EDITORIAL

Improving Outcomes for Patients With Epidermal Necrolysis

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Epidermal necrolysis (EN) encompassing spectrum of Stevens-Johnson syndrome and toxic EN, is a rare, severe cutaneous drug reaction with an estimated mortality in modern cohorts of 15% to 23%.[1-3] The rarity of the disease makes rigorous prospective clinical research difficult, highlighting the need for multicenter, multinational collaborations as well as iterative efforts to validate and build on prior work.

Related article

In this issue of *JAMA Dermatology*, Koh et al[4] compare the performance of 2 severity of illness scores for EN, the long-time reference standard Score of Toxic EN (SCORTEN)[5] and the recently published ABCD-10 score (age, bicarbonate, cancer, dialysis, 10% body surface area [BSA]),[6] using their single-institution cohort. Among 196 patients treated between 2003 and 2019 at a referral hospital in Singapore, disease severity was high (35% of patients met the definition of toxic EN [BSA >30%]), and mortality was significant (23%).[4] Applying the 2 scoring systems, the authors determined that the discrimination (ie, ability to stratify patients by mortality risk) of ABCD-10 and SCORTEN was equivalent. However, in this population, ABCD-10 underestimated mortality at lower score ranges and overestimated it at higher score ranges, while SCORTEN overestimated mortality at higher scores and in patients treated with immunomodulatory therapy across all score ranges.[4]

Variations in the predictive abilities of SCORTEN and ABCD-10 are expected. The rarity of EN limits study size and statistical power, which can lead to overestimation of effect sizes and a decreased reproducibility of results. Variations in mortality risk may also be secondary to population-specific genetic risk factors and local care practices, meaning the accuracy of risk assessment tools may be somewhat population dependent.

Despite these concerns regarding reproducibility and generalizability, retrospective cohort studies can nevertheless provide important information about rare diseases. For instance, the study by Koh et al[4] reaffirms several EN mortality risk factors reported previously in other populations, including age older than 50 years, BSA greater than 10%, active malignancy, and kidney dysfunction. However, unique, population-specific factors are also important and may contribute significantly to mortality risk.[7] These population-specific factors are likely because of variability in human leukocyte antigen (HLA) alleles, differences in medical comorbidities, and variations in supportive care and prescribing habits. Koh et al[4] note that the ethnic backgrounds of patients in their study, primarily Chinese and Malay, are different from those in the European and North American cohorts used to develop SCORTEN and ABCD-10, respectively, which may limit generalizability. In the Singaporean cohort, an unusually high proportion of patients presented with greater than 30% BSA involvement. This may explain why a BSA greater than 10% was the strongest predictor of mortality (odds ratio, 10.0; 95% CI, 3.0-33.8; $P < .001$)[4] and speaks to the need for improved understanding of EN biology and identification of treatments that can stop progression of keratinocyte necrosis.

Yet, while retrospective research can provide insights into rare diseases, there are also inherent weaknesses. When collecting information from medical record reviews, not all information may be available or recorded uniformly. Observational studies focused on treatment are shaped by important limitations and biases, with little to no standardization of comorbidities, supportive care, or clinician decision-making and treatment selection.[2,8] These limitations result in biased results and inaccurate determination of treatment effects. Koh et al[4] rightly indicate the danger of using either SCORTEN or ABCD-10 as an internal control to predict expected mortality in a cohort, calculate a standardized mortality ratio (observed divided by predicted mortality), and draw conclusions regarding the efficacy of specific therapies. These deficiencies illustrate the need for rigorous prospective clinical and translational research, including randomized clinical trials that account for relevant confounding factors and compare therapeutic interventions with the current standard of care.

Helping to guide future efforts, a recent article highlighted broad research priorities in EN, focusing on basic, translational, and clinical research needs.[9] The current understanding of EN pathogenesis suggests drug interaction with HLA proteins on keratinocytes activates drug-specific CD8+ cytotoxic T cells and natural killer cells, initiating an inflammatory cascade that ends in keratinocyte death.[10] Strong HLA gene associations have been elucidated for EN, although the precise mechanism for which these alleles are necessary but not sufficient for development of EN is yet to be understood.[10] Improved knowledge of disease pathophysiology may identify a serum biomarker that could be used for rapid diagnosis or aid identification of targeted therapies.

