DRESS syndrome

Part II. Management and therapeutics

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After completing this learning activity, participants should be able to distinguish DRESS syndrome from other severe cutaneous reactions; delineate the utility and limitations of the patch and lymphocyte transformation tests; and select the appropriate management based on presentation.

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The appropriate management of the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is paramount because it is associated with significant morbidity and mortality. This syndrome shares clinical features with other dermatologic conditions, including other severe cutaneous drug reactions, requiring the clinician to carefully examine the proposed criteria to make the appropriate diagnosis. Once the diagnosis of DRESS syndrome has been established, the next step in management is immediate cessation of the causative medication(s). In cases in which the culprit drug is not obvious, clinicians must use their clinical judgment to select which medication to discontinue. They may also utilize patch or lymphocyte transformation tests to aid in identification when appropriate. Topical corticosteroids can be used for symptomatic relief, but systemic steroid therapy is generally required. Other immunosuppressants have also been employed in treatment and show promise in future therapy. Patients with DRESS syndrome should be managed in an intensive care or burn unit for appropriate care and infection control. In addition, appropriate specialists should be consulted based on the affected organ systems. Most patients recover completely after drug withdrawal and appropriate therapy. However, some patients with DRESS syndrome suffer from chronic complications and approximately 10% die, primarily from visceral organ compromise. Controlled clinical trials investigating the most appropriate therapies and their risks, particularly intravenous corticosteroids, are lacking, and would be invaluable in determining the optimal future treatment regimen for DRESS syndrome. (J Am Acad Dermatol 2013;68:709.e1-9.)

Upon clinical diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, management centers on immediate withdrawal of the offending medication(s). This can be challenging at times, especially in the inpatient setting where patients may be started on multiple new medications. The patient should be provided supportive care, ideally in an intensive care or burn unit. There should be a low threshold for administering systemic corticosteroids, particularly in cases with extensive visceral involvement. Prognosis is generally good with early diagnosis and treatment, although some patients sustain considerable life-long complications or even death.

CAPSULE SUMMARY

- Withdrawal of causative drug, commencement of systemic corticosteroids, and supportive care are the mainstay of treatment of drug reaction with eosinophilia and systemic symptoms syndrome.
- The majority of patients recover completely after drug withdrawal and appropriate therapy; some patients suffer from chronic sequelae or even death.
- Controlled clinical trials investigating the effectiveness and potential long-term complications of corticosteroids and other therapies for drug reaction with eosinophilia and systemic symptoms syndrome would be helpful.

DIFFERENTIAL DIAGNOSIS

Key points

- **DRESS syndrome can usually be distinguished from other severe drug-induced dermatologic conditions, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythroderma, based on characteristic cutaneous findings, the onset of symptoms, and visceral involvement**
- **It is important to distinguish DRESS syndrome from dermatologic findings associated with acute viral infections and vasculitides accompanied by eosinophilia**

Distinguishing DRESS syndrome from the other major potentially life-threatening cutaneous drug reactions with similar clinical features—Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and erythroderma (exfoliative dermatitis)—is an important concern because treatment varies among these conditions (Table I). Although clinical signs of SJS/TEN, AGEP,

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Abbreviations used:

AGEP:	acute generalize exanthematous pustulosis
CMV:	cytomegalovirus
DRESS:	drug reaction with eosinophilia and systemic symptoms
EBV:	Epstein–Barr virus
HHV-6:	human herpesvirus-6
IVIG:	intravenous immunoglobulin
LTT:	lymphocyte transformation test
NPV:	negative predictive value
PPV:	positive predictive value
SJS:	Stevens–Johnson syndrome
TEN:	toxic epidermal necrolysis

erythroderma, and DRESS syndrome are usually distinct, there may be ambiguity, especially with overlap of features.[1-6] Clinically, the onset of eruption of SJS/TEN, AGEP, and erythroderma after drug ingestion is shorter and subsides sooner than in DRESS syndrome. Histologically, there is epidermal necrolysis in SJS/TEN and subcorneal pustules in AGEP, whereas in DRESS syndrome there is predominantly a lymphocytic infiltrate. Abnormal laboratory values indicating hepatitis, eosinophilia, and atypical lymphocytes are much more commonly seen in DRESS syndrome.[7]

AGEP is first evident as an edematous erythema in the body folds and face before generalizing to widespread nonfollicular sterile pustules.[5] It is associated with fever and neutrophilia, and spontaneously resolves in a few days. Like SJS/TEN and DRESS syndrome, it may result from a medication, often antibiotics, although it may be caused by a viral infection. AGEP's 5% mortality rate is most often related to secondary infection.

