroids, while EBV loads were higher in patients not receiving systemic corticosteroids [219]. Antiviral medications such as ganciclovir can be given in addition to steroids and/or IVIg in cases of severe disease with confirmation of viral reactivation [220]. Several previous studies have reported the effectiveness of treatment with IVIg [221]. However, the premature discontinuation of a prospective study regarding the role of IVIg treatment occurred due to severe adverse effects [222]. Plasmapheresis and other immunosuppressive drugs, such as cyclophosphamide, cyclosporine, interferons, muromonab-CD3, mycophenolate mofetil, and rituximab, may also be potential therapies [221]. Among the above treatments, the use of cyclosporine was successful in 2 recent cases with rapid response, and so, its use could be considered for patients with concerns about using longer courses of systemic corticosteroids [223]. Supportive treatment with topical steroid-based treatments for AGEP is suggested due to the mostly benign and self-limiting course of the condition [224, 225]. Meanwhile, the administration of systemic steroids for a short period can be considered for severe and refractory cases [175].

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Yi-Giien Tsai and Wen-Hung Chung contributed equally to this work.

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References

[1] W. J. Pichler, "Delayed drug hypersensitivity reactions," *Annals of Internal Medicine*, vol. 139, no. 8, pp. 683–693, 2003.

[2] M. I. Montañez, C. Mayorga, G. Bogas et al., "Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis," *Frontiers in Immunology*, vol. 8, p. 614, 2017.

[3] B. Schnyder and W. J. Pichler, "Mechanisms of drug-induced allergy," *Mayo Clinic Proceedings*, vol. 84, no. 3, pp. 268–272, 2009.

[4] S. G. Johansson, T. Bieber, R. Dahl et al., "Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003," *The Journal of Allergy and Clinical Immunology*, vol. 113, no. 5, pp. 832–836, 2004.

[5] M. Mockenhaupt, "Epidemiology of cutaneous adverse drug reactions," *Chemical Immunology and Allergy*, vol. 97, pp. 1–17, 2012.

[6] G. A. Wong and N. H. Shear, "Adverse drug interactions and reactions in dermatology: current issues of clinical relevance," *Dermatologic Clinics*, vol. 23, no. 2, pp. 335–342, 2005.

[7] C. C. Vittorio and J. J. Muglia, "Anticonvulsant hypersensitivity syndrome," *Archives of Internal Medicine*, vol. 155, no. 21, pp. 2285–2290, 1995.

[8] F. Arellano and J. A. Sacristan, "Allopurinol hypersensitivity syndrome: a review," *Annals of Pharmacotherapy*, vol. 27, no. 3, pp. 337–343, 1993.

[9] H. Bocquet, M. Bagot, and J. C. Roujeau, "Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS)," *Seminars in Cutaneous Medicine and Surgery*, vol. 15, no. 4, pp. 250–257, 1996.

[10] T. Shiohara, M. Iijima, Z. Ikezawa, and K. Hashimoto, "The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations," *British Journal of Dermatology*, vol. 156, no. 5, pp. 1083-1084, 2007.

[11] Y. Ushigome, Y. Kano, K. Hirahara, and T. Shiohara, "Human herpesvirus 6 reactivation in drug-induced hypersensitivity syndrome and DRESS validation score," *The American Journal of Medicine*, vol. 125, no. 7, pp. e9–e10, 2012.

[12] S. Bastuji-Garin, B. Rzany, R. S. Stern, N. H. Shear, L. Naldi, and J. C. Roujeau, "Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme," *Archives of Dermatology*, vol. 129, no. 1, pp. 92–96, 1993.

[13] A. Sidoroff, A. Dunant, C. Viboud et al., "Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR)," *British Journal of Dermatology*, vol. 157, no. 5, pp. 989–996, 2007.

[14] M. Lerch and W. J. Pichler, "The immunological and clinical spectrum of delayed drug-induced exanthems," *Current Opinion Allergy and Clinical Immunology*, vol. 4, no. 5, pp. 411–419, 2004.

[15] F. E. Simons, L. R. Ardusso, M. B. Bilò et al., "World Allergy Organization anaphylaxis guidelines: summary," *The Journal of Allergy and Clinical Immunology*, vol. 127, no. 3, pp. 587–593.e22, 2011.

[16] E. J. Jares, C. E. Baena-Cagnani, M. Sánchez-Borges et al., "Drug-induced anaphylaxis in Latin American countries," *The Journal of Allergy and Clinical Immunology: in Practice*, vol. 3, no. 5, pp. 780–788, 2015.

[17] Y. S. Lee and W. Z. Sun, "Epidemiology of anaphylaxis: a retrospective cohort study in Taiwan," *Asian Journal of Anesthesiology*, vol. 55, no. 1, pp. 9–12, 2017.

[18] L. H. Garvey, "Old, new and hidden causes of perioperative hypersensitivity," *Current Pharmaceutical Design*, vol. 22, no. 45, pp. 6814–6824, 2016.

[19] M. Iammatteo, T. Keskin, and E. Jerschow, "Evaluation of periprocedural hypersensitivity reactions," *Annals of Allergy Asthma & Immunology*, vol. 119, no. 4, pp. 349.e2–355.e2, 2017.

[20] N. Blanca-Lopez, D. Perez-Alzate, I. Andreu et al., "Immediate hypersensitivity reactions to ibuprofen and other arylpropionic acid derivatives," *Allergy*, vol. 71, no. 7, pp. 1048–1056, 2016.

[21] M. G. Canto, I. Andreu, J. Fernandez, and M. Blanca, "Selective immediate hypersensitivity reactions to NSAIDs," *Current Opinion in Allergy and Clinical Immunology*, vol. 9, no. 4, pp. 293–297, 2009.

[22] K. Brockow, L. H. Garvey, W. Aberer et al., "Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper," *Allergy*, vol. 68, no. 6, pp. 702–712, 2013.

[23] R. Munoz-Cano, C. Picado, A. Valero, and J. Bartra, "Mechanisms of anaphylaxis beyond IgE," *Journal of Investigational Allergology and Clinical Immunology*, vol. 26, no. 2, pp. 73–82, 2016.

[24] F. D. Finkelman, M. V. Khodoun, and R. Strait, "Human IgE-independent systemic anaphylaxis," *The Journal of Allergy and Clinical Immunology*, vol. 137, no. 6, pp. 1674–1680, 2016.

[25] H. Subramanian, K. Gupta, and H. Ali, "Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases," *The Journal of Allergy and Clinical Immunology*, vol. 138, no. 3, pp. 700–710, 2016.

[26] D. Laroche, F. Namour, C. Lefrancois et al., "Anaphylactoid and anaphylactic reactions to iodinated contrast material," *Allergy*, vol. 54, Supplement 58, pp. 13–16, 1999.

[27] K. Farnam, C. Chang, S. Teuber, and M. E. Gershwin, "Nonallergic drug hypersensitivity reactions," *International Archives of Allergy and Immunology*, vol. 159, no. 4, pp. 327–345, 2012.

[28] M. L. Kowalski, R. Asero, S. Bavbek et al., "Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs," *Allergy*, vol. 68, no. 10, pp. 1219–1232, 2013.

[29] S. H. Kardaun, A. Sidoroff, L. Valeyrie-Allanore et al., "Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist?," *British Journal of Dermatology*, vol. 156, no. 3, pp. 609–611, 2007.

[30] J. R. Sullivan and N. H. Shear, "The drug hypersensitivity syndrome: what is the pathogenesis?," *Archives of Dermatology*, vol. 137, no. 3, pp. 357–364, 2001.

[31] P. Cacoub, P. Musette, V. Descamps et al., "The DRESS syndrome: a literature review," *The American Journal of Medicine*, vol. 124, no. 7, pp. 588–597, 2011.

[32] S. H. Kardaun, P. Sekula, L. Valeyrie-Allanore et al., "Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study," *British Journal of Dermatology*, vol. 169, no. 5, pp. 1071–1080, 2013.

[33] C. H. Wei, R. Chung-Yee Hui, C. J. Chang et al., "Identifying prognostic factors for drug rash with eosinophilia and systemic symptoms (DRESS)," *European Journal of Dermatology*, vol. 21, no. 6, pp. 930–937, 2011.

[34] J. C. Roujeau and R. S. Stern, "Severe adverse cutaneous reactions to drugs," *The New England Journal of Medicine*, vol. 331, no. 19, pp. 1272–1285, 1994.

