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REVIEW

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Patch testing in drug reaction with eosinophilia and systemic symptoms (DRESS): A literature review

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Abstract

The literature on positive patch test results in drug reaction with eosinophilia and systemic symptoms (DRESS) is reviewed. One hundred and five drugs were identified that have together caused 536 positive patch tests in 437 DRESS patients. By far, the most reactions (n = 145) were caused by carbamazepine, followed by amoxicillin, isoniazid, phenytoin, ethambutol, fluindione, phenobarbital, rifampicin, and ceftriaxone; 43 drugs each caused a single case only. The drug classes causing the highest number of reactions were anticonvulsants (39%), beta-lactam antibiotics (20%), antituberculosis agents (11%), non-beta-lactam antibiotics (6%), and iodinated contrast media (5%). The sensitivity of patch testing (percentage of positive reactions) is high for anticonvulsants (notably carbamazepine), beta-lactam antibiotics (notably amoxicillin), and, possibly, iodinated contrast media. Allopurinol and sulfasalazine frequently cause DRESS but never give positive patch tests. Patch testing in DRESS appears to be safe, although mild recurrence of DRESS symptoms, mostly skin reactions, may not be rare. Multiple drug hypersensitivity was found to occur in 16% of all patients, but it is argued that the true frequency is higher. Clinical aspects of DRESS, including diagnosing the disease and identifying culprit drugs (patch tests, intradermal tests, in vitro tests, challenge tests) are also provided, emphasizing the role of patch testing.

KEYWORDS

anticonvulsant hypersensitivity syndrome, delayed-type hypersensitivity, DRESS, drug reaction with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome, multiple drug hypersensitivity, positive patch tests

1 | INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is one of the severe cutaneous adverse drug reactions (SCARs). In its characteristic form, DRESS manifests with fever, skin rash (usually a maculopapular eruption), lymphadenopathy, organ dysfunction (most frequently liver or kidneys), and blood abnormalities such as leucocytosis, eosinophilia, and atypical lymphocytes. There are strong indications that delayed-type (type IV) hypersensitivity plays an important role in its pathophysiology. This includes the finding of positive patch tests and/or delayed intradermal tests to (suspected) culprit drugs and the demonstration of drug-specific T cells in patients with DRESS.[1-3]

This article provides a review of reported positive drug patch tests in patients diagnosed with DRESS. The aims of the literature study were to find answers to the following questions: (a) which drugs have induced positive patch tests in patients with DRESS; (b) which pharmaceuticals are the most frequent culprits; (c) what is the sensitivity of patch testing (i.e., the percentage of positive reactions) when testing groups of patients with DRESS and when testing specific drugs; (d) what is the evidence for optimal patch test concentrations and vehicles; (e) how safe is patch testing in DRESS; and (f) how

frequent is multiple drug hypersensitivity in DRESS (here defined as positive patch test reactions to two or more unrelated drugs that have caused an initial episode of DRESS, induced a flare during the period, or later caused a new DRESS episode or another drug hypersensitivity reaction). In addition, the study aimed at providing an extensive bibliography of the available relevant literature for the readers of *Contact Dermatitis*.

To this end, a literature review was performed of positive patch tests in patients with DRESS by searching PubMed/MEDLINE, EMBASE, and SCOPUS with no time limits. Search terms in PubMed/MEDLINE were "DRESS", "drug reaction with eosinophilia and systemic symptoms", "DRESS syndrome", "drug rash with eosinophilia and systemic symptoms", "drug hypersensitivity syndrome", "drug-induced hypersensitivity syndrome", and "anticonvulsant hypersensitivity syndrome", combined with "patch test." In SCOPUS and EMBASE, the search strategy was limited to "DRESS" AND "patch test." All articles found and relevant references in their literature lists (and in the literature lists of these secondary articles, etc.) were screened for positive results of patch tests. Much relevant information (including articles not found by these searches) had already been identified while the author was searching data for his book[4] using multiple, unrelated search terms. Details of case reports on DRESS and positive patch tests can be found in that publication.[4] Hypersensitivity reactions to the antiviral drug abacavir exhibit earlier onset and different symptoms from those of classic DRESS; they are rather classified as abacavir hypersensitivity syndrome and are not discussed here.[5,6]

As DRESS is an infrequent drug reaction and, consequently, not all readers may be familiar with this severe and potentially life-threatening disease, some general information on DRESS (largely based on review articles) given first.

2 | DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

2.1 | Introduction to DRESS

The term, 'drug reaction with eosinophilia and systemic symptoms' was first used in 1996, when the R stood for "rash."[7] Later, it was found that cases of DRESS may also occur without skin eruption, and the meaning of the "R" in the acronym was changed to "reaction."[8] Synonyms for DRESS include hypersensitivity syndrome (HSS) and drug-induced hypersensitivity syndrome (DiHS), the latter used especially in Japan.[1] Similar reactions to antiepileptic drugs were, and are, sometimes still called anticonvulsant hypersensitivity syndrome.[9]

DRESS is a serious, sometimes fatal reaction to drugs characterised by a non-specific rash, often of the maculopapular type, fever, and organ involvement, notably of the liver and kidneys. A viral reactivation of herpesviruses characteristically follows the onset of the disease. A limited number of drugs cause DRESS, in particular, antiepileptics, anti-infective drugs, and allopurinol. Prompt withdrawal of suspected drugs and administration of systemic prednisolone early in the disease is crucial.

In this article, the most important practical aspects of DRESS are presented, but it falls outside the scope of the article to provide a detailed discussion. Recent review articles, discussing DRESS and other severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and acute generalized exanthematous pustulosis (AGEP) can be found in references[1-3,10-16] (focus on epidemiology); reference[17] (focus on epidemiology and risk factors); epidemiology and risk factors, reference[18] (focus on biomarkers of disease severity and HHV-6 reactivation), reference[19] (focus on clinical manifestations); reference[20] (focus on management); and reference[21] (Spanish guidelines for diagnosis, management, treatment, and prevention).