Erythroderma, also referred to as generalized exfoliative dermatitis, is a potentially life-threatening disease that is characterized by erythema and scaling of >90% of the body surface area. It is classified as being caused by 1 of 4 etiologies: a flare of a preexisting skin disorder, such as psoriasis or atopic dermatitis; a drug eruption; a lymphoma/leukemia, such as mycosis fungoides; or idiopathic. Allopurinol is one of the most common causes of drug-induced erythroderma. It first manifests as erythematous patches, which expand and coalesce to form extensive areas of erythema, later involving most of the skin surface.[8]

Although uncommon, erythema multiforme can be considered in cases of DRESS presenting with targetoid lesions. DRESS syndrome can also mimic acute viral infections. Such viral infections include primary HIV, human herpesvirus-6 (HHV-6), Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis A virus, hepatitis B virus, and influenza.[1,7,9] In primary HIV infection, there is often a mononucleosis-like syndrome associated with systemic symptoms, including a nonspecific morbilliform eruption of the trunk with buccal erosions or diffuse erythema and genital ulceration.[1] Primary or reactivated HHV-6 can also cause a mononucleosis-like illness with fever and skin rash.[1] EBV causes mononucleosis and is often associated with a morbilliform rash.[1]

Hematologic and lymphocytic conditions should also be considered in the differential diagnosis of DRESS syndrome. Angioimmunoblastic lymphadenopathy shares many clinical features.[1,7,9] It is considered a subtype of peripheral T-cell lymphoma with hypergammaglobulinemia and Coombs-positive hemolytic anemia. However, it differs from DRESS syndrome in lymph node histologic pattern and evolution and the lack of eosinophilia.[1] Other conditions to consider include lymphoma, pseudolymphoma, and idiopathic hypereosinophilic syndrome.[7,10,11]

Cutaneous eruptions associated with multiorgan involvement with eosinophilia can also be seen in vasculitides, such as polyarteritis nodosa, Wegener granulomatosis, and especially Churg–Strauss syndrome.[12,13] Systemic lupus erythematosus also exhibits varied cutaneous manifestations with systemic symptoms.[1] Still disease, Kawasaki disease, and staphylococcal scalded skin syndrome also share clinical features with DRESS syndrome.[1,10,11]

CLINICAL TESTING

Key point

- **Patch and lymphocyte transformation testing are 2 available methods of establishing the culprit drug of DRESS syndrome. However, positive values for these are more informative than negative ones. Neither is widely accepted or used**

Determining the culprit medication in DRESS syndrome can be challenging, especially in hospitalized patients who may have been treated with several new medications during their admission. Physicians often rely on clinical judgment to determine the drug that is most likely responsible for the reaction. Several clinical tests have been developed to assist in determining the causative agent in DRESS syndrome, but their use is often limited and unreliable. Nonetheless, drug sensitivity information derived from these tests can be useful in preventing future episodes of DRESS in patients by strict avoidance of the culprit drug. Such investigations include skin patch tests and lymphocyte transformation tests (LTTs). In patch testing, the suspect drug is diluted and applied to the skin. The site is then observed for the appearance of a local reaction after a specified time period.[14] Positive reactions rely on the