[35] Y. Kano, T. Ishida, K. Hirahara, and T. Shiohara, "Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome," *Medical Clinics of North America*, vol. 94, no. 4, pp. 743–759, 2010.

[36] O. Matsuno, "Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches," *Respiratory Research*, vol. 13, no. 1, p. 39, 2012.

[37] T. Thongsri, L. Chularojanamontri, and W. J. Pichler, "Cardiac involvement in DRESS syndrome," *Asian Pacific Journal Allergy and Immunology*, vol. 35, no. 1, pp. 3–10, 2017.

[38] G. P. Bourgeois, J. A. Cafardi, V. Groysman, and L. C. Hughey, "A review of DRESS-associated myocarditis," *Journal of the American Academy of Dermatology*, vol. 66, no. 6, pp. e229–e236, 2012.

[39] M. Ben m'rad, S. Leclerc-Mercier, P. Blanche et al., "Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients," *Medicine*, vol. 88, pp. 131–140, 2009.

[40] J. C. Roujeau, J. C. Guillaume, J. P. Fabre, D. Penso, M. L. Flechet, and J. P. Girre, "Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985," *Archives of Dermatology*, vol. 126, no. 1, pp. 37–42, 1990.

[41] E. Schopf, A. Stuhmer, B. Rzany, N. Victor, R. Zentgraf, and J. F. Kapp, "Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany," *Archives of Dermatology*, vol. 127, no. 6, pp. 839–842, 1991.

[42] D. Y. Hsu, J. Brieva, N. B. Silverberg, and J. I. Silverberg, "Morbidity and mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults," *Journal of Investigative Dermatology*, vol. 136, no. 7, pp. 1387–1397, 2016.

[43] N. Frey, J. Jossi, M. Bodmer et al., "The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK," *Journal of Investigative Dermatology*, vol. 137, no. 6, pp. 1240–1247, 2017.

[44] J. Diphoorn, S. Cazzaniga, C. Gamba et al., "Incidence, causative factors and mortality rates of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry," *Pharmacoepidemiology and Drug Safety*, vol. 25, no. 2, pp. 196–203, 2016.

[45] W. H. Chung, S. I. Hung, H. S. Hong et al., "Medical genetics: a marker for Stevens-Johnson syndrome," *Nature*, vol. 428, no. 6982, p. 486, 2004.

[46] D. Y. Hsu, J. Brieva, N. B. Silverberg, A. S. Paller, and J. I. Silverberg, "Pediatric Stevens-Johnson syndrome and toxic epidermal necrolysis in the United States," *Journal of the American Academy of Dermatology*, vol. 76, no. 5, pp. 811.e4–817.e4, 2017.

[47] P. B. Ferrell Jr. and H. L. McLeod, "Carbamazepine, *HLA-B* 1502* and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations," *Pharmacogenomics*, vol. 9, no. 10, pp. 1543–1546, 2008.

[48] E. J. Phillips, W. H. Chung, M. Mockenhaupt, J. C. Roujeau, and S. A. Mallal, "Drug hypersensitivity: pharmacogenetics and clinical syndromes," *The Journal of Allergy and Clinical Immunology*, vol. 127, no. 3, pp. S60–S66, 2011.

[49] A. Auquier-Dunant, M. Mockenhaupt, L. Naldi et al., "Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis - results of an international prospective study," *Archives of Dermatology*, vol. 138, no. 8, pp. 1019–1024, 2002.

[50] G. Yildirim Cetin, H. Sayar, F. Ozkan, S. Kurtulus, F. Kesici, and M. Sayarlioglu, "A case of toxic epidermal necrolysis-like skin lesions with systemic lupus erythematosus and review of the literature," *Lupus*, vol. 22, no. 8, pp. 839–846, 2013.

[51] D. Olson, L. K. Watkins, A. Demirjian et al., "Outbreak of mycoplasma pneumoniae-associated Stevens-Johnson syndrome," *Pediatrics*, vol. 136, no. 2, pp. e386–e394, 2015.

[52] W. H. Chung, S. R. Shih, C. F. Chang et al., "Clinicopathologic analysis of coxsackievirus a6 new variant induced widespread mucocutaneous bullous reactions mimicking severe cutaneous adverse reactions," *The Journal of Infectious Diseases*, vol. 208, no. 12, pp. 1968–1978, 2013.

[53] M. Mockenhaupt, C. Viboud, A. Dunant et al., "Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study," *Journal of Investigative Dermatology*, vol. 128, no. 1, pp. 35–44, 2008.

[54] A. C. Rosen, Y. Balagula, D. W. Raisch et al., "Life-threatening dermatologic adverse events in oncology," *Anti-Cancer Drugs*, vol. 25, no. 2, pp. 225–234, 2014.

[55] E. Dika, G. M. Ravaioli, P. A. Fanti et al., "Cutaneous adverse effects during ipilimumab treatment for metastatic melanoma: a prospective study," *European Journal of Dermatology*, vol. 27, no. 3, pp. 266–270, 2017.

[56] K. L. Vivar, M. Deschaine, J. Messina et al., "Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy," *Journal of Cutaneous Pathology*, 2016.

[57] C. Y. Lin, C. W. Wang, C. R. Hui et al., "Delayed-type hypersensitivity reactions induced by proton pump inhibitors: a clinical and in vitro T-cell reactivity study," *Allergy*, 2017.

[58] B. Sassolas, C. Haddad, M. Mockenhaupt et al., "ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis," *Clinical Pharmacology & Therapeutics*, vol. 88, no. 1, pp. 60–68, 2010.

[59] J. C. Roujeau, J. P. Kelly, L. Naldi et al., "Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis," *The New England Journal of Medicine*, vol. 333, no. 24, pp. 1600–1608, 1995.

[60] P. Sekula, A. Dunant, M. Mockenhaupt et al., "Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 133, no. 5, pp. 1197–1204, 2013.

[61] S. Bastuji-Garin, N. Fouchard, M. Bertocchi, J. C. Roujeau, J. Revuz, and P. Wolkenstein, "SCORTEN: a severity-of-illness score for toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 115, no. 2, pp. 149–153, 2000.

[62] S. Guegan, S. Bastuji-Garin, E. Poszepczynska-Guigne, J. C. Roujeau, and J. Revuz, "Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 126, no. 2, pp. 272–276, 2006.

[63] A. Beck, K. P. Quirke, R. L. Gamelli, and M. J. Mosier, "Pediatric toxic epidermal necrolysis: using SCORTEN and predictive models to predict morbidity when a focus on mortality is not enough," *Journal of Burn Care & Research*, vol. 36, no. 1, pp. 167–177, 2015.

[64] A. Sidoroff, S. Halevy, J. N. Bavinck, L. Vaillant, and J. C. Roujeau, "Acute generalized exanthematous pustulosis

(AGEP) - a clinical reaction pattern," *Journal of Cutaneous Pathology*, vol. 28, no. 3, pp. 113–119, 2001.

[65] E. H. Saissi, F. Beau-Salinas, A. P. Jonville-Bera, G. Lorette, E. Autret-Leca, and Centres Régionaux de Pharmacovigilance, "Drugs associated with acute generalized exanthematic pustulosis," *Annales de Dermatologie et de Venereologie*, vol. 130, no. 6-7, pp. 612–618, 2003.

[66] J. L. Gueant, A. Romano, J. A. Cornejo-Garcia et al., "*HLA-DRA* variants predict penicillin allergy in genome-wide fine-mapping genotyping," *The Journal of Allergy and Clinical Immunology*, vol. 135, no. 1, pp. 253–259.e10, 2015.

[67] A. J. Apter, H. Schelleman, A. Walker, K. Addya, and T. Rebbeck, "Clinical and genetic risk factors of self-reported penicillin allergy," *The Journal of Allergy and Clinical Immunology*, vol. 122, no. 1, pp. 152–158, 2008.

[68] R. M. Gueant-Rodriguez, A. Romano, M. Beri-Dexheimer, M. Viola, F. Gaeta, and J. L. Gueant, "Gene–gene interactions of IL13 and IL4RA variants in immediate allergic reactions to betalactam antibiotics," *Pharmacogenetics and Genomics*, vol. 16, no. 10, pp. 713–719, 2006.