The most pressing need in EN clinical research is understanding whether immunomodulatory therapies can alter the natural course of the disease. Two clinical trials exploring treatment efficacy are registered in the US (NCT03585946 and NCT02987257), but, to our knowledge, neither has started recruiting patients. Before initiating any prospective trial, it will be imperative to standardize interventions, instruments, and outcome measures whenever possible. The Society of Dermatology Hospitalists has recently published standardized supportive care guidelines for this purpose,[11] and a Delphi effort to do the same with various pharmacotherapeutic treatment

options is under way. Even procedures as seemingly straightforward as estimation of BSA involvement in EN (defined in SCORTEN as the sum of detached and detachable epidermis[5]) are subject to interobserver variability depending on the specific formula used and the extent of cutaneous involvement.[12] Similarly, while in-hospital mortality is an objective, defined outcomes and proxy outcomes like time-to-reepithelization are often poorly defined or of uncertain significance as surrogate markers of treatment response. Consistent terminology, rigorous disease metrics, and meaningful, evidence-based outcomes are essential for successful conduct of EN-related research around the world. Understanding and addressing the long-term physical and psychological effects of this disease on survivors is another area of ongoing need.

Finally, it is important to develop safe and accurate allergy testing for EN. Because it can be impossible to identify a specific medication trigger with certainty, frequently 2 or more medications are labeled as allergies, limiting future therapeutic options. Combined in vivo and ex vivo testing via patch testing and interferon-γ release assay, respectively, have been used safely in a pilot study to assign drug causality with moderate sensitivity and high specificity. Further investigation is needed to devise a personalized approach to drug hypersensitivity testing and safe medication prescribing among survivors of EN.[13]

In conclusion, future clinical and translational research in EN should focus on improving and standardizing prevention, diagnosis, and treatment options for patients. Multi-institutional, international collaborations with standardized, evidence-based definitions, instruments, and outcome measures will improve the generalizability of research findings and applicability to diverse populations around the world. The work by Koh et al[4] is an important reminder of the need for continued validation and improvement of key disease severity tools and other metrics.

ARTICLE INFORMATION

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REFERENCES

1. Bettuzzi T, Penso L, de Prost N, et al. Trends in mortality rates for Stevens-Johnson syndrome and toxic epidermal necrolysis: experience of a single centre in France between 1997 and 2017. *Br J Dermatol*. 2020;182(1):247-248.

2. Micheletti RG, Chiesa-Fuxench Z, Noe MH, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. *J Invest Dermatol*. 2018;138(11):2315-2321. doi:10.1016/j.jid.2018.04.027

3. Sekula P, Dunant A, Mockenhaupt M, et al; RegiSCAR Study Group. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol*. 2013;133(5):1197-1204. doi:10.1038/jid.2012.510

4. Koh HK, Fook-Chong S, Lee HY. Assessment and comparison of performance of ABCD-10 and SCORTEN in prognostication of epidermal necrolysis. *JAMA Dermatol*. Published online October 21, 2020. doi:10.1001/jamadermatol.2020.3654

5. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115(2):149-153. doi:10.1046/j.1523-1747.2000.00061.x

6. Noe MH, Rosenbach M, Hubbard RA, et al. Development and validation of a risk prediction model for in-hospital mortality among patients with Stevens-Johnson syndrome/toxic epidermal necrolysis-ABCD-10. *JAMA Dermatol*. 2019;155(4):448-454. doi:10.1001/jamadermatol.2018.5605

7. Kannenberg SMH, Jordaan HF, Koegelenberg CF, Von Groote-Bidlingmaier F, Visser WI. Toxic epidermal necrolysis and Stevens-Johnson syndrome in South Africa: a 3-year prospective study. *QJM*. 2012;105(9):839-846. doi:10.1093/qjmed/hcs078

8. Noe MH, Mostaghimi A, Rosenbach M, Shinkai K, Micheletti RG. Selective use of cyclosporine for Stevens-Johnson syndrome/toxic epidermal necrolysis may exclude patients with poor prognostic factors. *J Invest Dermatol*. 2018;138(9):2068-2072. doi:10.1016/j.jid.2018.03.1496

9. Manolio TA, Hutter CM, Avigan M, et al. Research directions in genetic predispositions to Stevens-Johnson syndrome/toxic epidermal necrolysis. *Clin Pharmacol Ther*. 2018;103(3):390-394. doi:10.1002/cpt.890

10. Peter JG, Lehloenya R, Dlamini S, 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(3):547-563. doi:10.1016/j.jaip.2017.01.025

11. Seminario-Vidal L, Kroshinsky D, Malachowski SJ, 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;82(6):1553-1567. doi:10.1016/j.jaad.2020.02.066

12. Wachtel TL, Berry CC, Wachtel EE, Frank HA. The inter-rater reliability of estimating the size of burns from various burn area chart drawings. *Burns*. 2000;26(2):156-170. doi:10.1016/S0305-4179(99)00047-9

13. Trubiano JA, Strautins K, Redwood AJ, et al. The combined utility of ex vivo IFN-γ release enzyme-linked ImmunoSpot Assay and in vivo skin testing in patients with antibiotic-associated severe cutaneous adverse reactions. *J Allergy Clin Immunol Pract*. 2018;6(4):1287-1296.e1. doi:10.1016/j.jaip.2017.09.004