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DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS: A COMPREHENSIVE REVIEW OF THE LITERATURE

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ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or drug-induced hypersensitivity syndrome is a serious form of cutaneous drug reactions resulting from a cell-mediated immune process with characteristic delay in onset, fever, edematous morbilliform rash, lymphadenopathy, eosinophilia or atypical lymphocytes, and typical involvement of internal organs. The diagnostic criteria consist of a structured assessment according to the RegiSCAR score or Japanese consensus criteria with differential exclusion of look-alikes followed by identification of the drug trigger. It is attributed to the presentation of antigens from the offending drug to specific HLA molecules with predominance of cytotoxic and type 2 lymphocyte responses. High-risk drugs include aromatic anti-epileptics, allopurinol, sulfonamide antibiotics and dapsone, tetracyclines and vancomycin, anti-tubercular drugs, and selected anti-retroviral drugs. Withdrawing the offending drug immediately and hospital care is primary. Cyclosporin is sometimes considered as second-line treatment for corticosteroid-refractoriness or corticosteroid-contraindications. In turn IVIG and targeted therapy against IL-5 or IL-5 receptors could have role in carefully chosen patients. Primary causes of cases leading to death include acute hepatopathy, myocarditis resultant to respiratory insufficiency or sepsis. Others include type-1 diabetes mellitus or autoimmunity to thyroid or chronic renal diseases. A very large proportion of cases could be certainly prevented with pharmacogenetics screening methods such as analysis for allopurinol and/or HLA-B*58:01 or screening for Abacavir with HLA-B*57:01 before their administration.

KEYWORDS

DRESS, DIHS, Severe Cutaneous Adverse Reactions, Eosinophilia

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS, also drug-induced hypersensitivity syndrome - DIHS), is a rare, complex, potentially life-threatening, severe adverse drug reaction. This effect is mediated by T cells and is characterized by various combinations of skin rash, hematologic abnormalities, eosinophilia, atypical lymphocytosis, lymphadenopathy, and internal organ involvement (most often hepatitis, nephritis, pneumonitis, and myocarditis). The usual latency is 2-6 weeks after initiation of the culprit medicine, longer than for most morbilliform drug eruptions [1–3]. Along with Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis, (AGEP), DRESS belongs to the group of severe cutaneous adverse reactions (SCAR). These syndromes share resembling pathogenetic mechanisms, are rare yet potentially fatal, and feature severe cutaneous and systemic manifestations caused by delayed type hypersensitivity reactions, type IV, to a range of medications. Unlike those entities, DRESS has more diverse clinical features, which greatly complicates diagnosis.

The first descriptions of the triad of drug fever, rash, and eosinophilia appeared in the 1930 and for a long time, various terms were used, such as anticonvulsant hypersensitivity syndrome, drug-induced pseudolymphoma, and drug-induced hypersensitivity syndrome, until in 1996 Bocquet proposed the term Drug Rash with Eosinophilia and Systemic Symptoms to embrace related reactions and distinguish them from other severe drug reactions without eosinophilia. Subsequently, the word “rash” in DRESS was replaced with “reaction,” reflecting the significant variability of cutaneous manifestations. It is worth noting that the “e” in DReSS is often lowercase to indicate that eosinophilia is not always present and other hematologic abnormalities may be seen. The term DRESS has gained international recognition and is widely used, though not universally. Recently, proposals have appeared to reconsider the word “drug,” since vaccines and biologics can also trigger DRESS [1–4]. Diagnostic frameworks from the European RegiSCAR group and the Japanese consensus group, J-SCAR, provide operational case definitions and scoring systems that have enabled epidemiological study, risk stratification, and therapeutic evaluation [1,3–6]. This review summarises current DRESS comprehension including pathophysiology, risk factors, epidemiology, diagnosis, differential diagnosis, management and outcomes, integrating contemporary evidence and consensus guidance.

