DRESS Syndrome: Drug Reaction With Eosinophilia and Systemic Symptoms

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Abstract: DRESS syndrome is a cutaneous and systemic drug reaction with severe complications and a long course that can be fatal. Recognition may be difficult, and the condition is just rare enough that clinicians will eventually see it but may not be familiar with it. This review will focus on key elements to help clinicians with the challenges of recognition and differential diagnosis.

Key Words: drug allergy, drug hypersensitivity, drug reaction, drug eruption, febrile exanthem

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TARGET AUDIENCE

This article is intended for health care providers who see children and adolescents in acute care settings. Pediatric emergency medicine providers, emergency medicine providers, and those working in acute care pediatric offices and urgent centers will have particular interest in this article.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. List the most common drugs or drug classes associated with this syndrome.
2. Describe the clinical features of this syndrome that best distinguish it from related or similar-seeming conditions.
3. Discuss the evaluation, laboratory tests, and initial management of this syndrome.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a serious cutaneous and systemic drug reaction with multiple complications, a prolonged course, and a mortality rate of up to 10%.[1] Uncommon but not rare, the syndrome is not universally known or easily recognized, and is thus prone to misdiagnosis.

Sometimes called drug-induced hypersensitivity syndrome, the condition is not new; it was first described in the 1930s in association with phenytoin and, for many years, was considered linked to that drug.[2] Recognition of other drug triggers and more understanding of pathophysiology led over the years to a series of names and classifications.[3]

DRESS syndrome presents a series of challenges for the clinician, who must distinguish it from the many rashes seen in severe illness, recognize it as a drug reaction, and separate it from milder drug reactions. Then too, the clinician must consider other severe dermatoses, look for confirmatory and complicating features of DRESS syndrome, and separate it from other severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)[4] and acute generalized exanthematous pustulosis.[5]

ETIOLOGY

The drugs most often associated with DRESS syndrome in children include especially the so-called aromatic anticonvulsants (those with an aromatic amine structure). These include phenytoin, phenobarbital, carbamazepine, lamotrigine, felbamate, oxcarbazepine, and zonisamide.[6]

A host of other drugs may be involved as well. A 12-year review of reported cases found 44 suspected inciting drugs[7]; by far, the most common was carbamazepine, accounting for approximately a quarter of all the case reports. A list of potential trigger drugs (Table 1) may be helpful to the clinician considering DRESS syndrome.[2] Note that most cases occur with a limited subset of these agents, including carbamazepine, phenytoin, and, especially in adults, allopurinol.[8]

Although a delayed onset is typical, those treating children should be aware that DRESS syndrome may appear earlier after starting an antibiotic[9]; it has been suggested that, much as amoxicillin may trigger a rash in mononucleosis, antibiotics may act as promoters of DRESS syndrome owing to another agent. If DRESS syndrome appears early after an antibiotic, clinicians should also look for another drug started in prior weeks.[8]

EPIDEMIOLOGY

Drug reaction with eosinophilia and systemic symptoms syndrome affects both children and adults. Its frequency has been estimated at 1 in 1000 to 10,000 drug exposures.[10,11] A key feature is somewhat delayed onset, most often between 2 and 6 weeks after drug inception, perhaps earlier on reexposure, and sometimes as late as 8 to 16 weeks.[12] Both presentation and recognition may be delayed by a chronic, progressive course.[13]

For the clinician, delayed onset can help distinguish DRESS syndrome from other drug eruptions but may also make it easier to overlook the diagnosis of a drug reaction altogether. Also, its long course, with progression and flare-ups even after withdrawal of the trigger drug, may further confuse or delay clinical recognition.

PATHOPHYSIOLOGY

Researchers continue to clarify the exact mechanisms underlying DRESS syndrome; this discussion will focus on features that may aid clinical understanding and recognition. Readers will recall that drug reactions are traditionally divided into 4 classes,[14] summarized in Table 2. DRESS syndrome falls into type IV, which typically involves the skin with features not seen in urticarial or vasulitic reactions.

