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When Common Medications Trigger a Rare Reaction: A Review of Clinical Features, Diagnosis, and Treatment Options of DRESS Syndrome

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ABSTRACT

Introduction and purpose: Drug-induced reaction with eosinophilia and systemic symptoms (DRESS) is a severe, life-threatening systemic drug reaction. The challenges in identifying DRESS syndrome result from its symptoms being variable, diverse, and unspecific. Due to the potentially lethal consequence, any clinician should be aware of the symptomatology and be prepared to initiate the appropriate steps. This review summarizes the clinical manifestations and provides essential information on the management of the illness.
State of knowledge: DRESS appears to be a rare reaction that frequently remains undetected due to its atypical clinical presentation. Fever, skin rash, lymphadenopathy, eosinophilia, and organ involvement as well as other manifestations, may occur. The onset may be delayed by weeks after exposure to the offending drug. DRESS syndrome is classified as a type IV hypersensitivity. It is thought to be triggered by antiepileptic drugs and antibiotics although many other medications can cause the condition. Certain genetic factors may also predispose some individuals to develop DRESS. Combining clinical and laboratory findings can help confirm the diagnosis. Discontinuation of the offending drug is the fundamental component of treatment such as supportive care

including the use of antihistamines and corticosteroids, but recent research has discovered additional promising therapy options.
Conclusions: Detecting DRESS syndrome early is crucial to ensure prompt treatment, prevent serious complications, and improve patient outcomes. Healthcare providers should be aware of the signs and symptoms of DRESS syndrome, especially in patients taking particular medications, and be prepared to investigate further if it is suspected.

Keywords
DRESS, drug reaction, eosinophilia, cutaneous reaction, hypersensitivity

1. EPIDEMIOLOGY

The incidence of DRESS syndrome varies depending on the population studied and the medications involved. There isn't much data on the precise prevalence of DRESS syndrome in the general population. It is estimated to occur in about 1,2 - 6: 1 000 000 a year in the general population, but it is noticeably more common in people who use a particular medication (1:1,000 to 1:10,000 a year) [1],. For new users of phenytoin and carbamazepine, the probability of developing hypersensitivity was calculated to be 2.3-4.5:10,000 and 1-4.1:10,000, respectively .[2] Compared to Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), the DRESS syndrome is more frequent, and around 95% of DRESS patients need to be hospitalized. [3]
However, data on the number of cases of DRESS syndrome are underestimated due to the syndrome's uncommon diagnosis in clinical practice. DRESS syndrome has been reported in patients of all ages and ethnicities, but some studies have suggested that it may be more common in adults than in children and has no predilection for sex. [4]
The most common comorbidities are epilepsy (20%), atopy (21.9%), and HIV infection (28.8%). [5,6]
In the US approximately at least 17,000 USD are spent on each patient's medical care for in-hospital management in DRESS. [7]

2. PATHOGENESIS

The pathogenesis of DRESS syndrome is not completely understood, but it is thought to involve a complex interplay between genetic, immunological, and environmental factors. It is a T-cell-mediated, classified as a type IV hypersensitivity reaction also known as delayed-type hypersensitivity. [8] Drug-specific CD4+ and CD8+ T-cell activation may selectively stimulate eosinophils by producing specific cytokines, such as IL5. [9]
Up to 80% of DRESS patients have a strong probability of drug causation. No correlated factor can be identified in 10 to 20 percent of cases. [10]
Some of the most commonly DRESS-related drugs include:

- Antiepileptic drugs, such as carbamazepine, phenytoin, phenobarbitone, and lamotrigine
- Antibiotics, such as sulfonamides, minocycline, ampicillin, cefotaxime, and vancomycin
- Allopurinol, a medication used to treat gout
- Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen
- Antiretroviral drugs used to treat HIV, such as nevirapine and abacavir [11, 12]

However, the most often mentioned medications associated with DRESS are aromatic anticonvulsants and antibiotics. [13] It is important to note that any medication has the potential to cause DRESS syndrome, and the risk may vary depending on the individual's genetic and immunological factors.
Genetic factors may also play a role in the development of DRESS syndrome. Certain genetic variations have been associated with an increased risk of developing DRESS syndrome in response to specific drugs. The correlation between HLA*B57:01 and the antiviral drug abacavir represents the prime example. [14] We can see similar dependencies between HLA-B*58:01 and allopurinol or HLA-A*31:01 and Carbamazepine but this list will keep expanding as searching for HLA alleles associated with the risk of drug hypersensitivity reaction has grown into a significant field of study. [15] In addition, the pathophysiology of DRESS syndrome has been associated with the reactivation of herpes **viruses** (HHV-6, HHV-7), HSV, EBV, and CMV, which correlate with the clinical signs of DRESS syndrome. [16, 17]

