

Medical algorithm: Diagnosis and treatment of Drug reaction with eosinophilia and systemic symptoms

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as Drug-induced hypersensitivity syndrome (DIHS), is a rare but severe delayed-type drug hypersensitivity reaction [1]. Its reported incidence ranges between 2 and 5 cases per million per year and the mortality between 5 and 10% [2]. DRESS is characterized by the occurrence of an extensive rash with face edema, lymphadenopathy and fever and organ damage, all of which seems to result from massive drug-directed T cell response and associated eosinophilia. DRESS is a complex condition, its clinical presentation varies depending on the cutaneous manifestation(s), affected target organ(s) and reaction severity. The diagnosis of DRESS is further challenged by the clinical overlay with autoimmune, infectious and lymphoproliferative conditions, which have to be considered in the differential diagnosis (Table 1). Eosinophilia is detected in only 80 % of DRESS patients and can be masked by e.g. the administration of systemic glucocorticoids (GCS). Furthermore, there are various differences in the DRESS diagnostic criteria (Table 1) developed by the Japanese SCAR (JSPS) [3] and RegiSCAR [4] groups, the most notable being the inclusion of herpes viremia in the criteria developed by the JSPS. All these clinical challenges underline the importance of a systematic and comprehensive approach when encountering a patient with suspected DRESS. Based on the most recent literature and our clinical expertise, we therefore suggest the medical algorithm depicted in Figure 1. DRESS should be evoked as a differential diagnosis in patients with a rash suspected to be drug-related and associated with head-and-neck edema [5]. Clinical history-taking is a critical element to consolidate or discard a drug-related etiology: most importantly, this should explore the dynamics of both possible DRESS clinical symptoms and drug exposure(s) (date of onset, way and length of administration, previous exposures / reactions). A long drug exposure prior to disease onset, i.e. 2-8 weeks, is indicative for DRESS rather than other drug hypersensitivities – but the duration may vary depending on the causative drug. A thorough clinical examination, basic laboratory work-up, electrocardiogram, and - if a rash is present - a skin biopsy should also be performed. If the clinical presentation and drug exposure history substantiate the DRESS diagnosis, additional investigations should be performed depending on the suspected target organ damage (cf. case “complementary, patient-specific work-up”). Once the diagnosis is established, a severity assessment is warranted, since DRESS can range from mild forms with very limited organ damage to fulminant ones, e.g. characterized by (multi-)organ failure. There are no consensual severity scoring. In this algorithm, we suggest the scoring system used in France (RCT DRESSCODE, <https://clinicaltrials.gov/NCT01987076>).

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Manuscript

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as Drug-induced hypersensitivity syndrome (DIHS), is a rare but severe delayed-type drug hypersensitivity reaction [1]. Its reported incidence ranges between 2 and 5 cases per million per year and the mortality between 5 and 10% [2]. DRESS is characterized by the occurrence of an extensive rash with face edema, lymphadenopathy and fever and organ damage, all of which seems to result from massive drug-directed T cell response and associated eosinophilia.

DRESS is a complex condition, its clinical presentation varies depending on the cutaneous manifestation(s), affected target organ(s) and reaction severity. The diagnosis of DRESS is further challenged by the clinical overlay with autoimmune, infectious and lymphoproliferative conditions, which have to be considered in the differential diagnosis (Table 1). Eosinophilia is detected in only 80 % of DRESS patients and can be masked by e.g. the administration of systemic glucocorticoids (GCS). Furthermore, there are various differences in the DRESS diagnostic criteria (Table 1) developed by the Japanese SCAR (JSPS) [3] and RegiSCAR [4] groups, the most notable being the inclusion of herpes viremia in the criteria developed by the JSPS.