2.2 | Epidemiology

DRESS is an infrequently occurring disease with an estimated 10 cases per million per year.[1,21] However, its incidence in new users of antiepileptic drugs (notably carbamazepine and phenytoin) may be 1/1000 to 1/10 000.[2,9-11,22] It is possible that cases of DRESS have been undiagnosed due to its variable clinical features and laboratory abnormalities. There may be a slight female predominance (male/female ratio 0.7-0.8). Median age at diagnosis is approximately 50–55 years (women slightly younger than men); less than 10% of patients are younger than 20 years.[1] A high frequency of previous rheumatic or collagen vascular disease has been observed.[23]

2.3 | Aetiology and pathophysiology

DRESS develops in the setting of a complex interaction of genetic, viral, and environmental factors. The exact pathophysiology of DRESS is unknown, but it is generally regarded as a T cell-mediated hypersensitivity reaction to drugs. Three non-mutually-exclusive models have been proposed to explain the interactions between drugs or metabolites and immunological synapses, namely, the hapten/pro-hapten model, the pharmacological interaction (p-i) model, and the altered peptide repertoire model. These models are not specific to DRESS, but also apply to all other T cell immune-mediated adverse drug reactions.[24] In the hapten/pro-hapten model, drugs or metabolites bind covalently to endogenous proteins, being processed and presented by antigen-presentation cells, and are recognized as foreign antigens. In the p-i model, it is hypothesized that drugs or metabolites can bind non-covalently to major histocompatibility complex (MHC) proteins or T cell-receptors in a peptide-independent manner to elicit T cell responses. In the altered peptide repertoire model, drugs and metabolites bind directly to the binding groove of MHC proteins, changing the peptide specificity of MHC binding. These peptides are then recognized as foreign, evoking T cell responses.[15]

Drugs implicated in DRESS include allopurinol, antiepileptic drugs (especially carbamazepine), antibacterial drugs (antibiotics, antituberculosis agents), sulfonamides (especially sulfasalazine and dapsone), antiviral drugs, antipyretics/analgesics, mexiletine, and fluindione (Table 1).

TABLE 1 Drugs that have caused DRESS[a]

Category	Drugs[b]
Antiepileptic drugs	Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin
Antibiotics	Amoxicillin, amoxicillin-clavulanic acid, ampicillin, azithromycin, levofloxacin, minocycline, piperacillin-tazobactam, vancomycin
Antituberculosis agents	Ethambutol, isoniazid, pyrazinamide, rifampicin, streptomycin
Antiviral agents	Boceprevir, nevirapine, telaprevir
Sulfones/ sulfonamides	Dapsone, sulfamethoxazole-trimethoprim (cotrimoxazole), sulfasalazine
Antipyretics/ analgesics	Acetylsalicylic acid (Aspirin), celecoxib, diclofenac, ibuprofen
Targeted anticancer agents	Sorafenib, vemurafenib, vismodegib
Miscellaneous drugs	Allopurinol, amitriptyline, atorvastatin, fluindione, hydroxychloroquine, imatinib, mexiletine, olanzapine, omeprazole, strontium ranelate

[a]Adapted from refs.[2,15,21,25]
[b]Best known culprit drugs and some other examples, not a full review.

The development of the disease is independent of the dose given and may already occur during the first treatment cycle. Approximately half of the patients have had an episode of an infection within the previous month, particularly virus infections such as herpes zoster. Patients with DRESS have drug-specific T cells, and it is assumed that viruses have a critical role in the generation and activation of these cells. In the vast majority of the affected individuals, there is reactivation of human herpesvirus 6 (HHV-6) and/or other herpesviruses including Epstein–Barr virus, HHV-7, cytomegalovirus (CMV), and varicella zoster virus. Frequent deterioration or several flare-ups of clinical symptoms occurring after withdrawal of the causative drugs in DRESS may be explained by reactivation of such viruses in various organs in a sequential manner. How viral infections contribute to the pathogenesis of DRESS is as yet unknown.[1]

A genetic predisposition to DRESS associated with specific human leukocyte antigen (HLA) subtypes has been established. HLA-A*31:01, for example, is linked to DRESS induced by carbamazepine in northern European, Japanese, southern Chinese, and Korean populations. Patients carrying this allele have a 10–12 times higher risk of developing DRESS from taking carbamazepine than controls who do not have this allele. Another drug that has been linked to a specific HLA is allopurinol, especially to HLA-B*58:01, which is seen mostly in Asian populations and some European populations. Such patients may have an odds ratio of 85 of developing allopurinol-induced DRESS compared to the general population. Other drugs that cause DRESS and are associated with specific HLA-alleles include dapsone, lamotrigine, nevirapine, phenytoin, piperacillin/tazobactam, sulfasalazine, and vancomycin.[2,21,26]

DRESS generally occurs with greater frequency in situations where chemically reactive metabolites are accumulated due to renal or hepatic insufficiency. Polymorphisms in genes encoding drug-metabolizing enzymes, such as cytochrome P 450 enzyme and *N*-acetyltransferase, may also participate in the pathophysiology of DRESS.[1,3]

2.4 | Clinical features

DRESS usually starts abruptly with fever of 38°C–40°C, diffuse skin rash, and signs of organ involvement, from 2–3 weeks up to 12 weeks after the introduction of the causative drug. Sometimes, there may be an upper-airway infection-like prodrome. Fever is seen in 90%–100% of the patients, and skin rash in >85%. The eruption usually involves more than half of the body surface area and may progress into erythroderma. The cutaneous lesions are frequently of polymorphic presentation, described as maculopapular, urticarial, exfoliative, lichenoid, pustular, bullous, target-like, or eczema-like lesions. Facial/periorbital oedema may be observed in 75% of the patients, which should arouse suspicion of DRESS; in common cutaneous adverse drug reactions the face is usually spared. Mucosal involvement, mainly of the lips and oral cavity, can be present in over half of all patients.[2,15] Some complain of dryness of the mouth (xerostomia), which makes swallowing or even taking in food difficult.[1,3] The palms and soles are usually unaffected. Tender lymphadenopathy is present in >70% of DRESS cases, notably in the cervical, axillary, or inguinal regions, as is bilateral swelling of the salivary glands.[3]

