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

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.

D R E S S Syndrome: Drug Reaction With Eosinophilia and Systemic Symptoms
Howard M. Corneli, MD

D R E S S 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

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.

D R E S S 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

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 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 drugs7; 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.9

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

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

*Carbamazepine may account for approximately 25% of cases.

DRESS syndrome is a drug-induced hypersensitivity reaction characterized by fever, rash, and multiple organ involvement. It is often difficult to diagnose because the clinical features can overlap with other conditions. The onset of symptoms is usually within 2 weeks of starting the causative medication, and the severity can range from mild to life-threatening. Common co-morbidities include lymphadenopathy, hepatitis, and nephritis. Other symptoms may include fever, arthralgia, and angiopathy. The rash is often morbilliform, with a high incidence of target lesions. The differential diagnosis includes other drug hypersensitivity reactions, viral infections, and neoplasms. Management involves discontinuation of the causative agent and supportive care. The mortality rate is about 10%, and the outcome is often determined by the degree of organ involvement.
**TABLE 3. Typical Features of the SCARs**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Time of Onset</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRESS syndrome</td>
<td>2 to 8 weeks</td>
<td>Generalized maculopapular rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eosinophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis and other organ damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dusky “target-like” lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucosal erosion: multiple, severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible Nikolsky sign</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>3 days to 3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal or no mucosal involvement</td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis</td>
<td>2 to 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. Articles in the specialty literature focus on distinguishing DRESS syndrome from the other SCARS (Table 3) and from a long list of severe dermatoses.

The SCAR best known to clinicians is undoubtedly SJS/TEN, which has been reviewed in these pages. 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. 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.

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.

Very severe cases of SJS/TEN may develop renal or hepatic injury, 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.

Finally, if some features of DRESS syndrome at times overlap with the other SCARS 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.

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%. Eosinophilia may range as high as 2000 cells/μL. 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, and renal and pulmonary involvement may occur in over 30%. 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. Tests to establish the culprit drug and confirmatory tests such as biopsy are discussed elsewhere.

**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. 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. 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 anticonvulsants is common; non-anticonvulsants, such as topiramate, levetiracetam, gabapentin, ethosuximide, or valproic acid, may be suggested.

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. 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.

Long-term follow-up may further involve outpatient clinicians. Relapses may flare 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.
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.

REFERENCES