

DRESS Syndrome: Clinical Myths and Pearls

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PRACTICE POINTS

- Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a clinical diagnosis, and incomplete forms may not meet formal criteria-based diagnosis.
- Although DRESS syndrome typically has a morbiliform eruption, different rash morphologies may be observed.
- The myocarditis of DRESS syndrome may not present with chest pain; a high index of suspicion is warranted.
- Autoimmune sequelae are more frequent in patients who have had an episode of DRESS syndrome.

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is an uncommon severe systemic hypersensitivity drug reaction. It typically develops 2 to 6 weeks after exposure to a culprit medication and presents with widespread rash, facial edema, systemic symptoms (eg, fever, rigors, hypotension), lymphadenopathy, evidence of visceral organ involvement, and often eosinophilia. The clinical myths and pearls presented here highlight some of the commonly held assumptions regarding DRESS syndrome in an effort to illuminate subtleties of managing patients with this condition.

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Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is an uncommon severe systemic hypersensitivity drug reaction. It is estimated to occur in 1 in every 1000 to 10,000 drug exposures.¹ It can affect patients of all ages and typically presents 2 to 6 weeks after exposure to a culprit medication. Classically, DRESS syndrome presents with often widespread rash, facial edema, systemic symptoms such as

fever, lymphadenopathy, and evidence of visceral organ involvement. Peripheral blood eosinophilia is frequently but not universally observed.^{1,2}

Even with proper management, reported DRESS syndrome mortality rates worldwide are approximately 10%² or higher depending on the degree and type of other organ involvement (eg, cardiac).³ Beyond the acute manifestations of DRESS syndrome, this condition is unique in that some patients develop late-onset sequelae such as myocarditis or autoimmune conditions even years after the initial cutaneous eruption.⁴ Therefore, longitudinal evaluation is a key component of management.

The clinical myths and pearls presented here highlight some of the commonly held assumptions regarding DRESS syndrome in an effort to illuminate subtleties of managing patients with this condition (Table).

Myth: DRESS syndrome may only be diagnosed when the clinical criteria satisfy one of the established scoring systems.

Patients with DRESS syndrome can have heterogeneous manifestations. As a result, patients may develop a drug hypersensitivity with biological behavior and a natural history compatible with DRESS syndrome that does not fulfill published diagnostic criteria.⁵ The syndrome also may reveal its component manifestations gradually, thus delaying the diagnosis. The terms *mini-DRESS* and *skirt syndrome* have been employed to describe drug eruptions

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DRESS Syndrome Myths and Pearls

Myths

DRESS syndrome may only be diagnosed when the clinical criteria satisfy one of the established scoring systems.

If the eruption is not morbilliform, then it is not DRESS syndrome.

Patients who have had an allergic reaction to sulfonamide antibiotics will have a cross-reaction to nonantibiotic sulfonamides.

Myocarditis secondary to DRESS syndrome will present with chest pain at the time of the cutaneous eruption.

Pearls

The most commonly involved organ in DRESS syndrome is the liver.

New-onset proteinuria, hematuria, and sterile pyuria indicate acute interstitial nephritis that may be associated with DRESS syndrome.

Facial edema noted during physical examination is an important clue to DRESS syndrome.

Vancomycin is an important cause of DRESS syndrome.

Steroids are not the only treatment used to control DRESS syndrome.

DRESS patients need to be monitored for long-term sequelae such as autoimmune disease.

Small cases series suggest differences between adult and pediatric DRESS syndrome, but there are no large studies in children.

Abbreviation: DRESS, drug rash with eosinophilia and systemic symptoms.

that clearly have systemic symptoms and more complex and pernicious biologic behavior than a simple drug exanthema but do not meet DRESS syndrome criteria. Ultimately, it is important to note that in clinical practice, DRESS syndrome exists on a spectrum of severity and the diagnosis remains a clinical one.

Pearl: The most commonly involved organ in DRESS syndrome is the liver.

Liver involvement is the most common visceral organ involved in DRESS syndrome and is estimated to occur in approximately 45.0% to 86.1% of cases.^{6,7} If a patient develops the characteristic rash, peripheral blood eosinophilia, and evidence of liver injury, DRESS syndrome must be included in the differential diagnosis.

Hepatitis presenting in DRESS syndrome can be hepatocellular, cholestatic, or mixed.^{6,7} Case series are varied in whether the transaminitis of DRESS syndrome tends to be more hepatocellular⁸ or cholestatic.⁷ Liver dysfunction in DRESS syndrome often lasts longer than in other severe cutaneous adverse drug reactions, and patients may improve anywhere from a few days in milder cases to months to achieve resolution of abnormalities.^{6,7} Severe hepatic involvement is thought to be the most notable cause of mortality.⁹

Pearl: New-onset proteinuria, hematuria, and sterile pyuria indicate acute interstitial nephritis that may be associated with DRESS syndrome.