[69] H. L. Qiao, J. Yang, and Y. W. Zhang, "Relationships between specific serum IgE, cytokines and polymorphisms in the IL-4, IL-4Rα in patients with penicillins allergy," *Allergy*, vol. 60, no. 8, pp. 1053–1059, 2005.

[70] J. Yang, H. L. Qiao, and Z. M. Dong, "Polymorphisms of IL-13 and IL-4-IL-13-SNPs in patients with penicillin allergies," *European Journal of Clinical Pharmacology*, vol. 61, no. 11, pp. 803–809, 2005.

[71] L. Ming, Q. Wen, H. L. Qiao, and Z. M. Dong, "Interleukin-18 and *IL18*-607A/C and -137G/C gene polymorphisms in patients with penicillin allergy," *Journal of International Medical Research*, vol. 39, no. 2, pp. 388–398, 2011.

[72] A. Oussalah, C. Mayorga, M. Blanca et al., "Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review," *Allergy*, vol. 71, no. 4, pp. 443–462, 2016.

[73] A. C. Bursztejn, A. Romano, R. M. Gueant-Rodriguez et al., "Allergy to betalactams and nucleotide-binding oligomerization domain (NOD) gene polymorphisms," *Allergy*, vol. 68, no. 8, pp. 1076–1080, 2013.

[74] S. H. Kim, Y. M. Ye, S. K. Lee, and H. S. Park, "Genetic mechanism of aspirin-induced urticaria/angioedema," *Current Opinion in Allergy and Clinical Immunology*, vol. 6, no. 4, pp. 266–270, 2006.

[75] M. L. Pacor, G. Di Lorenzo, P. Mansueto et al., "Relationship between human leucocyte antigen class I and class II and chronic idiopathic urticaria associated with aspirin and/or NSAIDs hypersensitivity," *Mediators of Inflammation*, vol. 2006, Article ID 62489, 5 pages, 2006.

[76] N. Palikhe, S. H. Kim, E. M. Yang et al., "Analysis of high-affinity IgE receptor (FcεR1) polymorphisms in patients with aspirin-intolerant chronic urticaria," *Allergy and Asthma Proceedings*, vol. 29, no. 3, pp. 250–257, 2008.

[77] S. H. Kim, E. M. Yang, H. J. Park, Y. M. Ye, H. Y. Lee, and H. S. Park, "Differential contribution of the CysLTR1 gene in patients with aspirin hypersensitivity," *Journal of Clinical Immunology*, vol. 27, no. 6, pp. 613–619, 2007.

[78] J. A. Cornejo-Garcia, L. R. Jagemann, N. Blanca-Lopez et al., "Genetic variants of the arachidonic acid pathway in non-steroidal anti-inflammatory drug-induced acute urticaria," *Clinical & Experimental Allergy*, vol. 42, no. 12, pp. 1772–1781, 2012.

[79] P. Ayuso, M. Blanca, J. A. Cornejo-Garcia et al., "Variability in histamine receptor genes *HRH1*, *HRH2* and *HRH4* in patients with hypersensitivity to NSAIDs," *Pharmacogenomics*, vol. 14, no. 15, pp. 1871–1878, 2013.

[80] R. Y. Pan, R. L. Dao, S. I. Hung, and W. H. Chung, "Pharmacogenomic advances in the prediction and prevention of cutaneous idiosyncratic drug reactions," *Clinical Pharmacology & Therapeutics*, vol. 102, no. 1, pp. 86–97, 2017.

[81] S. I. Hung, W. H. Chung, Z. S. Liu et al., "Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese," *Pharmacogenomics*, vol. 11, no. 3, pp. 349–356, 2010.

[82] C. B. Man, P. Kwan, L. Baum et al., "Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese," *Epilepsia*, vol. 48, no. 5, pp. 1015–1018, 2007.

[83] C. Locharernkul, J. Loplumlert, C. Limotai et al., "Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population," *Epilepsia*, vol. 49, no. 12, pp. 2087–2091, 2008.

[84] C. B. Chen, Y. H. Hsiao, T. Wu et al., "Risk and association of *HLA* with oxcarbazepine-induced cutaneous adverse reactions in Asians," *Neurology*, vol. 88, no. 1, pp. 78–86, 2017.

[85] Y. W. Shi, F. L. Min, X. R. Liu et al., "Hla-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population," *Basic & Clinical Pharmacology & Toxicology*, vol. 109, no. 1, pp. 42–46, 2011.

[86] S. I. Hung, W. H. Chung, S. H. Jee et al., "Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions," *Pharmacogenetics and Genomics*, vol. 16, no. 4, pp. 297–306, 2006.

[87] E. Genin, D. P. Chen, S. I. Hung et al., "HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis," *The Pharmacogenomics Journal*, vol. 14, no. 3, pp. 281–288, 2014.

[88] T. Ozeki, T. Mushiroda, A. Yowang et al., "Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population," *Human Molecular Genetics*, vol. 20, no. 5, pp. 1034–1041, 2011.

[89] S. H. Kim, K. W. Lee, W. J. Song et al., "Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans," *Epilepsy Research*, vol. 97, no. 1-2, pp. 190–197, 2011.

[90] M. McCormack, A. Alfirevic, S. Bourgeois et al., "HLA-A* 3101 and carbamazepine-induced hypersensitivity reactions in Europeans," *The New England Journal of Medicine*, vol. 364, no. 12, pp. 1134–1143, 2011.

[91] W. H. Chung, W. C. Chang, Y. S. Lee et al., "Genetic variants associated with phenytoin-related severe cutaneous adverse reactions," *JAMA*, vol. 312, no. 5, pp. 525–534, 2014.

[92] S. I. Hung, W. H. Chung, L. B. Liou et al., "HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 11, pp. 4134–4139, 2005.

[93] C. Lonjou, N. Borot, P. Sekula et al., "A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs," *Pharmacogenetics and Genomics*, vol. 18, no. 2, pp. 99–107, 2008.

[94] N. Kaniwa, Y. Saito, M. Aihara et al., "HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis," *Pharmacogenomics*, vol. 9, no. 11, pp. 1617–1622, 2008.

[95] W. Tassaneeyakul, T. Jantararoungtong, P. Chen et al., "Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population," *Pharmacogenetics and Genomics*, vol. 19, no. 9, pp. 704–709, 2009.

[96] H. R. Kang, Y. K. Jee, Y. S. Kim et al., "Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans," *Pharmacogenetics and Genomics*, vol. 21, no. 5, pp. 303–307, 2011.

[97] C. Y. Ng, Y. T. Yeh, C. W. Wang et al., "Impact of the *HLA-B** 58:01 allele and renal impairment on allopurinol-induced cutaneous adverse reactions," *Journal of Investigative Dermatology*, vol. 136, no. 7, pp. 1373–1381, 2016.

[98] S. Hetherington, A. R. Hughes, M. Mosteller et al., "Genetic variations in *HLA-B* region and hypersensitivity reactions to abacavir," *The Lancet*, vol. 359, no. 9312, pp. 1121-1122, 2002.

[99] S. Mallal, D. Nolan, C. Witt et al., "Association between presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir," *The Lancet*, vol. 359, no. 9308, pp. 727–732, 2002.

[100] F. A. Shepherd, J. Rodrigues Pereira, T. Ciuleanu et al., "Erlotinib in previously treated non-small-cell lung cancer," *The New England Journal of Medicine*, vol. 353, no. 2, pp. 123–132, 2005.

[101] S. Chantarangsu, T. Mushiroda, S. Mahasirimongkol et al., "HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients," *Pharmacogenetics and Genomics*, vol. 19, no. 2, pp. 139–146, 2009.

[102] H. Gatanaga, H. Yazaki, J. Tanuma et al., "HLA-Cw8 primarily associated with hypersensitivity to nevirapine," *AIDS*, vol. 21, no. 2, pp. 264-265, 2007.

[103] B. Schnyder and W. J. Pichler, "Allergy to sulfonamides," *The Journal of Allergy and Clinical Immunology*, vol. 131, no. 1, pp. 256-257.e5, 2013.

[104] Y. F. Lin, C. H. Yang, H. Sindy et al., "Severe cutaneous adverse reactions related to systemic antibiotics," *Clinical Infectious Diseases*, vol. 58, no. 10, pp. 1377–1385, 2014.

[105] F. R. Zhang, H. Liu, A. Irwanto et al., "*HLA-B*13:01* and the dapsone hypersensitivity syndrome," *The New England Journal of Medicine*, vol. 369, no. 17, pp. 1620–1628, 2013.

