

Spanish Guidelines for Diagnosis, Management, Treatment, and Prevention of DRESS Syndrome

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■ Abstract

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a complex multisystemic severe drug hypersensitivity reaction whose diagnosis and management are troublesome. DRESS syndrome requires management by various specialists. The correct identification of the culprit drug is essential to ensure safe future therapeutic options for the patient. There are no previous Spanish guidelines or consensus statements on DRESS syndrome.

Aim: To draft a review and guidelines on the clinical diagnosis, allergy work-up, management, treatment, and prevention of DRESS syndrome in light of currently available scientific evidence and the experience of experts from multiple disciplines.

Methods: These guidelines were drafted by a panel of allergy specialists from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (SEAIC), together with other medical specialists involved in the management of DRESS syndrome and researchers from the PIELenRed consortium. A review was conducted of scientific papers on DRESS syndrome, and the expert panel evaluated the quality of the evidence of the literature and provided grades of recommendation. Whenever evidence was lacking, a consensus was reached among the experts.

Results: The first Spanish guidelines on DRESS syndrome are now being published. Important aspects have been addressed, including practical recommendations about clinical diagnosis, identification of the culprit drug through the Spanish pharmacovigilance system algorithm, and the allergy work-up. Recommendations are provided on management, treatment, and prevention. Algorithms for the management of DRESS in the acute and recovery phases have been drawn up. Expert consensus-based stepwise guidelines for the management and treatment of DRESS syndrome are provided.

Key words: DRESS syndrome. Drug reaction with eosinophilia and systemic symptoms. Drug-induced hypersensitivity syndrome. SCAR. Patch tests. Skin tests. Lymphocyte transformation test. Corticosteroids.

■ Resumen

Antecedentes: El síndrome DRESS (*Drug Reaction with Eosinophilia and Systemic Symptoms*) es una reacción cutánea grave inducida por hipersensibilidad a fármacos, compleja y multisistémica. Su diagnóstico y manejo es difícil e implica a diferentes especialistas. Es muy importante una correcta identificación del fármaco responsable para que el paciente disponga de opciones terapéuticas seguras en el futuro. No hay guías ni documentos de consenso españoles previos sobre el síndrome DRESS.

Objetivo: Realizar una revisión y guía sobre el diagnóstico clínico y alergológico, manejo, tratamiento y prevención del DRESS según la evidencia científica disponible y la experiencia de expertos de diferentes especialidades médicas.

Métodos: Esta guía ha sido elaborada por un grupo de alergólogos del Comité de Alergia a Fármacos de la SEAIC, junto a otros especialistas involucrados en el manejo del DRESS e investigadores del Consorcio PIELenRed. Se realizó una búsqueda de publicaciones científicas sobre DRESS y el grupo de expertos evaluó la evidencia científica de la literatura y aportaron grados de recomendación. Cuando no existía evidencia se alcanzó un consenso entre expertos.

Resultados: Se publica la guía española sobre DRESS. Incluye aspectos prácticos importantes sobre el diagnóstico clínico, la identificación de fármacos causales a través del algoritmo del Sistema Español de Farmacovigilancia y guía para el diagnóstico alergológico. Se realizan recomendaciones sobre el manejo, tratamiento y prevención del DRESS. Se aportan algoritmos sobre el manejo en la fase aguda y en la de recuperación. Se ha elaborado una guía terapéutica escalonada consensuada por expertos especialistas implicados en el tratamiento del DRESS.

Palabras clave: Síndrome DRESS. Reacción adversa a fármaco con eosinofilia y sintomatología sistémica. Síndrome de hipersensibilidad inducido por fármaco. Reacción cutánea grave por fármaco. Parches. Pruebas cutáneas. Test de transformación linfocitaria. Corticosteroides.

1. Preface and Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, complex, potentially life-threatening, drug-induced hypersensitivity reaction that often includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement [1-3]. It is considered a severe cutaneous adverse reaction (SCAR) to drugs, together with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and acute generalized exanthematous pustulosis (AGEP) [4-5]. Its diagnosis and management are troublesome and require the involvement of various specialists.

No English-language guidelines or consensus documents on the diagnosis (including the allergy work-up), management, treatment, or prevention of DRESS syndrome have been published to date.

The aim of this study is to guide treating physicians by providing guidelines based on scientific evidence and thus optimize the quality of care and the quality of life of patients who experience such reactions.

The many different terms used to describe DRESS syndrome include anticonvulsant hypersensitivity syndrome, drug-induced pseudolymphoma, drug-induced hypersensitivity syndrome (DIHS), and hypersensitivity syndrome (HSS) [6-8]. The term DRESS (drug rash with eosinophilia and systemic symptoms) was introduced by Bocquet et al in 1996 [1]; the “R” in DRESS was later changed from rash to reaction owing to its diverse cutaneous presentations [9]. This is the term most widely accepted nowadays and is the one that we will use throughout this paper.

2. Methods

These guidelines were drawn up by a panel of allergy specialists from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica; SEAIC), together with other medical specialists involved in the management of DRESS syndrome (dermatologists, nephrologists, hepatologists, clinical pharmacologists) and researchers from the PIELenRed consortium.

Questions about specific difficulties in the management and diagnosis of DRESS syndrome in clinical practice were raised by the authors. The participants designed a working protocol based on a number of items to define the key words and the methodology for selecting the publications included in this review. The literature search was performed using electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), and a systematic review database (Cochrane Library). The key terms used were as follows: *DRESS syndrome, Drug reaction with eosinophilia and systemic symptoms, Drug-induced hypersensitivity syndrome, Drug hypersensitivity syndrome, SCAR, in combination with antiviral, consensus, corticosteroids, cyclosporine, differential diagnosis, incidence, IVIG, follow up, HLA-B antigens, lymphocyte transformation test, patch tests, pharmacovigilance, prevalence, primary prevention, secondary prevention, registries, skin biopsy, skin tests, symptoms, and risk factors.*

The expert panel evaluated the quality of the evidence in the literature and provided grades of recommendation according to the Scottish Intercollegiate Guidelines Network [10] (Table 1).

Table 1. Revised Grading System for Recommendations in Evidence-Based Guidelines [3]

Levels of evidence
– 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
– 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
– 1–Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
– 2++ High quality systematic reviews of case-control or cohort studies or
– High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
– 2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
– 2–Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
– 3 Nonanalytical studies, eg, case reports, case series
– 4 Expert opinion
Grades of recommendations
– A At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or
– A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
– B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or
– Extrapolated evidence from studies rated as 1++ or 1+
– C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or
– Extrapolated evidence from studies rated as 2++
– D Evidence level 3 or 4 or
– Extrapolated evidence from studies rated as 2+

Abbreviation: RCT, randomized controlled trial.

In the text, we have added a level of evidence (LE) and a grade of recommendation (GR) after each recommendation. Wherever evidence was lacking, a consensus was reached among the experts. The evaluation was based on several online and in-person discussions.

Each author or group of authors produced a draft of the issue of the guidelines in which they had expertise, and the first author compiled and reviewed the work carried out to prepare the first draft of this paper. The final version of the manuscript

was revised by all the co-authors and external reviewers. The project was started in June 2016 and finished in May 2019.

3. Epidemiology

The lack of reliable data on DRESS syndrome may be due to the confusing nomenclature and the paucity of epidemiologic studies.

RegiSCAR, an international prospective, ongoing pharmaco-epidemiological registry on SCARs to drugs and collection of biological samples, was started in 2003 and now includes, for the first time, cases of DRESS syndrome [11]. The Spanish multidisciplinary and multicenter consortium for research on SCARs, PIELenRed [12], was created in 2010 and later integrated in RegiSCAR. PIELenRed is a major contributor of reliable epidemiologic data on DRESS syndrome in Spain.

Data on the incidence of DRESS syndrome are scarce. The reported annual incidence in the general population ranges from 0.9/100 000 [13] to 10 cases per million [14]. Prevalence ranges from 2.18 [15] to 9.63 cases per 100 000 inpatients [16]. An incidence rate of 3.89 per 10 000 patients was observed in Spain [17]. DRESS may occur in children, although most cases occur in adults, with no predilection for sex [18].

The most frequent associated comorbidities are HIV infection (28.8%) [16], atopy (21.9%) [17], and epilepsy (20%) [19].

Most patients who experience DRESS syndrome recover completely, although some may develop long-term sequelae. The percentage affected may reach 11.5% [20], especially in the case of autoimmune diseases in young patients and permanent end-organ failure in elderly patients [20,21].

Retrospective studies have reported a mortality rate of 3.8% [16] to 10% [22]. In one prospective multinational study, the mortality rate was 1.7% [23].

The causes of death were multiple organ failure, hepatic necrosis, shock, pulmonary hemorrhage, and sepsis [22]. The culprit drugs most commonly involved in deaths were antiepileptic drugs [24] and allopurinol [25,26].

3.1. Culprit Drugs

Anticonvulsants, allopurinol, sulfonamides, minocycline, and vancomycin are the most frequently reported culprit drugs [22,23,27]. Piperacillin/tazobactam has also been reported to be a major culprit drug in Spain [17].

A list of drugs implicated in the main reported case series of DRESS [16-19,28] is shown in Table 2.

3.2. Risk Factors

The various risk factors reported include viral infection, a few drug-specific human leukocyte antigen alleles, polymedication, and enzyme polymorphisms in genes encoding drug metabolizing enzymes, such as cytochrome P 450 enzyme and slow N-acetylator phenotype [29-31].