Acute interstitial nephritis (AIN) is a drug-induced form of acute kidney injury that can co-occur with DRESS syndrome. Acute interstitial nephritis can present with some

combination of acute kidney injury, morbilliform eruption, eosinophilia, fever, and sometimes eosinophiluria. Although AIN can be distinct from DRESS syndrome, there are cases of DRESS syndrome associated with AIN.¹⁰ In the correct clinical context, urinalysis may help by showing new-onset proteinuria, new-onset hematuria, and sterile pyuria. More common causes of acute kidney injury such as prerenal etiologies and acute tubular necrosis have a bland urinary sediment.



FIGURE 1. Morbilliform eruption on the arms in a patient with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.

Myth: If the eruption is not morbilliform, then it is not DRESS syndrome.

The most common morphology of DRESS syndrome is a morbilliform eruption (Figure 1), but urticarial and atypical targetoid (erythema multiforme–like) eruptions also have been described.⁹ Rarely, DRESS syndrome secondary to use of allopurinol or anticonvulsants may have a pustular morphology (Figure 2), which is distinguished from acute generalized exanthematous pustulosis by its delayed onset, more severe visceral involvement, and prolonged course.¹¹

Another reported variant demonstrates overlapping features between Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome. It may present with mucositis, atypical targetoid lesions, and vesiculobullous lesions.¹² It is unclear whether this reported variant is indeed a true subtype of DRESS syndrome, as Stevens-Johnson syndrome/toxic epidermal necrolysis may present with systemic symptoms, lymphadenopathy, hepatic, renal, and pulmonary complications, among other systemic disturbances.¹²

Pearl: Facial edema noted during physical examination is an important clue of DRESS syndrome.

Perhaps the most helpful findings in the diagnosis of DRESS syndrome are facial edema and anasarca (Figure 3), as facial edema is not a usual finding in sepsis. Facial edema can be severe enough that the patient's features are dramatically altered. It may be useful to ask family members if the patient's face appears swollen or to



FIGURE 2. Pustules within a morbilliform eruption on the arm in a patient with pustular drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

compare the current appearance to the patient's driver's license photograph. An important complication to note is laryngeal edema, which may complicate airway management and may manifest as respiratory distress, stridor, and the need for emergent intubation.¹³

Myth: Patients who have had an allergic reaction to sulfonamide antibiotics will have a cross-reaction to nonantibiotic sulfonamides.

A common question is, if a patient has had a prior allergy to sulfonamide antibiotics, then are nonantibiotic sulfones such as a sulfonyleurea, thiazide diuretic, or furosemide likely to cause a cross-reaction? In one study (N=969), only 9.9% of patients with a prior sulfone antibiotic allergy developed hypersensitivity when exposed to a nonantibiotic sulfone, which is thought to be due to an overall increased propensity for hypersensitivity rather than a true cross-reaction. In fact, the risk for developing a hypersensitivity reaction to penicillin (14.0% [717/5115]) was higher than the risk for developing a reaction from a nonantibiotic sulfone among these patients.¹⁴ This study bolsters the argument that if there are other potential culprit medications and the time course for a patient's nonantibiotic sulfone is not consistent with the timeline for DRESS syndrome, it may be beneficial to look for a different causative agent.

Pearl: Vancomycin is an important cause of DRESS syndrome.

Guidelines for treating endocarditis and osteomyelitis caused by methicillin-resistant *Staphylococcus aureus* infection recommend intravenous vancomycin for 4 to 6 weeks.¹⁵ This duration is within the relevant time frame of exposure for the development of DRESS syndrome de novo.

One case series noted that 37.5% (12/32) of DRESS syndrome cases in a 3-year period were caused by vancomycin, which notably was the most common medication associated with DRESS syndrome.¹⁶ There were caveats to this case series in that no standardized drug causality



FIGURE 3. Facial edema and anasarca with effacement of the nasolabial folds in a patient with drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Facial edema is a physical examination hallmark in DRESS syndrome.

score was used and the sample size over the 3-year period was small; however, the increased use (and misuse) of antibiotics and perhaps increased recognition of rash in outpatient parenteral antibiotic therapy clinics may play a role if vancomycin-induced DRESS syndrome is indeed becoming more common.

Myth: Myocarditis secondary to DRESS syndrome will present with chest pain at the time of the cutaneous eruption.

