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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Coordinating Research Priorities to Move the Field Forward

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Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) is the most life-threatening emergency managed by dermatologists. Although affecting only 1-5/million per year, mortality remains stable at 15%, and high-level evidence-based treatment options are lacking. The third biannual meeting[1, 2] "SJS/TEN 2021: Collaboration, innovation, and community" that was held virtually August 28 and 29, 2021, brought together multidisciplinary clinicians, scientists, and community members to share knowledge, research, stories, and support. In this viewpoint, we provide our perspective of the successes and gaps in research and clinical care of SJS/TEN highlighted at this meeting, and propose future opportunities for prioritization and optimization.

Historical perspective of SJS/TEN

In 1922, Stevens and Johnson defined SJS as a syndrome of fever, mucocutaneous lesions, and severe ocular involvement.[3] Although these early cases were assumed associated with infection and not drugs, the first reports of frequently fatal bullous dermatitis with mucosal involvement followed the subsequent discovery of phenobarbital, phenytoin, and sulfa antibiotics. In 1956, Lyell proposed the name "toxic epidermal necrolysis" to unify syndromes characterized histopathologically by epidermal necrosis that clinically showed epidermal detachment.[4] A consensus panel in 1993 considered SJS and TEN to be one disease across a spectrum of severity.[5] From the RegiSCAR data a probable drug cause is identified in 67% of SJS/TEN, possible drug cause in 13%, and unlikely or unidentifiable drug cause in 13%.[1]

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Current research and clinical priorities for SJS/TEN

Prevention, Prediction, and Regulation.

Human leukocyte antigen (HLA) class I genes are strongly associated with drug-induced SJS/TEN, providing insight into pathophysiology and prevention.[1, 2] FDA-approved labeling has recommended HLA-B*15:02 screening before carbamazepine therapy in at-risk patients since 2007, with reference to those of Asian ancestry.[6] However, those who carry HLA-B*15:02, regardless of known ancestry, are at risk for carbamazepine SJS/TEN. Furthermore, race-based screening where the decision to order an HLA test is based on perceived ancestry is unreliable.[7] Unlike abacavir hypersensitivity, where HLA-B*57:01 is the only identified HLA risk factor, a single HLA allele does not identify all individuals at risk for SJS/TEN associated with a specific drug.[6] To address this negative-predictive value gap there is a need to identify HLA alleles for all drugs associated with SJS/TEN, that are relevant to all ancestries, as well as genetic and other risk factors explaining the positive-predictive value gap of why, in general, only 2-8% of those carrying a drug-specific HLA risk allele develop SJS/TEN.[1, 6]

Earlier Diagnosis, Risk Stratification, and Identification of the Culprit Drug.

Prompt cessation of all potentially implicated drugs and immediate transfer to an appropriate supportive care environment such as burn unit or ICU positively impact SJS/TEN outcome. Our current approaches can be improved with enhanced provider education about early recognition and classification of SJS/TEN. Timely transfer of patients to specialized centers can be optimized by approaches that engage the expertise of dermatologists and burn surgeons before patient transfer such as telehealth triaging. In the future, point-of-care biomarkers such as granulysin may help with early identification and prognostication of SJS/TEN.[1] Percentage body surface area (%BSA) detached is a strong predictor of SJS/TEN outcomes, however, bedside measurements remain imprecise. Standardized photography and imaging combined with novel digital informatic approaches should be studied and validated to more accurately document SJS/TEN evolution and resolution.

Evidence-based acute clinical care and follow-up.

Supportive care remains the mainstay of SJS/TEN treatment and consensus-based recommendations for best supportive acute care including wound care, ocular, oral, and urogenital care, critical care management, pain management and infection surveillance have been published.[8] Evidence-based studies are needed to define best supportive wound, ocular and urogynecological care. This includes approaches to study SJS/TEN eye complications both acutely with amniotic membrane transplantation, and in follow-up in the community to identify lesser-known complications.[1, 2] Evidence-based approaches for acute treatment are needed to define the role of existing FDA-approved drugs. Mental health screening and resources should be provided in the hospital and outpatient setting. Continuity of care, including better education before hospital discharge and support to coordinate multidisciplinary outpatient care, should be routine. Coordinated approaches to study the short and long-term impact of SJS/TEN on the physical and psychosocial functioning of the patients and their family members are critical.

Understanding mechanisms and promoting innovation in care

Drug-induced SJS/TEN is a class I HLA restricted CD8+ T-cell-dependent process that results in keratinocyte death mediated by cytolytic cell killing peptides. We now can identify antigen-driven resident T cells at the site of tissue damage and the molecular and cellular basis of SJS/TEN at the single-cell level.[9, 10] Mechanistic studies at the site of tissue damage that define gene and protein expression profiles are needed to identify biological markers and novel targets for treatment.[9] To facilitate this collaborative effort, prospective collection of cellular samples including skin and blister fluid for long-term storage will be needed.