Table I. Characteristic findings of severe cutaneous drug reactions

	DRESS	SJS/TEN	AGEP	Erythroderma
Onset of eruption	2-6 weeks	1-3 weeks	48 hours	1-3 weeks
Duration of eruption (weeks)	Several	1-3	<1	Several
Fever	+++	+++	+++	+++
Mucocutaneous features	Facial edema, morbilliform eruption, pustules, exfoliative dermatitis, tense bullae, and possible target lesions	Bullae, atypical target lesions, and mucocutaneous erosions	Facial edema, pustules, tense bullae, possible target lesions, and possible mucosal involvement	Erythematous plaques and edema affecting >90% of the total skin surface with or without diffuse exfoliation
Histological pattern of skin	Perivascular lymphocytic infiltrate	Epidermal necrosis	Subcorneal pustules	Nonspecific, unless reflecting Sézary syndrome or other lymphoma
Lymph node enlargement	+++	−	+	+
Lymph node histology	Lymphoid hyperplasia	−	−	No, unless reflecting Sézary syndrome or other malignancy
Hepatitis	+++	++	++	−
Other organ involvement	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	Tubular nephritis and tracheobronchial necrosis	Possible	Possible
Neutrophils	↑	↓	↑↑↑	↑
Eosinophils	↑↑↑	−	↑	↑
Atypical lymphocytes	+	−	−	+
Mortality (%)	10	5-35	5	5-15

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *SJS*, Stevens–Johnson syndrome; *TEN*, toxic epidermal necrolysis.

development of a localized inflammatory response based on activation of drug-specific T cells acting as cytotoxic effector cells and the recruitment of inflammatory cells.[15] It is a safe procedure, and, to our knowledge, has not been associated with the development of a severe reaction. The diagnostic value of patch testing remains under investigation. Its negative predictive values (NPVs) and positive predictive values (PPVs) are unknown. An accurate determination of patch testing sensitivity and specificity is difficult to achieve because of the lack of a reliable standard test against which its results can be compared. In addition, several factors are known to affect the interpretation of a given patch test, such as the type of drug being evaluated, its concentration and vehicle used, time after exposure, and the clinical type of patch test reaction. The PPV of patch testing under optimal conditions was as high as 80% to 90% for certain drugs, but only around 10% to 20% for other medications.[15] For optimal results, patch testing should be performed 2 to 6 months after recovery from the symptoms.[15] Results of patch testing vary significantly based on the specific drug and appear to be most reliable for antiepileptic medications, such as carbamazepine and phenytoin, because of their high specificity.[15] In one series, Santiago et al[14] reported an overall 32.1% positive patch test result in patients with DRESS syndrome, with 51.5% reactivity among all antiepileptics and 72.2% with carbamazepine alone. This contrasts with the 0% reactivity seen with allopurinol as the causative agent. As a result, a positive patch test is a highly reliable indicator of an inflammatory cutaneous hypersensitivity reaction, while a negative test does not exclude it.

The LTT can help determine the causative agent in DRESS syndrome. This in vitro procedure assesses the activation of drug-specific T cells in response to culprit drugs in solution. It specifically measures ^{3}H-thymidine uptake by dividing T cells, which proliferate after encountering the antigen.[16] LTT has several advantages, such as absolute patient safety, a simultaneous assessment of T cell responses to multiple drugs, and the detection of drug reactions with different immunopathologic mechanisms.[17] In addition, there is no increased risk of developing

Table II. Management of drug reaction with eosinophilia and systemic symptoms syndrome

Clinical scenario	Treatment	Dose	Level of evidence
All cases of DRESS syndrome	Withdrawal of culprit drug	—	IV
Life-threatening cases with significant systemic involvement	Oral prednisone or intravenous methylprednisolone	Initiate at 1.0 mg/kg and gradually taper	IV
DRESS syndrome with exfoliative dermatitis	Admission and care in specialized unit, burn facility or ICU setting	—	IV

Level of evidence: IA evidence includes evidence from metaanalysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.
DRESS, Drug reaction with eosinophilia and systemic symptoms; *ICU*, intensive care unit.

additional drug allergies after testing.[16] The technique has a general sensitivity in the range of 60% to 70% and an overall specificity of at least 85%.[18] LTT has been shown to have better diagnostic value than patch tests in identifying offending drugs. However, the utility of its results vary based on when the test is performed during the course of the reaction. Kano et al[16] observed many false negative LTT reactions during the acute phase of DRESS syndrome, usually within 2 to 3 weeks after onset. However, after resolution of symptoms, there was a significant increase in the number of positive LTT reactions. Because of the low sensitivity and specificity of LTT during the acute phase, it is recommended to perform LTT 5 to 8 weeks after the onset of DRESS syndrome. Other limitations of LTT include its cumbersome nature, the need for significant experience with cellular techniques, expensive equipment, and the reliance upon an interpreter with a strong background in pharmacology and immunology.[18] Finally, the LTT is not currently commercially available and is unlikely to be available at most facilities. In summary, a positive LTT is valuable both in the diagnosis of DRESS syndrome and in determining the eliciting drug. However, because of its limited sensitivity, a negative LTT cannot exclude drug hypersensitivity.

