

Flaws and Limitations of Classification Criteria for Drug Reaction With Eosinophilia and Systemic Symptoms



Cathryn Sibbald, MD^a, Neil H. Shear, MD^b, and Ruud H.J. Versteegen, MD^{c,d} *Toronto, Ontario, Canada*

Drug reaction with eosinophilia and systemic symptoms (DReSS), also called drug-induced hypersensitivity syndrome (DIHS), is a severe multisystem inflammatory adverse drug reaction associated with high short-term and long-term morbidity most commonly caused by antibiotics, anticonvulsants, allopurinol, and sulfonamides.¹ Patients of all ages and ethnicities can be affected, although some have a predisposition based on (genetic) variations in drug metabolism and immune response (eg, human leukocyte antigen).¹

Although the classic presentation includes fever, a cutaneous eruption, hematologic abnormalities, and internal organ inflammation approximately 2 to 6 weeks after initiation of drug therapy, these features are not always present. More important, viral and inflammatory conditions can present similarly, and there is no reference standard for the diagnosis.

It is common for clinicians to rely on available classification criteria for diagnoses. However, this practice may lead to a missed or false diagnosis of DReSS/DIHS, which can be harmful. First, misdiagnosis may result in incorrect treatments with a risk for unmanaged disease and avoidable adverse drug reactions. Second, without the critical establishment of drug causality, inadvertent reexposure is possible with worse outcomes. Besides direct effects on patient care, inappropriate inclusion in research studies affects the validity of reported results and conclusions. Thus, a clear need exists for diagnostic criteria that ensure accurate diagnosis for clinical use and provide clear, unambiguous case definitions for inclusion in retrospective and prospective studies.

Table I lists three commonly used criteria for DReSS/DIHS, including the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) criteria, the Japanese Severe Cutaneous Adverse Reactions (J-SCAR) criteria, and criteria proposed by Bocquet in 1996.¹

The RegiSCAR criteria are the most used criteria for research studies, for which they were initially intended. However, they are also widely used in clinical practice although they were not developed or validated for this purpose, including in specific populations such as patients receiving immunosuppressive treatment, or children.

The RegiSCAR criteria include compatible skin biopsy results. However, features on skin biopsy in DReSS/DIHS have been reported to be nonspecific, with poor positive predictive values and no single universal finding.²

The hematologic and organ involvement elements in the RegiSCAR criteria are also problematic. Hematologic abnormalities including elevated peripheral eosinophils and atypical lymphocytes are common, but not specific. Eosinophilia is not universally present, and atypical lymphocytes are not specific; they are often detected in viral infections. In addition, pancytopenia may be present, preventing the development of eosinophilia and atypical lymphocytes. Finally, the requirements for organ involvement are not defined, leaving this determination to the discretion of clinicians and causing uncertainty about which organs to consider and when laboratory results are slightly above the cutoff level.

The RegiSCAR criteria require the exclusion of alternative diagnoses. However, many viral infections present with a widespread morbilliform cutaneous eruption that is clinically indistinguishable from that in DReSS/DIHS.³ Hepatitis serology is included, but not other viral mimickers such as Epstein-Barr virus, cytomegalovirus, parvovirus, measles, rubella, echovirus, and chikungunya. Chlamydia and mycoplasma are included but more commonly present with mucositis predominance. Although positive antinuclear antibody (ANA) is included, this may miss true cases because of the high prevalence in the general population (about 16%), which is never the sole feature of rheumatic disease.⁴

Finally, many elements do not account for the time required to develop or score them. First, some clinical features may be seen only later in the disease course (eg, eosinophilia). Second, biopsy results and ANA and microbiology test results may take days or weeks. Finally, resolution within 15 days does not consider the frequent necessity for empiric treatment and lacks clear parameters regarding what defines resolution, which is especially important in the context of patients receiving appropriate treatment.

^aDivision of Dermatology, Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada

^bDepartment of Medicine, Division of Dermatology, University of Toronto, Toronto, Ontario, Canada

^cDivision of Clinical Pharmacology and Toxicology, Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada

^dDivision of Rheumatology, Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada

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Corresponding author: Cathryn Sibbald, MD, Department of Paediatrics, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G1X8, Canada. E-mail: Cathryn.sibbald@sickkids.ca.

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TABLE I. Current diagnostic criteria for DReSS/DIHS

Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples					Japanese Severe Cutaneous Adverse Reactions	Bocquet et al ¹
	-1	0	1	2		
Fever ($\geq 38.5^{\circ}\text{C}$)	No/U	Yes	—	—	Maculopapular rash >3 wk after starting suspected drug Prolonged clinical symptoms after causative drug withdrawal (>2 wk) Fever ($>38^{\circ}\text{C}$) Liver abnormalities (ALT >100 U/L) Leukocyte abnormalities (at least one present): leukocytosis ($>11 \times 10^9/\text{L}$) atypical lymphocytes ($>5\%$) eosinophilia ($>1.5 \times 10^9/\text{L}$) Lymphadenopathy Human herpesvirus 6 reactivation	Cutaneous drug eruption Hematologic abnormalities (at least one): Eosinophilia ($\geq 1.5 \times 10^9/\text{L}$) Atypical lymphocytes Systemic manifestation (at least one): Adenopathy (≥ 2 cm) Hepatitis (alanine transaminase, AST $\geq 2 \times$ normal limits) Interstitial nephritis Interstitial pneumonitis Carditis
Lymphadenopathy (two or more sites, $>1\text{cm}$)		No/U	Yes			
Atypical lymphocytes		No/U	Yes			
Eosinophilia		No/U	$0.7\text{--}1.499 \times 10^9/\text{L}$	$\geq 1.5 \times 10^9/\text{L}$		
When leukocytes $<4.0 \times 10^9/\text{L}$			10% to 19.9%	$\geq 20\%$		
Skin eruption						
Skin eruption $\geq 50\%$ BSA		No/U	Yes			
Skin eruption suggesting DReSS	No	U	Yes			
Skin biopsy suggesting DReSS	No	Yes/U				
Internal organ involvement		No/U	One organ system	Two or more organ systems		
Resolution ≥ 15 d	No/U	Yes				
Evaluation of other causes			None positive and negative results for at least three			
Antinuclear antibody						
Blood cultures						
Hepatitis A/B/C serology						