DRESS syndrome generally occurs with greater frequency in situations where chemically reactive metabolites have accumulated owing to kidney or liver failure [31].

Table 2. Drugs Reported in Association With DRESS Syndrome [15,17,19,20,28]

Antibiotic and other anti-infective drugs	Sulfonamides Dapsone*, sulphamethoxazole/trimethoprim* Penicillins and cephalosporins Ampicillin/amoxicillin, ampicillin/ sulbactam, amoxicillin-clavulanic acid, cefadroxil, cefepime, cefixime, cefotaxime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam* Quinolones Levofloxacin Other Abacavir*, nevirapine*, boceprevir, telaprevir, benznidazole*, clindamycin, diaphenylsulfone, hydroxychloroquine, linezolid, metronidazole, minocycline*, teicoplanin, vancomycin*, voriconazole, zalcitabine
Anticonvulsant drugs	Carbamazepine*, lamotrigine*, levetiracetam* oxcarbazepine, phenytoin*, phenobarbital*, valproate, ethosuximide, zonisamide
Antineoplastic and immunomodulating agents	Azathioprine, chlorambucil, efalizumab, imatinib, vemurafenib Leflunomide Lenalidomide
Antidepressants and antipsychotic drugs	Amitriptyline, bupropion, clomipramine, fluoxetine, olanzapine
Cardiovascular system	Amlodipine, captopril, diltiazem, mexiletine, spironolactone, tribenoside
Musculoskeletal system drugs	Allopurinol*, aspirin, celecoxib, dexketoprofen, ibuprofen, metamizole, phenylbutazone
Treatment for tuberculosis	Ethambutol, isoniazid, pyrazinamide, rifampicin*, streptomycin
Miscellaneous	Ranitidine, esomeprazole, iodinated contrast media, rivaroxaban, atorvastatin, codeine phosphate, salazosulfapyridine*, sulfasalazine*, quinine, thiamine, epoetin alfa, cyanamide, vitamin B ₁₂ sitagliptin, strontium ranelate

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

*Frequent culprit drugs.

Table 3 summarizes the risk alleles predisposing to DRESS syndrome according to drug and ethnicity and the pharmacogenetic tests recommended by various medical organizations [30-50].

4. Pathogenesis

The precise pathogenesis of DRESS remains unclear, although a drug-specific immune response and virus reactivation are considered key factors [51]. The complex interplay between herpesviruses and antiviral and antidrug immune responses may also play a role [8]. DRESS syndrome is a type IV-b hypersensitivity reaction mediated by T cells (T_H2 profile), which, through the release of specific cytokines and chemokines such as IL-4, IL-5, and IL-13, preferentially activate and recruit eosinophils [52]. In this T_H2 immune reaction, thymus and activation-regulated chemokine (TARC) plays an important role by recruiting T_H2-polarized T lymphocytes into local inflammation sites [53,54]. IL-33, which is produced by skin macrophages in patients with DRESS syndrome, attracts innate type 2 lymphocytes to the skin through its specific receptor ST2, in addition to promoting eosinophilia [55]. Reactivation of viral infection concurrent with drug hypersensitivity is considered specific for DRESS syndrome [56,57]. The most prevalent of the viruses reported to reactivate is human herpesvirus 6 (HHV-6) [56,58], which

has been demonstrated in peripheral blood [8,58], skin [59], lymph nodes [60], and renal tissues [61,62]. In addition to HHV-6, other herpesvirus reactivations have been reported to be associated with the onset of DRESS syndrome [63-66].

Reactivation of HHV-6 requires immunosuppression, which is demonstrated as a decrease in serum immunoglobulin (Ig) levels, including IgG, IgM, and IgA, and of circulating B cells at onset in patients with DRESS syndrome [8,67,68].

Marked expansion of the regulatory CD4⁺CD25⁺FOXP3⁺ T-cell subset in the acute phase of DRESS syndrome could play an important role in inhibiting antiviral T lymphocytes and favoring viral reactivation [14,69,70].

5. Biopsy Findings

Skin histopathology is highly variable and nonpathognomonic for DRESS syndrome. Biopsy is useful and has been recommended for ruling out conditions for which histologic findings are pathognomonic. Histopathology findings in DRESS syndrome encompass a spectrum of changes, such as lichenoid dermatitis and nonspecific dermatitis, with erythema multiforme-like dermatitis being the most dominant type [71]. A lymphocytic infiltrate that is either predominantly dense and diffuse or superficial and perivascular is observed. In some cases, there is a band-like infiltrate with atypical lymphocytes simulating mycosis

Table 3. Risk Alleles According to Drug, Ethnicity, and Screening Prevention Strategies

Causative Drug	Ethnicity	Allele (NPV)	Pharmacogenetic Testing Recommendations
Allopurinol	Han Chinese, Korean, Japanese, Thai [41,42]	HLA B* 58:01 (100%)	American College of Rheumatology and Clinical Pharmacogenetics Implementation Consortium (CPIC) [36], Taiwanese Department of Health [43] None from FDA
	European Portuguese population [44,45]	HLA B* 58:01 (63%)	Not recommended for Caucasian population
Carbamazepine	Northern European; Japanese; Korean [43,46] Spanish Caucasian [47]	HLA-A* 31:01	Warning about possible association [42] (no FDA recommendation) Canadian Pharmacogenomics Network for drug safety recommends pharmacogenetics testing in patients of all ancestries [48].
	Caucasian [43]	8.1 AH (HLA A*01:01: Cw*07:01: B*08:01: DRB1*03:01: DQA1*05:01: DQB1*02:01)	None
Lamotrigine and phenytoin	Spanish Caucasian [47]	HLA-A* 24:02	None
Salazosulfapyridine	Chinese Han (49)	HLA B* 13:01	
Dapsone	Han Chinese patients treated for leprosy [43] [50]	HLA-B*13:01	None
Piperacillin/tazobactam	English population [51]	HLA- B62	None
Abacavir ^a	US [52,53] European, African [54]	HLA-B* 57:01 (100%)	Screening FDA population of risk [41,43]
Nevirapine /HIV ^a	Asian: Han Chinese, Thai [55]	HLA-B* 35:05	None
	Italian (Sardinian) [56]; Japanese [57]	Cw*8 or Cw*08-B*14 haplotype	None
	Australian	HLA-DRB1*01:01; B35:01 [58]	None
Vancomycin	North American	HLA-A*32:01 [59]	None

Abbreviations: FDA, United States Food and Drug Administration; HLA, human leukocyte antigen; NPV, negative predictive value.

^aAbacavir and nevirapine hypersensitivity do not completely fit the major criteria for DRESS syndrome.

fungoides [1]. Histopathological changes include basket-weave hyperkeratosis, dyskeratosis, lymphocytic exocytosis, and spongiosis. Eosinophils in the dermis or edema may or may not be present.

Histopathology of the skin can highlight various associated inflammatory patterns in a single biopsy [72].

Cutaneous effector lymphocytes comprise a high proportion of polyclonal CD8⁺ granzyme B⁺ T lymphocytes [72]. The findings in lymph node biopsies vary from benign reactive hyperplasia induced by viral processes to the presence of atypical lymphocytes that may suggest lymphoma [73]. Liver biopsy reveals an acute hepatitis pattern with lobular inflammation, foci of necrotic hepatocytes, and granulomatous infiltrates with eosinophils. Portal inflammation and cholestasis may also be present [74]. Renal biopsy shows tubulointerstitial nephritis with edema and infiltrates of lymphocytes, histiocytes, eosinophils, and plasma cells [75].

6. Clinical Symptoms

DRESS is characterized by a mixture of symptomatic and asymptomatic features that are variable in both course and time [23,76]. Clinical manifestations often develop 2 to 8 weeks after starting treatment with the causative drug, although rechallenge can result in a reaction within hours to days [23]. Asymptomatic laboratory abnormalities may appear before clinical symptoms. The usual sequence of presentation according to median data in a Spanish DRESS series was fever (11 days), hypogammaglobulinemia (12 days), visceral involvement (20 days), eosinophilia (21 days), and exanthema (23 days) [17].

6.1. Skin Symptoms

Dermatologic manifestations typically begin as a morbilliform eruption that is slightly pruritic and involves the

Table 4. Laboratory Findings in DRESS Syndrome

- Leukocytosis with eosinophils $>1500/\text{mm}^3$, even leukemoid reactions [18]
- Transient eosinophilia ($>700/\text{mm}^3$) [23]
- Leukocytosis with atypical lymphocytes [14,96]
- Leukopenia and/or lymphopenia at the onset of the syndrome [14,96]
- Low platelet levels and low hemoglobin levels [14,96]
- Low immunoglobulin levels [14,96]
- Liver abnormalities: alanine aminotransferase >100 U/L [62]^a or an increase of 2 times the upper limit of normal (ULN) on at least 2 successive dates or conjugated bilirubin $2 \times$ ULN on at least 2 successive dates or aspartate aminotransferase, total bilirubin, alkaline phosphatase, all $2 \times$ ULN at least [97]^b. Prothrombin alterations and bilirubin high levels [97].
- Renal disorders: High creatinine levels (more than 1.5 times above the baseline level of the patient), and/or proteinuria around 1 g/d, hematuria, decreased creatinine clearance and decreased glomerular flow rate [97]^b
- Amylase and/or lipase more than $2 \times$ ULN [97]^b
- Raised serum creatinine phosphokinase (CPK) > 2 ; raised isoenzyme fractions (CPK-MM [skeletal muscle], CPK-MB [heart muscle]) or raised troponin T (>0.01 mg/L) [97]^b
- Abnormal bronchoalveolar lavage fluid or biopsy specimen, abnormal blood gases and/or evidence of interstitial lung (computed tomography, x-ray) [97]^b

Abbreviation: DRESS, drug reaction with eosinophilia and systemic symptoms; ULN, upper limit of normal.