[106] M. M. Monshi, L. Faulkner, A. Gibson et al., "Human leukocyte antigen (HLA)-B*57:01-restricted activation of drug-specific T cells provides the immunological basis for flucloxacillin-induced liver injury," *Hepatology*, vol. 57, no. 2, pp. 727–739, 2013.

[107] M. I. Lucena, M. Molokhia, Y. Shen et al., "Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles," *Gastroenterology*, vol. 141, no. 1, pp. 338–347, 2011.

[108] S. H. Kim, M. Kim, K. W. Lee et al., "*HLA-B*5901* is strongly associated with methazolamide-induced Stevens–Johnson syndrome/toxic epidermal necrolysis," *Pharmacogenomics*, vol. 11, no. 6, pp. 879–884, 2010.

[109] A. K. Daly, G. P. Aithal, J. B. Leathart, R. A. Swainsbury, T. S. Dang, and C. P. Day, "Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes," *Gastroenterology*, vol. 132, no. 1, pp. 272–281, 2007.

[110] A. K. Daly and C. P. Day, "Genetic association studies in drug-induced liver injury," *Drug Metabolism Reviews*, vol. 44, no. 1, pp. 116–126, 2012.

[111] E. Padovan, T. Bauer, M. M. Tongio, H. Kalbacher, and H. U. Weltzien, "Penicilloyl peptides are recognized as T cell antigenic determinants in penicillin allergy," *European Journal of Immunology*, vol. 27, no. 6, pp. 1303–1307, 1997.

[112] C. Y. Wei, W. H. Chung, H. W. Huang, Y. T. Chen, and S. I. Hung, "Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome," *The Journal of Allergy and Clinical Immunology*, vol. 129, no. 6, pp. 1562–1569.e5, 2012.

[113] J. Yun, M. J. Marcaida, K. K. Eriksson et al., "Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01," *The Journal of Immunology*, vol. 192, no. 7, pp. 2984–2993, 2014.

[114] P. T. Illing, J. P. Vivian, N. L. Dudek et al., "Immune self-reactivity triggered by drug-modified HLA-peptide repertoire," *Nature*, vol. 486, no. 7404, pp. 554–558, 2012.

[115] D. A. Ostrov, B. J. Grant, Y. A. Pompeu et al., "Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 25, pp. 9959–9964, 2012.

[116] K. D. White, W. H. Chung, S. I. Hung, S. Mallal, and E. J. Phillips, "Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response," *The Journal of Allergy and Clinical Immunology*, vol. 136, no. 2, pp. 219–234, 2015.

[117] S. Watkins and W. J. Pichler, "Sulfamethoxazole induces a switch mechanism in T cell receptors containing TCRVβ20-1, altering pHLA recognition," *PLoS One*, vol. 8, no. 10, article e76211, 2013.

[118] K. W. Williams and H. P. Sharma, "Anaphylaxis and urticaria," *Immunology and Allergy Clinics of North America*, vol. 35, no. 1, pp. 199–219, 2015.

[119] D. MacGlashan Jr, "Expression of CD203c and CD63 in human basophils: relationship to differential regulation of piecemeal and anaphylactic degranulation processes," *Clinical & Experimental Allergy*, vol. 40, no. 9, pp. 1365–1377, 2010.

[120] D. W. MacGlashan Jr, "Basophil activation testing," *The Journal of Allergy and Clinical Immunology*, vol. 132, no. 4, pp. 777–787, 2013.

[121] P. Vadas, M. Gold, B. Perelman et al., "Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis," *The New England Journal of Medicine*, vol. 358, no. 1, pp. 28–35, 2008.

[122] J. van der Heijden, J. Geissler, E. van Mirre et al., "A novel splice variant of FcγRIIa: a risk factor for anaphylaxis in patients with hypogammaglobulinemia," *The Journal*

of Allergy and Clinical Immunology, vol. 131, no. 5, pp. 1408–1416.e5, 2013.

[123] R. R. Vassallo, "Review: IgA anaphylactic transfusion reactions. Part I. Laboratory diagnosis, incidence, and supply of IgA-deficient products," *Immunohematology*, vol. 20, no. 4, pp. 226–233, 2004.

[124] C. Steenholdt, M. Svenson, K. Bendtzen, O. O. Thomsen, J. Brynskov, and M. A. Ainsworth, "Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease," *Journal of Crohn's and Colitis*, vol. 6, no. 1, pp. 108–111, 2012.

[125] F. Baert, M. Noman, S. Vermeire et al., "Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease," *The New England Journal of Medicine*, vol. 348, no. 7, pp. 601–608, 2003.

[126] J. Szebeni, "Complement activation-related pseudoallergy: a stress reaction in blood triggered by nanomedicines and biologicals," *Molecular Immunology*, vol. 61, no. 2, pp. 163–173, 2014.

[127] T. K. Kishimoto, K. Viswanathan, T. Ganguly et al., "Contaminated heparin associated with adverse clinical events and activation of the contact system," *The New England Journal of Medicine*, vol. 358, no. 23, pp. 2457–2467, 2008.

[128] M. Veien, F. Szlam, J. T. Holden, K. Yamaguchi, D. D. Denson, and J. H. Levy, "Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells," *Anesthesiology*, vol. 92, no. 4, pp. 1074–1081, 2000.

[129] J. A. Blunk, M. Schmelz, S. Zeck, P. Skov, R. Likar, and W. Koppert, "Opioid-induced mast cell activation and vascular responses is not mediated by μ-opioid receptors: an *in vivo* microdialysis study in human skin," *Anesthesia & Analgesia*, vol. 98, no. 2, pp. 364–370, 2004.

[130] B. D. McNeil, P. Pundir, S. Meeker et al., "Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions," *Nature*, vol. 519, no. 7542, pp. 237–241, 2015.

[131] S. J. Posadas, A. Padial, M. J. Torres et al., "Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity," *The Journal of Allergy and Clinical Immunology*, vol. 109, no. 1, pp. 155–161, 2002.

[132] I. Viard, P. Wehrli, R. Bullani et al., "Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin," *Science*, vol. 282, no. 5388, pp. 490–493, 1998.

[133] A. Nassif, A. Bensussan, G. Dorothee et al., "Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 118, no. 4, pp. 728–733, 2002.

[134] I. Voskoboinik, J. C. Whisstock, and J. A. Trapani, "Perforin and granzymes: function, dysfunction and human pathology," *Nature Reviews Immunology*, vol. 15, no. 6, pp. 388–400, 2015.

[135] W. H. Chung, S. I. Hung, J. Y. Yang et al., "Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis," *Nature Medicine*, vol. 14, no. 12, pp. 1343–1350, 2008.

[136] R. Abe, N. Yoshioka, J. Murata, Y. Fujita, and H. Shimizu, "Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome," *Annals of Internal Medicine*, vol. 151, no. 7, pp. 514-515, 2009.

[137] M. Weinborn, A. Barbaud, F. Truchetet, P. Beurey, L. Germain, and B. Cribier, "Histopathological study of six types of adverse cutaneous drug reactions using granulysin expression," *International Journal of Dermatology*, vol. 55, no. 11, pp. 1225–1233, 2016.

[138] S. SC, M. Mockenhaupt, P. Wolkenstein et al., "Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 137, pp. 1065–1073, 2017.

[139] Z. G. Liu, "Molecular mechanism of TNF signaling and beyond," *Cell Research*, vol. 15, no. 1, pp. 24–27, 2005.

[140] P. Paquet, A. Nikkels, J. E. Arrese, A. Vanderkelen, and G. E. Pierard, "Macrophages and tumor necrosis factor a in toxic epidermal necrolysis," *Archives of Dermatology*, vol. 130, no. 5, pp. 605–608, 1994.

[141] C. Paul, P. Wolkenstein, H. Adle et al., "Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis," *British Journal of Dermatology*, vol. 134, no. 4, pp. 710–714, 1996.

[142] A. Nassif, H. Moslehi, S. Le Gouvello et al., "Evaluation of the potential role of cytokines in toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 123, no. 5, pp. 850–855, 2004.

[143] M. Caproni, D. Torchia, E. Schincaglia et al., "Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis," *British Journal of Dermatology*, vol. 155, no. 4, pp. 722–728, 2006.