Some researchers note that the delayed onset, progressive course, and multi-organ injury in DRESS syndrome may be due in part to the reactivation of host viruses, especially the human

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TABLE 1. A Partial List of Drugs Associated With DRESS Syndrome

Drug Class	Examples
Anticonvulsants	Carbamazepine,* lamotrigine, phenobarbital, phenytoin, valproic acid, zonisamide
Antibiotics	Ampicillin, cefotaxime, dapsone, ethambutol, isoniazid, linezolid, metronidazole, minocycline, pyrazinamide, quinine, rifampin, sulfasalazine, streptomycin, trimethoprim-sulfamethoxazole, vancomycin
Others	Allopurinol, abacavir, nevirapine, zalcitabine, bupropion, fluoxetine, amlodipine, captopril, efalizumab, imatinib, celecoxib, ibuprofen, mexiletine, ranitidine, epoetin alfa

*Carbamazepine may account for approximately 25% of cases.

herpesviruses, but also Epstein-Barr virus and cytomegalovirus.[15,16] The interaction of viral activation and T-cell response then creates a continued immune cascade, with the liberation of cytokines such as tumor necrosis factor and interferon, and, thus, to ongoing illness and organ damage.

Genetic predisposition appears to vary.[17] Specific human leukocyte antigen types may be linked to susceptibility to an individual drug; human leukocyte antigen typing is at times suggested to help identify patients at risk.[18]

CLINICAL FEATURES

The classic signs of DRESS syndrome include fever, rash, eosinophilia, atypical lymphocytosis, lymphadenopathy, and hepatitis. Carditis, pneumonitis, nephritis, and other systemic injury may be involved,[2] and such involvement may be severe.[13]

High fevers have been reported in up to 90% of cases and may precede the rash by several days.[19] The rash is frequently itchy; pruritus may also precede the actual eruption.

The skin features of DRESS syndrome can vary. The most typical rash is morbilliform.[2] Macules may dominate; early concentration on the face, neck, proximal trunk, and arms may be followed by extension to the legs. The rash may become generalized, thickened or infiltrated, violaceous or even purpuric, and may develop erosion, scaling, desiccation, and exfoliation. Edema, a characteristic feature, is most often facial and may be severe, suggesting angioedema. The rash sometimes persists for months, and an ongoing course may relapse and remit even after the offending agent is discontinued.

Lympadenopathy is present in approximately 75% of cases.[19] Patients may have focal or generalized lymphadenopathy, especially in the neck, axilla, and groin, and the swollen nodes may be tender.

Not only do the skin manifestations vary but also they may overlap with the other severe cutaneous drug reactions. Ang et al.[20] reviewed 27 cases of DRESS syndrome and found that, whereas approximately 80% had the morbilliform eruption over face, trunk, and extremities, and a third had facial edema, a third also showed mucositis, 7% developed pustules, and another 7% displayed target-type lesions.

DIAGNOSIS

Misdiagnosis is common, of course, if a physician is not familiar with DRESS syndrome.[19] Frequently too, though, misdiagnosis occurs because a drug reaction is not considered.[21] Patients with DRESS syndrome appear ill and febrile, and drug initiation may be remote by 3 to 6 weeks or longer; both factors may prompt a diagnosis of illness, such as sepsis, viral exanthem, or dermatosis, rather than drug hypersensitivity.

Another feature that may mislead the diagnostician is the long or progressive worsening of symptoms after withdrawal of the offending agent.[19] This may falsely lead clinicians to exclude drug reaction, when in fact such progression is common in DRESS syndrome.