DRESS syndrome organ involvement results from specific eosinophil or lymphocyte tissue infiltration. Different organs and systems can be affected, most commonly the liver (75%–94%), followed by the kidneys (12%–40%), lungs (30%–35%), heart (4%–27%), and neurological system, causing headaches, seizures, coma, and motor function impairment.[2] Liver involvement mainly manifests as hepatic cytolysis, sometimes cholestasis, and, rarely, hepatic failure. Kidney involvement is characterized by interstitial nephritis. When the lungs are affected, symptoms may be dyspnea, cough, eosinophilic pneumonitis, and, rarely, respiratory failure. Heart involvement (myocarditis, pericarditis) on electrocardiogram or computed tomography, or cardiac enzyme abnormalities, can be fatal.[10]

Laboratory features of DRESS are leucocytosis with atypical lymphocytes (early in the reaction), monocytosis, and "(transient) eosinophilia of various degrees" occurs in 95% of the patients, late in the reaction. However, a normal eosinophil count does not exclude the diagnosis of DRESS.[2] Elevated liver enzymes are found in up to 70%–80% of the patients in the acute phase. Human herpesvirus 6 (HHV-6) reactivation is shown in the vast majority of the patients 2 to 3 weeks after onset by a significant increase in serum IgG titres to HHV-6 and the detection of HHV-6 DNA in leukocytes.[1]

Worsening of clinical symptoms may occur 3 to 4 days after withdrawal of the causative drug and flare-ups can even be observed weeks later. Resolution of symptoms in one organ may be followed by a stepwise development of other organ failures. Neurological symptoms manifesting as limbic encephalitis, gastroenteritis, interstitial

pneumonia, and myocarditis may also occur long after resolution of the rashes.[1] Exacerbations may be the result of reactivation of herpesviruses in various organs,[1] rapid reduction of systemic steroids, administration of new drugs, or from previously tolerated drugs after dose increase.[27] Worsening of clinical symptoms is frequently interpreted as resulting from an infection, for which antibiotics are often administered. However, this may well increase the risk of developing additional drug reactions, leading to multiple drug hypersensitivity, which is frequent in DRESS.[27-31]

2.5 | Histology

The histopathological features of patients with DRESS syndrome are generally non-specific. There is no single unique finding that can be used to differentiate DRESS syndrome from other drug eruptions or inflammatory skin disorders.[15] Various inflammatory patterns can be found in a single skin biopsy, namely interface dermatitis, lichenoid, eczematous, AGEP-like vascular damage, superficial perivascular infiltration, peri-appendage infiltration, and erythema multiforme-like patterns. The co-existence of three histopathological patterns in a skin specimen has a higher likelihood of being a definite case of DRESS and is correlated with clinical severity.[5]

2.6 | Diagnosis

2.6.1 | Diagnosing DRESS

For diagnosing DRESS in a patient, the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) to Drugs and the Collection of Biological Samples validation score are most frequently used, both in practice and in scientific publications, ergo indeed research.[8,32] Based on multiple parameters (fever, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, time to resolution, and evaluation of other potential causes), each suspected DRESS reaction can be scored as no case, possible case, probable case, or definite case.[8,32] In Japan, HHV-6 reactivation is included in the diagnostic criteria for DRESS.[1,3] Other diseases which may present with fever, skin rashes, lymphadenopathy, and internal organ involvement include the following viral infections: infectious mononucleosis, parvovirus B19 infection, measles, dengue, and Coxsackie virus infection.[1,21] SJS/TEN, which also clinically manifests with fever, a skin eruption and systemic symptoms, can be differentiated by the detachable skin and epidermal necrosis in the histopathology in SJS/TEN, whereas a morbilliform/maculopapular eruption, eosinophilia, and atypical lymphocytes will support DRESS.[2,33]

2.6.2 | Diagnosing the culprit drug(s)

Patch tests

Assessment to identify the culprit drug(s) includes establishing the chronology of drug intake and patch testing. Indeed, patch tests can be very helpful in identifying the drugs that caused DRESS and should, in the opinion of this author, always be the first in vivo diagnostic aid to be performed. This subject is discussed in Section 4.3. When patch tests are negative, intradermal tests (IDTs) or prick tests are the second diagnostic step.

Intradermal tests

Intradermal tests can be used to identify both immediate and delayed hypersensitivity reactions to drugs. Until recently, these tests were generally considered to be contra-indicated in SCARs (DRESS, AGEP, SJS/TEN): despite the small doses applied, severe and even fatal reactions have arisen,[34] albeit very infrequently.[35] Currently, however, various authors consider IDTs in DRESS to be potentially useful and safe when performed by specialists.[21,35-40] Nevertheless, recent guidelines of the European Network in Drug Allergy state that IDTs are contraindicated in SCARs.[41] IDTs are performed only with drugs available in sterile parenteral commercially manufactured preparations. For the technique and interpretation of IDTs, which should – like patch tests – not be performed sooner than 6 months after regression of DRESS, see Barbaud et al.[41] Non-irritant drug concentrations for intradermal testing can be found in Brockow et al.[42] The use of IDT in SCARs has predominately been in the setting of hypersensitivity associated with anti-infective drugs that are commonly available as sterile preparations and for which there exists a great need to know whether they can be safely used.[39] IDTs generally have increased sensitivity over the patch test and this appears particularly true for antibiotic-associated DRESS.[35,43] However, similar to the patch test, a negative delayed IDT does not exclude the responsibility of a drug in a cutaneous adverse reaction.[36,39,44]

Prick tests

In delayed cutaneous adverse drug reactions (CADRs), skin prick tests with commercial drugs read after 24 hours have given some positive results in DRESS, AGEP, and maculopapular eruptions.[36,40] However, drug concentration, test protocol, specificity, sensitivity, and safety of prick testing in CADRs are largely unknown.[36,42] Nevertheless, skin prick tests are often proposed prior to IDTs because they may be safer than IDTs. Also, skin prick tests can be performed in cases where a sterile injectable form of the offending drug (necessary for IDTs) is unavailable.[36,41,42] General considerations for prick tests in suspected drug hypersensitivity and non-irritant drug concentrations can be found in Brockow et al.[42]

In vitro tests

In vitro tests include the lymphocyte transformation test (LTT) and the enzyme-linked immunosorbent spot assay (ELISPOT).[10] The LTT is often positive in DRESS and can help in identifying the culprit drug(s). However, positive LTT reactions can only be obtained 4 to 8 weeks after remission, but not in the acute phase of DRESS.[2] This method, as well as ELISPOT, which detects drug-specific T cells or identifies the culprit drug via drug-specific interferon γ, interleukin 4, or granulysin production, requires specific expertise, is not widely available, and is, therefore, not part of the diagnostic routine.[2,45]

