# Management of Adult Patients with Drug Reaction with Eosinophilia and Systemic Symptoms

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*Published in:*
JAMA Dermatology

*DOI:*
10.1001/jamadermatol.2023.4450



*Publication date:*
2024

JAMA Dermatology | Original Investigation

# Management of Adult Patients With Drug Reaction With Eosinophilia and Systemic Symptoms
## A Delphi-Based International Consensus

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**IMPORTANCE** Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but potentially fatal drug hypersensitivity reaction. To our knowledge, there is no international consensus on its severity assessment and treatment.

**OBJECTIVE** To reach an international, Delphi-based multinational expert consensus on the diagnostic workup, severity assessment, and treatment of patients with DRESS.

**DESIGN, SETTING, AND PARTICIPANTS** The Delphi method was used to assess 100 statements related to baseline workup, evaluation of severity, acute phase, and postacute management of DRESS. Fifty-seven international experts in DRESS were invited, and 54 participated in the survey, which took place from July to September 2022.

**MAIN OUTCOMES/MEASURES** The degree of agreement was calculated with the RAND-UCLA Appropriateness Method. Consensus was defined as a statement with a median appropriateness value of 7 or higher (appropriate) and a disagreement index of lower than 1.

**RESULTS** In the first Delphi round, consensus was reached on 82 statements. Thirteen statements were revised and assessed in a second round. A consensus was reached for 93 statements overall. The experts agreed on a set of basic diagnostic workup procedures as well as severity- and organ-specific further investigations. They reached a consensus on severity assessment (mild, moderate, and severe) based on the extent of liver, kidney, and blood involvement and the damage of other organs. The panel agreed on the main lines of DRESS management according to these severity grades. General recommendations were generated on the postacute phase follow-up of patients with DRESS and the allergological workup.

**CONCLUSIONS AND RELEVANCE** This Delphi exercise represents, to our knowledge, the first international expert consensus on diagnostic workup, severity assessment, and management of DRESS. This should support clinicians in the diagnosis and management of DRESS and constitute the basis for development of future guidelines.

*JAMA Dermatol*. 2024;160(1):37-44. doi:10.1001/jamadermatol.2023.4450
Published online November 15, 2023.

Supplemental content

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening drug hypersensitivity reaction. Its reported incidence lies between 2 and 5 cases per million per year.[1] Skin involvement with an infiltrated maculopapular exanthema paired with facial edema, lymphadenopathy, fever, organ damage, and hematological abnormalities (notably eosinophilia) are the main features of DRESS.[2,3] Although extracutaneous manifestations of DRESS most frequently affect the liver and kidney, other organs such as the lungs, heart, and nervous system may be affected. The severity of DRESS may vary from mild, with limited organ involvement, to severe life-threatening disease.[2,4]

There remain areas of major challenge in the management of patients with DRESS. These range from the initial diagnostic evaluation to the severity assessment and therapy. To date, no broadly accepted scoring system for grading DRESS severity exists. Different scores to grade disease severity have been published in the UK, Japan, and Spain,[2,4,5] and severity criteria were also suggested in France for a randomized clinical trial.[6]

Corticosteroids, either topically or systemic, are the current mainstay of DRESS treatment. Since DRESS relapses in about 10% to 15% of patients, it is current practice to slowly taper corticosteroids, usually over several months.[1,7,8] To our knowledge, there is no consensus on corticosteroid dose tapering or the appropriate treatment regimen, including the dose and length of administration. In patients with evidence of robust human herpes virus (HHV) replication, especially

cytomegalovirus (CMV), antiviral agents may be considered, but little guidance exists to date.[4,9] Furthermore, in severe corticosteroid-refractory cases, additional treatment approaches have been proposed, including immunosuppressants or, more recently, targeted treatments (anti-IL-5/anti-IL-5R antibodies or Janus kinase inhibitors).[1,5,8,10-12] Lastly, very little data and guidance are available to clinicians concerning follow-up care in DRESS, a matter of importance given the risk of relapse, and uncertain the optimal allergy workup.

Taken together, there is a major unmet need for an international expert consensus on diagnosis, severity assessment, treatment, and postacute patient management in DRESS. Such a consensus would provide valuable guidance for clinicians confronted with this severe adverse cutaneous drug reaction.