Few patients with DRESS syndrome–associated myocarditis actually are symptomatic during their hospitalization.⁴ In asymptomatic patients, the primary team and consultants should be vigilant for the potential of subclinical myocarditis or the possibility of developing cardiac involvement after discharge, as myocarditis secondary to DRESS syndrome may present any time from rash onset up to 4 months later.⁴ Therefore, DRESS patients should be especially attentive to any new cardiac symptoms and notify their provider if any develop.

Although no standard cardiac screening guidelines exist for DRESS syndrome, some have recommended that baseline cardiac screening tests including electrocardiogram, troponin levels, and echocardiogram be considered at the time of diagnosis.⁵ If any testing is abnormal, DRESS syndrome–associated myocarditis should be suspected and an endomyocardial biopsy, which is the diagnostic gold standard, may be necessary.⁴ If the cardiac screening tests are normal, some investigators recommend serial outpatient echocardiograms for all DRESS patients, even those who remain asymptomatic.¹⁷ An alternative is an empiric approach in which a thorough review of systems is performed and testing is done if patients develop symptoms that are concerning for myocarditis.

Pearl: Steroids are not the only treatment used to control DRESS syndrome.

A prolonged taper of systemic steroids is the first-line treatment of DRESS syndrome. Steroids at the equivalent of 1 to 2 mg/kg daily (once or divided into 2 doses) of prednisone typically are used. For severe and/or recalcitrant DRESS syndrome, 2 mg/kg daily (once or divided into 2 doses) typically is used, and less than 1 mg/kg daily may be used for mini-DRESS syndrome.

Clinical improvement of DRESS syndrome has been demonstrated in several case reports with intravenous immunoglobulin, cyclosporine, cyclophosphamide, mycophenolate mofetil, and plasmapheresis.¹⁸⁻²¹ Each of these therapies typically were initiated as second-line therapeutic agents when initial treatment with steroids failed. It is important to note that large prospective studies regarding these treatments are lacking; however, there have been case reports of acute necrotizing eosinophilic myocarditis that did not respond to the combination of steroids and cyclosporine.^{4,22}

Although there have been successful case reports using intravenous immunoglobulin, a 2012 prospective

open-label clinical trial reported notable side effects in 5 of 6 (83.3%) patients with only 1 of 6 (16.6%) achieving the primary end point of control of fever/symptoms at day 7 and clinical remission without steroids on day 30.²³

Pearl: DRESS patients need to be monitored for long-term sequelae such as autoimmune disease.

Several autoimmune conditions may develop as a delayed complication of DRESS syndrome, including autoimmune thyroiditis, systemic lupus erythematosus, type 1 diabetes mellitus, and autoimmune hemolytic anemia.²⁴⁻²⁶ Incidence rates of autoimmunity following DRESS syndrome range from 3% to 5% among small case series.^{24,25}

Autoimmune thyroiditis, which may present as Graves disease, Hashimoto thyroiditis, or painless thyroiditis, is the most common autoimmune disorder to develop in DRESS patients and appears from several weeks to up to 3 years after DRESS.²⁴ Therefore, all DRESS patients should be monitored longitudinally for several years for signs or symptoms suggestive of an autoimmune condition.^{5,24,26}

Because no guidelines exist regarding serial monitoring for autoimmune sequelae, it may be reasonable to check thyroid function tests at the time of diagnosis and regularly for at least 2 years after diagnosis.⁵ Alternatively, clinicians may consider an empiric approach to laboratory testing that is guided by the development of clinical symptoms.

Pearl: Small cases series suggest differences between adult and pediatric DRESS syndrome, but there are no large studies in children.

Small case series have suggested there may be noteworthy differences between DRESS syndrome in adults and children. Although human herpesvirus 6 (HHV-6) positivity in DRESS syndrome in adults may be as high as 80%, 13% of pediatric patients in one cohort tested positive for HHV-6, though the study size was limited at 29 total patients.²⁷ In children, DRESS syndrome secondary to antibiotics was associated with a shorter latency time as compared to cases secondary to nonantibiotics. In contrast to the typical 2- to 6-week timeline, Sasidharanpillai et al²⁸ reported an average onset 5.8 days after drug administration in antibiotic-associated DRESS syndrome compared to 23.9 days for anticonvulsants, though this study only included 11 total patients. Other reports have suggested a similar trend.²⁷

The role of HHV-6 positivity in pediatric DRESS syndrome and its influence on prognosis remains unclear. One study showed a worse prognosis for pediatric patients with positive HHV-6 antibodies.²⁷ However, with such a small sample size—only 4 HHV-6–positive patients of 29 pediatric DRESS cases—larger studies are needed to better characterize the relationship between HHV-6 positivity and prognosis.

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