Drug provocation tests

Generally speaking, drug provocation tests in patients with DRESS and other SCARs are contraindicated because of the risk of recurrence of the hypersensitivity reaction.[10,35,37,44,46] In special circumstances, however, when other diagnostic procedures such as in vivo skin testing and in vitro laboratory tests do not lead to conclusive results, drug provocation tests may, according to some authors, be performed.[35,36] This applies when there is a compelling need for testing (e.g., treatment is necessary and there are no safe and efficacious treatment alternatives) and the benefit of the provocation is far greater than the risk.[35,36] Of course, optimal safety measures must be taken and evidence-based recommendations followed. Provocation tests are usually restricted to certain specialist centres in which patients are carefully selected and equipment, supplies, and well-trained and experienced personnel are present to manage serious reactions.[44]

2.7 | Management

All drugs used by the patient at the time DRESS developed should – whenever possible and responsible – be stopped immediately. Systemic corticosteroids (prednisolone 1 mg/kg/day) are the gold standard treatment in the acute phase in patients with severe organ involvement. Rapid resolution of rashes and fever occur within several days after starting treatment. The steroids have to be tapered very slowly, over at least 12 weeks, to prevent the relapse of various symptoms and the emergence of the so-called immune reconstitution inflammatory syndrome (IRIS), ranging from cytomegalovirus disease to autoimmune disease.[1,2]

2.8 | Prognosis

The prognosis of DRESS, either in the short- or long-term, is highly variable and unpredictable. About 25% of all patients with DRESS will present with one or more exacerbations/flare-ups after the initial episode, and, therefore, with a prolonged course that can last up to 1 year.[2] Mortality in DRESS has been reported to range from 5% to 10%,[5,10] but appears to be lower (2%) in strictly validated cases.[23,33] A composite score has been created using demographic data, medical history, and clinical variables, by which disease severity and treatment efficacy can be assessed and disease progression to a more aggressive stage can be predicted.[47] Generally speaking, allopurinol and anticonvulsants are associated with a poorer, and antibiotics with a better, prognosis.[21]

Complications leading to morbidity and mortality include myocarditis, *Pneumocystis jirovecii* pneumonia, sepsis, liver failure, and gastrointestinal bleeding. Reactivation of CMV may be the cause of some of these complications and most patients who die from DRESS are CMV-positive.[1] There is growing evidence that autoimmune diseases, such as systemic sclerosis, lupus erythematosus, diabetes, thyroiditis, autoimmune haemolytic anaemia, reactive arthritis, alopecia areata, and vitiligo may follow DRESS a few months to several years after remission in >10% of patients.[1,2,10,15,21] The exact mechanism for the development of these autoimmune diseases is still unknown; treatment of DRESS with systemic corticosteroids may limit their development.[2,10,15]

3 | RESULTS OF LITERATURE REVIEW

The results of the literature review of positive patch tests in DRESS are summarized in Table 2. In some cases (indicated in the Table), the drugs did not cause DRESS, but induced a secondary non-DRESS hypersensitivity reaction during or after an episode of DRESS caused by another drug (non-DRESS means that there were insufficient symptoms to label the secondary reaction as a probable or definite case of DRESS[8,32]). Details of most case reports can be found in the author's book.[4]

"Culprit drug" means that the drug either caused the first DRESS episode (alone or with one or more other drugs), caused an exacerbation in this episode, or – far less frequently – induced a second episode of DRESS after full recovery. It should be mentioned that in some studies, no clinical details were provided, only drugs causing DRESS and inducing a positive patch test were tabulated. The data on patch test concentrations, vehicles and times of reading were in many reports incomplete, not specific, or even completely absent. Also, it was frequently unclear whether the drugs taken by the patient (indicated in Table 2, column 3 as 'CP' [Commercial Preparation]) had been used for patch testing or whether pure drug material had been tested. Because of this frequent lack of specific data, the author cannot guarantee that all information provided in Table 2 is fully accurate.

3.1 | Drugs causing DRESS and showing positive patch tests

In this literature review, the author found 105 drugs that have together caused 536 positive patch tests in 437 patients with DRESS (Table 3). The number of positive patch tests exceeds the number of patients, as 75 individuals had two or more positive reactions (totalling 174 tests). A total of 362 patients each had one positive patch test, 60 individuals had two positive reactions, eleven had 3, one had 4, two had five, and one had 7 positive patch tests (more details presented in Section 3.5).

By far, most reactions (n = 145) were caused by the antiepileptic drug carbamazepine, followed by amoxicillin (n = 34), isoniazid (n = 22), phenytoin (n = 21), ethambutol (n = 18), fluindione (n = 16; an anticoagulant mainly used in France), phenobarbital (n = 13), rifampicin (n = 12), ceftriaxone (n = 11), meropenem (n = 11), vancomycin (n = 11), piperacillin-tazobactam (n = 10), and valproic acid (n = 10). Following these, one drug caused 9 reactions, two caused 8, two caused 7, one caused 5, nine caused 4, 12 caused three, 22 caused two and the remaining 43 drugs (41%) each caused one positive patch test.