### Key Points

**Question** What is the optimal diagnostic and severity assessment as well as management of patients with drug reaction with eosinophilia and systemic symptoms (DRESS)?

**Findings** In this 2-round international Delphi exercise, a panel of 54 experts agreed on 93 statements regarding DRESS diagnosis and management. These statements included recommendations on diagnostic workup and multidisciplinary involvement, severity assessment, drug management, treatment, and follow-up care, as well as allergological workup.

**Meaning** DRESS is a complex, severe cutaneous adverse drug reaction that poses diagnostic and management challenges for clinicians; this consensus is aimed at providing needed support in diagnosis, assessment, and treatment of patients with DRESS.

## Methods

### Steering Committee, Literature Review, and Statement Development

The steering committee (S.I.-H.-O., S.W., L.E.F., and M.-C.B) agreed on the addressed categories (diagnostic workup, professionals involved, drug management, severity assessment, treatment, follow-up care, and allergological workup) and were in charge of guiding the Delphi process. They reviewed the literature and drafted and developed the initial statements. They assessed the results and comments from both Delphi rounds and adapted the new suggested statements based on them.

A literature review was performed in PubMed, Embase, CINAHL, the Cochrane Library, and ClinicalTrials.gov with the following search terms: *DRESS*, *DIHS*, *DRESS treatment*, *DRESS corticosteroids*, *DRESS management*, *DRESS diagnosis*, *DRESS severity*, and *DRESS complications*. Original articles, case reports/series, meta-analyses, clinical trials, and open studies published from 2002 to 2022 and considered of interest for this Delphi exercise were included. Articles that were not in English were excluded. The literature that was considered is indicated under the respective statements. Eleven topics were developed within the scope of the guidelines. The Delphi exercise took place from July to September 2022. The study was exempt from institutional review board approval since there was no research involving patient samples or data.

### Panel Selection and Participation

An international panel of experts in the field of DRESS was invited to participate in this Delphi exercise. Experts were identified based on their publication record and/or participation in expert networks in DRESS. Geographical diversity was considered, but due to the identification and publication-based selection process of participants, not all countries/continents were equally represented. A total of 57 experts were invited via email to participate in this Delphi exercise. The experts were dermatologists and/or allergologists from 21 different countries across 4 continents. A detailed summary of the participants, their specialization(s), and their country of practice is provided in eTable 1 in Supplement 1.

Invited experts who did not respond to the initial invitation were not solicited again. For both Delphi rounds, a deadline for entering responses was set and communicated in the invitation. Within this period, 2 automated reminders were sent out to participants who had not yet given their evaluations of the respective Delphi statements.

### First Round

In the first round (**Figure 1**), participants received an online survey consisting of 100 statements regarding DRESS diagnosis workup, severity assessment, and management. Statements were organized into 7 topic categories: (1) diagnostic workup, (2) professionals involved in the acute phase, (3) drug management, (4) disease severity assessment, (5) treatment, (6) follow-up care, and (7) allergological workup. For the disease severity assessment, statements were based on Japanese and French severity criteria (eTable 2 in Supplement 1), as well as on values of the Sepsis-Related Organ Failure Assessment score.[4,13] Participants evaluated the level of appropriateness of statements on a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). The questionnaire for round 1 is presented in eTable 3 in Supplement 1.

### Second Round

During the second round, participants were asked to rate 13 statements: 11 were a revision of the uncertain (with or without agreement) statements from the previous round, and 2 were additional statements within 2 categories (diagnosis and allergological workup). The workflow is shown in Figure 1. The questionnaire for round 2 is presented in eTable 4 in Supplement 1.

### Statistical Analysis

The RAND/UCLA Appropriateness Method was used to analyze the responses of the Delphi exercise, as previously described.[14,15] We calculated the median rating for appropriateness, interpercentile range (IPR), IPR adjusted for symmetry, and disagreement index (DI) for each statement (DI = IPR/IPR adjusted for symmetry). Median appropriateness values were assessed as follows: 1 to 3.4 was considered inappropriate, 3.5 to 6.9 as uncertain, and 7 to 9 as appropriate. A DI less than 1 indicated a consensus, whereas a DI of 1 or higher was considered to indicate a lack of consensus for a statement's appropriateness.