3. CLINICAL MANIFESTATIONS AND PROGNOSIS

DRESS typically appear within 2 to 8 weeks after initiation of one of the particular drug. [18]
Clinical features include a skin rash, lymphocytosis, fever, eosinophilia, and organ involvement. [19]
In 96%–100% of cases, DRESS syndrome has a specific phenotype characterized by a fever of ≥ 38.5°C. [20]
Such fever typically precedes the cutaneous eruption by several days. [21]
Hematologic symptoms are a common feature of DRESS syndrome. The most prevalent hematological outcome, observed in 52–92% of individuals across several studies, is hypereosinophilia with an average eosinophil count of 3.5 (×109 L−1) [22, 23, 24] 50-75% of patients have lymphadenopathy. [25]
The next frequent condition is leukocytosis with early neutrophilia and delayed monocytosis, which is followed by atypical lymphocytosis around (65-80%). [26, 27]
Other, less common findings include thrombocytopenia and pancytopenia which can occur due to bone marrow suppression or drug-induced immune destruction of blood cells and platelets. [28, 29]
The severity of the condition has been correlated to facial edema, which is present in 76% of patients. [30] Most frequently symmetrical and persistent, facial edema manifests in the periorbital and midfacial regions. [31]
It can be distinguished from other frequent types of drug-induced dermatitis by the continual worsening that occurs after medication withdrawal. [32]
The interval between drug exposure and the start of symptoms (often 2 to 8 weeks) is also longer than it is for other SCARs (severe cutaneous adverse reactions). After re-exposure to the culprit substance, symptoms may appear within hours or days. [33]
Organ failure and sepsis are among the most common conditions that contribute to the 10% mortality rate from DRESS. [34]

3.1. The skin manifestations

In most cases, more than 50% of the body's total surface area (BSA) is affected. [35]
The most frequent kind of cutaneous medication response is of the morbilliform or maculopapular type . [36]
Cutaneous eruptions appear as diffuse, pruritic, or nonpruritic lesions in 85%–100% of cases. Around 85% of patients have polymorphic cutaneous signs, other noticeable skin changes include targetoid, urticarial, pustular, blistering, lichenoid, exfoliative, or eczematous lesions. [37, 38] Additional features may include purpura, vesicles, bullae, and cheilitis. [39, 40]
Patients often have erythematous papules and macules throughout the upper part of their bodies first. Commonly beginning on the face, upper trunk, and upper extremities before moving down to the lower extremities. Distribution is generally symmetric. [41] It is also worth noting that the skin rash spares the palms and soles. [42]
Although less severe than in SJS/TEN, mucous membranes may also be affected in 56% of cases. [43,44] The rash could turn into erythroderma and exfoliative dermatitis if the culprit drug continues to be administered. [45]
Children are more likely to develop a morbilliform exanthem, fever, and lymphadenopathy in pediatric DRSS, but are less probable to experience facial edema. [46]

3.2. Visceral manifestations

Internal organ involvement is the most concerning DRESS symptom.
85%–96% of patients experience internal organ involvement, which determines the severity; in 50%–60% of individuals, two or more organs are involved. Any internal organ can be affected. [47, 48, 49]
In up to 97% of cases, the liver was the organ most severely damaged, and reports of cholestatic, mixed, and hepatocellular types of liver injury have been recorded. While hepatosplenomegaly is possible, liver involvement is more frequently asymptomatic and is found via routine liver function tests. Eventual hepatitis is often anicteric, and it may take months for the elevation of liver enzymes to decrease entirely. [50] Hepatic necrosis may also be discovered in some cases, which can cause liver failure that requires transplantation and even lead to death. [51]
It is important to monitor liver function tests in patients with suspected or confirmed DRESS syndrome, as well as to avoid drugs known to be associated with DRESS syndrome in patients with pre-existing liver disease.
Kidneys are the second most affected organ. [52, 53] Kidney injury can range from proteinuria to renal failure [54]. Some cases of DRESS result in permanent end-stage renal disease. The highest risk of renal impairment is seen in elderly individuals with allopurinol-associated DRESS, and those who already have kidney disease. [55]
It is important to pay attention to potential symptoms including the decreased output of urine, ankle and leg edema, high blood pressure, and increased creatinine levels.
The lung involvement ranges from interstitial pneumonitis to acute respiratory distress syndrome [56]. A greater incidence of pneumonitis has been linked to DRESS related to minocycline. [57] Patients with pulmonary manifestations may complain of symptoms such as cough, shortness of breath, and chest pain.
An increasing number of cases of cardiac involvement in DRESS are also being identified.