All these clinical challenges underline the importance of a systematic and comprehensive approach when encountering a patient with suspected DRESS. Based on the most recent literature and our clinical expertise,

we therefore suggest the medical algorithm depicted in Figure 1. DRESS should be evoked as a differential diagnosis in patients with a rash suspected to be drug-related and associated with head-and-neck edema [5]. Clinical history-taking is a critical element to consolidate or discard a drug-related etiology: most importantly, this should explore the dynamics of both possible DRESS clinical symptoms and drug exposure(s) (date of onset, way and length of administration, previous exposures / reactions). A long drug exposure prior to disease onset, i.e. 2-8 weeks, is indicative for DRESS rather than other drug hypersensitivities – but the duration may vary depending on the causative drug. A thorough clinical examination, basic laboratory work-up, electrocardiogram, and - if a rash is present - a skin biopsy should also be performed. If the clinical presentation and drug exposure history substantiate the DRESS diagnosis, additional investigations should be performed depending on the suspected target organ damage (cf. case “complementary, patient-specific work-up”). Once the diagnosis is established, a severity assessment is warranted, since DRESS can range from mild forms with very limited organ damage to fulminant ones, e.g. characterized by (multi-)organ failure. There are no consensual severity scoring. In this algorithm, we suggest the scoring system used in France (RCT DRESSCODE, <https://clinicaltrials.gov/NCT01987076>).

In terms of treatment, steroids, either topically applied (TCS) or systemically administered (GCS) are, besides the retrieval of the culprit drug(s), the current mainstay of DRESS treatment [6]. There is no consensus on the dosage of either GCS or TCS, but there is evidence supporting that very high-potency TCS are sufficient to treat mild, maybe even moderate DRESS [7, 8]. GCS are the cornerstone of the management of severe DRESS cases. In therapy-refractory patients, systemic immunosuppressants and more recently JAK inhibitors and anti-IL5R or anti-IL5 antibodies can be used as a second-line treatment [1, 9]. The benefit of antivirals (e.g. valacyclovir) to treat herpes virus reactivations (especially cytomegalovirus) is debated, since the use of a new medication in a DRESS patient may bear the risk of multiple drug hypersensitivity [10]. TCS/GCS should be tapered very carefully over months. Given the risk of DRESS relapses and/or autoimmune sequelae, patients should be regularly monitored for these.

Our medical algorithm highlights the importance of a systematic diagnostic approach to patients with suspected DRESS. With regard to the presented treatment algorithm, we should keep in mind that so far, the use of all drugs to treat DRESS relies on case reports / case series and retrospective analyses, prospective clinical trials are missing.

Author contribution statement:

M.-C.B. has developed the concept, designed the algorithm drafted the manuscript. S.I.O. has contributed to the concept, edited the algorithm and the manuscript. Y.M., S.O. S.T. and E.M. have contributed to the concept, edited the algorithm and the manuscript.

Conflict of interest statement:

The authors have no conflicts of interest to declare.

Figure Legends

Figure 1. Medical algorithm: Diagnosis and treatment of DRESS.

Suspicious skin rashes with or without eosinophilia should be investigated by comprehensive medical history, examination and lab work. If the results from this investigation are in line with the diagnosis of DRESS and other organ involvement is suspected, a complementary, patient-specific work-up is indicated. This includes individual, symptom-specific examination of liver, lung, heart, kidney, gastrointestinal tract, pancreas, and the nerve system. Based on the extent of organ involvement, mild, moderate and severe DRESS can be differentiated. These are treated by high potent topical steroids or systemic glucocorticoids, respectively. The culprit drug must be stopped. In case of steroid-refractory DRESS, second line therapy is indicated. The first follow up visits shall be scheduled one month after discharge and include clinical and laboratory controls. Patch testing, intracutaneous testing and, if available, lymphocyte transformation test (LTT) or ELISPOT, shall be performed. AP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, CNS: Central nervous system, CT: Computed tomography, IVIG: Intravenous immunoglobulins, JAK:

janus kinases, MRI: Magnetic resonance imaging, PNS: Peripheral nervous system.

§Severity assessment: According those of the French RCT DRESSCODE <https://clinicaltrials.gov/NCT01987076>.

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