## Results

### Participants and Delphi Exercise

Three of the 57 experts (eFigure in the Supplement) did not respond to the invitation to participate, 0 declined, and the remaining 54 agreed to participate and responded (from 19 countries across 4 continents; the response rate was 93%). In the second round, 45 of the 54 experts responded (response rate, 83.3%).

### First Round

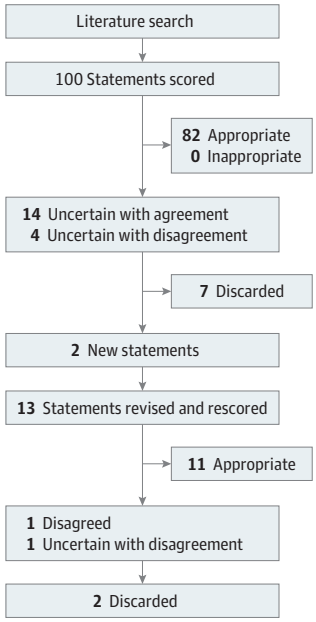
In total, for 82 of 100 statements (82%), a consensus (DI <1) was reached in the first round. All of the initial statements as well as their respective DI and median of appropriateness are summarized in eTable 3 in Supplement 1. For 18 statements, the experts were uncertain. For 4 of 18 statements, experts disagreed (DI ≥1), and for the other 14 statements, they agreed (DI <1; Figure 1 and eTable 3 in Supplement 1). The category with the most disagreement for the proposed statements was diagnosis (3 statements; eTable 3 in Supplement 1). Seven statements were discarded (eTable 5 in Supplement 1). This led to 11 unclear statements for the second round.

### Second Round

As a result of incorporating 2 additional statements, the second round of the process consisted of a total of 13 statements. For 11 of 13 revised statements (92%), consensus (DI <1) was reached. For 1 statement, experts were uncertain (median rating of 6), and for another experts disagreed, despite a median rate being appropriate (median rating of 7) (eTable 4 in Supplement 1). Both of these statements were discarded based on discussion and comments (eTable 5 in Supplement 1).

After the 2 rounds, a consensus was reached for 93 statements (**Table** and eTable 6 in Supplement 1). A summary of the consensus statements in the category diagnostic workup is shown in **Figure 2**. DRESS severity degrees as agreed on in the Delphi consensus are displayed in **Figure 3**.

Figure 1. Flowchart of the 2-Round DELPHI Process




In the first round, 100 statements were scored, of which 82 were appropriate and 7 were discarded. In the second round, the 11 statements from the first round that exhibited uncertain levels of agreement and disagreement were revised. Two additional statements were introduced. As a result, 93 statements achieved consensus.

## Discussion

The main goal of this Delphi-based exercise was to reach a consensus to support clinicians in the management of patients with DRESS. It provides a basis of elements to consider in diagnosing, treating, and following up patients with DRESS. It was not designed to cover all aspects of DRESS management in detail.

Consensus was reached for 93 statements. The topic of greatest uncertainty within the diagnostic workup section and overall was the assessment of HHV reactivation. The panel agreed on the value of measuring the viral load of Epstein-Barr virus, CMV, and HHV-6 in all patients with suspected DRESS. However, a viral polymerase chain reaction (PCR) for HHV-7, which is not universally available in clinical laboratories, was only viewed as an optional investigation in patients with a suspected viral reactivation. This means a situation in which another viral reactivation has already been confirmed (Epstein-Barr virus, CMV, HHV-6), since HHV-7 has mostly been reported in combination with other reactivations and is rarer.[16] Testing for herpes simplex virus 1/2 and parvovirus B19 was not recommended by the panel. The divergent opinions of experts regarding the value of viral PCR for DRESS diagnosis reflect the ongoing debate and uncertainty concerning HHV reactivation in DRESS. It is not clear whether it is a causative factor vs consequence of DRESS.[17] In addition, this difference in opinion may also be related to region-specific differences in availability of certain laboratory investigations and differences in the prevalence of certain viral strains. The recommendations on performing viral PCRs as part of the basic workup provided in this Delphi exercise should be viewed and interpreted in the context of the treating clinician's available resources. Whereas viral replications are not an essential criterion for the diagnosis of DRESS, the therapeutic effect of their positivity is heavily debated.