[144] S. Halevy, "Acute generalized exanthematous pustulosis," *Current Opinion in Allergy and Clinical Immunology*, vol. 9, no. 4, pp. 322–328, 2009.

[145] P. Schaerli, M. Britschgi, M. Keller et al., "Characterization of human T cells that regulate neutrophilic skin inflammation," *The Journal of Immunology*, vol. 173, no. 3, pp. 2151–2158, 2004.

[146] M. Britschgi and W. J. Pichler, "Acute generalized exanthematous pustulosis, a clue to neutrophil-mediated inflammatory processes orchestrated by T cells," *Current Opinion in Allergy and Clinical Immunology*, vol. 2, no. 4, pp. 325–331, 2002.

[147] A. A. Navarini, L. Valeyrie-Allanore, N. Setta-Kaffetzi et al., "Rare variations in *IL36RN* in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis," *Journal of Investigative Dermatology*, vol. 133, no. 7, pp. 1904–1907, 2013.

[148] H. S. Song, S. J. Kim, T. I. Park, Y. H. Jang, and E. S. Lee, "Immunohistochemical comparison of IL-36 and the IL-23/Th17 axis of generalized pustular psoriasis and acute generalized exanthematous pustulosis," *Annals of Dermatology*, vol. 28, no. 4, pp. 451–456, 2016.

[149] S. A. Walsh and D. Creamer, "Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking," *Clinical and Experimental Dermatology*, vol. 36, no. 1, pp. 6–11, 2011.

[150] T. Komatsu-Fujii, Y. Chinuki, H. Niihara et al., "The thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption is a prognostic biomarker of severity of systemic inflammation," *Allergology International*, 2017.

[151] K. Ogawa, H. Morito, A. Hasegawa et al., "Identification of thymus and activation-regulated chemokine (TARC/CCL17)

as a potential marker for early indication of disease and prediction of disease activity in drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS)," *Journal of Dermatological Science*, vol. 69, no. 1, pp. 38–43, 2013.

[152] B. Tapia, A. Padial, E. Sanchez-Sabate et al., "Involvement of CCL27-CCR10 interactions in drug-induced cutaneous reactions," *The Journal of Allergy and Clinical Immunology*, vol. 114, no. 2, pp. 335–340, 2004.

[153] O. Correia, L. Delgado, I. L. Barbosa, F. Campilho, and J. Fleming-Torrinha, "Increased interleukin 10, tumor necrosis factor α, and interleukin 6 levels in blister fluid of toxic epidermal necrolysis," *Journal of the American Academy of Dermatology*, vol. 47, no. 1, pp. 58–62, 2002.

[154] P. Paquet, F. Paquet, W. Al Saleh, P. Reper, A. Vanderkelen, and G. E. Pierard, "Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis," *The American Journal of Dermatopathology*, vol. 22, no. 5, pp. 413–417, 2000.

[155] W. H. Chung, W. C. Chang, S. L. Stocker et al., "Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin," *Annals of the Rheumatic Diseases*, vol. 74, no. 12, pp. 2157–2164, 2015.

[156] R. Takahashi, Y. Kano, Y. Yamazaki, M. Kimishima, Y. Mizukawa, and T. Shiohara, "Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome," *The Journal of Immunology*, vol. 182, no. 12, pp. 8071–8079, 2009.

[157] T. Shiohara, M. Inaoka, and Y. Kano, "Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses," *Allergology International*, vol. 55, no. 1, pp. 1–8, 2006.

[158] T. Shiohara, M. Kurata, Y. Mizukawa, and Y. Kano, "Recognition of immune reconstitution syndrome necessary for better management of patients with severe drug eruptions and those under immunosuppressive therapy," *Allergology International*, vol. 59, no. 4, pp. 333–343, 2010.

[159] T. Shiohara, Y. Ushigome, Y. Kano, and R. Takahashi, "Crucial role of viral reactivation in the development of severe drug eruptions: a comprehensive review," *Clinical Reviews in Allergy & Immunology*, vol. 49, no. 2, pp. 192–202, 2015.

[160] T. Yoshikawa, A. Fujita, A. Yagami et al., "Human herpesvirus 6 reactivation and inflammatory cytokine production in patients with drug-induced hypersensitivity syndrome," *Journal of Clinical Virology*, vol. 37, Supplement 1, pp. S92–S96, 2006.

[161] T. Shiohara and Y. Kano, "A complex interaction between drug allergy and viral infection," *Clinical Reviews in Allergy & Immunology*, vol. 33, no. 1-2, pp. 124–133, 2007.

[162] F. E. Simons, L. R. Ardusso, M. B. Bilo et al., "2012 update: World Allergy Organization guidelines for the assessment and management of anaphylaxis," *Current Opinion in Allergy and Clinical Immunology*, vol. 12, no. 4, pp. 389–399, 2012.

[163] R. Y. Lin, L. B. Schwartz, A. Curry et al., "Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study," *The Journal of Allergy and Clinical Immunology*, vol. 106, no. 1, pp. 65–71, 2000.

[164] F. E. Simons, A. J. Frew, I. J. Ansotegui et al., "Risk assessment in anaphylaxis: current and future approaches," *The Journal of Allergy and Clinical Immunology*, vol. 120, no. 1, Supplement, pp. S2–S24, 2007.

[165] E. Gomez, M. J. Torres, C. Mayorga, and M. Blanca, "Immunologic evaluation of drug allergy," *Allergy, Asthma & Immunology Research*, vol. 4, no. 5, pp. 251–263, 2012.

[166] M. Blanca, C. Mayorga, M. J. Torres et al., "Clinical evaluation of Pharmacia CAP system™ RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy," *Allergy*, vol. 56, no. 9, pp. 862–870, 2001.

[167] I. Dona, M. J. Torres, M. I. Montanez, and T. D. Fernandez, "*In vitro* diagnostic testing for antibiotic allergy," *Allergy, Asthma & Immunology Research*, vol. 9, no. 4, pp. 288–298, 2017.

[168] C. Mayorga, I. Dona, E. Perez-Inestrosa, T. D. Fernandez, and M. J. Torres, "The value of in vitro tests to diminish drug challenges," *International Journal of Molecular Sciences*, vol. 18, no. 6, 2017.

[169] C. Mayorga, G. Celik, P. Rouzaire et al., "*In vitro* tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper," *Allergy*, vol. 71, no. 8, pp. 1103–1134, 2016.

[170] H. J. Hoffmann, A. F. Santos, C. Mayorga et al., "The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease," *Allergy*, vol. 70, no. 11, pp. 1393–1405, 2015.

[171] J. Leysen, V. Sabato, M. M. Verweij et al., "The basophil activation test in the diagnosis of immediate drug hypersensitivity," *Expert Reviews of Clinical Immunology*, vol. 7, no. 3, pp. 349–355, 2011.

[172] E. C. McGowan and S. Saini, "Update on the performance and application of basophil activation tests," *Current Allergy and Asthma Reports*, vol. 13, no. 1, pp. 101–109, 2013.

[173] A. L. De Week, M. L. Sanz, P. M. Gamboa et al., "Diagnosis of immediate-type β-lactam allergy in vitro by flow-cytometric basophil activation test and sulfidoleukotriene production: a multicenter study," *Journal of Investigational Allergology & Clinical Immunology*, vol. 19, no. 2, pp. 91–109, 2009.

[174] N. Saito, R. Abe, N. Yoshioka, J. Murata, Y. Fujita, and H. Shimizu, "Prolonged elevation of serum granulysin in drug-induced hypersensitivity syndrome," *British Journal of Dermatology*, vol. 167, no. 2, pp. 452-453, 2012.

[175] L. Feldmeyer, K. Heidemeyer, and N. Yawalkar, "Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy," *International Journal of Molecular Sciences*, vol. 17, no. 8, 2016.

[176] S. SC, S. I. Hung, W. L. Fan, R. L. Dao, and W. H. Chung, "Severe cutaneous adverse reactions: the pharmacogenomics from research to clinical implementation," *International Journal of Molecular Sciences*, vol. 17, p. 1890, 2016.

[177] A. A. Elzagallaai and M. J. Rieder, "*In vitro* testing for diagnosis of idiosyncratic adverse drug reactions: implications for pathophysiology," *British Journal of Clinical Pharmacology*, vol. 80, no. 4, pp. 889–900, 2015.