^aIncluded as diagnostic criteria in a Japanese consensus group [96]

^bIncluded as diagnostic criteria in the RegiSCAR scoring system [97]

face, neck, upper extremities, and trunk, progressing towards diffuse, confluent, and infiltrated erythema. The rash can become edematous and includes purpuric lesions, pustules, and even vesicles or bullae in certain cases [19,77]. If the drug is not withheld, the rash may progress to erythroderma or exfoliative dermatitis.

The cutaneous phenotype in DRESS syndrome can be categorized as an urticarial papular exanthem, morbilliform erythema, exfoliative erythroderma, or erythema multiforme-like lesions, which in DRESS syndrome may be prognostic of more severe liver involvement [78]. Skin involvement in DRESS syndrome usually affects more than 50% of the body surface area (BSA). Facial edema usually appears in the periorbital and midfacial region and is symmetric and persistent. Disfiguring facial swelling is recorded in 25% of patients [2]. Mild mucosal involvement (50% of patients) usually involves a single site, most often the mouth or pharynx, and in 15% of cases more than 1 mucous membrane is affected [23].

6.2. Systemic Symptoms

Fever is seen in $>90\%$ of patients and generally precedes cutaneous eruptions by several days. It is usually high ($>38^\circ\text{C}$) and spiking [79].

Internal organ involvement occurs in 85%-96% of patients and determines severity; in 50% to 60% of patients, 2 or more organs are involved [18,23,77,80,81]. Any internal organ can be affected. The most common findings are abnormalities of the lymphatic system, blood, and liver followed by the kidneys, heart, and lungs. Severe cases can result in neurologic, gastrointestinal, and endocrine dysfunction [2].

Lymphadenopathy (30%-60% of cases) is often diffuse, with slightly enlarged and tender nodes at various locations [18].

Although any medication can affect any organ, certain drugs have a predilection for specific organs [82].

Liver involvement is frequent in DRESS syndrome (75% of cases) [23]. Hepatosplenomegaly may be present, although involvement is more often asymptomatic and detected in routine liver function tests. While the cholestatic type is the most common, mixed or hepatocellular types can also be detected [80]. DRESS-related liver injury manifests as reversible abnormal liver function results only, although hepatic necrosis may also be found and can lead to liver failure requiring transplantation and even lead to death [80]. Liver involvement is the leading cause of death from DRESS syndrome [18,80,81,83,84].

Renal involvement is found in 10% to 30% of cases, more often in those induced by allopurinol, followed by carbamazepine and dapsone [22]. Older age and preexisting alterations of renal function may be predisposing factors [85-87].

Lung manifestations appear in 5% to 25% of cases, with minocycline being the most common drug affecting the lungs. Respiratory complications include acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome [2,86-88].

Involvement of the heart can take the form of eosinophilic myocarditis or pericarditis, with minocycline and ampicillin being the most frequent culprit drugs [2]. Myocarditis is potentially fatal and can appear months after resolution of the laboratory abnormalities. Patients may present with chest pain, tachycardia, dyspnea, and hypotension [89].

The most frequent gastrointestinal manifestation is gastroenteritis; mucosal erosions can develop and contribute to acute bleeding. Gastrointestinal complications include chronic protein-losing enteropathy, colitis, and pancreatitis [2,87,90].

Brain disorders are unusual in DRESS syndrome and include encephalitis, meningitis [87,91], and even cerebral vasculitic-like lesions [92].

Endocrine disorders are rare in the acute phase, being more frequent as long-term sequelae and affecting the thyroid. Pancreatic involvement ranges from pancreatitis to type 1 diabetes mellitus that can develop 3 weeks to 10 months after the onset of DRESS syndrome [2,18,87,93].

Additional manifestations such as myositis, peripheral nerve disorders, uveitis, and salivary gland inflammation may be present [18,87].

Rare cases of shock and multiple organ failure have also been reported [94,95].

6.3. Laboratory Findings

The laboratory findings for DRESS syndrome are shown in Table 4.

7. Prognosis and Outcome

The outcome of DRESS is often unpredictable. Early diagnosis and prompt withdrawal of the culprit drug are often followed by complete recovery [18]. Some culprit drugs, such as allopurinol and anticonvulsants, are associated with a poorer prognosis, and others, such as antibiotics, are associated with a better prognosis [98,99].

A lower BSA affected and milder skin and mucosal involvement correlate with a better prognosis [18].

Severe liver injury and presence of atypical lymphocytes [99], as well as reactivation of herpesvirus, especially HHV-6 [62], and reactivation of cytomegalovirus (CMV) are associated with a worse prognosis. The Mizukawa scoring system was developed to predict CMV disease and complications and to ensure early intervention with anti-CMV agents [100]. In cases of reactivation of herpesvirus, patients may go on to develop autoimmune disease [58,69], even after resolution of the syndrome.

Serum TARC/CCL17 levels are elevated during acute DRESS syndrome, and TARC/CCL17 has been proposed as a prognostic and diagnostic biomarker [54,101].

The concentration of serum soluble ST2 (an innate type 2 lymphocyte-specific receptor) was proposed as a biomarker of disease, as it correlated with IL-33 and alanine aminotransferase levels at the onset of DRESS syndrome [55].

Elevations in TNF- α and TARC/CCL17 levels during the early stages of the disease enable early recognition of reactivation of HHV-6 [102]. TNF- α and TARC levels also reflect therapeutic responses and may be useful markers of the course of DRESS syndrome [102].

8. Clinical Diagnosis

8.1. When Should We Suspect DRESS Syndrome?

DRESS syndrome should be suspected in any patient under treatment with a new drug initiated in the previous 2-8 weeks who presents any combination of the following: skin eruption

Table 5. Recommended Laboratory Investigations in Patients With Suspected DRESS Syndrome and in Their Follow-up [5,8,19,23,104].

On Admission	Follow-up in Acute Phase (at least 2 times/wk) According to Initial Blood Abnormalities and Clinical Course
Complete differential Blood Count including evaluation of atypical lymphocytes	-
Inflammation markers (CRP, LDH)	-
Liver function tests (AST, ALT, GGT, alkaline phosphatase, total bilirubin) prothrombin time/INR	(Repeat in follow-up if liver involvement)
Kidney function tests (creatinine, serum urea, urine albumin-to-creatinine ratio or protein-to-creatinine ratio, urine sediment, urinary protein and cells)	(Repeat in follow-up if kidney involvement)
Other:	
Blood electrolytes: sodium, potassium.	
Lipase, amylase	
Creatine kinase	
Troponin I	
Proteinogram and immunoglobulins	
Herpes virus serology and PCR for HHV-6, HHV-7, CMV, EBV ^a	
Exclusion of alternative diagnosis	
Serology for mycoplasma, chlamydia, HAV, HBV, HCV, parvovirus B19, VHS 1/2. Blood culture	
Antinuclear antibodies	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ -glutamyl transpeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; HSV, herpes simplex virus.

^aTesting for herpesvirus infection should be performed at admission and repeated one or more times at 2- to 3-week intervals to detect a change in the antibody titer [5,8].

(mainly if facial edema is associated), fever, lymphadenopathy, eosinophilia, atypical lymphocytes, and signs of liver or kidney involvement. Suspicion will be higher if the patient is on treatment with drugs known to induce DRESS syndrome frequently (Table 2) [1,19,103] (LE3, GRD).

8.2. Which Laboratory Investigations Should Be Performed for the Diagnosis and Follow-up of DRESS Syndrome?

The authors of these guidelines recommend a series of laboratory investigations for diagnosis, assessment of severity, and follow-up (Table 5) and skin biopsy whenever DRESS syndrome is suspected [5,8,19,23,104] (LE4 expert opinion consensus, GRD).

Additional tests that can be performed according to the patient's symptoms include abdominal ultrasonography, chest x-ray, EKG, echocardiography, computed tomography scan of the brain, neurological evaluation, pulmonary function testing, computed tomography scan of the chest, and evaluation by various specialists (eg, nephrologist, hepatologist, and cardiologist) [79].

8.2.1. Evaluation of kidney injury

Laboratory investigations are recommended for the assessment of renal function and kidney disease (Table 5). Acute kidney injury should be assessed and its severity staged according to the KDIGO clinical practice guideline [105] (LE4 expert opinion consensus, GRD) (Table 6)

8.2.2. Evaluation of liver injury

Liver function tests should be performed (Table 5). Liver injury should be assessed and severity staged according to the DILI Expert Working Group [106] (Table 7) (LE4 expert opinion consensus, GR D).