TREATMENT

Key points

- **Immediate withdrawal of the causative drug and initiation of systemic corticosteroids is the mainstay in the management of DRESS syndrome**
- **Commencement of corticosteroid therapy generally results in an improvement of clinical symptoms and laboratory abnormalities, but prolonged courses may be associated with variant DRESS syndrome secondary to immunosuppression**
- **DRESS syndrome complicated by exfoliative dermatitis benefits from intensive care or burn unit settings**

Therapy of DRESS syndrome is challenging (Table II). The most important measures are early recognition of this syndrome and immediate withdrawal of the suspected drug. Delay may be associated with poorer outcomes.[1,10,11] Supportive therapy should be provided to stabilize the patient, including antipyretics to reduce the effects of fever and topical steroids to alleviate the cutaneous symptoms. The patient should not be given empiric antibiotics or anti-inflammatory drugs during the acute stages of DRESS syndrome because it may confound or exacerbate the clinical condition as a result of an unexplained cross-reactivity between drugs.[19] When exfoliative dermatitis is present, therapy is similar to that of major burns and may be provided in a specialized intensive care or burn unit. Such measures include fluid replacement, correction of electrolyte abnormalities, warming the environmental temperature, providing high caloric intake, treatment of superinfections and bacteremias with antibiotics, and skin care with appropriate dressings. If cutaneous blood flow is significantly increased because of erythroderma, cardiac failure may occur, especially in the elderly or those with cardiac disease.[11,20]

Systemic corticosteroid therapy for DRESS syndrome is currently the most widely accepted and used treatment.[21] Significant improvement in both clinical symptoms and laboratory abnormalities is often seen within several days after initiating steroid therapy. The early administration of systemic steroids is generally recommended for all cases of DRESS syndrome.[21] Topical corticosteroids may be applied to skin lesions for symptomatic relief.[22] Systemic steroid therapy should begin with a minimum dose of 1.0 mg/kg/day of prednisone or equivalent. Gradual taper over 3 to 6 months after

clinical and laboratory stabilization is recommended to avoid relapse. There is often significant improvement of symptoms and laboratory abnormalities within several days after initiating steroid treatment.[7,19,23] In cases where there is no improvement or exacerbation of symptoms with oral corticosteroids or significant visceral involvement, patients can be treated with intravenous methylprednisolone. A course of pulsed methylprednisolone, 30 mg/kg intravenously for 3 days, can be administered.[19] During this time, complete blood cell count, liver function tests, lymph nodes, and other organ-specific laboratory tests should be monitored carefully to detect potential relapse, and steroid doses should be adjusted accordingly. Significant cutaneous and systemic symptoms have been reported after accidental withdrawal or a rapid reduction in corticosteroid dose.[7,19,22] Although steroid therapy is generally effective in the acute setting, its effect on the long-term disease course is unknown; there have been no controlled clinical trials to our knowledge. Immunosuppression from steroid therapy may promote the reactivation of viruses, such as HHV-6 or CMV, and can be associated with a rare long-lasting, steroid-dependent variant of DRESS syndrome.[11]

Alternative steroid-sparing therapies may be used to treat DRESS syndrome, especially in cases that do not respond to systemic steroids.[19,24] Patients have been effectively treated with adjunctive high dose intravenous immunoglobulin (IVIG). Several cases have been reported in the literature, including nevirapine-induced DRESS syndrome successfully treated with IVIG (1 g/kg for 2 days).[25,26] However, a recent study of 6 patients with DRESS syndrome did not support a beneficial effect of IVIG; 5 of 6 patients experienced severe adverse effects and 4 patients had to be treated with oral corticosteroids because of the adverse effects of IVIG or uncontrolled DRESS syndrome. Consequently, the authors did not recommend the use of IVIG monotherapy in the treatment of DRESS syndrome.[27] IVIG is thought to be effective in DRESS syndrome therapy because it replenishes the low immunoglobulin levels in the patient's blood, supports immune protection against HHV-6, and has antiinflammatory properties.[24]