Pathophysiology

As mentioned above DRESS is a prototypical T cell mediated, type IV hypersensitivity, with drug-specific cytotoxic T-cell responses directed against peptide–HLA complexes on keratinocytes and diverse parenchymal cells. Several mechanisms have been proposed. One view holds that an early expansion of immunosuppressive regulatory T cells, particularly CD4+CD25+FoxP3+, reduces antiviral T-cell function, enabling viral reactivation. Others suggest reactivation is linked to steroid-induced immunosuppression. A recent hypothesis posits that drug-reactive, DRESS-inducing T cells are in fact virus-specific memory T cells. T cells previously engaged in antiviral responses become aberrantly stimulated by HLA–drug complexes, triggering DRESS. Small-molecule drugs or their metabolites can act as haptens or bind non-covalently to HLA or T-cell receptor, according to the hapten–protein, pharmacological interaction, or altered peptide repertoire models, producing an immunogenic neoantigen landscape [2,7]. Antigen presentation is constrained by specific HLA risk alleles that confer high positive predictive value for some culprit–phenotype pairs. For example, HLA-A*32:01 is strongly associated with vancomycin-induced DRESS, with near-complete negative predictive value in European ancestry cohorts [8]. HLA-B*58:01 confers large effect size risk for allopurinol-induced SCAR, including DRESS, with high allele frequencies in East Asian, some Oceanian, and African populations [9–12]. HLA-A*31:01 increases risk of carbamazepine hypersensitivity phenotypes that include DRESS, whereas HLA-B*15:02 is more predictive of SJS/TEN in Han Chinese and Southeast Asian populations [10,13]. HLA-B*13:01 is a validated marker for dapsone hypersensitivity syndrome, a DRESS-like entity prevalent in settings where dapsone is used for leprosy or as Pneumocystis prophylaxis [10,14]. Non-HLA determinants include drug dose and rapid dose escalation, reduced renal function for renally cleared drugs such as allopurinol and vancomycin, and metabolic polymorphisms that modify reactive metabolite formation, for example CYP2C9 for phenytoin [9–11,15].

Downstream, activated CD4+ and CD8+ T cells produce IL-5, IL-4, IFN-γ, TNF-α, and IL-17, which drives eosinophilopoiesis, recruitment of eosinophils into affected tissues, keratinocyte injury, and multi-organ damage [2,7]. Regulatory T cell expansion in early disease may be followed by functional impairment during human herpesvirus reactivation, facilitating relapses and autoimmunity [2,3]. The common comorbidities in DRESS are HIV infection, atopy, and epilepsy. Most patients recover completely, but long-term consequences develop in 11.5% of cases, such as autoimmune diseases or persistent failure of target organs. Additionally,

the relationship between DRESS and viral reactivation has been widely studied and despite abundant research, it remains unclear whether viral reactivation is causal or should be viewed as a complication of the reaction. The most common virus associated with DReSS is human herpesvirus 6, HHV-6, though reactivation of HHV-7, cytomegalovirus, CMV, Epstein–Barr virus, EBV, and herpes simplex virus, HSV, has been reported. Viral reactivation usually occurs 2–4 weeks after DRESS symptom onset and is associated with longer illness duration, frequent relapses during steroid taper, and more severe outcomes. Virologic flares correlate with disease activity and may herald complications such as fulminant hepatitis or haemophagocytic lymphohistiocytosis [2–4]. The interplay between drug-specific T cells and herpesvirus reactivation likely accounts for the prolonged and fluctuating clinical course and the delayed onset relative to exposure.

The most common culprit drugs that is associated with the reaction embrace aromatic anticonvulsants, allopurinol, sulfonamide antibiotics and dapsone, tetracyclines, glycopeptides including vancomycin, antituberculosis regimens, antiretrovirals such as abacavir and nevirapine, and anti-inflammatory or disease-modifying agents including sulfasalazine and, less consistently, proton pump inhibitors [25]. In pediatrics, the most common drugs are antiepileptics and antimicrobials, with vancomycin followed by trimethoprim-sulfamethoxazole [1,3,16–18]. Recent initiation within the previous two to eight weeks, dose dependence for some agents, polypharmacy, and intercurrent infections form the clinical context for causality assessment. Non-drug precipitants are uncommon, although DIHS-like presentations associated with herpesvirus reactivation without an identifiable drug have been reported, and should prompt scrutiny for unrecognised exposures and consideration of alternative diagnoses [3]. A complete list of drugs associated with DRESS is provided in Table 1.