Table 6. Staging of Acute Kidney Injury for Severity [105]

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L) OR Initiation of renal replacement therapy OR In patients <18 y, decrease in eGFR to <35 mL/min per 1.73 m ²	<0.3 mL/kg/h for ≥24 h

Table 7. Clinical Chemistry Criteria for Drug-Induced Liver Injury (DILI) and Staging DILI. Modified from Aithal, Clinical Pharmacology & Therapeutics 2011 [106]

DILI Severity Index

Degree of Severity

1. MILD
 - Elevated alanine aminotransferase (ALT)/alkaline phosphatase (ALP) concentration reaching criteria for DILI^a but bilirubin concentration <2× upper limit of normal (ULN).
2. MODERATE
 - Elevated ALT/ALP concentration reaching criteria for DILI^a and bilirubin concentration ≥2× ULN, or symptomatic hepatitis.
3. SEVERE
 - Elevated ALT/ALP concentration reaching criteria for DILI^a, bilirubin concentration ≥2× ULN, and one of the following:
 - International normalized ratio ≥1.5
 - Ascites and/or encephalopathy, disease duration <26 wk, and absence of underlying cirrhosis
 - Other organ failure considered to be due to DILI
4. FATAL OR TRANSPLANTATION
 - Death or transplantation due to DILI
 - Level of evidence, 2b (exploratory/retrospective cohort studies)

^aDILI if any of the following:

- ≥5× ULN for ALT
- ≥2× ULN for ALP (particularly with accompanying elevations in concentrations of 5'-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone disease driving the rise in ALP level)
- >3× ULN for ALT and total bilirubin exceeding 2× ULN

8.3. Confirmation of a Diagnosis of DRESS Syndrome: Scoring Systems

Different diagnostic scores have been developed to help clinicians to confirm or exclude DRESS syndrome [1,8,19].

RegiSCAR devised a scoring system for DRESS syndrome that is widely accepted and is shown in Table 8 [19]. This group has published a document on the practical application of the diagnostic score, including the specifics for evaluation of the diagnostic features of DRESS syndrome [97]. We strongly recommend the use of the RegiSCAR scoring system for diagnosing DRESS syndrome (LE3, GRD) (Table 8).

8.4. Differentiating DRESS Syndrome From Other Cutaneous and Systemic Diseases and Other SCARs

The differential diagnosis should be made with other diseases that may present with skin rash, systemic symptoms, adenopathy, and fever. These include other SCARs (SJS/TEN and AGEP) (Table 9), bacterial and viral infections (Epstein-Barr virus, CMV, measles, hepatitis virus, influenza virus, parvovirus, and HIV) [1,5,57,67,107]. Other conditions that should also be taken into account include autoimmune diseases (eg, Kikuchi-Fujimoto syndrome, Kawasaki syndrome [108],

Table 8. RegiSCAR Validation Score for DRESS Syndrome 2007 [19]^a

Score	-1	0	1	2	Min	Max
Fever ≥ 38.5 (core) or $>38^{\circ}\text{C}$ (axillary)	N	Y			-1	0
Enlarged lymph nodes (>1 cm size, at least 2 sites)		N/U	Y		0	1
Eosinophilia		N/U	700-1499/ μL 10%-19.9% (if leukopenia)	$\geq 1500/\mu\text{L}$ $\geq 20\%$ (if leukopenia)	0	2
Atypical lymphocytes		N/U	Y		0	1
Skin involvement						
– Rash extent (%BSA)		N/U	$>50\%$			
– Rash suggesting DRESS (≥ 2 of facial edema, purpura, infiltration, desquamation)	N	U	Y		-2	2
– Biopsy suggesting DRESS	N	Y/U				
Organ involvement						
L/K/Lu/M-H/Pa/Other		N/U	Y/Y/Y/Y/Y*		0	2
Resolution >15 days	N	Y			-1	0
Evaluation of other potential causes:			Y (None [+] and at least 3 [-])			
– Serology for HAV/HBV/HCV; blood culture;					0	1
– Antinuclear antibody; Chlamydia/Mycoplasma						
Total score	<2, Excluded; 2-3, Possible; 4-5, Probable; >5, Definite				-4	9

Abbreviations: N, no; Y, yes; U, Unknown; L, liver; K, kidney, Lu, lung; M, muscle; H, heart; Pa, pancreas.

^aSee reference [97] and text for details about evaluation of organ involvement

Still disease, and acute cutaneous lupus erythematosus), hypereosinophilic syndromes [109], Sézary syndrome, and angioimmunoblastic T-cell lymphoma [27,110].

Taking photographs of the skin lesions and the whole body surface (to evaluate the BSA affected) is of the utmost importance. Sending the images to an expert center may facilitate an earlier diagnosis. This approach also allows a better retrospective evaluation and validation of the case.

It is important not to forget the overlap between SCARs. These cases, while very rare, fulfil the criteria for a definitive or probable diagnosis of at least 2 of AGEPE, DRESS syndrome, and SJS-TEN [96,103,113]. An overlap between maculopapular exanthema and DRESS syndrome has also been identified and characterized [114].

Drug-induced eosinophilia may occur with or without other manifestations of adverse drug reactions, such as exanthema or drug fever. Eosinophilia alone requires close observation, because resolution usually occurs within a week or two of drug cessation [17].

9. Identifying the Culprit Drug

9.1. Assessment of Causality Using the Spanish Pharmacovigilance System Algorithm

Many methods have been proposed to assess the causal relationship between an adverse event and a medication taken by a patient [115-117]. The parameters evaluated in the algorithm of the Spanish Pharmacovigilance System

(ASPS) [118] are shown in Table 10. The final case evaluation of each drug is listed as not related (improbable, conditional) or related (possible, probable, or definite).

Whenever possible, we must interview the patient and/or their relatives to obtain more details of all the drugs taken, including over-the-counter drugs and the consumption of herbal or homeopathic products, and dechallenge or rechallenge information (if available). All drugs taken during exposure windows must be recorded (including chronology of drug intake, dose, indication, and clinical course after withdrawal).

The chronology is considered suggestive if the drug was initiated less than 6 months previously and stopped less than 14 days before the index day [23]. The index day is considered to be the day on which prodromal symptoms/signs first occurred, or in their absence, the day of acute rash [17].

We strongly recommend calculating the index day and performing a causality assessment according to the ASPS criteria (Table 10) as soon as DRESS syndrome is suspected (with a score of at least “possible” according to the RegiSCAR criteria shown in Table 8). All drugs in the category of “possible to definite” should be stopped and prohibited provisionally (LE4 expert opinion consensus, GRD).

When a drug is classed as being associated with DRESS syndrome in Spain, a complete adverse reaction report must be submitted to the pharmacovigilance center of the Autonomous Community in order to conduct a second evaluation and to be included in the Spanish Pharmacovigilance System Registry.

Table 9. Differential Diagnosis of DRESS, SJS/TEN, AGEP, and Other Cutaneous Diseases^a

	DRESS Syndrome	SJS/TEN	AGEP	Hyper eosinophilic Syndrome	Kawasaki Disease	Still Disease
Typical onset of eruption	2-6 wk	1-3 wk	Hours to 2 d (antibiotics) 4-12 d (other drugs)			
Cutaneous lesions	Facial edema Morbilloform/maculopapular exanthema with scaling Erythroderma/exfoliative dermatitis Rare blisters Rare pustules Mucosal lesions infrequent Purpuric eruption Infiltrated erythema Nikolsky (-)	Dusky red, coalescent macular exanthema Atypical target lesions Bullous and blister lesions Mucosal involvement in nearly all cases Nikolsky (+) Epidermal necrosis: - <10%: SJS - 10%-30%: overlap - SJS/TEN - >30% TEN	Several dozen small nonfollicular pustules on a background of widespread edematous erythema. Predominant in main skinfolds. Mucosal involvement rare. No blisters Nikolsky (-)	Urticaria, angioedema, morbilliform exanthema, papular or nodular infiltrate	Conjunctival involvement, cleft palate, strawberry tongue, palmar erythema, hand edema, periungual desquamation, and polymorphous rash	Salmon colored bumpy rash
Skin biopsy	Nonspecific: Lymphocytic infiltrate. Eosinophils, dermal edema may be present	Epidermal necrosis with full thickness loss of epidermis	Subcorneal and/or intraepidermal pustules and perivascular infiltrate with neutrophils and edema of the papillary dermis			
Hematological abnormalities						
- Eosinophilia	Yes	No	No	Yes (>1500/ μ L) Possible	No	Possible
- Atypical lymphocytes	Yes	No	No		No	No
			Leukocytosis with neutrophilia (>7000/ mm^3)			
Systemic involvement						
- Lymphadenopathy	Yes	No	No	Yes	Yes	Yes
- Hepatitis	Yes	Yes	Possible but rare	Yes	Possible	Possible
- Other organs	Interstitial nephritis, pneumonitis, carditis, Pancreatitis, bone marrow	Tubular nephritis, tracheobronchial necrosis	Internal organ involvement Transient prerenal failure	Carditis, pneumonitis, encephalopathy, diarrhea, vomiting, and abdominal pain	Cardiovascular abnormality, diarrhea, vomiting, and abdominal pain	Pleurisy, pericarditis

^aModified from Fernandez et al. Tratado de Alergología 2016 [1, 12, 23, 111].

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS/TEN, Steven-Johnson syndrome/toxic epidermal necrolysis.