Plasmapharesis and immunosuppressive drugs, such as cyclophosphamide, cyclosporine, interferons, muromonab-CD3, mycophenolate mofetil, and rituximab, may also be potential therapies.[28] A case of vancomycin-induced DRESS syndrome with hepatitis and interstitial nephritis was successfully treated with a 5-day course of cyclosporine after there was no response with vancomycin withdrawal and steroid therapy.[28] Laban et al[29] reported a case of corticosteroid-resistant DRESS syndrome with acute interstitial nephritis and eye involvement that was treated with a 6-month course of oral cyclophosphamide, resulting in complete resolution of symptoms. The use of N-acetylcysteine, especially in anticonvulsant-induced DRESS syndrome, may aid in drug detoxification and limit reactive metabolites.[11] However, there are no randomized clinical trials for this use. It may be associated with the severe adverse effect of angioedema.[11] Antiherpesvirus medications, such as valganciclovir, may be helpful in preventing or minimizing complications related to HHV-6 reactivation. Moling et al[30] proposed a novel treatment regimen combining prednisone, N-acetylcysteine, and valganciclovir for the treatment of DRESS syndrome, with each drug targeting different pathogenic mechanisms.

A consensus group of the French Society of Dermatology has published recommendations for the management of DRESS syndrome.[31] A decisional tree of treatment options was proposed based on the severity of visceral involvement. The first step in management is immediate withdrawal of the culprit drug. In the absence of signs of severity (transaminase levels >5 times normal, renal involvement, pneumonia, hemophagocytosis, and cardiac severity, etc), patients can be treated with topical corticosteroids in addition to supportive therapy including emollients and H_1-antihistamines. In the presence of signs of severity, treatment with systemic corticosteroids equivalent to 1 mg/kg/day of prednisone is warranted. In addition, multidisciplinary evaluation with appropriate specialists is in order. Patients with life-threatening signs (ie, hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure) can be treated with steroids and IVIG at a dose of 2 g/kg over 5 days. The IVIG should not be administered without associated steroids. In cases with signs of severity with confirmation of major viral reactivation, antiviral medications such as ganciclovir can be given in addition to steroids and /or IVIG. Long-term follow up with laboratory testing is important to monitor relapse.

Although individual organ abnormalities frequently resolve after withdrawing the offending drug and implementing systemic steroids and immunosuppressive therapy, it is advised to order system-specific laboratory, imaging, and other diagnostic studies. Descamps et al[31] recommend the following laboratory tests at admission: complete blood cell count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma-glutamyltransferase, alkaline phosphatase, sodium, potassium, creatinine, and creatinine clearance, 24-hour urine protein and urinary eosinophil count, creatine phosphokinase, lactate dehydrogenase,