[178] C. M. Rive, J. Bourke, and E. J. Phillips, "Testing for drug hypersensitivity syndromes," *The Clinical Biochemist Reviews*, vol. 34, no. 1, pp. 15–38, 2013.

[179] G. Porebski, "In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already?," *International Journal of Molecular Sciences*, vol. 18, no. 8, p. 1737, 2017.

[180] W. J. Pichler and J. Tilch, "The lymphocyte transformation test in the diagnosis of drug hypersensitivity," *Allergy*, vol. 59, no. 8, pp. 809–820, 2004.

[181] A. T. Nagao-Dias, F. M. Teixeira, and H. L. Coelho, "Diagnosing immune-mediated reactions to drugs," *Allergologia et Immunopathologia*, vol. 37, no. 2, pp. 98–104, 2009.

[182] Y. Kano, K. Hirahara, Y. Mitsuyama, R. Takahashi, and T. Shiohara, "Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption," *Allergy*, vol. 62, no. 12, pp. 1439–1444, 2007.

[183] Y. Srinoulprasert and W. J. Pichler, "Enhancement of drug-specific lymphocyte proliferation using $CD25^{hi}$-depleted $CD3^{+}$ effector cells," *International Archives of Allergy and Immunology*, vol. 163, no. 3, pp. 198–205, 2014.

[184] K. Kato, A. Kawase, H. Azukizawa et al., "Novel interferon-γ enzyme-linked immunospot assay using activated cells for identifying hypersensitivity-inducing drug culprits," *Journal of Dermatological Science*, vol. 86, no. 3, pp. 222–229, 2017.

[185] L. Valeyrie-Allanore, M. Mockenhaupt, P. Sekula et al., "Mechanisms that limit proliferative potential of drug-specific LTT in drug-induced severe cutaneous adverse reaction patients," *Clinical and Translational Allergy*, vol. 4, Supplement 3, pp. O1–P149, 2014.

[186] W. H. Chung, R. Y. Pan, M. T. Chu et al., "Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions," *Journal of Investigative Dermatology*, vol. 135, no. 9, pp. 2237–2248, 2015.

[187] A. Barbaud, E. Collet, B. Milpied et al., "A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions," *British Journal of Dermatology*, vol. 168, no. 3, pp. 555–562, 2013.

[188] Y. T. Lin, Y. C. Chang, R. C. Hui et al., "A patch testing and cross-sensitivity study of carbamazepine-induced severe cutaneous adverse drug reactions," *Journal of the European Academy of Dermatology and Venereology*, vol. 27, no. 3, pp. 356–364, 2013.

[189] M. J. Torres, A. Romano, G. Celik et al., "Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America," *Clinical and Translational Allergy*, vol. 7, no. 1, p. 7, 2017.

[190] Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology et al., "Drug allergy: an updated practice parameter," *Annals of Allergy, Asthma & Immunology*, vol. 105, no. 4, pp. 259–273.e78, 2010.

[191] K. Brockow, A. Romano, M. Blanca, J. Ring, W. Pichler, and P. Demoly, "General considerations for skin test procedures in the diagnosis of drug hypersensitivity," *Allergy*, vol. 57, no. 1, pp. 45–51, 2002.

[192] T. A. Duong, L. Valeyrie-Allanore, P. Wolkenstein, and O. Chosidow, "Severe cutaneous adverse reactions to drugs," *The Lancet*, vol. 390, no. 10106, pp. 1996–2011, 2017.

[193] M. Alrasbi and A. Sheikh, "Comparison of international guidelines for the emergency medical management of anaphylaxis," *Allergy*, vol. 62, no. 8, pp. 838–841, 2007.

[194] A. Sheikh, Y. A. Shehata, S. G. Brown, and F. E. Simons, "Adrenaline for the treatment of anaphylaxis: Cochrane systematic review," *Allergy*, vol. 64, no. 2, pp. 204–212, 2009.

[195] T. Kawano, F. X. Scheuermeyer, R. Stenstrom, B. H. Rowe, E. Grafstein, and B. Grunau, "Epinephrine use in older patients with anaphylaxis: clinical outcomes and cardiovascular complications," *Resuscitation*, vol. 112, pp. 53–58, 2017.

[196] M. Thomas and I. Crawford, "Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers," *Emergency Medicine Journal*, vol. 22, no. 4, pp. 272-273, 2005.

[197] K. J. Choo, F. E. Simons, and A. Sheikh, "Glucocorticoids for the treatment of anaphylaxis," *Cochrane Database of Systematic Reviews*, no. 4, article CD007596, 2012.

[198] K. A. Michelson, M. C. Monuteaux, and M. I. Neuman, "Glucocorticoids and hospital length of stay for children with anaphylaxis: a retrospective study," *The Journal of Pediatrics*, vol. 167, no. 3, pp. 719–724.e3, 2015.

[199] A. Sheikh, V. Ten Broek, S. G. Brown, and F. E. Simons, "H_1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review," *Allergy*, vol. 62, no. 8, pp. 830–837, 2007.

[200] P. Lieberman, R. A. Nicklas, C. Randolph et al., "Anaphylaxis-a practice parameter update 2015," *Annals of Allergy, Asthma & Immunology*, vol. 115, no. 5, pp. 341–384, 2015.

[201] R. P. Dodiuk-Gad, W. H. Chung, C. H. Yang, L. CW, R. C. Hui, and N. H. Shear, "The 8th International Congress on Cutaneous Adverse Drug Reactions, Taiwan, 2013: focus on severe cutaneous adverse reactions," *Drug Safety*, vol. 37, no. 6, pp. 459–464, 2014.

[202] H. Y. Lee, A. Dunant, P. Sekula et al., "The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies," *British Journal of Dermatology*, vol. 167, no. 3, pp. 555–562, 2012.

[203] E. H. Law and M. Leung, "Corticosteroids in Stevens-Johnson syndrome/toxic epidermal necrolysis: current evidence and implications for future research," *Annals of Pharmacotherapy*, vol. 49, no. 3, pp. 335–342, 2015.

[204] Y. C. Huang, Y. C. Li, and T. J. Chen, "The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis," *British Journal of Dermatology*, vol. 167, no. 2, pp. 424–432, 2012.

[205] Y. C. Huang, Y. N. Chien, Y. T. Chen, Y. C. Li, and T. J. Chen, "Intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis," *Giornale Italiano di Dermatologia e Venereologia*, vol. 151, no. 5, pp. 515–524, 2016.

[206] P. Tristani-Firouzi, M. J. Petersen, J. R. Saffle, S. E. Morris, and J. J. Zone, "Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children," *Journal of the American Academy of Dermatology*, vol. 47, no. 4, pp. 548–552, 2002.

[207] L. Valeyrie-Allanore, P. Wolkenstein, L. Brochard et al., "Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis," *British Journal of Dermatology*, vol. 163, no. 4, pp. 847–853, 2010.

[208] H. Y. Lee, S. Fook-Chong, H. Y. Koh, T. Thirumoorthy, and S. M. Pang, "Cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis: retrospective analysis of a cohort treated in a specialized referral center," *Journal of the American Academy of Dermatology*, vol. 76, no. 1, pp. 106–113, 2017.

[209] Y.-T. H. Chen, C. Y.-N. Che-Yuan, W.-R. Lee, and Y.-C. Huang, "Efficacy of cyclosporine for the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: systemic review and meta-analysis," *Dermatologica Sinica*, vol. 35, no. 3, pp. 131–137, 2017.

[210] A. Wojtkiewicz, M. Wysocki, J. Fortuna, M. Chrupek, M. Matczuk, and A. Koltan, "Beneficial and rapid effect of infliximab on the course of toxic epidermal necrolysis," *Acta Dermato-Venereologica*, vol. 88, no. 4, pp. 420-421, 2008.

[211] A. Paradisi, D. Abeni, F. Bergamo, F. Ricci, D. Didona, and B. Didona, "Etanercept therapy for toxic epidermal necrolysis," *Journal of the American Academy of Dermatology*, vol. 71, no. 2, pp. 278–283, 2014.

[212] M. Fischer, E. Fiedler, W. C. Marsch, and J. Wohlrab, "Antitumour necrosis factor-α antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis," *British Journal of Dermatology*, vol. 146, no. 4, pp. 707–709, 2002.

