

New Clinical Insights Into Pediatric DRESS to Tailor Future Care?



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Severe cutaneous adverse reactions (SCAR), a group of presumed T-cell-mediated conditions, are associated with significant morbidity and mortality.¹ There has been increased interest in understanding the epidemiology and immunopathogenesis of these conditions, in particular drug reaction with eosinophilia and systemic symptoms (DRESS), to improve applied diagnostics and treatments.²⁻⁵ Bedouelle et al⁶ present a modern examination of DRESS in a pediatric cohort (n = 49) from 15 French university hospitals. Although limited by the retrospective data and single region, unfortunately inherent to many studies of rare T-cell-mediated hypersensitivities such as DRESS, the authors provide a unique examination of the disease process in children. The authors highlight the high degree of morbidity (ie, internal organ involvement) yet almost absent mortality, with antibiotics the primary implicated drugs, similar to that seen in adult populations.⁷ Further similarities to the adult literature and clinical practice were noted, including primary use of steroids as a therapeutic intervention and high rate of disease relapse. The shorter latency period is also informative in shifting opinion that DRESS can occur earlier than the frequently quoted 14-day latency period.⁸ The work by Bedouelle et al takes a significant step forward in describing the pediatric phenotypic characteristics of DRESS that help the broader drug hypersensitivity community in pursuing research into disease pathogenesis, diagnostics, and treatments.

In regard to pathogenesis, Bedouelle et al demonstrate potential herpesvirus 6 (HHV-6) reactivation in 22% of children in this study, an often investigated mediator in DRESS pathogenesis and diagnosis, reflected by its status in the revised J-SCAR criteria.⁹ The role of HHV-6 reactivation in DRESS pathogenesis, outcomes, and sequelae remains ill defined. Several studies illustrate that viremia generally occurs in a greater amount 2 weeks after symptom onset,¹⁰ encouraging the debate of cause or effect in DRESS. It has been demonstrated that HHV-6

positivity is associated with greater severity and longer hospitalizations in the pediatric population.¹¹ Furthermore, although reaction of other herpesviruses is also noted (eg, cytomegalovirus), as in the case series by Bedouelle et al, the need for directed antiviral treatments remains unknown. Defining the role of viral pathogens in DRESS, and the role of targeted herpesvirus therapies, will be a paradigm shift in care.

One of the known limitations of SCAR research is identification of the causal drug, with the absence of a gold-standard diagnostic test and inability to undertake direct drug provocation noted. In the study by Bedouelle et al, allergy assessment was performed in 53% of children, *ex vivo* testing in the form of the lymphocyte transformation test performed in 2 patients. Recent publications have highlighted the emerging role of *ex vivo* diagnostics;^{12,13} however, the pediatric populations are generally underrepresented in these cohorts. From the adult literature, younger age was associated with a positive *ex vivo* result, with potential favorable implications for *ex vivo* diagnostics in pediatrics. For the most part, oral provocation tests are contraindicated in DRESS because of the risk of recurrence,¹⁴ which did occur in 1 patient in this study. Obverting these scenarios in the future might be via the combination of *in vitro* and *ex vivo* testing,¹³ before rechallenge. Patch testing (PT) has a sensitivity of 32% to 80% in DRESS,¹⁵ noting that a negative PT result does not exclude drug causality. Intradermal testing (IDT) is more difficult to employ in a pediatric population and is generally recommended 6 months after acute reactions;⁴ however, it has been performed earlier in some centers. It is important to note that the range for testing was 2 to 39 months after discharge in this study; hence use of IDT before the 6-month timeframe does challenge historical recommendations of testing time points.

In regard to treatment, corticosteroids have historically been considered the mainstay of care, with intravenous immunoglobulin (IVIG) being used in severe cases. However, the use of IVIG is controversial. Although some studies have shown that IVIG in combination with corticosteroids has been used successfully in pediatric patients with severe DRESS, another case series of 6 adults who only received IVIG at the beginning of their treatment and not corticosteroids had a high rate of severe adverse effects.¹⁶ This may suggest that the timing of IVIG administration is crucial, as some hypothesize that severe liver damage and defective regulatory T-cell during the early phase contribute to autoantibody production.¹⁷ IVIG administration during this time can accelerate the rapid recovery of B cells resulting in subsequent expansions of more autoantibodies, possibly explaining why IVIG given during the acute phase may have more adverse effects.¹⁸ Furthermore, the early use of corticosteroid therapy during the acute phase may prevent the development of these autoantibodies,¹⁷ and hence the consensus of using the combination of

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 22, 2021; accepted for publication October 22, 2021.