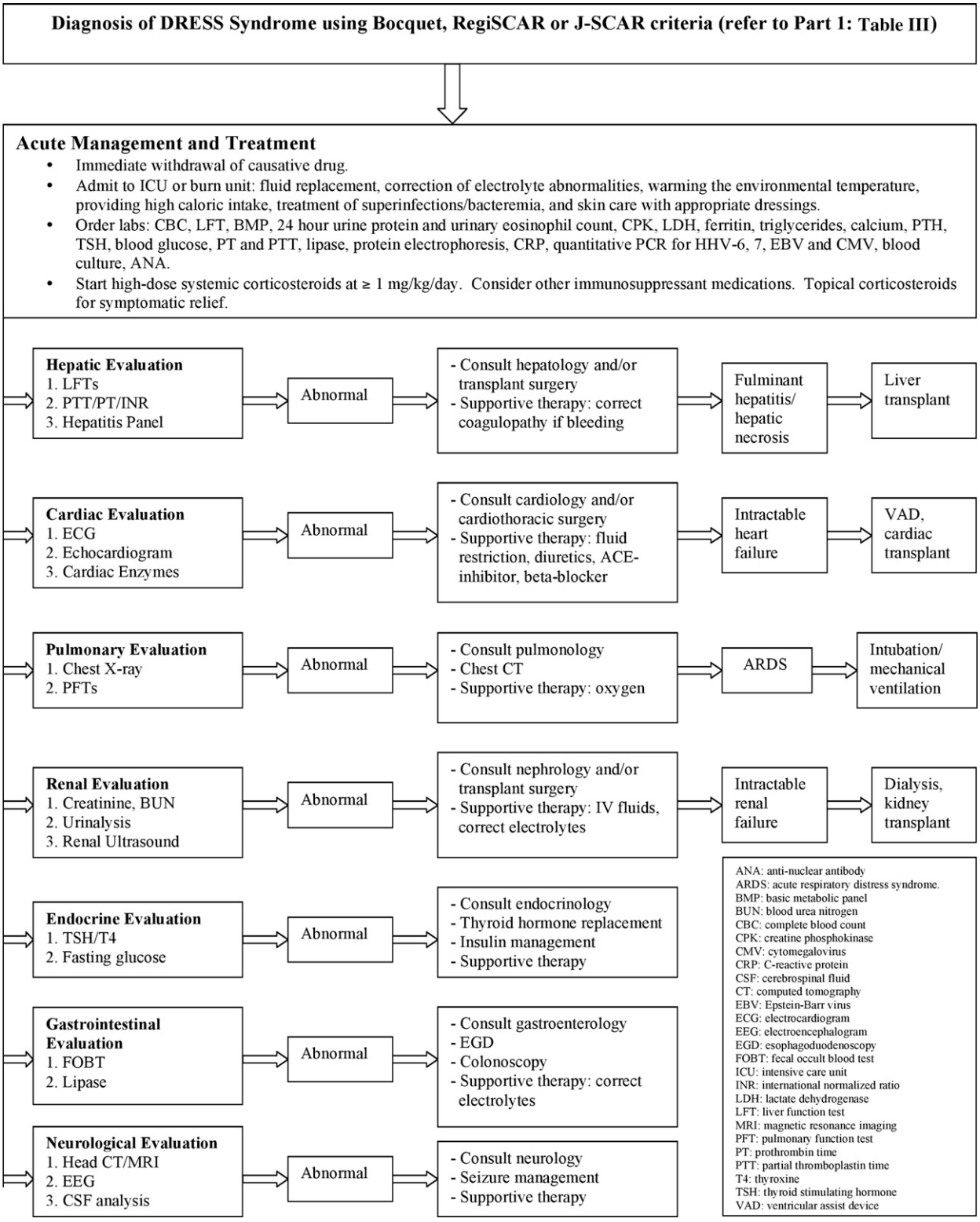

Fig 1. Alogrithm for the diagnosis, management, and treatment of drug reaction with eosinophilia and systemic symptoms syndrome.

ferritin, triglycerides, calcium, parathyroid hormone, thyroid-stimulating hormone, blood glucose, prothrombin time and partial thromboplastin time, lipase, protein electrophoresis, C-reactive protein, quantitative polymerase chain reaction studies for HHV-6 and -7, EBV, and CMV, blood culture, and

antinuclear factor. Follow-up laboratory tests (twice per week) for complete blood cell count, alanine aminotransferase, aspartate aminotransferase, creatinine, lactate dehydrogenase, and other organ-specific laboratory values concerning from admission is recommended. Evolutive follow-up tests should include quantitative polymerase chain reaction studies for HHV-6 and -7, EBV, and CMV, complete blood cell count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, lactate dehydrogenase, ferritin, and triglycerides.[31]

It is also prudent to consult the appropriate specialists, especially in the management of complicated visceral involvement. Instituting timely supportive and medical measures to prevent organ failure is critical in patients with DRESS syndrome. Once organ failure is recognized, organ-specific therapy and supportive measures must be administered immediately. For instance, treatment for DRESS syndrome—associated myocarditis consists of high-dose corticosteroids in conjunction with heart failure therapy, including diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and digoxin.[32,33] Severe cases have also been successfully treated with the implantation of a left-ventricular assist device.[32]An algorithm summarizing the diagnosis, management, and treatment of DRESS syndrome is provided (Fig 1).