Table 1. High-risk medications for DRESS.

Generic drug	Class	Common indications	Relative risk for DRESS
Allopurinol	Xanthine oxidase inhibitor	Gout, hyperuricemia	High
Carbamazepine	Antiepileptic (aromatic)	Seizures, trigeminal neuralgia	High
Oxcarbazepine	Antiepileptic (ketone)	Seizures, neuropathic pain	Intermediate
Lamotrigine	Antiepileptic	Seizures, bipolar disorder	High
Phenytoin	Antiepileptic (aromatic)	Seizures, status epilepticus	High
Phenobarbital	Antiepileptic (barbiturate)	Seizures	High
Valproate	Antiepileptic	Seizures, bipolar disorder	Uncertain
Trimethoprim/sulfamethoxazole	Antibiotic (sulfonamide)	Bacterial infections (UTI, pneumonia)	High
Minocycline	Antibiotic (tetracycline)	Acne, Rickettsia, atypical infections	High
Doxycycline	Antibiotic (tetracycline)	Bacterial infections	Intermediate
Vancomycin	Antibiotic (glycopeptide)	MRSA, resistant Gram-positives	High
Linezolid	Antibiotic (oxazolidinone)	MRSA, VRE infections	Intermediate
Dapsone	Antibiotic/sulfone	Leprosy, dermatitis herpetiformis	High
Isoniazid	Antituberculosis	Tuberculosis	High
Rifampin	Antituberculosis	Tuberculosis, staphylococcal infections	High
Pyrazinamide	Antituberculosis	Tuberculosis	Intermediate
Ethambutol	Antituberculosis	Tuberculosis	Intermediate
Abacavir	Antiretroviral (NRTI)	HIV infection	High
Nevirapine	Antiretroviral (NNRTI)	HIV infection	High
Sulfasalazine	Immunomodulator (sulfa)	Ulcerative colitis, rheumatoid arthritis	High
Terbinafine	Antifungal	Onychomycosis, dermatophytosis	High
Hydroxychloroquine	Antimalarial/DMARD	Malaria, lupus, rheumatoid arthritis	Intermediate
Amoxicillin-clavulanate	Antibiotic (penicillin)	Bacterial infections	Uncertain
Mexiletine	Antiarrhythmic	Ventricular arrhythmias, neuropathic pain	Intermediate

Epidemiology

DRESS is uncommon but clinically significant. Population-based and inpatient estimates vary with ascertainment method, medication utilisation patterns, and ethnicity. Incidence in the general population has been estimated at approximately 0.9 per 100,000 person-years to 10 per million, while inpatient incidence ranges from 2 to 40 per 100,000 admissions [1]. Mortality is typically reported between 3.8 and 10 percent, most often due to fulminant hepatitis or multiorgan failure [1,3]. Hospital length of stay commonly exceeds one week and readmissions within 30 to 365 days are frequent, reflecting disease relapses or late complications; small cohort data suggest readmission rates around one third [26]. Although DRESS can occur in children, it is mainly observed in adults with mean onset at 40–60 years of age, without a significant sex difference. Risk differs by ancestry as a function of HLA allele frequencies and by drug utilisation. For example, allopurinol-associated SCAR burden is higher in East Asian and some African ancestry populations due to higher HLA-B*58:01 frequency and prescribing patterns [9,11,12,26]. Beyond acute mortality, morbidity extends to late autoimmune sequelae. Autoimmune thyroid disease and thyroiditis are well recognised within months, and type 1 diabetes, autoimmune haemolytic anaemia, alopecia, and chronic kidney disease with interstitial nephritis have been reported; surveillance for at least two years is advised to detect evolving endocrinopathy [1–4,22,27]. Pulmonary sequelae, including interstitial changes and impaired diffusion capacity, and quality-of-life decrements are described, though robust longitudinal estimates remain limited [22,28]. Psychosocial and mental health impacts are not negligible, arising from prolonged courses, systemic steroid exposure, and recurrent relapses.