Table 10. Algorithm of the Spanish Pharmacovigilance System [118]

Algorithm of the Spanish Pharmacovigilance System

- Chronology, referred to as the interval between drug administration and effect:
 - Compatible (score +2)
 - Not fully supported (+1)
 - No information (0)
 - Incompatible chronology (-1)
 - Specific case of withdrawal syndrome (+2).
- According to the literature, defining the degree of knowledge of the relationship between the drug and the effect:
 - Known in the reference literature (+2): recorded in the summary of product characteristics, or the adverse drug reaction was found in clinical trials, or the association has been found in cohort studies or in case-control studies.
 - Occasionally known (+1): only found in published case reports.
 - Unknown (0)
 - Unrelated to the drug (-1): presence of confounding variables. Confounding variables appear when the estimate of a measure of association between the drug exposure and health status is distorted by the effect of ≥ 1 other variables that are also risk factors for the outcome of interest.
- Evaluation of drug withdrawal:
 - Improvement on withdrawal (+2)
 - No improvement on withdrawal (-2)
 - Not withdrawing does not improve the effect (+1)
 - Not withdrawing improves the effect (-2)
 - No information (0)
 - Death or irreversible effect (0)
 - Not withdrawn, but there is a tolerance effect (+1)
 - Not withdrawn, improves with symptomatic treatment (+1)
- Rechallenge effect:
 - Reappearance of the positive effect (+3)
 - Negative, the effect does not reappear (-1)
 - No re-exposure or no information (0)
 - Death or irreversible effect (0)
 - Positive for a different agent with the same active ingredient or parent drug (+1)
- Alternative causes:
 - Yes, a medical condition or other drugs (-3).
 - Similar likelihood for drug and other causes (-1)
 - Missing information (0)
 - No alternative cause (+1)

Categories according to final score:

Not classified (lack of data) /Improbable <0/Conditional 1-3/Possible 4-5/Probable 6-7/Definite>8

9.2. Causality Assessment by the Allergist

9.2.1. Clinical History

A detailed clinical history is an essential first step towards an accurate diagnosis of DRESS syndrome [119]. The history must be meticulous, with the full medical background of the patient and the family history of SCARs.

A timeline chart should be constructed to bring together signs and symptoms (eg, fever, eosinophilia, cutaneous symptoms, increase in transaminases), time of onset and resolution, and all of the drugs taken with a latency period that is compatible with DRESS syndrome (ie, initiated less than 6 months previously and stopped less than 14 days

Table 11. Cut-off Values for Lymphocyte Transformation Test Positivity According to Pichler and Tilch [122]

Drug	Result	SI
β-Lactams	Negative	<3
	Positive	>3
Iodinated contrast media	Negative	<4
	Positive	>4
Other drugs	Negative	<2
	Doubtful	2-3
	Positive	>3

Abbreviation: SI, stimulation index.

before the index day). The details recorded of the drugs administered should include formulation, dose, route, timing of administration and effect of stopping treatment [23]. This approach and the result of applying the ASPS (Table 10) will enable us to identify the suspect drugs with which to perform our allergy work-up. It is important to take into account that in 18% of cases of DRESS syndrome in the multicenter study by Barbaud et al [120] there were at least 2 different culprit drugs.

9.2.2. Assessment of Causality Using In Vitro Allergy Tests

In vitro diagnostic tests have the advantage over in vivo tests of being absolutely safe. They are based on the property of antigen-specific T cells being activated upon stimulation with the nominal antigen in sensitized patients [121]. They should not be performed before a minimal time interval of 4-8 weeks after the reaction and at least 4 weeks after stopping treatment with systemic corticosteroids. Analysis in the first 6 months to 1 year is recommended, although subsequent test results may be positive [122].

A positive result reflects specific sensitization to the test drug, which is a risk factor but does not prove causality. However, it can support the diagnosis and pinpoint the responsible agent if the patient took several drugs.

The lymphocyte transformation test (LTT) is the most widely used in vitro test. Detailed technical aspects of the LTT have been described [122]. A stimulation index (SI) is calculated as the ratio of ^3H incorporated by drug-stimulated cultures and baseline incorporation of ^3H by unstimulated cells. An SI ≥ 2 is considered positive, with some exceptions (Table 11).

Small studies involving few patients and case reports pointed to the usefulness of LTT in the evaluation of the cause of DRESS syndrome [98,123-129]. Pichler and Tilch [122] reported positive LTT results in more than 50% of cases of DRESS syndrome. Cabañas et al [130] reported data on the sensitivity (73%) and specificity (82%) of LTT in the recovery phase of DRESS syndrome in a series of 41 patients. Comparison of skin tests and LTT confirms a higher sensitivity and specificity of LTT in DRESS syndrome. LTT showed high sensitivity and specificity for anticonvulsants (100% and 100%; $P=.008$), antituberculosis drugs (87.5% and 100%; $P=.004$), and β-lactams (73% and 100%; $P=.001$) [130]. Performance of LTT requires a specialized laboratory and skilled personnel. Laboratories have reached a consensus regarding the protocol and cut-offs for positivity, although there are no standard values for each drug [122].

The fluorescent dye 5,6-carboxyfluorescein diacetate succinimidyl ester may be used as an alternative to the radioactive label for LTT; however, very few reports have been published, and there is no consensus on the analysis of the SI [123,131]. No agreement has been reached on the cut-off for positivity in flow cytometry analysis of CD69 upregulation, as few cases have been published [132].

The analysis of cytokine release by enzyme-linked immunosorbent assay or enzyme-linked immunospot assay (ELISPOT) upon drug-induced stimulation of peripheral blood mononuclear cells is also used by several laboratories. However, no consensus exists on the protocol or criteria for positivity. Positive ELISPOT assays for IFN- γ production have been reported in DRESS syndrome [50,133-135].

At present, LTT is the best documented assay for in vitro diagnosis of DRESS syndrome [136,137]; the ENDA/EAACI Drug Allergy Interest Group position paper indicates that it might be advisable to perform LTT before in vivo tests in severe reactions with a suspected T-cell mechanism [136].

We strongly recommend that LTT and/or ELISPOT should be available in reference centers managing DRESS syndrome to identify the culprit drug. The tests should be performed before skin tests and incubation with all the drugs indicated by the allergist and with the category of “possible to definite” according to the ASPS [136,137] (LE3, GRD)

9.3.3. Assessment of Causality Using In Vivo Allergy Tests

Skin tests (mainly delayed intradermal reaction) and patch tests are of value in the investigation of T cell-mediated hypersensitivity reactions such as DRESS syndrome [120,138-140].

9.3.3.1. Patch tests

Patch tests can prove helpful, with positive results reported in 32% [141] to 64% of cases in a French multicenter study [120]. Positivity depends to a large extent on the drug. Patch tests are very useful with anticonvulsants [120,141], antibiotics (highest reactivity to β -lactams and quinolones) [120,139], and proton pump inhibitors [120]. Patch tests always yield negative results with sulfasalazine and allopurinol [120,141].

Results from the largest patch testing series in DRESS syndrome showed this to be a safe procedure with no adverse reactions [120,141-143].

Patch tests should be performed according to European guidelines for skin tests [138,144-146] for a minimum of 4 to 6 weeks after the acute reaction [147] and 4 weeks after stopping treatment with systemic corticosteroids or immunosuppressive therapy [144,148]. Topical corticosteroids should not be applied to the patch test area in the week before the test [144]. Patch testing should be performed 2-6 months after recovery [120] (LE3, GRD).

All culprit drugs suspected according to the clinical history, especially those with the ASPS category of “related”, should be included (LE4 expert opinion consensus, GRD). Testing of chemically or pharmacologically related drugs may provide information on cross-reactivity [133,149,150], and testing available metabolites may improve the results [149] (LE3, GRD).

We recommend using a 10% concentration in petrolatum with the active ingredient. When the commercialized form of the drug is used, it is recommended to test up to a 30% concentration of the final product [120,144] (LE3, GRD).

Concentrations and vehicles previously considered as most adequate for certain drugs should also be chosen. As for β -lactams, European guidelines and the authors of the present guidelines suggest a concentration of 5% in petrolatum [151,152]. A list with drug concentrations and vehicles used in reported cases of DRESS syndrome is provided in Supplementary File 1 of the online material.

The authors of these guidelines strongly recommend not testing different concentrations of the same suspect drug or using different vehicles simultaneously for safety reasons, because systemic reactions reported after patch tests were the result of such an approach [111,133,153,154] (LE3, GRD).

Special caution is recommended in immunocompromised patients [153,155,156], and testing should start at lower concentrations (LE3, GRD).

Patch tests should be preceded by LTT or performed as the first-line approach if in vitro tests are not available [136] (LE3, GRD).

9.3.3.2. Prick and intradermal tests

If a patch test yields a negative result and a suitable injectable form is available, then prick testing should be performed. If this is negative, subsequent intradermal testing is recommended [98,120,138,157] (LE3, GRD).

Delayed positive reactions to skin prick tests have occasionally been described in patients with DRESS syndrome [120]. Immediate readings should be taken at 20 minutes and delayed readings at 6 and 24 hours according to the European guidelines [145]. The higher sensitivity of intradermal tests compared with patch tests has been reported [120], mainly in reactions to β -lactams [158].

Although recent studies and case reports support the safety of prick and intradermal tests in DRESS syndrome [42,98,120,157,159], isolated systemic reactions after intradermal tests [120] and prick testing have been reported in HIV-infected patients [155].