[213] R. E. Hunger, T. Hunziker, U. Buettiker, L. R. Braathen, and N. Yawalkar, "Rapid resolution of toxic epidermal necrolysis with anti-TNF-α treatment," *The Journal of Allergy and Clinical Immunology*, vol. 116, no. 4, pp. 923-924, 2005.

[214] B. Kreft, J. Wohlrab, I. Bramsiepe, R. Eismann, M. Winkler, and W. C. Marsch, "Etoricoxib-induced toxic epidermal necrolysis: successful treatment with infliximab," *The Journal of Dermatology*, vol. 37, no. 10, pp. 904–906, 2010.

[215] L. C. Zarate-Correa, D. C. Carrillo-Gomez, A. F. Ramirez-Escobar, and C. Serrano-Reyes, "Toxic epidermal necrolysis successfully treated with infliximab," *Journal of Investigational Allergology & Clinical Immunology*, vol. 23, no. 1, pp. 61–63, 2013.

[216] S. Zimmermann, P. Sekula, M. Venhoff et al., "Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis," *JAMA Dermatology*, vol. 153, no. 6, pp. 514–522, 2017.

[217] R. S. Stern and S. J. Divito, "Stevens-Johnson syndrome and toxic epidermal necrolysis: associations, outcomes, and pathobiology-thirty years of progress but still much to be done," *Journal of Investigative Dermatology*, vol. 137, no. 5, pp. 1004–1008, 2017.

[218] Y. T. Cho, C. W. Yang, and C. Y. Chu, "Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system," *International Journal of Molecular Sciences*, vol. 18, no. 6, 2017.

[219] T. Ishida, Y. Kano, Y. Mizukawa, and T. Shiohara, "The dynamics of herpesvirus reactivations during and after severe drug eruptions: their relation to the clinical phenotype and therapeutic outcome," *Allergy*, vol. 69, no. 6, pp. 798–805, 2014.

[220] V. Descamps, B. Ben Said, B. Sassolas et al., "Management of drug reaction with eosinophilia and systemic symptoms (DRESS)," *Annales de Dermatologie et de Vénéréologie*, vol. 137, no. 11, pp. 703–708, 2010.

[221] Z. Husain, B. Y. Reddy, and R. A. Schwartz, "DRESS syndrome: part II. Management and therapeutics," *Journal of the American Academy of Dermatology*, vol. 68, no. 5, pp. 709.e1–709.e9, 2013.

[222] P. Joly, B. Janela, F. Tetart et al., "Poor benefit/risk balance of intravenous immunoglobulins in DRESS," *Archives of Dermatology*, vol. 148, no. 4, pp. 543-544, 2012.

[223] M. G. Kirchhof, A. Wong, and J. P. Dutz, "Cyclosporine treatment of drug-induced hypersensitivity syndrome," *JAMA Dermatology*, vol. 152, no. 11, pp. 1254–1257, 2016.

[224] C. Hotz, L. Valeyrie-Allanore, C. Haddad et al., "Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients," *British Journal of Dermatology*, vol. 169, no. 6, pp. 1223–1232, 2013.

[225] S. Ingen-Housz-Oro, C. Hotz, L. Valeyrie-Allanore et al., "Acute generalized exanthematous pustulosis: a retrospective audit of practice between 1994 and 2011 at a single centre," *British Journal of Dermatology*, vol. 172, no. 5, pp. 1455–1457, 2015.

[226] T. Y. Mehta, L. M. Prajapati, B. Mittal et al., "Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians," *Indian Journal of Dermatology, Venereology and Leprology*, vol. 75, no. 6, pp. 579–582, 2009.

[227] C. C. Chang, C. L. Too, S. Murad, and S. H. Hussein, "Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population," *International Journal of Dermatology*, vol. 50, no. 2, pp. 221–224, 2011.

[228] K. W. Chong, D. W. Chan, Y. B. Cheung et al., "Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B*1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore," *Archives of Disease in Childhood*, vol. 99, no. 6, pp. 581–584, 2014.

[229] D. V. Nguyen, H. C. Chu, D. V. Nguyen et al., "HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese," *Asia Pacific Allergy*, vol. 5, no. 2, pp. 68–77, 2015.

[230] P. K. Kwan, M. H. Ng, and S. V. Lo, "Association between HLA-B*15:02 allele and antiepileptic drug-induced severe cutaneous reactions in Hong Kong Chinese: a population-based study," *Hong Kong Medical Journal*, no. 20, Supplement 7, pp. S16–S18, 2014.

[231] E. Ramírez, T. Bellón, H. Y. Tong et al., "Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population," *Pharmacological Research*, vol. 115, pp. 168–178, 2017.

[232] N. Kaniwa, Y. Saito, M. Aihara et al., "*HLA-B*1511* is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients," *Epilepsia*, vol. 51, no. 12, pp. 2461–2465, 2010.

[233] D. Sun, Y. CH, Z. S. Liu et al., "Association of HLA-B*1502 and *1511 allele with antiepileptic drug-induced Stevens-Johnson syndrome in central China," *Journal of Huazhong University of Science and Technology Medical Sciences*, vol. 34, pp. 146–150, 2014.

[234] H. Ikeda, Y. Takahashi, E. Yamazaki et al., "HLA class I markers in Japanese patients with carbamazepine-induced cutaneous adverse reactions," *Epilepsia*, vol. 51, no. 2, pp. 297–300, 2010.

[235] W. Tassaneeyakul, N. Prabmeechai, C. Sukasem et al., "Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population," *Pharmacogenetics and Genomics*, vol. 26, no. 5, pp. 225–234, 2016.

[236] C. C. Chang, C. C. Ng, C. L. Too et al., "Association of HLA-B*15:13 and HLA-B*15:02 with phenytoin-induced severe

cutaneous adverse reactions in a Malay population," *The Pharmacogenomics Journal*, vol. 17, no. 2, p. 170, 2016.

[237] T. Zeng, Y. S. Long, F. L. Min, W. P. Liao, and Y. W. Shi, "Association of HLA-B*1502 allele with lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: a meta-analysis," *International Journal of Dermatology*, vol. 54, no. 4, pp. 488–493, 2015.

[238] G. R. Kazeem, C. Cox, J. Aponte et al., "High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients," *Pharmacogenetics and Genomics*, vol. 19, no. 9, pp. 661–665, 2009.

[239] B. K. Kim, J. W. Jung, T. B. Kim et al., "HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population," *Annals of Allergy Asthma & Immunology*, vol. 119, no. 5, pp. 629-630, 2017.

[240] A. M. Martin, D. Nolan, I. James et al., "Predisposition to nevirapine hypersensitivity associated with HLA-DRB1* 0101 and abrogated by low CD4 T-cell counts," *AIDS*, vol. 19, no. 1, pp. 97–99, 2005.

[241] R. Littera, C. Carcassi, A. Masala et al., "HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients," *AIDS*, vol. 20, no. 12, pp. 1621–1626, 2006.

[242] D. F. Carr, M. Chaponda, A. L. Jorgensen et al., "Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a Malawian HIV-infected population," *Clinical Infectious Diseases*, vol. 56, no. 9, pp. 1330–1339, 2013.

[243] J. Yang, H. L. Qiao, Y. W. Zhang, L. J. Jia, X. Tian, and N. Gao, "HLA-DRB genotype and specific IgE responses in patients with allergies to penicillins," *Chinese Medical Journal*, vol. 119, no. 6, pp. 458–466, 2006.

[244] T. Kongpan, S. Mahasirimongkol, P. Konyoung et al., "Candidate HLA genes for prediction of co-trimoxazole-induced severe cutaneous reactions," *Pharmacogenetic and Genomics*, vol. 25, no. 8, pp. 402–411, 2015.

[245] J. Revuz, D. Penso, J. C. Roujeau et al., "Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients," *Archives of Dermatology*, vol. 123, no. 9, pp. 1160–1165, 1987.

[246] J. Quiralte, F. Sanchez-Garcia, M. J. Torres et al., "Association of HLA-DR11 with the anaphylactoid reaction caused by nonsteroidal anti-inflammatory drugs," *The Journal of Allergy and Clinical Immunology*, vol. 103, no. 4, pp. 685–689, 1999.

[247] H. L. Qiao, J. Yang, and Y. W. Zhang, "Specific serum IgE levels and FcεRIβ genetic polymorphism in patients with penicillins allergy," *Allergy*, vol. 59, no. 12, pp. 1326–1332, 2004.