It usually manifests as myocarditis or pericarditis. Between 4% and 21% of patients with DRESS have cardiac involvement. [58] According to the searches, 71.4% of the patients had abnormal electrocardiograms, and 45% of those with cardiac involvement had decreased left ventricular ejection fraction. [59] Myocarditis can cause symptoms such as chest pain, shortness of breath, palpitations, and fluid buildup in the lungs. Pericarditis can cause chest pain and difficulty breathing. In addition, there have been reports of thyroiditis, colitis, pancreatitis, cholangitis, encephalitis/meningoencephalitis, hemophagocytic syndrome, and endocrine disorders. [60, 61, 62] It is important to note that these visceral manifestations can occur in isolation or combination, and the severity and presentation can vary widely among individuals.

3.3. The prognosis

The prognosis, or expected outcome, of DRESS syndrome, can vary widely depending on the severity of the condition and the underlying cause.

Studies suggest that the mortality rate for DRESS syndrome is generally around 10% [63], but this can vary depending on factors such as age, underlying health conditions, and the severity of the symptoms. [64, 65] Some patients might suffer from long-term autoimmune consequences. In patients who have recovered from DRESS syndrome, retrospective cohort studies have documented autoimmune sequelae like Graves' disease, Hashimoto's thyroiditis, type 1 diabetes, systemic lupus erythematosus, alopecia areata, and autoimmune hemolytic anemia. [66, 67] It is important to note that the prognosis for DRESS syndrome can be difficult to predict, and patients may require ongoing monitoring and follow-up care to assess for potential complications or long-term effects of the illness. [68]

4. DIAGNOSIS

Due to its delayed start, progressive presentation, and various clinical characteristics, DRESS can be difficult to diagnose. The RegiSCAR (Registry of Severe Cutaneous Adverse Reactions) scoring system is a validated tool based on symptoms, organs affected, and clinical course to support the diagnosis. It consists of clinical and laboratory criteria that are assigned points based on their severity and relevance to the diagnosis of DRESS syndrome. DRESS Syndrome is more likely to occur the higher the score.

RegiSCAR DRESS validation score [69, 70]

RegiSCAR Criteria	Score

	-1	0	1	2	Min.	Max.
Fever ≥ 38.5 °C	N/U	Y			-1	0
Enlarged lymph nodes) (>1 cm size, at least 2 sites)		N/U	Y		0	1
Eosinophilia		N/U	700–1499/μL (10–19.9% if leukopenia)	≥1500/μL (≥20% if leukopenia)	0	2
Atypical lymphocytes		N/U	Y		0	1
Skin involvement: - Body surface area ≥ 50% - Rash consistent with DRESS - Biopsy consistent with DRESS	 N N	 N/U U Y/U	 Y Y		-2	2
Organ involvement -liver, kidney, lung, muscle/heart, pancreas, and other organs		N/U	Y/Y/Y/Y/Y/Y		0	2
Resolution ≥ 15 days	N/U	Y			-1	0
Evaluation of other potential causes (ANA, blood culture, serology for HAV/HBV/HCV, Chlamydia, Mycoplasma pneumoniae) If none positive and ≥3 negative		Y			0	1

Total: <2, Excluded; 2–3, Possible; 4–5, Probable; >5, Definite

*N, no; Y, yes; U, unknown

The RegiSCAR scoring system has been validated in several studies, demonstrating good sensitivity and specificity for the diagnosis of DRESS syndrome. For example, one study found that the RegiSCAR score had a positive predictive value of 98.3% for the diagnosis of severe DRESS syndrome as definite/probable. [71]

5. MANAGEMENT

The treatment of DRESS syndrome depends on the symptoms' severity and the reaction's underlying cause.
In general, treatment involves stopping the causative medication and providing supportive care. [72]
Complete blood count with differential, liver enzyme, and liver function tests, renal function including creatinine and urea, electrolytes, pancreatic enzymes including lipase and amylase, and viral serology for HHV-6 should all be performed at the initial evaluation. [73]
DRESS syndrome is frequently treated with the following methods:

- **Discontinuation of the Causative Medication**

The first step in treating DRESS syndrome is to identify and discontinue the medication that triggered the reaction. This may involve switching to a different medication, but in some cases, all medications may need to be stopped temporarily to allow for recovery. [74]

- **Supportive Care**

DRESS syndrome can cause a range of symptoms, including fever, rash, and organ inflammation. The intensity of skin eruptions and other organ involvement usually determines the next course of action. Treatment is symptomatic in mild illness cases (no organ involvement or only minor liver involvement). [75]
Due to the Spanish Guidelines, except for minor cases, hospitalization is advised for all patients, with the possibility of close clinical and analytical monitoring at regular intervals. [76]
Supportive care measures may include using antipyretics to reduce fever, topical or oral steroids to reduce inflammation and control the rash, and monitoring for signs of organ dysfunction, such as liver or kidney involvement. [77]

- **Complications management:**

For patients with moderate to severe DRESS with considerable visceral organ injury, systemic corticosteroids, immunosuppressive drugs, and intravenous immunoglobulins are reserved. [78, 79, 80]
Corticosteroids are the mainstay of treatment for DRESS Syndrome. They are used to suppress the immune system and reduce inflammation. The dosage and duration of corticosteroid therapy depend on the severity of the patient's symptoms and response to treatment.
There are many different dosing methods employed, from early intravenous methylprednisolone pulse therapy through oral prednisone administration, reduced over at least 2-3 months or occasionally longer. [81, 82]
However, recent studies have concentrated on looking “beyond corticosteroids” and suggesting the possibility of targeted therapy considering the specific pathogenesis of DRESS in different individuals. [83]
Other immunosuppressive drugs may be used when corticosteroids are either ineffective or contraindicated. Cyclosporine, mycophenolate mofetil, and azathioprine are often reserved for the most severe conditions that do not improve with corticosteroids or for individuals who are unable to take corticosteroid dosages that are too high due to side effects.
An algorithm based on the Spanish Guideline states, treatments such as intravenous immunoglobulin (IVIG), plasmapheresis, or cyclophosphamide may also be applied.
The French Society of Dermatology recommends systemic steroids with intravenous immunoglobulin (IVIG) at a dose of 2 g/kg over five days for life-threatening symptoms like bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure. [84]
It is also advised to add an antiviral such as IV ganciclovir or oral valganciclovir if viral reactivation and life-threatening symptoms appear, or if viral reactivation is suspected of causing serious consequences such as encephalitis, hemophagocytosis, or severe erosive colitis. [85]
Targeted fluid and electrolyte replacement, maintaining a warm environment temperature, monitoring patient core temperature, careful monitoring for secondary infections, providing high-calorie nutritional support to keep up with rising demand, prompt initiation of targeted antimicrobial therapy when indicated, skin care and dressing changes are all examples of critical care-based interventions. [86]

- **Follow-Up Care:**

Patients who have experienced DRESS syndrome should be cautiously watched for any complications or signals of recurrence. In some cases, patients may need to avoid certain medications or receive desensitization treatment if they need to take a medication that caused a previous episode of DRESS. [87]
In addition to medical treatment, patients with DRESS Syndrome may benefit from nutritional and psychological support. Patients with severe symptoms may experience weight loss and malnutrition and may require nutritional supplementation. Psychological support may be needed to help patients cope with the stress and anxiety associated with the illness. Additionally, advice on avoiding the medicine should be given to all first-degree relatives until more extensive genetic susceptibility testing becomes possible to help clarify the danger to family members [88]

6. CONCLUSIONS

Clinicians must be aware of DRESS Syndrome because it is a potentially life-threatening drug-induced hypersensitivity reaction that can involve multiple organs. Some patients may also experience long-term sequelae, even after the acute phase of the illness has resolved. It can present with a wide range of symptoms that can mimic other conditions, such as viral infections or autoimmune diseases, making it challenging to diagnose. Doctors who prescribe medications, especially those with a high potential for causing DRESS Syndrome, should be aware of the potential risks and be prepared to recognize and manage this condition promptly. Furthermore, clinicians should have a good understanding of the various treatment options, including the use of corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, and other immunosuppressive agents, to ensure the best possible outcome for their patients. Early recognition, appropriate management, and close monitoring are essential in the management of DRESS because delayed or misdiagnosis can lead to a delay in treatment, which can increase the risk of severe complications or even lead to death.

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