Once entertained, the diagnosis of DRESS syndrome may be supported by the typical skin findings, time of onset, visceral involvement, and hematologic features.[22]

At least 3 different sets of diagnostic criteria for DRESS syndrome have been proposed.[3,23,24] A 2014 study[25] compared these in 48 patients and suggested that the simplest set, originally proposed by Bocquet in 1996,[3] might be efficient and accurate in clinical use. The Bocquet criteria comprise just 3 features: (1) a skin eruption, (2) eosinophilia greater than 1500/μL, and (3) internal organ involvement signified by transaminase elevation greater than 2× normal, lymphadenopathy greater than 2 cm in diameter, or nephritis, interstitial pneumonia, or carditis.

Clinicians treating children should be mindful of the anticonvulsants associated with DRESS syndrome such as phenytoin and especially carbamazepine (Table 1). If a clinician carefully reviews the medication history, considers drug reactions, and is aware of the course and features of DRESS syndrome, misdiagnosis is less likely.

DIFFERENTIAL DIAGNOSIS

DRESS syndrome has been noted as a great mimicker of other conditions.[21] Clinicians seeing children must consider DRESS syndrome in a host of patients on medications who develop illness with fever and rash. DRESS syndrome may be confused with an array of infectious, rheumatologic, and hematologic diseases.[8]

A complete discussion of febrile exanthems in children would be difficult; luckily, clinicians who treat children have developed heuristics to aid in sorting out the typical features of diseases from simple viral exanthems to toxic shock syndrome and hundreds of others. The important element is to add DRESS syndrome to those diagnostic considerations.

In children especially, DRESS syndrome shares features with many serious illnesses such as Kawasaki disease, staphylococcal scalded skin syndrome, or systemic juvenile inflammatory arthritis.[22] Fernando[6] touches on possible differences between DRESS

TABLE 2. Overview of Drug Hypersensitivity Categories

Category	Primary Mechanism	Typical Manifestations
Type I	IgE	Hives, bronchospasm, anaphylaxis
Type II	Cytotoxic reaction	Blood dycrasias
Type III	Immune complexes	Vasculitis (as in serum sickness)
Type IV*	T-cell activation	Skin reactions (exanthema)

*Type IV reactions can be further divided according to the type of T-cells involved.

TABLE 3. Typical Features of the SCARs

Disease	Time of Onset	Distinguishing Features
DRESS syndrome	2 to 8 weeks	Generalized maculopapular rash Edema Eosinophilia Hepatitis and other organ damage
SJS/TEN	3 days to 3 weeks	Dusky "target-like" lesions Mucosal erosion: multiple, severe Possible Nikolsky sign
Acute generalized exanthematous pustulosis	2 to 3 days	Multiple discrete sterile pustules Minimal or no mucosal involvement

syndrome and other childhood illnesses with rash; for instance, eosinophilia would not be expected in Kawasaki disease or in most viral exanthems.

Estimates suggest that up to half of all adverse drug reactions involve the skin.[26] Articles in the specialty literature focus on distinguishing DRESS syndrome from the other SCARS (Table 3) and from a long list of severe dermatoses.[27]

The SCAR best known to clinicians is undoubtedly SJS/TEN, which has been reviewed in these pages.[28] Stevens-Johnson syndrome and TEN are now seen as 2 levels of severity in the same clinical syndrome, with TEN being more severe and involving a larger percentage of body surface area.[4] Simple erythema multiforme (so-called *EM minor*) was sometimes considered as the mildest end of the same spectrum, but most experts now view it as a separate entity, noting its benign course and that few cases, even in children, are owing to drugs.[29]

Some clinical features of DRESS syndrome and SJS/TEN may overlap (eg, mucositis, skin erosion, or target lesions), but SJS/TEN usually occurs earlier than DRESS syndrome, within 1 to 3 weeks after drug inception. When erosion or exfoliation occurs in DRESS syndrome, they seldom involve sheet-like sloughing of intact skin as seen with the Nikolsky sign in SJS/TEN. Furthermore, the edema, lymphadenopathy, eosinophilia, and systemic involvement in DRESS syndrome may be helpful distinguishing features.[1]

Very severe cases of SJS/TEN may develop renal or hepatic injury[30]; some authors have suggested that, when apparent SJS/TEN has severe systemic involvement, such as hepatitis, it should be treated as a variant of DRESS syndrome.[31]

Finally, if some features of DRESS syndrome at times overlap with the other SCARs,[20] for the front-line clinician, the exact distinction may be less important than the recognition of a serious drug reaction.