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J Allergy Clin Immunol Pract 2022;10:275-6.
2213-2198

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<https://doi.org/10.1016/j.jaip.2021.10.045>

corticosteroids and IVIG together in severe cases. Although this paper explores the use of therapies in DRESS, the heterogeneity of therapies and unknowns regarding choice of treatment remains in both adult and pediatric populations.

Prospective cohort studies, international registries, and randomized controlled trials, including both adult and pediatric DRESS patients, are urgently required to address an illness that, as underlined by Bedouelle et al, continues to have significant morbidity, and potential identifiable targets for disease modification. Although we recognize that many unknowns exist in DRESS, similarities between the adult and pediatric experience are noted. Future translational research needs to address DRESS across the age spectrum and use clinical observations such as those presented in the discussed manuscript to tailor translational research that potentially advances adult and pediatric drug hypersensitivity care simultaneously.

REFERENCES

- Adler NR, Aung AK, Ergen EN, Trubiano J, Goh MSY, Phillips EJ. Recent advances in the understanding of severe cutaneous adverse reactions. *Br J Dermatol* 2017;177:1234-47.
- 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;98:2-12.
- 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.
- Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, et al. Controversies in drug allergy: testing for delayed reactions. *J Allergy Clin Immunol* 2019;143:66-73.
- Lehloanya RJ, Peter JG, Copescu A, Trubiano JA, Phillips EJ. Delabeling delayed drug hypersensitivity: how far can you safely go? *J Allergy Clin Immunol Pract* 2020;8: 2878-95.e6.
- Bedouelle E. Drug reaction with eosinophilia and systemic symptoms (DRESS): series of 49 French pediatric cases. *J Allergy Clin Immunol Pract* 2022;10: 267-74.
- Trubiano JA, Aung AK, Nguyen M, Fehily SR, Graudins L, Cleland H, et al. A comparative analysis between antibiotic- and nonantibiotic-associated delayed cutaneous adverse drug reactions. *J Allergy Clin Immunol Pract* 2016;4:1187-93.
- Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169:1071-80.
- Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007;156:1083-4.
- 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.
- Ahluwalia J, Abuabara K, Perman MJ, Yan AC. Human herpesvirus 6 involvement in paediatric drug hypersensitivity syndrome. *Br J Dermatol* 2015; 172:1090-5.
- Copaescu A, Mouhtouris E, Vogrin S, James F, Chua KYL, Holmes NE, et al. The role of in vivo and ex vivo diagnostic tools in severe delayed immune-mediated adverse antibiotic drug reactions. *J Allergy Clin Immunol Pract* 2021;9: 2010-5.e4.
- Copaescu A, Gibson A, Li Y, Trubiano JA, Phillips EJ. An updated review of the diagnostic methods in delayed drug hypersensitivity. *Front Pharmacol* 2021; 11:573573.
- Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis* 2013;26: 526-37.
- Barbaud A. Skin testing and patch testing in non-IgE-mediated drug allergy. *Curr Allergy Asthma Rep* 2014;14:442.
- Giavina-Bianchi P, Huang SW. Intravenous immunoglobulin may be beneficial as an add-on therapy in DRESS. *J Allergy Clin Immunol Pract* 2018;6:1243-5.
- Takehara A, Aoyama Y, Kurosawa M, Shirafuji Y, Umemura H, Kamiya K, et al. Longitudinal analysis of antibody profiles against plakins in severe drug eruptions: emphasis on correlation with tissue damage in drug-induced hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms. *Br J Dermatol* 2016;175:944-52.
- Morita C, Yanase T, Shiohara T, Aoyama Y. Aggressive treatment in paediatric or young patients with drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is associated with future development of type III polyglandular autoimmune syndrome. *BMJ Case Rep* 2018;2018:bcr2018225528.