PROGNOSIS

Key points

- **Most patients with DRESS syndrome will undergo complete recovery after withdrawal of the causative drug**
- **Cutaneous lesions typically regress with topical steroid treatment**
- **The most common dermatologic sequela observed in patients with DRESS syndrome is chronic exfoliative dermatitis**
- **The estimated mortality of DRESS syndrome is 10%; the most common cause of death is related to hepatic necrosis**

DRESS syndrome is a potentially life-threatening drug reaction, with an estimated mortality of 10%, primarily because of hepatic necrosis.[10,11,21,34] In general, prognosis is more guarded in elderly individuals, whereas children recover more quickly and completely from the syndrome.[35] In a recent study from the Republic of China, septic shock was found to be a significant cause of mortality in patients with DRESS syndrome, who developed bacteremia and fungemia during hospitalization.[36] The identified pathogens included *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Candida albicans*. Poor prognostic indicators associated with higher mortality in patients with DRESS syndrome include high absolute eosinophil counts (>6000/uL), thrombocytopenia, pancytopenia, a history of chronic renal insufficiency, multiorgan involvement, and multiple underlying diseases.[36,37] In a retrospective study of prognostic factors in DRESS syndrome, Wei et al[37] determined that tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome were associated with poor outcomes.

Fortunately, the majority of patients with DRESS syndrome have complete recovery after withdrawal of the culprit drug. The clinical course is variable, with some cases resolving quickly with no long-term sequelae, whereas others may have life-long, extensive systemic damage.[9] Symptoms are generally present for several weeks after discontinuing the offending agent and beginning treatment. Cutaneous findings usually respond well to topical steroid therapy.[7] The major cutaneous sequela seen in DRESS is chronic exfoliative dermatitis, but there can be pigmentary alterations and cutaneous scarring.[38]

CONCLUSION

DRESS syndrome is a potentially fatal cutaneous drug reaction with a 10% mortality rate. Prompt diagnosis using clinical criteria, laboratory values, histopathology, and diagnostic testing is imperative. The offending drug should be immediately discontinued and the patient given supportive care in an inpatient setting to minimize complications. Severe cases of DRESS syndrome require systemic corticosteroids or other immunotherapeutic treatments. Future randomized controlled trials evaluating the efficacy of corticosteroids and other immunotherapies are warranted. Most patients have complete recovery after drug withdrawal, but some suffer long-term sequelae as a result of extensive systemic damage. Consequently, it is important to routinely monitor patients for organ system dysfunction. Clinicians are encouraged to report all cases of DRESS syndrome as adverse drug reactions to the US Food and Drug Administration.

REFERENCES

1. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol 2003;4:561-72.
2. Dmochowski M, Schwartz RA. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Demis DJ, editor. Clinical dermatology. Philadelphia (PA): Lippincott Williams & Wilkins; 1999. pp. 1-20.