TABLE 2 Reported cases of DRESS/DiHS/DHS/AHS with positive patch tests

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Acetaminophen (paracetamol)	1	5% water	Secondary non-DRESS hypersensitivity reaction (fever, generalized pruritic exfoliative rash, leucocytosis) after DRESS from carbamazepine with positive patch test	28
	1	10% water and pet.	Secondary non-DRESS hypersensitivity reaction (generalized maculopapular eruption, eosinophilia) after DRESS from carbamazepine with positive PT	48
Acetylsalicylic acid	1	CP 10% and 20% pet.	2-year-old boy with Kawasaki disease	49
Acyclovir	2	CP 30% pet. (n = 1); CP 30% or 10% pet. (n = 1)	One patient also had a positive PT to ceftriaxone[a]	50
	1	CP diluted to 10% a.i. in water or pet. (ns)	The patient also had positive patch tests to the culprit drugs amoxicillin and carbamazepine; a repeat patch test after nearly 4 years was again positive to acyclovir	51
Allopurinol			Allopurinol is a well-known and frequent cause of DRESS, but patch tests are always negative	50,52
Amitriptyline	1	1% pet.	Secondary non-DRESS hypersensitivity reaction (generalized maculopapular eruption) after DRESS from carbamazepine with positive patch test	28
Amikacin	1	CP 30% or 10% pet. (ns)		50
	1	2,5 mg/mL saline prepared from i.v. powder	Generalized skin eruption from patch testing without involvement of other organs	53
	1	CP pure		54
Aminosalicylic acid (PAS, *p*-aminosalicylic acid)	1	Sodium aminosalicylate 5% water	The patient also had a positive patch test reaction to the culprit drug isoniazid; generalized maculopapular eruption after patch tests (far too soon performed)	55
	1	Unknown	No details available, data cited in ref.[55]	56
	1	Sodium salicylate	No details provided on PT concentration and vehicle	57
Amoxicillin	6	CP 30% or 10% pet. (ns)	One patient had also a positive PT to lansoprazole, another to "cephalosporins"[a]	50
	6	Trihydrate, 10% pet.	In five patients, amoxicillin was given during DRESS caused by carbamazepine and in one caused by allopurinol; unknown how amoxicillin contributed; in five cases cross-reaction to ampicillin; 2/3 repeat PTs after 2-5 y positive	58
	6	Not specified		59
	4	Trihydrate, 10% pet.	Three cross-reactions to ampicillin, one to benzylpenicillin; probably overlap with ref.[58]	60
	3	Probably 10% pet.	Also positive PT to the culprit drug ioversol	61

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	Trihydrate, 10% pet.	The patient also had positive patch tests to the culprit drugs carbamazepine and acyclovir; a repeat patch test after nearly 4 y was negative to amoxicillin at D2	51
	1	CP 10%–30% pet. (ns)	Also positive patch test to the culprit drug carbamazepine; later (time period not specified) the patient had a "relapse"[b] of DRESS from valproic acid	27,30
	1	Trihydrate, 10% pet.	Also positive patch test to culprit drug clindamycin	62
	1	Trihydrate, 10% pet.	Cross-reactions to benzylpenicillin and penicillin V	63
	1	Not specified	Also positive PT to culprit drug metamizole	64
	1	Trihydrate, 10% pet. and CP 30% pet.	Both PTs with the pure chemical and the test material made from the commercial tablets were positive	65
	1	5% water	Secondary reaction to amoxicillin in DRESS induced by allopurinol	32
	1	5% water, 10% pet.		66
	1	Not specified		38
Amoxicillin-clavulanic acid	2	CP 30% or 10% pet. (ns)	One patient also had pos. PTs to esomeprazole and "quinolones"[a] (not specified which; cross-reactions between ciprofloxacin, norfloxacin and pefloxacin)	50
	1	CP 20% and 50% pet.	Pediatric case	67
	1	Not specified	The culprit constituent was amoxicillin; also positive patch test to culprit drug oxacillin	68
	1	Not specified	Also positive PT reactions to piperacillin-tazobactam and meropenem; not stated which of these had caused DRESS and whether the other positive PTs were beta-lactam cross-reactions	69
	1	Not specified	The patient first had a maculopapular exanthema during mononucleosis infectiosa and had a positive patch test; 6 months later, the drug was administered again and after day 2 DRESS developed	70
	1	Not specified		38
	1	Not specified		59
Ampicillin	1	10% pet.		60
Atovaquone	1	Not specified	Also positive patch test to the culprit drug penicillin V	71
Benznidazole	1	5% pet.		72
	1	Not specified	Diagnosis described as DRESS/SJS	73
Benzylpenicillin	1	CP 30% pet.	Cross-reaction to amoxicillin	62
	1	10% pet.		74

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Captopril	1	1% pet.		75
	1	1% pet.		76
	1	10% water (CP?)	A repeat PT was again positive	77
	1	Not specified		78
Carbamazepine	13	1%, 5%, 10% and 20% pet.	The 1% concentration detected all sensitized patients; one had also a pos. PT to the culprit drug phenytoin	52
	11	CP 30% or 10% pet. (ns)	One patient also had a positive patch test to cloxacillin CP 30% pet. and two to spironolactone CP 30% pet.[a]	50
	7	CP 10% and 30% pet.	Five patients had cross-reactions to oxcarbazepine	79
	6	CP 10%, 20% and 40% pet.	Six of a group of seven were positive	80
	5	CP 10% pet.[c]	All five patients had co-sensitization to amoxicillin which was given during the DRESS episode caused by carbamazepine; three repeat patch tests after 2-5 years were all positive; probably overlap with ref.[60]	
	5	CP 10%, 20% and 30% pet.		81
	5	10% pet.		82
	5	Not specified		83
	4	CP 10% pet.	Pediatric cases	84
	4	3% and 10% in pet., water and alcohol		85
	4	100%, 10%, 1% and 0.1% in pet. and acet.	Strongly positive patch test reactions to all concentrations in both vehicles	86
	4	1%–5% pet. (CP?)		87
	4	1% pet.	Uncertain whether these were all cases of DRESS	88
	3	5% pet. (n = 2); 1% and 10% pet. (n = 1)	Later other non-DRESS hypersensitivity reactions to acetaminophen (paracetamol) (n = 1) and amitriptyline (n = 1) with positive patch tests	28
	3	CP 5% pet.	One also had a positive PT to the culprit drug valproic acid; this patient had a generalized rash from PT carbamazepine	89
	3	CP 1% and 10% a.i.		65
	3	CP 5% or 10% pet.		90
	2	CP 10% pet.[c]	Probably overlap with ref.[58] (see above)	60
	2	CP 10% pet.	One of these patients after 7 months developed a maculopapular eruption from valproic acid with a positive patch test	91
	2	5%, 10%, 15% and 20% pet.		92
	2	1% and 10% Phlojel base and pet.	The patient also reacted to phenobarbital (culprit drug?); Phlojel ® Ultra is an organic gel made from lecithin	93
	2	CP pulverized in 30 μL saline	Two positives in a group of eight tested	22
	2	Data unknown	Article in Japanese, data cited in ref.[94]	95