Therefore, we recommend that for intradermal testing, the drug should be initially administered at the highest dilution (usually 1/100 of the skin prick test concentration) [145,151], the interval between tests should be extended [145], different concentrations should not be tested on the same day, and special precautions should be adopted with HIV-infected patients [155] (LE3, GRD).

More precise guidelines have been drafted for nonimmediate β -lactam reactions including SCARs [145,151,158].

9.3.3.3. Controlled re-exposure Test

Since DRESS syndrome is a severe and sometimes life-threatening condition, challenge testing with the suspected culprit drug and cross-reactive drugs is contraindicated [138,147,160].

A search of the literature reveals cases of DRESS syndrome induced by β -lactams [159,161,162], amikacin [133], and antituberculosis drugs [155,163] in which controlled re-exposure tests were performed under special circumstances.

Controlled re-exposure tests with β -lactams

We recommend controlled exposure testing with an alternative β -lactam (not the culprit) if the benefit outweighs or at least equals the risk. This approach should be guided by the allergy study [98,159,161] (LE3, GRD).

The graded challenge exposure test recommended by Romano et al [158] for nonimmediate β -lactam allergic reactions is an initial dose of 1/100 of the therapeutic one. In cases with negative results 3 days to 1 week later, a dose of one tenth is given and, if the result is again negative, a full dose can be given after the same interval as used before. We recommend this approach if controlled exposure testing is indicated and with clinical and laboratory monitoring (LE4 expert opinion consensus, GRD).

Controlled re-exposure tests with antituberculosis drugs

In special cases of DRESS syndrome induced by 3 or 4 first-line antituberculosis drugs, challenge testing may be indicated for adequate management of tuberculosis. The availability of in vivo and ex vivo testing to guide rechallenge choices would be extremely helpful in these settings [147]. Two main series of DRESS syndrome induced by antituberculosis drugs have been reported [155,163]. In both series, all antituberculosis drugs were stopped until normalization of skin findings and laboratory values, and then careful re-exposure to each drug was performed independently [155,163]; in the series of Lehloenya et al [155] in particular, this approach was followed after performing allergy tests.

In reference to rechallenge with drugs in patients with SCARs induced by HIV and antituberculosis drugs in low- and middle-income countries, a recent international consensus document [147] stated that if the risk of morbidity and mortality from the disease outweighs or at least equals the risks from the drug reaction, the risk-benefit ratio sways toward sequential rechallenge with potentially implicated drugs. Allergy testing to guide rechallenge choices would be extremely helpful [147] (LE3, GRD).

Given the high specificity and sensitivity of LTT [130,164], we recommend this approach with antituberculosis drugs as a first step in the management of DRESS syndrome induced by these agents followed by patch tests and prick and intradermal tests according to the previous results (LE4 expert opinion consensus, GRD).

Controlled exposure tests should be performed after consulting with an infectious disease specialist if there are no adequate second-line alternatives and guided by the negative results in the allergy tests. The rechallenge should be sequential and cumulative when symptoms resolve and laboratory parameters return to normal [155,163]. Clinical and biological surveillance (temperature and blood tests) should be performed before each administration (LE4 expert opinion consensus, GRD).

As for doses, we recommend the criteria of the French Investigators of Skin Adverse Reactions to Drugs [165], ie, to rechallenge with 1 drug each time, starting with 10^{-2} on day 1, 10^{-1} on day 3, a full dose on day 5, and treatment on day 7 (LE4 expert opinion consensus, GRD).

As for other groups of drugs, the authors of the present guidelines recommend controlled re-exposure tests only when different drugs are involved in the reaction and after negative in vitro tests, if available, and in vivo tests, considering that the benefit of treatment with the drug outweighs or at least equals the risk of morbidity and mortality from the drug reaction (LE4 expert opinion consensus, GRD).

Careful risk-benefit assessment in discussion with the patient and informed consent is strongly recommended (LE4 expert opinion consensus, GRD).

We suggest beginning at 10^{-5} to 10^{-3} of the full dose and gradually increasing 10-fold with an interval of 3 days to 1 week at 10^{-2} and 10^{-1} until the full dose is reached with clinical and laboratory monitoring before each dose. The drug can be reauthorized if the results are negative (LE4 expert opinion consensus, GRD).

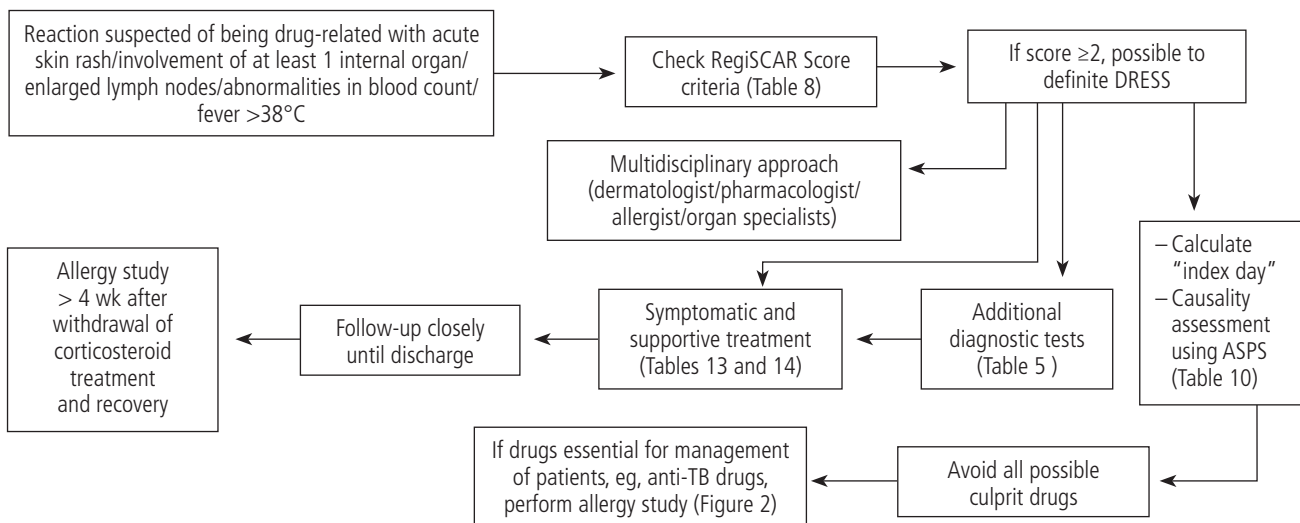


Figure 1. Management of DRESS in the acute phase. DRESS indicates drug reaction with eosinophilia and systemic symptoms; ASPS, algorithm of the Spanish Pharmacovigilance System.

10. Management and Treatment Recommendations

Management of DRESS syndrome in the acute and recovery phases is summarized in Figures 1-3.

10.1. Withdrawal of the Culprit and Cross-Reacting Drugs

Identification and prompt withdrawal of the offending drug is the mainstay of treatment for patients with DRESS syndrome. It may be enough to obtain remission in some

cases [3]. Prognosis is better with earlier cessation [3,76]. All potentially involved drugs should be stopped. The patient should be educated about the need for a strict avoidance of the offending drug, as well as cross-reacting drugs in the future. Patients who recover from DRESS syndrome may have an increased risk of reaction, even to unrelated drugs; this risk appears to be higher in the first few months following the occurrence of DRESS syndrome [166] and also during the acute phase. Empiric treatment with antibiotics (especially amoxicillin) and NSAIDs should be avoided [167].

Below, we provide specific recommendations for management of DRESS syndrome induced by various groups

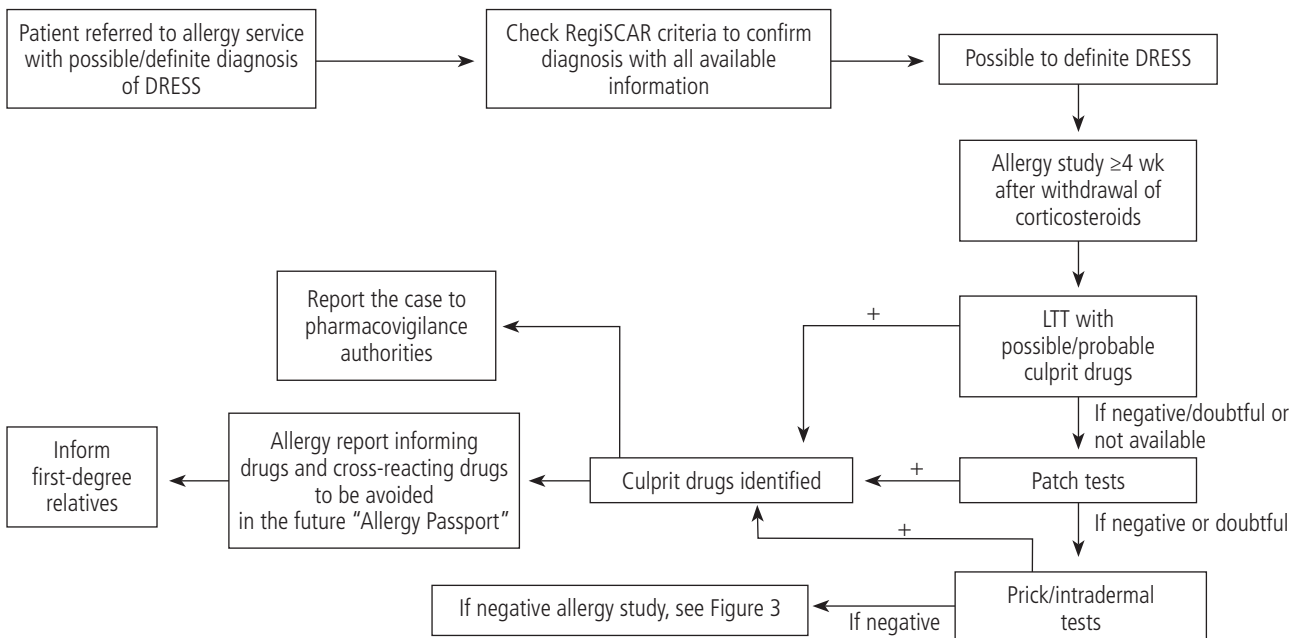


Figure 2. Management of DRESS in the recovery phase by the allergist (part 1). DRESS indicates drug reaction with eosinophilia and systemic symptoms; LTT, lymphocyte transformation test.