The second most debated topic was whether to perform serological screening for hepatitis A, B, and/or C. We initially proposed screening for hepatitis A, B, and C for all patients, as in the Spanish guidelines.[5] The panel, however, rejected this proposal but accepted, in case of liver involvement, a screening for hepatitis A, B and C, and prior to initiation of a systemic treatment, a screening for hepatitis B and C only. The HIV antibody screening was not recommended, even when limited to patients who would receive systemic treatment.

For cardiac involvement, consensus was obtained to perform an electrocardiogram in all patients, but measurement serum levels of B-type natriuretic peptide/pro-B-type natriuretic

Table. DRESS Acute Phase Management and Follow-Up Care

| | |
|---|---|
| **Consensus on DRESS treatment**[a] | |
| General recommendations | • Treatment should be based on disease severity assessment<br>• Corticosteroids should be initiated in all patients with confirmed DRESS |
| Mild DRESS[b] | • Topical very high potency steroids should be initiated<br>• Steroids should be tapered over 6 wk to 3 mo |
| Moderate DRESS[b] | • Topical very high potency steroids can be considered<br>• Systemic glucocorticoids can be considered in patients with moderate disease<br>• Steroids should be tapered over 6 wk to 3 mo |
| Severe DRESS[b] | • Systemic glucocorticoids should be initiated in all patients<br>• Systemic glucocorticoids should be tapered over 3 to 6 mo |
| Corticosteroid-refractory DRESS | • Cyclosporine can be considered<br>• Antibodies interfering with the IL-5 axis (anti-IL-5 or anti-IL-5R) can be considered<br>• Intravenous immunoglobulins can be considered |
| DRESS with high serum CMV viral load | • Antiviral treatment (ganciclovir/valganciclovir) can be considered |
| **Consensus on follow-up care**[a] | |
| Timing of follow-up | • Regular follow-up consultations beginning in the first month after discharge<br>• Regular follow-up consultations during the first 6 mo after onset and thereafter according the patients' needs |
| Content of follow-up consultations | • Blood tests according to the initial organ involvement<br>• Screening for autoantibodies in the convalescence phase<br>• Screening for thyroid dysfunction in the convalescence phase<br>• Screening for steroid adverse effects in patients receiving prolonged systemic steroids<br>• Active offering of psychological support |

Abbreviations: CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms.

[a] Summary of the full consensus statements are displayed in eTable 2 in Supplement 1.

[b] DRESS severity degrees as agreed on in the Delphi consensus, as displayed in Figure 3.

peptide and troponin only in case of suspected cardiac involvement. Screening serum troponin levels was first proposed for all patients, based on other national diagnostic guidelines,[5,9] but the statement did not reach agreement and was therefore revised. Despite this, the expert panel emphasized that caution is warranted since cardiac involvement in DRESS may occur without clinical signs or symptoms during the acute phase.[18]

Almost all statements dealing with severity assessment obtained consensus after the first round. The use of thymus and activation-regulated chemokine (CCL17)—previously suggested to be a serologic marker for DRESS—as part of the diagnostic workup was the only statement that did not reach consensus and was thus removed.[19,20] Its implementation in clinical practice, however, may, as evidenced by the present Delphi results, require further validation in patient cohorts.