3. Schwartz RA, Dmochowski M. The erythema multiforme spectrum: pathogenesis, pathology and links with the pemphigus spectrum. Post Dermatol Alergol 1998;15:7-23.
4. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. Int J Dermatol 2011;50:221-4.
5. Guevara-Gutierrez E, Uribe-Jimenez E, Diaz-Canchola M, Tlacuilo-Parra A. Acute generalized exanthematous pustulosis: report of 12 cases and literature review. Int J Dermatol 2009; 48:253-8.
6. Miteva L, Kadurina M, Schwartz RA. Childhood acute generalized exanthematous pustulosis induced by oral ketoconazole. Acta Dermatovenerol Croat 2010;18:267-70.
7. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg 1996;15:250-7.
8. Okoduwa C, Lambert WC, Schwartz RA, Kubeyinje E, Eitokpah A, Sinha S, et al. Erythroderma: review of a potentially life-threatening dermatosis. Indian J Dermatol 2009;54:1-6.
9. Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges 2009; 7:142-60.
10. Tas S, Simonart T. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Acta Clinica Belgica 1999;54: 197-200.
11. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. Dermatology 2003;206:353-6.
12. Schwartz RA, Churg J. Churg-Strauss syndrome. Br J Dermatol 1992;127:199-204.
13. Morgan AJ, Schwartz RA. Cutaneous polyarteritis nodosa: a comprehensive review. Int J Dermatol 2010;49:750-6.
14. Santiago F, Goncalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Derm 2010;62:47-53.
15. Elzagallaai AA, Knowles SR, Rieder MJ, Bend JR, Shear NH, Koren G. Patch testing for the diagnosis of anticonvulsant hypersensitivity syndrome: a systematic review. Drug Safety 2009;32:391-408.
16. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy 2007;62:1439-44.
17. Lee JH, Park HK, Heo J, Kim TO, Kim GH, Kang DH, et al. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome induced by celecoxib and anti-tuberculosis drugs. J Korean Med Sci 2008;23:521-5.
18. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004;59:809-20.
19. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. Allergol Int 2006;55:1-8.
20. Bachot N, Roujeau JC. Physiopathology and treatment of severe drug eruptions. Curr Opin Allergy Clin Immunol 2001;1: 293-8.
21. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol 2008;22: 1044-9.
22. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J 2002;8:5.
23. Gentile I, Talamo M, Borgia G. Is the drug-induced hypersensitivity syndrome (DIHS) due to human herpesvirus 6 infection or to allergy-mediated viral reactivation? Report of a case and literature review. BMC Infect Dis 2010;10:49.
24. Kito Y, Ito T, Tokura Y, Hashizume H. High-dose intravenous immunoglobulin monotherapy for drug-induced hypersensitivity syndrome. Acta Derm Venereol 2012;92:100-1.
25. Scheuerman O, Nofech-Moses Y, Rachmel A, Ashkenazi S. Successful treatment of antiepileptic drug hypersensitivity syndrome with intravenous immune globulin. Pediatrics 2001;107:E14.
26. Fields KS, Petersen MJ, Chiao E, Tristani-Firouzi P. Case reports: treatment of nevirapine-associated dress syndrome with intravenous immune globulin (IVIG). J Drugs Dermatol 2005;4: 510-3.
27. Joly P, Janela B, Tetart F, Rogez S, Picard D, D'Incan M, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol 2012;148:543-4.
28. Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. Clin Nephrol 2005;64:155-8.
29. Laban E, Hainaut-Wierzbicka E, Pourreau F, Yacoub M, Sztermer E, Guillet G, et al. Cyclophosphamide therapy for corticoresistant drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a patient with severe kidney and eye involvement and Epstein-Barr virus reactivation. Am J Kidney Dis 2010;55:e11-4.
30. Moling O, Tappeiner L, Piccin A, Pagani E, Rossi P, Rimenti G, et al. Treatment of DIHS/DRESS syndrome with combined N-acetylcysteine, prednisone and valganciclovir—a hypothesis. Med Sci Monit 2012;18:CS57-62.
31. Descamps V, Ben Saïd B, Sassolas B, Truchetet F, Avenel-Audran M, Girardin P, et al. Management of drug reaction with eosinophilia and systemic symptoms (DRESS) [in French]. Ann Dermatol Venereol 2010;137:703-8.
32. Bourgeois GP, Cafardi JA, Groysman V, Pamboukian SV, Kirklin JK, Andea AA, et al. Fulminant myocarditis as a late sequela of DRESS: two cases. J Am Acad Dermatol 2011;65:889-90.
33. Zaidi AN. Anticonvulsant hypersensitivity syndrome leading to reversible myocarditis. Can J Clin Pharmacol 2005;12:e33-40.
34. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2006;155:422-8.
35. Criado PR, Criado RF, Avancini Jde M, Santi CG. Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS): a review of current concepts. An Bras Dermatol 2012;87:435-49.
36. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146:1373-9.
37. Wei CH, Chung-Yee Hui R, Chang CJ, Ho HC, Yang CH, Lin YJ, et al. Identifying prognostic factors for drug rash with eosinophilia and systemic symptoms (DRESS). Eur J Dermatol 2011; 21:930-7.
38. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology 2005;209:123-9.