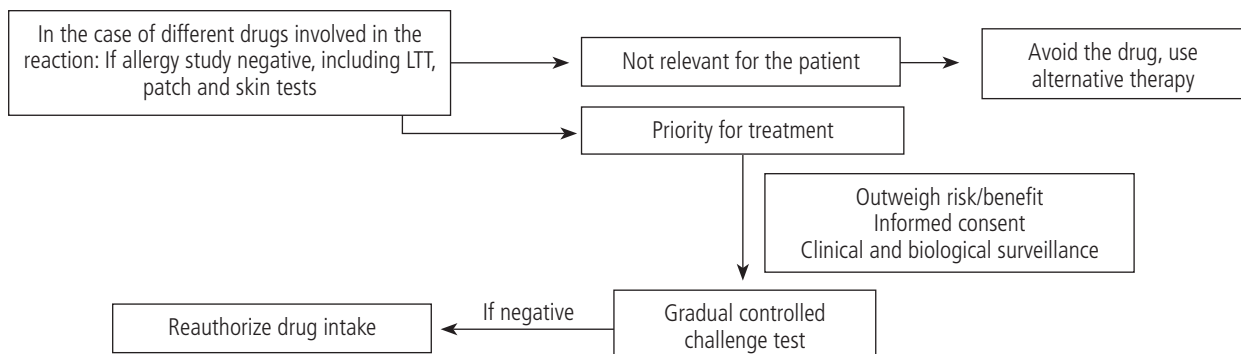


Figure 3. Management of DRESS syndrome in the recovery phase by the allergist (part 2). DRESS indicates drug reaction with eosinophilia and systemic symptoms; LTT, lymphocyte transformation test.

of drugs (eg, which drugs should be prohibited, available alternatives).

10.1.1. Anticonvulsants

Cross-reactivity between aromatic anticonvulsant drugs (eg, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, felbamate, zonisamide, and primidone) is well documented, varying between 40% and 80% [25,168,169]. These agents should be avoided in the future for antiepileptic drug therapy, as should tricyclic antidepressant agents, which cross-react mainly with amitriptyline [170-171]. Nonaromatic anticonvulsant drugs (gabapentin, topiramate, tiagabine, ethosuximide, pregabalin, and valproic acid) are considered safe [169], as are benzodiazepines and vigabatrin. Given that valproic acid and divalproex are hepatotoxic, caution is advised in patients with liver injury [172,173].

An allergy work-up may prove helpful for identifying the anticonvulsant culprit drug and studying cross-reactivity [173]. It can also guide the introduction of safe alternatives (LE3, GRD).

10.1.2. β -Lactam antibiotics

Until more evidence becomes available, in cases of β -lactam-induced DRESS syndrome, we advise against the administration of β -lactams as a group and performing an allergy study that will guide our decision if the patient needs a drug from this group (see also “*Controlled re-exposure tests with β -lactams*” above) (LE4 expert opinion consensus, GRD).

10.1.3. Sulfonamide group

Cross-reactivity between sulfonamide drugs is controversial [174,175]. However, for patients who experience a serious drug reaction with a specific sulfonamide antimicrobial, cross-reactivity would be expected for sulfonamide antimicrobials as a class [176] and should be avoided [5], as should sulfasalazine [176].

Dapsone is a sulfone drug and cross-reactivity could also occur with sulfonamide antimicrobials. However, it is often tolerated in HIV-infected patients with a history of intolerance to sulfonamide antibiotic [177]. The allergy work-up enables us to assess cross-reactivity between sulfa drugs in a specific patient and can guide our decisions on therapy [178].

Another important concern about dapsone is that this drug can persist for up to 35 days in organs; therefore, slow tapering of corticosteroid therapy over at least 1 month with close monitoring of organ function is required in the management of dapsone-induced DRESS syndrome [179].

10.1.4. Antituberculosis drugs

The authors of this guideline provide recommendations on the management of antituberculosis drug-induced DRESS in Table 12.

10.1.5. Iodinated radiocontrast media (IRCM)

DRESS induced by IRCM is rarely reported [180-182], and it is difficult to be aware of it [180]. Cross-reactivity between

Table 12. Management of DRESS Syndrome Induced by Antituberculosis Drugs, Expert Consensus

- 1 Stop all antituberculosis drugs until eosinophilia has almost disappeared and rash and toxic hepatitis have resolved [155,156,163] (LE3, GRD)
- 2 Symptomatic treatment according to treatment guidelines^a
- 3 Perform LTT in the acute phase before starting treatment with corticosteroids, if possible, to identify the culprit drug [130,164]
Perform LTT [130,164] and allergy work-up in recovery phase (LE4, GRD)
- 4 Start treatment with alternative antituberculosis drugs if possible and/or oral controlled re-exposure (see also in section Controlled re-exposure tests with antituberculosis drugs), independently with first-line agents after negative allergy tests, starting with those less often involved in DRESS syndrome induced by antituberculosis drugs and according to the indications of the infectious disease specialist (LE4 expert consensus, GRD)

^aSee Table 14. Stepwise Spanish Guidelines for DRESS Management and Treatment

IRCM is possible, as is the case with other nonimmediate reactions induced by these agents [182].

We recommend performing allergy tests to identify the specific culprit and to provide an alternative agent that could be safely administered in case of absolute necessity (LE4 expert opinion consensus, GRD).

Table 13. Supportive Measures in the Management of DRESS Syndrome^a

- Hospital admission or outpatient monitoring in mild cases (with possibility of close monitoring every 48 h) (see also Table 14) (evaluate admission in critical care unit)
- Fluid and electrolyte replacement, nutritional supplementation
- Hemodynamic balance
- Life support measures
- Gastric protection
- Anticoagulation prophylaxis of venous thromboembolism for adult inpatients if needed
- Pain control
- Fever management
- Avoid empiric NSAIDs (during acute period)
- Avoid empiric antibiotic therapy. Avoid amoxicillin (during acute period)
- Skin care and topical treatment
- Clinical and laboratory monitoring of organ involvement
- Organ specialist consultation to provide timely supportive and medical measures to prevent organ failure (see also Table 14)

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug.

^aAdapted from Clin Mol Allergy, 2016 [3,8,14,23,27,187,188].

Table 14. Stepwise Spanish Guidelines for Management and Treatment of DRESS Syndrome: Expert Consensus

We recommend early management measures (see also Figure 1):

- Prompt withdrawal of suspected and cross-related drugs
- Avoid empiric NSAIDs and antibiotics (specially amoxicillin) [8,188]
- Evaluation by a multidisciplinary specialist group (dermatologist/pharmacologist/allergist)
- Assessment of cutaneous and organ involvement: evaluation for signs of severity
- Hospitalization “except mildest nonserious cases” with possibility of close follow-up and laboratory and clinical monitoring every 48 h (LE4 expert opinion consensus, GRD)
- Supportive therapy
 - Antipyretics, H₁-antihistamines, emollients, other (see Table 13).

A. If nonserious DRESS syndrome: patients with no organic involvement or only stage 1 DILI [106] or liver involvement below threshold for the definition of DILI (Table 7) (or stage 1 AKI [105] (Table 6):

- Symptomatic treatment:
 - Topical corticosteroids (very high or high potency^a) 2-3 times a day for 1 wk [27,104,189,190,191] (LE2+, GRC)
 - Close CLINICAL and ANALYTICAL follow up (clinical control every 24 h and analytical control at 48-72 h) for reevaluation of severity.