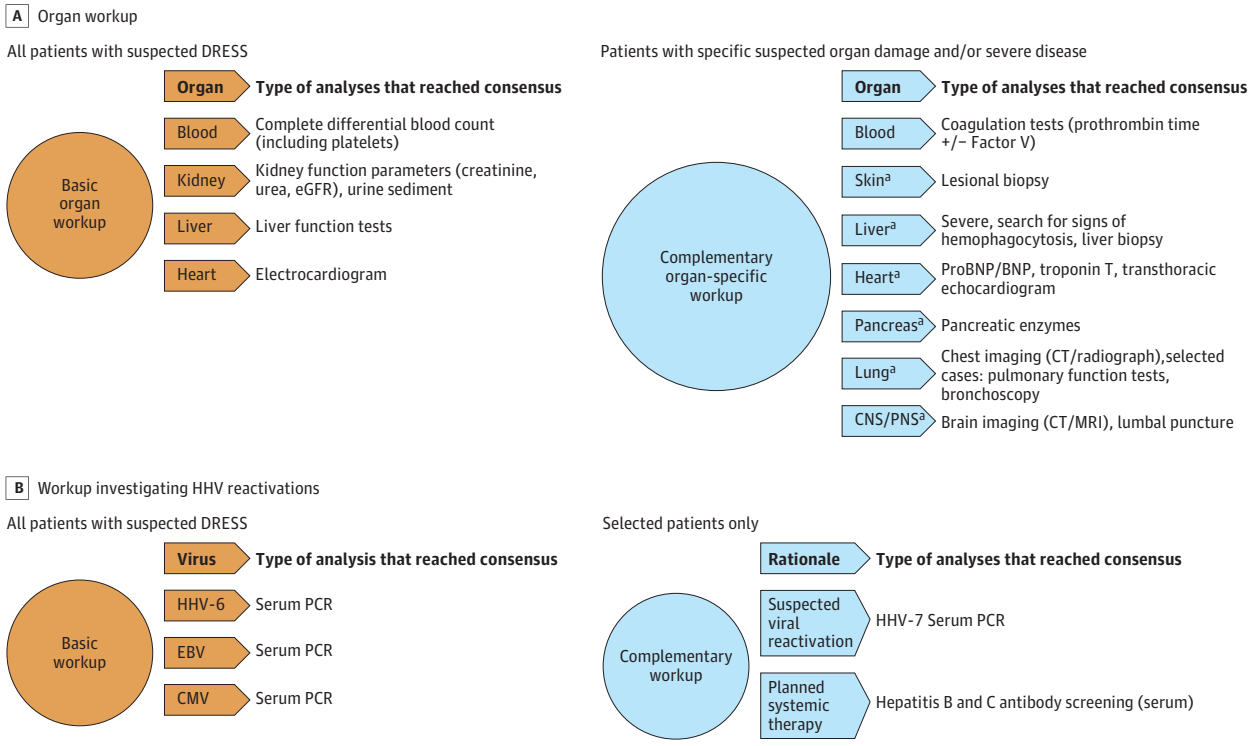
To date, and to our knowledge, no consensus on criteria of severity has been published for DRESS. The DRESSCODE randomized clinical trial[6] and Japanese severity criteria[4,21] delineate 3 levels of DRESS severity (eTable 2 in Supplement 1). These severity criteria, used in France, routinely and in clinical research,[22] were proposed herein and agreed on by the panel of experts. Briefly, these severity criteria define ranges for liver and kidney function test anomalies as well as hematological disturbances that differentiate between mild, moderate, and severe DRESS and define DRESS with any other organ damage as severe. Importantly, despite support from the expert panel for these severity criteria, the thresholds defined and their correlation with outcomes need to be validated in a multicenter revised statement that recommends performing antibody screening in prospective cohorts and possibly adapted where necessary.

Experts reached consensus in the first round for all 12 proposed statements for the treatment of DRESS. Corticosteroids as a cornerstone of DRESS treatment and immediate cessation of the culprit drug(s) were accepted for all patients. Regarding the form of administration, very high potency topical corticosteroids were recommended in mild DRESS. For moderate DRESS, both very high potency topical corticosteroids and systemic glucocorticoids were suggested as statements and accepted by the expert panel. A French retrospective study has previously shown that very high potency topical steroids were efficacious to treat skin and internal organ disease in nonsevere cases and were associated with few relapses.[7] The efficacy of a blood passage of high-potent topical steroids on nonsevere organ involvements is hypothesized. An additional ongoing trial (DRESSCODE[6]) addresses the question of very high potency topical vs low-dose systemic steroids for moderate DRESS. However, caution should be taken when switching from systemic glucocorticoids to topical steroids; this may, according to a recent study, carry the risk of relapses.[22] For severe DRESS, experts agreed that systemic glucocorticoid therapy should be first line. Dosage suggestions were not included in the statements.