Clinical presentation

The cutaneous eruption is typically a diffuse morbilliform exanthem with oedematous infiltration, frequently starting on the face and upper trunk and spreading caudally, often with confluent erythema, follicular accentuation, and progression to erythroderma in 20 to 30 percent. Skin involvement usually affects more than 50% of body surface area. Facial oedema is symmetrical and periorbital, and mucosal involvement occurs in up to half, usually limited to cheilitis or mild erosions rather than the extensive mucositis seen in SJS/TEN [1–3]. Fever is present in most patients and lymphadenopathy is common. Haematologic features include eosinophilia in 60 to 70 percent, sometimes delayed, atypical lymphocytes, leukocytosis after an initial leukopenic phase, and occasionally thrombocytopenia [1,3]. Organ involvement occurs in the majority, the liver being most frequently affected, with asymptomatic transaminase elevations to severe hepatitis and coagulopathy. Renal involvement embrace both mild creatinine rise and eosinophiluria to acute interstitial nephritis and renal failure. Pulmonary disease may present with dyspnoea, hypoxaemia, and interstitial pneumonitis; radiology often shows ground-glass or interstitial infiltrates [1,22,28]. Cardiac involvement, particularly eosinophilic myocarditis, may occur during the acute phase or weeks after apparent clinical improvement and is associated with significant mortality; symptoms include chest pain, dyspnoea, hypotension, arrhythmia, and elevated cardiac biomarkers [1,21,29]. The time course is protracted, with resolution over weeks to months and risk of relapse upon premature withdrawal of systemic corticosteroids or intercurrent infections [1–3].

Diagnosis

There are no universally accepted diagnostic criteria for DRESS and diagnosis is challenging because of the long latency from drug initiation, stepwise development of organ involvement, and varied clinical features. Diagnosis relies on a compatible exposure history, clinical phenotype, laboratory abnormalities, and exclusion of mimics. The RegiSCAR group proposed a weighted scoring system that classifies cases as definite, probable, possible, or negative based on fever, enlarged lymph nodes, eosinophilia thresholds, atypical lymphocytes, extent and morphology of rash, organ involvement across hepatic, renal, pulmonary, cardiac, pancreatic, and other systems, disease duration of at least 15 days, and exclusion of alternative causes by cultures and serology; scoring tables and thresholds are widely reproduced and have been externally compared with J-SCAR criteria [1,4,5]. J-SCAR criteria emphasise HHV-6 reactivation, facial oedema, atypical lymphocytosis, and internal organ involvement, and have a variant classification for “atypical DIHS” when virologic data are absent or negative but the clinical picture is concordant [3,5]. In practice, RegiSCAR scoring is used for case definition in research and clinical audits, while clinicians integrate elements from both frameworks when adjudicating difficult cases or when HHV-6 testing is unavailable [1,4,5].

Initial laboratory assessment includes complete blood count with differential, liver enzymes, bilirubin, INR, creatinine, urinalysis with microscopy, and CRP. Cardiac troponin and ECG are indicated in the presence

of chest pain, dyspnoea, hypotension, or marked eosinophilia; echocardiography and cardiac MRI may be required if myocarditis is suspected [1,21,29]. Pulmonary symptoms warrant chest RTG and, if hypoxaemia or infiltrates are present - HRCT [22,28]. Suggested virology includes HHV-6/7 PCR or serology, EBV and CMV PCR or serology, acknowledging that interpretation is complex and test availability variable [2,3]. Skin biopsy is not mandatory but may help exclude mimics; histology often shows spongiotic interface dermatitis with perivascular lymphocytic infiltrates and variable eosinophils [1,3]. Ancillary tests such as patch testing and lymphocyte transformation testing, LTT, can assist culprit identification after clinical resolution; patch testing is ideally deferred four to six weeks after recovery and has variable sensitivity by drug class, while LTT sensitivity and specificity in DRESS have been reported around 73 percent and 85 percent respectively when performed within months of the reaction [1].