[248] Y. H. Nam, J. E. Kim, S. H. Kim et al., "Identifying genetic susceptibility to sensitization to cephalosporins in health care workers," *Journal of Korean Medical Science*, vol. 27, no. 11, pp. 1292–1299, 2012.

[249] H. L. Qiao, Q. Wen, N. Gao, X. Tian, and L. J. Jia, "Association of IL-10 level and IL-10 promoter SNPs with specific antibodies in penicillin-allergic patients," *European Journal of Clinical Pharmacology*, vol. 63, no. 3, pp. 263–269, 2007.

[250] N. Gao, H.-L. Qiao, L.-J. Jia, X. Tian, and Y.-W. Zhang, "Relationships between specific serum IgE, IgG, IFN-γ level and IFN-γ, IFNR1 polymorphisms in patients with penicillin allergy," *European Journal of Clinical Pharmacology*, vol. 64, no. 10, pp. 971–977, 2008.

[251] C.-Z. Huang, J. Yang, H.-L. Qiao, and L.-J. Jia, "Polymorphisms and haplotype analysis of IL-4Rα Q576R and I75V in patients with penicillin allergy," *European Journal of Clinical Pharmacology*, vol. 65, no. 9, pp. 895–902, 2009.

[252] C. Z. Huang, D. Zou, J. Yang, and H. L. Qiao, "Polymorphisms of STAT6 and specific serum IgE levels in patients with penicillin allergy," *International Journal of Clinical Pharmacology and Therapeutics*, vol. 50, no. 07, pp. 461–467, 2012.

[253] L. Guglielmi, C. Fontaine, C. Gougat et al., "IL-10 promoter and *IL4-R* α gene SNPs are associated with immediate β-lactam allergy in atopic women," *Allergy*, vol. 61, no. 8, pp. 921–927, 2006.

[254] R. M. Gueant-Rodriguez, J. L. Gueant, M. Viola, D. Tramoy, F. Gaeta, and A. Romano, "Association of tumor necrosis factor-α -308G>A polymorphism with IgE-mediated allergy to betalactams in an Italian population," *The Pharmacogenomics Journal*, vol. 8, no. 2, pp. 162–168, 2008.

[255] J. A. Cornejo-Garcia, R. M. Gueant-Rodriguez, M. J. Torres et al., "Biological and genetic determinants of atopy are predictors of immediate-type allergy to betalactams, in Spain," *Allergy*, vol. 67, no. 9, pp. 1181–1185, 2012.

[256] S. H. Kim, J. H. Choi, J. W. Holloway et al., "Leukotriene-related gene polymorphisms in patients with aspirin-intolerant urticaria and aspirin-intolerant asthma: differing contributions of ALOX5 polymorphism in Korean population," *Journal of Korean Medical Science*, vol. 20, no. 6, pp. 926–931, 2005.

[257] J.-S. Bae, S.-H. Kim, Y.-M. Ye et al., "Significant association of FcεRIα promoter polymorphisms with aspirin-intolerant chronic urticaria," *The Journal of Allergy and Clinical Immunology*, vol. 119, no. 2, pp. 449–456.

[258] H. J. Park, Y. M. Ye, G. Y. Hur, S. H. Kim, and H. S. Park, "Association between a TGFβ1 promoter polymorphism and the phenotype of aspirin-intolerant chronic urticaria in a Korean population," *Journal of Clinical Pharmacy and Therapeutics*, vol. 33, no. 6, pp. 691–697, 2008.

[259] J. H. Choi, S. H. Kim, B. Y. Cho et al., "Association of TNF-α promoter polymorphisms with aspirin-induced urticaria," *Journal of Clinical Pharmacy and Therapeutics*, vol. 34, no. 2, pp. 231–238, 2009.

[260] S. H. Kim, Y. M. Kang, S. H. Kim et al., "Histamine *N*-methyltransferase 939A>G polymorphism affects mRNA stability in patients with acetylsalicylic acid-intolerant chronic urticaria," *Allergy*, vol. 64, pp. 213–221, 2009.

[261] S. H. Kim, J. K. Son, E. M. Yang, J. E. Kim, and H. S. Park, "A functional promoter polymorphism of the human *IL18* gene is associated with aspirin-induced urticaria," *British Journal of Dermatology*, vol. 165, no. 5, pp. 976–984, 2011.

[262] N. S. Palikhe, S. H. Kim, H. Y. Lee, J. H. Kim, Y. M. Ye, and H. S. Park, "Association of thromboxane A2 receptor (*TBXA2R*) gene polymorphism in patients with aspirin-intolerant acute urticaria," *Clinical & Experimental Allergy*, vol. 41, no. 2, pp. 179–185, 2011.

[263] N. S. Palikhe, H. J. Sin, S. H. Kim et al., "Genetic variability of prostaglandin E2 receptor subtype EP4 gene in aspirin-intolerant chronic urticaria," *Journal of Human Genetics*, vol. 57, no. 8, pp. 494–499, 2012.

[264] L. Mastalerz, M. Setkowicz, M. Sanak, H. Rybarczyk, and A. Szczeklik, "Familial aggregation of aspirin-induced urticaria and leukotriene C_4 synthase allelic variant," *British Journal of Dermatology*, vol. 154, no. 2, pp. 256–260, 2006.

[265] M. Sanchez-Borges, N. Acevedo, C. Vergara et al., "The A–444C polymorphism in the leukotriene C_4 synthase gene is associated with aspirin-induced urticaria," *Journal of Investigational Allergology and Clinical Immunology*, vol. 19, no. 5, pp. 375–382, 2009.

[266] J. A. Agundez, P. Ayuso, J. A. Cornejo-Garcia et al., "The diamine oxidase gene is associated with hypersensitivity response to non-steroidal anti-inflammatory drugs," *PLoS One*, vol. 7, no. 11, article e47571, 2012.

[267] C. Vidal, L. Porras-Hurtado, R. Cruz et al., "Association of thromboxane A1 synthase (*TBXAS1*) gene polymorphism with acute urticaria induced by nonsteroidal anti-inflammatory drugs," *The Journal of Allergy and Clinical Immunology*, vol. 132, no. 4, pp. 989–991, 2013.

[268] C. Plaza-Seron Mdel, P. Ayuso, N. Perez-Sanchez et al., "Copy number variation in ALOX5 and PTGER1 is associated with NSAIDs-induced urticaria and/or angioedema," *Pharmacogenetics and Genomics*, vol. 26, no. 6, pp. 280–287, 2016.

[269] L. M. Ferreira Vasconcelos, R. O. Rodrigues, A. A. Albuquerque et al., "Polymorphism of *IL10*, *IL4*, *CTLA4*, and *DAO* genes in cross-reactive nonsteroidal anti-inflammatory drug hypersensitivity," *The Journal of Clinical Pharmacology*, 2017.

[270] A. Beeler, O. Engler, B. O. Gerber, and W. J. Pichler, "Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions," *Journal of Allergy and Clinical Immunology*, vol. 117, no. 2, pp. 455–462, 2006.

[271] D. Nishio, K. Izu, K. Kabashima, and Y. Tokura, "T cell populations propagating in the peripheral blood of patients with drug eruptions," *Journal of Dermatological Science*, vol. 48, no. 1, pp. 25–33, 2007.

[272] M. Hertl, H. Bohlen, F. Jugert, C. Boecker, R. Knaup, and H. F. Merk, "Predominance of epidermal CD8+ T lymphocytes in bullous cutaneous reactions caused by β-lactam antibiotics," *Journal of Investigative Dermatology*, vol. 101, no. 6, pp. 794–799, 1993.

[273] K. Ogawa, H. Morito, A. Hasegawa et al., "Elevated serum thymus and activation-regulated chemokine (TARC/CCL17) relates to reactivation of human herpesvirus 6 in drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS)," *British Journal of Dermatology*, vol. 171, no. 2, pp. 425–427, 2014.

[274] I. Viard-Leveugle, O. Gaide, D. Jankovic et al., "TNF-α and IFN-γ are potential inducers of Fas-mediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis," *Journal of Investigative Dermatology*, vol. 133, no. 2, pp. 489–498, 2013.

[275] P. Paquet and G. E. Pierard, "Erythema multiforme and toxic epidermal necrolysis: a comparative study," *The American Journal of Dermatopathology*, vol. 19, no. 2, pp. 127–132, 1997.