The role of HHV reactivation and in particular reactivation of HHV-6 and HHV-7 remains debated. The expert panel, however, agreed that antiviral drugs (ganciclovir, valganciclovir) could be considered in patients with high CMV viral load. This recommendation was previously suggested in the Japanese guidelines.[4,21] In the Spanish and French guidelines, antivirals are suggested in case of high viral load and/or life-threatening CMV-related manifestations.[5,9]

For patients with corticosteroid-refractory disease, experts agreed that cyclosporine and intravenous immunoglobulins (IVIGs) may be clinically helpful. Evidence is based only on small retrospective case series. In the latter, IVIGs are either combined with systemic corticosteroid therapy in steroid-refractory cases[23,24] or with cyclosporine as a first-line regimen.[23,25,26] For IVIGs, toxic effects have been reported when these were used as single agents without corticosteroids in DRESS.[27] Experts also agreed that the more recently

Figure 2. Baseline and Complementary Diagnostic Workup Based on the Delphi Consensus




A, Investigations that should be performed in all patients with suspected drug reaction with eosinophilia and systemic symptoms (DRESS) and complementary examinations that are recommended in patients with specific suspected organ damage and/or severe disease. B, Workup investigating human herpes virus (HHV) reactivations, including serological investigations of HHV reactivations associated with DRESS in the basic workup and serological investigations of viral reactivations associated with DRESS in selected patients only. HHV-7 reactivation can be suspected in patients with DRESS with another confirmed HHV reactivation. CMV indicates cytomegalovirus; CNS, central nervous system; CT, computed tomography; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PNS, peripheral nervous system; ProBNP, Pro–B-type natriuretic peptide.

[a] Involve specialists of the respective disciplines.

reported use of anti-IL-5 or anti-IL-5R antibodies should be considered as a therapeutic option in corticosteroid-refractory DRESS.[28,29] The use of all of these agents in corticosteroid-refractory DRESS relies on case reports or small retrospective case series; therefore, prospective trials, although difficult to perform, are urgently needed.

Allergy workup for DRESS was the last category, in which divergent practices were evident. Skin prick tests were rejected as an option in DRESS workup, and intradermal tests were accepted when used with caution. Patch tests were agreed on as an option.[30] Overall, this study also highlights that there are divergent practices in the use of in vitro vs skin tests. It points out the need for more thorough, drug-specific recommendations. Such recommendations are difficult to obtain in a Delphi exercise, as the data for decision-making is currently insufficient.[31,32]

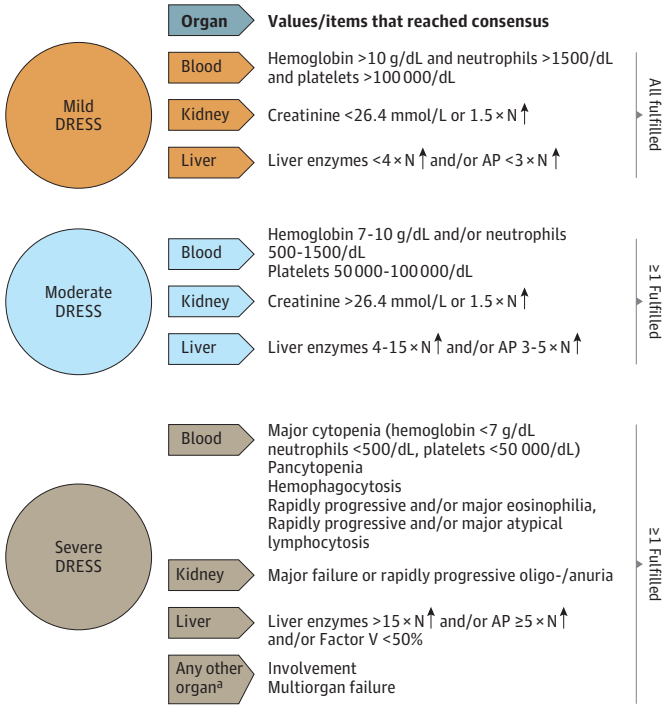
## Limitations

It must be emphasized that due to the low prevalence of DRESS, the literature evidence for these Delphi statements on treatment is limited. The reached consensus statements thus need to be handled with caution and context/expertise of the treating physician. This Delphi exercise aimed to provide a common ground of consensus. Each of the addressed categories needs more in-depth follow-up studies to improve the clinical management of patients. This work's aim was to provide a broad basis management plan for patients with DRESS but cannot cover all nuances of DRESS. The expert panel assessing this Delphi was objectively selected but showed an imbalance in terms of specialties. It consisted of about 80% dermatologists (45 of 54 participants), and the other participants were specialists in allergy/immunology, pharmacology, and hepatology. The expert composition may have influenced the reached consensus. Finally, this study points out the need to further explore ethnicity- and/or region-associated differences in DRESS (eg, in the spectrum of viral reactivation, which may affect patient management).