The differential diagnosis includes SJS/TEN, AGEP, hypereosinophilic syndromes, eosinophilic granulomatosis with polyangiitis, viral exanthems, acute graft-versus-host disease, and drug rash with eosinophilia without systemic organ involvement [1,6].

Management

There are no universally accepted international recommendations for the treatment of DRESS at present. The gold standard is identification of the causative drug and its withdrawal, together with supportive care. When multiple potential triggers exist, a comprehensive review of the medication history focusing on drugs introduced within the previous two to eight weeks, known high-risk agents, and dose changes is required, and where uncertainty persists, specialist allergy input and post-recovery testing can refine causality [1,3]. Appropriate monitoring depends on severity. Patients with systemic involvement, marked eosinophilia, coagulopathy, cardiac or pulmonary symptoms, renal impairment, or significant hepatocellular injury should be admitted to an inpatient setting with capability for multidisciplinary care and access to intensive care support [1–3,21]. Supportive therapy includes fluid and electrolyte management, temperature control, pruritus relief with emollients and potent topical corticosteroids, pain control avoiding non-steroidal anti-inflammatory drugs if possible, nutritional support in erythroderma, and early mobilisation with thromboprophylaxis according to institutional protocols given the pro-inflammatory state and reduced mobility [1,3]. Systemic corticosteroids remain first-line for moderate to severe DRESS with internal organ involvement. Systemic glucocorticoids are usually used as first line therapy in moderate to high doses, to reduce clinical symptoms and normalize laboratory parameters Prednisone or prednisolone at approximately 0.5 to 1 mg/kg/day, or equivalent, is commonly initiated, with intravenous methylprednisolone pulses considered for life-threatening organ dysfunction. Taper should be slow over at least six to eight weeks to minimise relapse, guided by clinical response, eosinophil count, and laboratory markers of organ injury [1–3]. Observational evidence and expert consensus support this approach, although high-quality randomised trials are lacking [1,3].

Bacterial infection is a recognised risk under systemic corticosteroids; culture-directed antibiotics should be used rather than empirical broad-spectrum therapy, and clinical vigilance is necessary [1–3]. In patients with suspected myocarditis, management according to heart failure and arrhythmia protocols should occur in parallel with immunosuppression; vasopressors and mechanical circulatory support are considered in cardiogenic shock [21,29]. Pulmonary failure requires supplemental oxygen, ventilatory support if needed, and avoidance of unnecessary fluid overload [22].

In steroid-refractory, steroid-dependent, or contraindicated cases, cyclosporine appears effective and can shorten time to disease control and hospital length of stay compared with corticosteroids alone in case–control and cohort series. Typical dosing is 3 to 5 mg/kg/day with close monitoring for nephrotoxicity and hypertension [18,30,31]. A randomised comparison of cyclosporine versus high-dose systemic corticosteroids is underway and will better define relative efficacy and safety [7,32]. Intravenous immunoglobulin - IVIG has been used as an adjunct in severe disease, particularly with life-threatening hepatitis, myocarditis, or suspected virus-associated complications [33]. Targeted biologics directed at type 2 inflammation, including anti-IL-5, mepolizumab and reslizumab, and anti-IL-5 receptor, benralizumab, have been reported in difficult cases with prominent hypereosinophilia, with rapid declines in eosinophil counts and clinical improvement [18]. Targeted therapy aimed at the JAK–STAT signaling pathway, which transduces signals for many cytokines including IL-4, IL-5, and IL-13 involved in the pathogenesis of DRESS, is also of interest. Janus kinase inhibition, for example tofacitinib, has been used in severe DIHS/DRESS, including myocarditis, based on mechanistic rationale and single-centre experiences showing clinical responses; use should be individualised and preferably within specialist centres [34,35].