B. If serious DRESS syndrome: patients with moderate/severe organ involvement: stage ≥ 2 DILI [106] (Table 7) or grade ≥ 2 AKI [105] (Table 6), hemophagocytosis, lung, cardiac or other internal organ involvement or initially nonserious DRESS with unfavorable outcome:

- *We strongly recommend consultation with an organ specialist*
- Consider ICU admission in severe cases
- We strongly recommend systemic corticosteroid treatment:
 - If renal injury stage ≥ 2 AKI (Table 6):
 - Oral prednisone 0.8-1 mg/kg/d for 2-3 wk; tapered down as soon as renal function improves for 4-6 wk (<8 wk) [192] (LE2+, GRC)
 - If liver injury stages 2 or 3 or 1 DILI (Table 7) [106] but without improvement or worsening after 1 wk of culprit drug withdrawal under close surveillance by hepatologist [193,194] (LE2+, GRC)
 - Oral methylprednisolone 60-120 mg/d or prednisone 40-60 mg/d 3-5 d and then 20 mg/d and taper by 5-10 mg weekly [193] (LE2+, GRC)
 - If lung or other organ injury oral prednisone or prednisone equivalent 0.5-2 mg/kg/d [3,27,58,104] until clinical improvement and normalization of laboratory parameters are obtained and then tapered 10 mg/wk over the ensuing 6-12 wk [8,14,27,169] (LE3, GRD)
 - If relapse when tapering corticosteroids, return to previous dose and taper more slowly; if this is not effective, then use sparing agents: cyclosporine [195,196] or IVIG [76,197] (LE3, GRD)
- *In absence of control with corticosteroids or if corticosteroids are contraindicated:*
 - Cyclosporine [27,195,198,199,200,201] 4-5 mg/kg/d for 5-7 d (LE3, GRD)
 - Tapering 50 mg every wk when clinical improvement for approximately 6 wk (LE3, GRD)
 - Others with lower evidence:
 - IVIG 2 g/kg over 5 d combined with systemic corticosteroids [3,76,104,202-5] (LE3, GRD)
 - Plasmapheresis (especially if DRESS with multiple organ injury) [169, 206-8] (LE3, GRD)
- *In absence of response to previous treatments:*
 - Cyclophosphamide [209-10] (LE3, GRD)
- *If confirmation of major viral reactivation and life-threatening signs or viral reactivation suspected of contributing to severe complications (eg, encephalitis, hemophagocytosis, or severe erosive colitis):*
 - Add 1 antiviral to the other treatments [27,104,211-2] (LE3, GRD)
 - Treatment for at least 1 wk. Perform viral load weekly; when 2 consecutive negative results, stop antiviral (LE4 expert consensus, GRD)
 - Ganciclovir iv: 5 mg/kg
 - Valganciclovir po: 900 mg/12 h
- *Organ-specific specialist consultation. Special concern for renal replacement therapy and liver transplantation. (See also Table 15 and Table 16, respectively, for management of renal and liver injury)*

Abbreviations: AKI, acute kidney injury; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic syndromes; GR, grade of recommendation; IVIG, intravenous immunoglobulin; LE, level of evidence; NSAID, nonsteroidal anti-inflammatory drugs.

^aTopical corticosteroids of very high potency (betamethasone dipropionate cream or ointment 0.05%; clobetasol 0.05%; or halobetasol propionate cream or ointment 0.05%) or high potency (triamcinolone acetonide ointment 0.5%; methylprednisolone aceponate cream, lotion, or solution 0.1%; and furoate mometasone ointment 0.1%)

10.1.6. Allopurinol

Allopurinol is a frequent culprit of DRESS syndrome. Febuxostat, whose chemical structure is completely different to that of allopurinol, was expected to be a safe option for treatment of affected patients. Nevertheless, cases of febuxostat-allopurinol cross-reactions, probably due

Table 15. Treatment of Acute Interstitial Nephritis in DRESS Syndrome: Expert Consensus [105,192,213-217]

1. Rapid identification and discontinuation of the offending drug is the cornerstone of the treatment of drug-induced AIN.
2. Early administration of corticosteroids (unless rapid renal function recovery after drug withdrawal [less than 3-5 d], in the case of a stage 1 AKI) (see Table 6 for staging). Renal function must be monitored every day.
 - If renal function does not recover after 3-5 d or stage 2-3 AKI, the patient must be sent to nephrology for evaluation:
 - Start oral prednisone 0.8-1 mg/kg/d for 2-3 wk, tapered down as soon as renal function improves for 4–6 weeks (< 8 wk).
 - Patients who relapse after discontinuation of corticosteroids or do not respond to corticosteroid therapy (after other causes of AIN have been excluded) must be evaluated for change of immunosuppressive drugs.
 - The nephrologist may indicate renal replacement therapy.

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; DRESS, drug reaction with eosinophilia and systemic symptoms.

Table 16. Treatment of Liver Injury in DRESS Syndrome: Consensus Experts^a

- Prompt discontinuation of the suspected drugs, supportive, and symptomatic therapy. Avoid hepatotoxic drugs and manage in conjunction with the hepatologist. Monitor liver function every day or every other day.
- If mild DILI or stage 1 [106] or below threshold for the definition of DILI (see Table 7): Follow as indicated in the previous point and if favorable outcome in less than 1 wk, continue monitoring and close follow-up [193,194] (LE3, GRD).
- If moderate or severe DILI (stages 2 or 3) (Table 7) or initially milder stages but without improvement or worsening after 1 week of withdrawal of the culprit drug, treatment with corticosteroids is recommended under surveillance by a hepatologist [193,194] (LE3, GRD).
Methylprednisolone 60-120 mg/d or prednisone 40-60 mg/d 3-5 d and then 20 mg/d and taper to 5-10 mg weekly [82,83].
- In the absence of improvement: Cyclosporine or consider other immunosuppression.

Abbreviations: DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia; GR, grade of recommendation; LE, level of evidence.
^aNote: At the earliest signs of liver failure (INR >1.5, development of ascites, or any grade of hepatic encephalopathy), prompt referral to a liver transplant unit is indicated [218].

to a nonimmunological mechanism, have been reported [183,184]. Patients with renal insufficiency under treatment with febuxostat should be closely monitored, especially if the patient is hypersensitive to allopurinol [184] (LE4 expert opinion consensus, GRD).

10.1.7. Nonsteroidal antiinflammatory drugs (NSAIDs)

DRESS induced by an NSAID is a T cell-mediated reaction in which cross-reactivity with NSAIDs belonging to other groups is not expected [185,186].

Guidelines for the allergy work-up in delayed hypersensitivity reactions induced by NSAIDs have been published elsewhere [186]. If the allergy work-up reveals a specific NSAID to be the culprit drug, the recommendation is to avoid the culprit NSAID and drugs from a chemically related group (LE4 expert opinion consensus, GRD).

10.2. Supportive Treatment

Hospitalization is recommended for all patients except in mild cases, with the possibility of close clinical and analytical follow up every 48 hours [8,14] (LE4 expert opinion consensus, GRD).

Management depends on the severity of the manifestations. Supportive therapy should be provided to stabilize the patient [3]. Those with erythroderma, exfoliative dermatitis, and overlap SJS-TEN require fluids, electrolytes, nutritional support, and even specialized treatment in intensive care or burn units. Cardiac failure may occur [23]. Additional measures include a warm and humid environment and gentle skin care with warm baths/wet dressings and emollient [27].

Recommended supportive measures are shown in Table 13.

10.3. Symptomatic Treatment

A review and update document of the different symptomatic treatments used for DRESS is shown in the online material (File 2), as is the classification based on evidence level regarding treatment with corticosteroids (File 3) and other treatments (File 4).

10.4. Stepwise Spanish Guidelines For Management and Treatment of DRESS Syndrome. Expert Consensus

As an expert committee on adverse drug reactions of the SEAIC and of the consortium PIELenRed and after the review of the most recent scientific publications for the therapeutic management of DRESS syndrome, we make the recommendations that are shown in Table 14.

Specific management of renal and liver injury are also addressed in Tables 15 and 16, respectively.

11. How to Prevent DRESS Syndrome

Primary and secondary prevention recommendations are shown in Table 17 and Table 18, respectively.

Table 17. Primary Prevention of DRESS Syndrome

- Pre-prescription HLA screening in identified risk populations with specific drugs in which different studies have proved their usefulness and yield:
 - Allopurinol: HLA B* 58:01 screening in Han Chinese, Thai, and Korean populations and descendants, especially if chronic kidney disease is present. In the case that no HLA-B*5801 genotyping is available, the benefits should be thoroughly assessed and outweigh the possible higher risks before starting therapy [147,219,220] (LE1, GRA)
 - An alternative to allopurinol, such as febuxostat or probenecid should be offered to these patients [221].
 - Carbamazepine: HLA*31:01 screening in Caucasian European patients and patients of Japanese origin. If positive for this allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks [222] (LE1, GRA)
 - Phenytoin and lamotrigine: HLA-A*24:02 has been associated with DRESS syndrome induced by phenytoin or lamotrigine in the Spanish population. The authors of these guidelines recommend screening in the Spanish population with limited evidence [223] (LE4, GRD)
 - Dapsone: HLA-B*13:01 screening in patients of Asian descent [41,147,219] (LE1, GRA)
 - Abacavir: HLA-B*57:01 screening to prevent abacavir hypersensitivity syndrome (a DRESS-like syndrome) already in routine HIV clinical practice in developed countries [147,225] (LE1, GRA)
- Avoid unnecessary treatments.

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; GR, grade of recommendations; HLA, human leukocyte antigen; LE, level of evidence.

Table 18. Secondary Prevention of DRESS. Expert Consensus

- Correct identification of culprit drugs through allergy study.
- A detailed medical report shall be produced indicating clearly which drugs to avoid in the future (as well as those with cross-reactivity) and which alternative drugs will be safely tolerated by the patient
- The patient will carry an allergy passport and a medical allergy report to be shown when attending medical facilities.
- Drug allergy alerts must be recorded in the electronic medical history.
- Avoidance of the causative drug should also be recommended to first-degree family members of patients with DRESS because of genetic factors.
- Any case of drug-induced DRESS must be notified to pharmacovigilance agencies.
- Promoting large collaborative networks researching projects on DRESS and including the cases in national and international registries to promote wider analysis and progression in the knowledge of DRESS and other SCARs is strongly recommended

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reaction.

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Conflicts of Interest

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