How to move the field forward

The number of SJS/TEN-associated publications has increased more than 50% over the last 10 years. Although this is cause for optimism and excitement, advancing SJS/TEN research and clinical care requires multidisciplinary leadership, collaboration, and coordination including a critical review of patient-centered clinical and research priorities and unmet evidence-based research needs (Table 1). Engagement is commanded from dermatologists and other clinical, research, and community stakeholders. The development of a robust research network infrastructure that will facilitate the study of new treatments and approaches to physical and mental health complications is critical to further advances. The veracity of genetic and epidemiological studies rely on the ability to accurately identify SJS/TEN as a clinical phenotype within the electronic health record (EHR). These approaches that rely on ICD-9 and 10 coding and case verification should be validated across different healthcare systems. International biorepositories of stored samples from diverse populations will fuel mechanistic research to support preventive, diagnostic, and treatment efforts. Current studies have been country or population-specific, and these are not necessarily generalizable based on genetic risk, causal drugs or infections, or the most effective treatment strategies. Since SJS/TEN is an uncommon disease it is important to design studies that will include adequate representation of sex, age, and ancestry.

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References

1. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. J Allergy Clin Immunol Pract 2018; 6:38–69. [PubMed: 29310768]

2. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: From science to translation. J Dermatol Sci 2020.

3. Stevens AM JF. A New Eruptive Fever Associated with Stomatitis and Ophthalmia: Report of Two Cases in Children. Am J Dis Child 1922; 24:526–33.

4. Lyell A Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol 1956; 68:355–61. [PubMed: 13374196]

5. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129:92–6. [PubMed: 8420497]

6. Deshpande P, Hertzman RJ, Palubinsky AM, Giles JB, Karnes JH, Gibson A, et al. Immunopharmacogenomics: Mechanisms of HLA-Associated Drug Reactions. Clin Pharmacol Ther 2021; 110:607–15. [PubMed: 34143437]

7. Goodman CW, Brett AS. Race and Pharmacogenomics-Personalized Medicine or Misguided Practice? JAMA 2021; 325:625–6. [PubMed: 33492362]

8. Seminario-Vidal L, Kroshinsky D, Malachowski SJ, Sun J, Markova A, Beachkofsky TM, et al. Society of Dermatology Hospitalists supportive care guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. J Am Acad Dermatol 2020.

9. Kim D, Kobayashi T, Voisin B, Jo JH, Sakamoto K, Jin SP, et al. Targeted therapy guided by single-cell transcriptomic analysis in drug-induced hypersensitivity syndrome: a case report. Nat Med 2020; 26:236–43. [PubMed: 31959990]

10. Redwood AJ, Rwandamuriye F, Chopra A, Leary S, Ram R, McDonnell W, et al. Single-cell transcriptomics reveal polyclonal memory T-cell responses in skin with positive abacavir patch test results. J Allergy Clin Immunol 2019; 144:1413–6 e7. [PubMed: 31574267]

Table 1:

Gaps, priorities, and opportunities to move SJS/TEN forward

Current Gap(s)	Priorities and Opportunities
Prevention, Prediction and Regulation	
• Generalizability of genetic findings • Evidence-based pre-prescription genetic tests • Few drugs and targets • Low positive predictive value of genetic testing • Lack of real-time information of new drug causes of SJS/TEN • Risk factors for infectious causes of SJS/TEN	• Studies across diverse ancestries • Cohorts for genetic studies and enhanced availability of cost-effective testing • Networks to study multiple drugs • Studies for risk factors outside of HLA • Enhanced pharmacovigilance including for immunomodulatory therapy • Studies to examine genetic and ecological risk factors.
Earlier diagnosis, risk stratification and identification of the culprit drug	
• Early recognition in community • Timely transfer to specialized centers • Biological markers to aid early diagnosis and prognostication • In vitro/ex vivo/in vivo testing methods s to identify the culprit drug • **Bedside and photographic measurements to improve risk assessment and prognostication**	• Provider education and decision support • Telehealth triage services • Studies for point-of-care markers for earlier diagnosis and prognostication • Validation of assays for different drugs across different cohorts • Study and validation of measurements in large studies. Development of artificial intelligence algorithms to help facilitate
Evidence-based acute clinical care and follow-up	
• Evidence-based studies to define best supportive care practice • Evidence-based acute treatment • Definition of long-term physical and mental health complications • Coordinated clinical care and multidisciplinary support services for follow-up SJS survivors and families	• Large collaborative networks to establish evidence-based best practices • Collaborative networks and clinical trials • Collaborative networks for long-term follow-up • Coordination amongst multi-disciplinary specialty societies*
Understanding mechanisms and promoting innovation in care	
• Mechanistic studies at site of SJS/TEN tissue damage to identify cellular and molecular signals to identify biological markers and novel targets for treatment	• Collaborative efforts to develop precisely phenotyped international cohorts of prospectively collected samples for long-term storage and study by specialized basic science groups