Antiviral therapy, ganciclovir, is considered in documented HHV-6 or CMV disease with compatible organ involvement, ideally with infectious disease consultation [1–3]. Plasmapheresis and mycophenolate mofetil have been used in refractory instances. Decisions should be individualised in multidisciplinary discussion, balancing risks of immunosuppression against disease severity and trajectory [1,18].

Pharmacogenetic screening has a preventive and sometimes therapeutic role. Strong evidence supports HLA-B*58:01 testing before allopurinol initiation in high-prevalence populations or in individuals of East Asian or certain African ancestries, with guidelines from CPIC and regional policy statements recommending avoidance of allopurinol in carriers and use of alternative urate-lowering therapy [9,11–13]. HLA-B*57:01 screening before abacavir is internationally standard of care and eliminates the risk of systemic hypersensitivity; it should be documented before any abacavir exposure [23,24]. Emerging data support consideration of HLA-A*32:01 testing in individuals of European ancestry who require prolonged vancomycin therapy and have access to timely genotyping, recognising that implementation frameworks and cost-effectiveness remain in evaluation [8,19,20].

Complications and outcomes

Acute complications include fulminant hepatic failure, acute kidney injury with interstitial nephritis, respiratory failure from pneumonitis or acute respiratory distress syndrome, eosinophilic myocarditis with cardiogenic shock, and haematologic abnormalities such as severe eosinophilia, pancytopenia, or haemophagocytic lymphohistiocytosis [1-3,21,22,29, 36]. Mortality in hospital is driven by these organ failures and by sepsis under immunosuppression. Relapse is common when corticosteroids are tapered rapidly, when hidden culprit drugs remain in use, or with viral reactivation; serial reassessment during taper is therefore essential [1–3]. Long-term sequelae include thyroiditis and autoimmune thyroid disease, type 1 diabetes, chronic kidney disease after interstitial nephritis, interstitial lung disease, ocular and mucosal morbidity, nail and hair abnormalities, and reduced quality of life [1–4,22,27,28]. Mental health symptoms related to prolonged illness and corticosteroid exposure warrant attention.

Severity assessment informs disposition and immunosuppressive strategy. RegiSCAR provides a diagnostic score, and its elements correlate with severity. The J-SCAR practice framework incorporates a severity scale that stratifies risk of fatal CMV disease and guides initiation of systemic corticosteroids and antivirals [1,3,5]. Clinical predictors of adverse outcomes include marked hepatic dysfunction with alanine aminotransferase more than 5 to 10 times the upper limit of normal or coagulopathy, rising bilirubin, renal failure, cardiac involvement with elevated troponin or reduced ventricular function, very high eosinophil counts above approximately 6,000 per microlitre, thrombocytopenia, leucocytosis, and older age or significant comorbidity [1,3,29]. Early troponin measurement and electrocardiography at baseline and during early follow-up are essential even in the absence of overt cardiac symptoms [21,29]. Severity should be re-evaluated at least weekly during the first month and at each steroid dose change; biochemical relapses often precede clinical deterioration.

Conclusions

DRESS is a distinct, delayed-type, T cell mediated hypersensitivity syndrome with characteristic clinical features, prolonged latency, and a tendency to relapse and to generate late autoimmune sequelae. Diagnosis is secured by structured criteria, notably RegiSCAR and J-SCAR, integrated with systematic exclusion of mimics and careful identification of the culprit drug. The successful management of DRESS relies entirely on the rapid identification and cessation of the responsible medication. Systemic corticosteroids currently serve as the primary intervention, but clinical practice is expanding to include targeted biologics and alternative immunosuppressants for resistant presentations. It must be considered that the danger does not end with skin clearance. Patients face a high risk of acute organ failure and delayed autoimmune conditions requiring extended observation over many months. Moving forward, the medical community needs large prospective registries and controlled trials to establish standardized treatment protocols and reduce our dependence on prolonged steroid use.

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