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	2	1% pet.		96
	1	CP 5% pet.	Five years later, the patient developed a generalized maculopapular rash with eosinophilia after using paracetamol; a patch test was positive (ref.[48])	7
	1	CP diluted to 10% a.i. in water or pet. (ns)	The patient also had positive patch tests to the culprit drugs amoxicillin and acyclovir; a repeat patch test after nearly 4 years was again positive to carbamazepine	51
	1	10% pet.	The patient also had a positive PT to the culprit drug cloxacillin	54
	1	CP 10%–30% pet.	Later maculopapular eruption from ceftriaxone, cefuroxime and flucloxacillin with positive patch tests	27,30
	1	CP 10%–30% pet.	Also positive patch test to the culprit drug amoxicilline; later (time period not specified) the patient had a relapse of DRESS from valproic acid	27,30
	1	CP 20% and 50% pet.	Pediatric case	67
	1	Not specified	Pediatric case	98
	1	CP 10% pet.[c]		58
	1	20% PBS	Also positive patch tests to the culprit drugs fluvoxamine and oxcarbazepine	99
	1	5% pet.	Six months later, the patient became sensitized from treatment with lamotrigine and developed a new episode of DRESS	100
	1	CP 5 mg in 50 μL alc.	The paediatric patient later developed another episode of DRESS while using oxcarbazepine and had a positive PT to it; this reaction was from neo-sensitization rather than from cross-reactivity to carbamazepine	101
	1	1% and 10% pet.	Flare-up from phenytoin, which had previously been well tolerated, with positive patch test	102
	1	Not specified	Later, secondary reaction to valproic acid with positive patch tests to both antiepileptic drugs	103
	1	1% pet.		104
	1	1%, 5% and 10% pet.		105
	1	Not specified	Apparently also a positive patch test to primidone, but the patient had not used this drug	106
	26		Additional single cases/case reports can be found in refs.[94,107-131]	
Cefadroxil	1	CP 30% pet. and water	Patch tests were performed on 10x tape-stripped skin	132
	1	Not specified		133
Cefonicid	1	Not specified	Also positive PT to culprit drug oxcarbazepine	134

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Cefotaxime	1	Not specified	Pediatric case	98
	1	Not specified	Positive patch-scratch test	135
Cefoxitin	1	10% pet. (ns whether from CP or pure drug)	The patient was diagnosed with DRESS from allopurinol (a well-known cause of DRESS which is always patch test-negative) worsened by co-sensitization to cefoxitin	136
	1	10% pet.		63
	1	10% pet.	Cefoxitin was given during an episode of DRESS caused by phenytoin and caused a flare-up; repeated patch test after 2-5 years was again positive; also reaction to vancomycin with positive patch test	58
	1	10% pet.	Cefoxitin was given during an episode of DRESS caused by allopurinol and caused a flare-up	58
Ceftriaxone	2	CP 30% pet.	One patient also had a positive PT to acyclovir[a]	50
	1	CP 10%–30% pet. (ns)	Also positive PT to culprit drug flucloxacillin; secondary hypersensitivity reaction from iobitridol with positive patch tests[27]; in ref.[30] iobitridol was mentioned as a culprit drug of the first DRESS episode	27,30
	1	CP 10%-30% pet. (ns)	Later, the patient developed a maculopapular eruption from iomeprol with a positive patch test	27
	1	5% pet.		137
	1	i.v. powder 10% pet. active ingredients	Also positive patch test to culprit drug ciprofloxacin; probably the same patient as in ref.[58]	60
	1	CP 25% pet.	Induced flare-up of DRESS caused by phenobarbital	138
	1	i.v. powder 10% pet.	Given during DRESS episode caused by allopurinol; unknown how it influenced the clinical picture	58
	1	5% and 10% pet.		139
	1	Not specified		59
	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from carbamazepine with positive patch test	27,30
Cefuroxime	1	CP 15% and 30% pet.	May have contributed to DRESS caused by vancomycin and rifampicin (but only used for 3 d), later developing into TEN	140
	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from carbamazepine with positive patch test	27,30

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Celecoxib	1	CP 30% pet.		50
	1	CP 10% and 50% pet.	Also positive patch test to culprit drug ethambutol	141
	1	CP 30% pet.		142
Cephalosporins (ns)	1	CP 30% or 10% pet. (ns)	The patient had also a positive PT to amoxicillin[a]	50
Chloroquine	1	2 mg/mL (vehicle ns)		143
Ciprofloxacin	1		See Amoxicillin-clavulanic acid, ref.[50]	
	1	10% pet.	Cross-reaction with ofloxacin; also positive patch test to culprit drug ceftriaxone	60
	1	Not specified	Also positive patch test reactions to culprit drugs piperacillin-tazobactam and vancomycin	38
Citalopram	1	CP 30% pet.		50
Clarithromycin	1	10% pet.	Also secondary hypersensitivity reaction from gadobutrol (maculopapular eruption) with positive patch test	27,30
Clindamycin	1	CP 20% and 50% pet.	Pediatric case	67
	1	10% pet.	Also positive patch test to culprit drug amoxicillin	62
	1	CP 10% pet.[c]		144
Clobazam	1	CP 30% pet.		50
Cloxacillin	1	CP 30% pet.	The patient also had a positive PT to carbamazepine	50
	1	CP 30% pet.	The patient also had a positive PT to the culprit drug carbamazepine	54
	1	i.v. powder 0.2% and 2% water and pet.		145
	1	CP 15% and 30% pet.	May have contributed to DRESS caused by vancomycin and rifampicin (but only used for 3 days), later developing into TEN	140
Codeine	1	CP codeine phosphate	Concentration and vehicle of the patch test material not specified	146
Cotrimoxazole		See Sulfamethoxazole-trimethoprim		
Cyanamide	1	CP (liquid cyanamide 1%) undiluted		147
	1	Data not available		148
Dabrafenib	1	CP 30% pet.		27
Dapsone	7	Not specified	Seven positives among 16 patients with dapsone hypersensitivity syndrome	149
Diclofenac	1	CP emulgel pure and diclofenac 1% pet.	Pictures of positive patch tests in article not very convincing	150
	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from sulfamethoxazole with positive patch test	27,30
Dicloxacillin	1	CP 30% pet.		50