## Conclusions

In conclusion, this Delphi exercise provides, to our knowledge, the first international expert consensus on the

Figure 3. Proposed DRESS Severity Grading Based on the Delphi Consensus Statements




AP indicates alkaline phosphatase; DRESS, drug reaction with eosinophilia and systemic symptoms; N ↑, fold increase of the normal upper limit value.

[a] Involvement of other organ(s) of any severity.

diagnostic workup, severity assessment, and treatment of DRESS, aimed at helping clinicians optimally manage patients with DRESS. The Delphi exercise also highlights gaps in knowledge that need to be addressed with additional collaborative studies to consolidate and expand the current consensus, but also address areas of uncertainty.

ARTICLE INFORMATION

**Accepted for Publication:** August 28, 2023.

**Published Online:** November 15, 2023. doi:10.1001/jamadermatol.2023.4450

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**Conflict of Interest Disclosures:** Prof Brüggen reported grants and research funding from the Swiss National Science Foundation, the Christine Kühne-Center for Allergy Research and Education, the FreeNovation Foundation, the LEO Foundation, the Olga Mayenfisch Foundation, the University of Zurich, LEO Pharma, and the Eczema Foundation of Pierre Fabre; speaking and/or consultation fees from Eli Lilly, LEO Pharma, AbbVie, GSK, and AstraZeneca; and honoraria from speaking/presentation and educational events for the Christine Kühne-Center for Allergy Research and Education, FOMF, and ADR-AC. Dr Bernal reported personal fees from Versantis and Flagship Pioneering outside the submitted work. Dr Chua reported nonfinancial support from Novartis, Almirall, and UCB, as well as personal fees from Boehringer Ingelheim, Novartis, and UCB outside the submitted work. Dr Divito reported grants from the National Institutes of Health during the conduct of the study, personal fees from Adaptimmune outside the submitted work, and a provisional patent issued. Prof Dodiuk-Gad reported serving as a consultant/investigator for Sanofi, AbbVie, Pfizer, Janssen, Novartis, La Roche-Posay, Dexcel, and Eli Lilly. Prof Horváth reported personal fees paid to their institution from Janssen-Cilag, UCB, and Argenx, as well as grants paid to their institution from AbbVie and Novartis outside the submitted work. Dr Kaffenberger reported grants from the Dermatology Foundation outside the submitted work. Prof Lehloenya reported grants from the National Research Foundation during the conduct of the study. Dr Micheletti reported personal fees from Vertex and grants from Acelyrin, Pfizer, Amgen, and Cabaletta Bio outside the submitted work. Dr Mostaghimi reported personal fees from hims and hers, AbbVie, Sun Pharma, Pfizer, Digital Diagnostics, Lilly, Equillium, ASLAN, Boehringer Ingelheim, and Acom outside the submitted work. Dr Phillips reported personal fees from Verve, Novavax, Janssen, AstraZeneca, Biocryst, Regeneron, and UpToDate outside the submitted work. Dr Rosenbach reported personal fees from Merck, Janssen, and Novartis during the conduct of the study. Dr Salavastru reported royalties from Springer Nature. Dr Staumont-Salle reported grants from AstraZeneca and personal fees from GSK outside the submitted work. Dr Tiplica reported personal fees from LEO Pharma, Antibiotice SA, and Genesis Pharma outside the submitted work. Dr Traidl reported grants from Sanofi and personal fees from LEO Pharma, Janssen, Lilly, and La Roche-Posay outside the submitted work. Dr Cho reported personal fees from Novartis, AbbVie, Sanofi, and Viatris outside the submitted work. No other disclosures were reported.

**Disclaimer:** Dr Micheletti is an Images in Dermatology Editor and Dr Shinkai is Editor of *JAMA Dermatology*, but they were not involved in any of the decisions regarding review of the manuscript or its acceptance.

**Data Sharing Statement:** See Supplement 2.

**Additional Contributions:** We thank Neil Shear, MD, PhD, of the University of Toronto, for his participation in the Delphi exercise. No compensation was received for these contributions.

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