LABORATORY AND IMAGING FEATURES

Laboratory features can be vital in the evaluation of possible DRESS syndrome. At a minimum, testing should include a complete blood count, a metabolic panel with liver and renal functions, and urinalysis.[1]

Hematologic features in a 10-year registry study of over 100 validated cases of DRESS syndrome included eosinophilia in 95% and atypical lymphocytosis in 67%.[19] Eosinophilia may range as high as 2000 cells/μL.[2] Overall leukocytosis up to 50,000 white blood cells/μL, as well as elevations of C-reactive protein and the erythrocyte sedimentation rate, is typical but not distinctive.

Elevation of liver enzymes is seen in 70% to 90% of cases,[2] and renal and pulmonary involvement may occur in over 30%.[19] If pulmonary or cardiac involvement is considered, a chest x-ray is indicated. Other directed laboratory or ultrasound evaluation may be needed.

Viral testing may demonstrate viral activation, for instance, to human herpesvirus 6 or Epstein-Barr virus.[13] Tests to establish the culprit drug and confirmatory tests such as biopsy are discussed elsewhere.[22]

MANAGEMENT

Once a clinician suspects or diagnoses DRESS syndrome, admission or transfer to a center that can care for severely ill children may follow. The clinician should seek consultation in sicker patients as to level of care. Intensive care may be needed if shock, sepsis, or other physiologic derangements are suspected. In cases with extensive exfoliation, care in a burn unit or similar setting has been considered.[22] Because these cases lack a direct thermal insult, however, burn or dermatology consultation in a setting experienced with pediatric critical care may at times be preferred.

A key initial step in management of DRESS syndrome is withdrawal of the causative drug; delay in doing so can be harmful.[27] Identifying the culprit drug, however, may be challenging, especially where multiple drugs have been started over recent months and weeks.

When DRESS syndrome is suspected, further doses of most medicines may be held pending hospitalization and consultation. Drugs that are suspicious, such as carbamazepine or phenytoin, as well as those that can be stopped without risk, should be withdrawn. Withdrawal or replacement of clearly required anticonvulsants may require neurologic consultation. Cross-reaction to other aromatic anticonvulsants is common; non-aromatic alternatives, such as topiramate, levetiracetam, gabapentin, ethosuximide, or valproic acid, may be suggested.[6]

Active treatment is aimed at interrupting the immune response. The key component of such therapy is corticosteroid administration, recommended for almost all patients with serious or systemic involvement. This should be started as soon as possible in a dose of 1 mg/kg/day of prednisone or the equivalent.[8,10] Corticosteroids are continued for many weeks or months and tapered very slowly to decrease the risk of relapse.

In cases with life-threatening complications, additional therapies including intravenous immunoglobulin and antivirals have been recommended.[6,8]

Long-term follow-up may further involve outpatient clinicians. Relapses may flare up for weeks or months, sometimes with the introduction of other drugs, even when the causative drug has been withdrawn. Complications of DRESS syndrome besides ongoing progression and viral reactivation illness may include later autoimmune disease.[32]

SUMMARY

DRESS syndrome is a severe and progressive condition that may be life threatening. It requires early recognition and aggressive treatment, but recognition and differential diagnosis can be challenging. A number of factors may lead to misdiagnosis. An awareness of possible drug reaction, a careful review of the medication history, and familiarity with the triggers, time course, and cutaneous, systemic, and laboratory features of DRESS syndrome will aid in recognition.

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