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Diltiazem	1	CP 30% pet.		50
Doxofylline	1	CP 10% pet.	Also positive PT to culprit drug erdosteine	151
Enoxaparin	1	CP undiluted		50
	1	CP 20% and 50% pet.	Pediatric case	67
Erdosteine	1	CP 10% pet.	Also positive PT to culprit drug doxofylline	151
Eslicarbazepine	2	CP 30% pet.	Cross-reaction to carbamazepine in one patient	152
Esomeprazole	2	CP 30% pet.	One also reacted to culprit drugs amoxicillin-clavulanic acid and "quinolones"	50
	1	CP 30% water, pet. and alcohol	The patient also had a positive PT to vancomycin (not a culprit drug)	54
	1	1%–10% solution (ns)	Cross-reactions to omeprazole and pantoprazole; mild erythroderma with facial oedema and desquamation 3 d after patch tests	153
Ethambutol	3	CP 30% water and olive oil	Two also had positive PT reactions to culprit drug isoniazid; great risk of generalized reactions after patch testing antituberculosis drugs in HIV-infected patients	154
	2	Not specified	One also had a positive PT to isoniazid	155
	1	CP 50% pet.	Also positive patch test to culprit drug celecoxib	141
	1	CP 50% pet.	Also tested with isoniazid and rifampicin which the patient had also used (multidrug therapy); at day 2 there was diffuse erythema around all patches; the authors admitted these may have been irritant reactions; apparently no PT readings performed after day 2	156
	1	CP 20% pet.		157
	1	1%, vehicle ns	Also positive PT to the culprit drug isoniazid	158
	1	CP 10% pet.	Early features of SJS	159
	1	CP 3% pet.	Also positive patch tests to the culprit drugs isoniazid and pyrazinamide	160
	1	CP 30% pet.	Also reaction to culprit drug isoniazid	161
	1	CP 30% pet.	Also reaction to culprit drug isoniazid	162
	1	Not specified		163
	1	CP 30% pet.		164
	1	1% pet.	Also positive patch tests to culprit drugs pyrazinamide, pyridoxine, isoniazid and rifampicin	165
	1	Not specified		166
	1	CP 20% pet.		167
Ethosuximide	1	CP 20% water	Also pos. PT to culprit drug valproic acid	168

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Flucloxacillin	1	CP 10%–30% pet. (ns)	Also positive PT to culprit drug ceftriaxone; secondary hypersensitivity reaction from iobitridol with positive patch test; in ref.[30] it was mentioned that iobitridol was a culprit drug in the first DRESS episode	27
	1	10% pet.	Cross-reactions to dicloxacillin, benzylpenicillin and amoxicillin; later, the patient developed occupational allergic contact dermatitis followed by maculopapular eruption caused by airborne contact with flucloxacillin and cross-reacting penicillin in her work as a nurse	169
	1	1%, 5% and 10% pet.		139
	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from carbamazepine with positive patch test	27,30
Fluindione	7	Not specified	Possibly there were two more cases; all these and other cases of DRESS were reported from France, where this drug is widely used as an anticoagulant	170
	5	CP 30%, 5% and 2% water and pet.	One patient had photo-augmentation of DRESS by UVB-light	171
	2	CP 30% or 10% pet. (ns)		50
	1	CP 1% and 10% water and pet.		54
	1	CP 30% and 5% pet.		172
Fluvoxamine	1	12.5% PBS	Also positive patch tests to the culprit drugs carbamazepine and oxcarbazepine	99
Gadobutrol	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from clarithromycin with positive patch test	27,30
Hydroxychloroquine	1	CP 20% water and pet.		173
Imipenem - cilastatin	1	CP 30% pet.	Also positive patch test to vancomycin[a]	50
	1	CP 30% pet.		61
Iobitridol	5	Not specified	Four had cross-reactions to other iodinated contrast media; French pharmacovigilance database	174
	2	CP 10%–30% saline or undiluted (ns)		61
	1	CP undiluted	Also positive patch tests to culprit drugs ceftriaxone and flucloxacillin; this patient was presented in ref.[27] as having a *secondary* drug hypersensitivity reaction	30
	1	CP 10%–30% pet. (ns)	Relapse[b] undefined period after DRESS episode caused by ceftriaxone and flucloxacillin	27

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Iodixanol	1	CP undiluted		50
	1	Not specified	Previously (period unknown) the patient had suffered an episode of DRESS caused by ioversol and ioxitalamic acid	175
Iohexol	3	CP 10%-30% saline or undiluted (ns)	One had two, another three and the third had six cross-reactions to other iodinated contrast media	61
Iomeprol	1	CP 10%–30% saline or undiluted (ns)	Five cross-reactions to other iodinated contrast media; also pos. PT to culprit drug omeprazole	61
	1	Not specified		38
	1	CP 10%–30% pet. (ns)	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) during or after DRESS from ceftriaxone with positive patch test	27,30
Iopromide	1	CP undiluted	The patient had DRESS on two occasions when treated with iopromide; after the first time, a patch test was negative, but positive after the second DRESS episode	176
Ioversol	4	CP 10%–30% saline or undiluted (ns)	One had five and two had six cross-reactions to other iodinated contrast media; three had also positive patch test reactions to the culprit drug amoxicillin	61
	1	Not specified	Also positive patch test to the culprit drug ioxitalamic acid and cross-reactions to various other iodinated contrast media; later, the patient would develop a new episode of DRESS from using iodixanol	175
	1	Not specified	Cross-reaction to iohexol	177
	1	Not specified	Multiple cross-reactions to iodinated contrast media	38
Ioxaglic acid	1	CP sodium meglumine ioxaglate undiluted	The patient had suffered an episode of DRESS 7 years before from the same drug; at that moment, the PT was negative but an intradermal test positive[179]	178
Ioxitalamic acid	1	Not specified	Also positive patch test to the culprit drug ioversol and cross-reactions to various other iodinated contrast media; later, the patient would develop a new episode of DRESS caused by iodixanol	175
	1	CP sodium meglumine ioxitalamate undiluted and 30% water		180
Isoniazid	5	Not specified	One also had a positive PT to ethambutol	155
	4	CP 30% water and olive oil	Two also had positive PT reactions to culprit drug ethambutol; great risk of generalized reactions after patch testing antituberculosis drugs in HIV-infected patients	154,181