Chlamydia/ mycoplasma serology		
Final score	Typical DIHS: all seven criteria; atypical DIHS: first five criteria	DIHS: all three criteria required
<2: no case		
2-3: possible case		
4-5: probable case		
>5: definite case		

ALT, alanine transaminase; AST, aspartate transaminase; BSA, body surface area; DIHS, drug-induced hypersensitivity syndrome; DReSS, drug reaction with eosinophilia and systemic symptoms; U, units.

The J-SCAR and Bocquet criteria share shortcomings with the RegiSCAR criteria, notably the lack of important exclusion of infectious mimickers. The J-SCAR has several additional limitations. It requires a maculopapular morphology for cutaneous rash, despite the large range of exanthems that have been reported in DReSS/DIHS, including urticarial, lichenoid, pustular, bullous, and eczematous.¹ It also requires a 3-week latency after starting the suspected drug, despite recent data reporting cases with much shorter latency periods.^{5,6} Although the J-SCAR defines liver organ dysfunction as alanine transaminase level greater than 100, this misses other presentations of liver involvement and includes no other solid organs despite data demonstrating that the kidney, lungs, and heart are involved in up to 42%, 33%, and 27% of patients, respectively.⁵ Finally, a positive human herpesvirus 6 result is included, although this test is unavailable at many centers.

All three criteria have important limitations. They are cross-sectional and do not reflect the characteristic sequential development of features. None include a probability score based on drug exposure or genetic predisposition. None have been updated in the past 10 years, despite new studies and published data with newly recognized features including facial edema, potential mucosal involvement, overlap syndromes (especially with other severe drug reactions), associated predisposing genetic mutations, and drug-specific presentations. Considerations regarding skin of color should be highlighted, including variations in clinical presentation and genetic predisposition.

The availability of a diagnostic tool is helpful to enhance the recognition and diagnosis of DReSS/DIHS and may direct the choice of treatment modalities in the future. Therefore, we call for the development of new criteria using a Delphi process mimicking that recently used to classify systemic lupus erythematosus.⁷ Key elements should include a drug causality assessment using newly recognized features considering basic science and molecular, cellular, and genetic criteria. Appropriate selection of experts should ensure representation from different specialties (dermatology, clinical pharmacology, allergy/immunology, pediatrics, and others) from a large range of geographic locations, as well as patients. Finally, the criteria should undergo validation in an international cohort. Although this endeavor may be resource- and time-intensive, only with improved criteria can we ensure that optimal clinical care and future research are accurately informed. Until these are developed, clinicians must be aware of the pitfalls of current criteria and be guided by the clinical presentation of their patients.

KEY POINTS

Caveats of current DReSS/DIHS classification criteria

Drugs:

- Drug exposure is not included as a required criterion for diagnosis.

- Low versus high-risk drug exposures are not assessed.
- Drug causality is not addressed.
- Drug-specific latency period is not included.

Skin:

- Less common skin morphologies are not included, including overlap syndromes.
- Rash may be missed in skin of color.
- Histopathology criteria are nonspecific.

Hematologic involvement:

- Eosinophilia is often late or absent or may be suppressed by corticosteroid treatment.
- Atypical lymphocytes can be seen in other illnesses.

Organ involvement:

- Definitions are lacking, incomplete, or imprecise.

Exclusion criteria:

- Common viral mimickers are not included.
- A positive ANA is nonspecific, does not exclude DReSS, and by itself does not indicate any other alternative clinical diagnosis.
- Additional investigations may not be available or may take too long for results.

Diagnostic and prognostic value:

- Not validated for diagnostic use.
- Characteristic (drug-specific) sequential development of disease features is not included.
- Duration of disease criterion is inappropriate for diagnostic use.
- Lacks prediction of recurrence or relapse.

REFERENCES

- Cardones AR. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *Clin Dermatol* 2020;38:702-11.
- Skowron F, Bensaid B, Balme B, Depaepe L, Kanitakis J, Nosbaum A, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): clinicopathological study of 45 cases. *J Eur Acad Dermatol Venereol* 2015;29:2199-205.
- Korman AM, Alikhan A, Kaffenberger BH. Viral exanthems: an update on laboratory testing of the adult patient. *J Am Acad Dermatol* 2017;76:538-50.
- Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, et al. Increasing prevalence of antinuclear antibodies in the United States. *Arthritis Rheumatol* 2022;74:2032-41.
- Martinez-Cabriales SA, Rodriguez-Bolanos F, Shear NH. Drug reaction with eosinophilia and systemic symptoms (DRESS): how far have we come? *Am J Clin Dermatol* 2019;20:217-36.
- Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: a retrospective study. *J Am Acad Dermatol* 2020;82:606-11.
- Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:1400-12.