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	CP powder, moistened	The patient also had a positive PT reaction to the culprit drug (*p*-) aminosalicylic acid (PAS); generalized maculopapular eruption after patch tests (far too soon performed)	56
	1	CP 50% pet.	Also tested with ethambutol and rifampicin which the patient had also used (multidrug therapy); at D2 there was diffuse erythema around all patches; the authors admitted these may have been irritant reactions; apparently no PT readings done after day 2	156
	1	1%, vehicle ns	Also positive PT to the culprit drug ethambutol	158
	1	1% pet.	Also positive patch tests to the culprit drugs ethambutol and pyrazinamide	160
	1	CP pulverized "as is" and 30% in water and pet.		160
	1	50% pet.	Result of day 4 PT not mentioned (although read)	182
	1	1% water		183
	1	Not specified	Patch test positive on three occasions	184
	1	CP 30% pet.	Also reaction to culprit drug ethambutol	161
	1	CP 30% pet.	Also reaction to culprit drug ethambutol	162
	1	1% pet.	Also positive patch tests to culprit drugs pyrazinamide, pyridoxine, ethambutol and rifampicin	165
	1	Not specified	Also positive patch test to culprit drug streptomycin	185
	1	1% pet.		186
Lamotrigine	1	CP 30% pet.		50
	1	10% pet.		187
	1	5% pet.	Six months earlier, the patient had suffered an episode of DRESS from carbamazepine hypersensitivity	100
	1	CP 10% pet.	Pediatric case	84
	1	1% and 10% pet.		52
	1	CP 30% water and pet.	Pediatric case	188
	1	Not specified	Pediatric case	189
	1	5% pet.	Pediatric case	89
Lansoprazole	1	CP 30% pet.	Also positive patch test to amoxicillin[a]	50
	1	CP 10% pet.		190
Levofloxacin	1	10% pet.		191
Meropenem	2	5% pet.	In one, there were multiple cross-reactions to penicillins and cephalosporins	139
	1	CP 10%–30% pet. (ns)		27,30
	1	Not specified	Same patient as in[27,30]; conflicting data regarding co-sensitization to vancomycin (pos. PT in ref.[192], negative in refs.[27] and [30])	192

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	1% and 20% pet.	Probably primary sensitization to phenytoin, but this drug was not patch tested or intradermally tested	193
	1	10% pet.		194
	1	CP 15 and 30% pet.	May have contributed to DRESS caused by vancomycin and rifampicin, later developing into TEN	140
	1	Not specified	Also positive PT reactions to amoxicillin-clavulanic and piperacillin-tazobactam; not stated which of these had caused DRESS and whether the other positive PTs were beta-lactam cross-reactions	69
	1	Not specified		38
	1	Not specified	Also positive PT to culprit drug vancomycin	195
	1	Not specified		196
Metamizole	2	CP 10% pet.	In one case also pos. PT to culprit drug amoxicillin	64
	1	CP 10% water		197
Metronidazole	1	CP 15% and 30% pet.	May have contributed to DRESS caused by vancomycin and rifampicin, later developing into TEN	140
Mexiletine	1	CP 1%, 2%, 5% 10% and 20% pet.		198
	1	Not specified		199
	1	Not specified		200
	1	Not specified		201
	1	Not specified		202
Miconazole	1	Oral gel 30% pet.	The patient was diagnosed with AGEP/DRESS overlap, but probably had (only) AGEP	203
Minodronic acid	1	Not specified	Patch test incorrectly performed in the acute phase	204
Nifurtimox	1	Not specified		205
Norfloxacin			See Amoxicillin-clavulanic acid, ref.[50]	
Olanzapine	1	CP 30% pet.		50
	1	CP 30% pet.		206
	1	CP 10% water and pet.		207
	1	CP 30% pet.	Previously, the patient had suffered an episode of DRESS caused by carbamazepine	128
Omeprazole	1	CP 30% pet.	Also positive PT to culprit drug iomeprol	61
Oxacillin	1	CP 20% and 50% pet.	Pediatric case	67
	1	Not specified	Also positive patch test to culprit drug amoxicillin in amoxicillin-clavulanic acid	68
Oxcarbazepine	1	12.5% PBS	Also positive patch tests to the culprit drugs fluvoxamine and carbamazepine	99

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	CP 5 mg in 50 μL alc.	The paediatric patient had DRESS while on carbamazepine previously and had a positive PT to it; the reaction to oxcarbazepine was from neo-sensitization rather than from cross-reactivity to carbamazepine	101
	1	CP 30% pet.	Cross-reactions to eslicarbazepine and carbamazepine	152
	1	Not specified	Also positive PT to culprit drug cefonicid	134
Pantoprazole	2	CP 30% pet. (n = 1); pure drug 10% pet. (n = 1)	One patient also had a positive PT to vancomycin[a]	50
	1	CP 15% and 30% pet.	May have contributed to DRESS caused by vancomycin and rifampicin, later developing into TEN; suspected to have played a role in the transition of DRESS into TEN; cross-reactions to omeprazole, lansoprazole, esomeprazole and rabeprazole	140
Pefloxacin			See Amoxicillin-clavulanic acid, ref.[50]	
Penicillin V (phenoxymethyl-penicillin)	1	Not specified	Also positive patch test to the culprit drug atovaquone	71
	1	1%, 5% and 10% pet.		139
Phenindione	1	Not specified		71
Phenobarbital	3	CP 10% pet.	One of these patients had a relapse from valproic acid with a positive patch test	91
	3	CP 10%, 20% and 30% pet.		81
	2	1% and 10% Phlojel base and pet.	Also positive PT to culprit drug carbamazepine in one patient and to phenytoin in the other	93
	1	CP 20% and 50% pet.	Pediatric case	67
	1	CP 30% pet.	Flare-up from ceftriaxone with positive patch test	138
	1	CP 30% pet.		82
	1	CP 20% pet.	The patch test became positive only at day 11	208
	1	Not specified	Later, the patient developed DRESS from carbamazepine	127
Phenytoin	7	CP 10%, 20% and 30% pet.		81
	2	5% water	One patient also had a positive patch test to carbamazepine, but this drug had apparently not been used by the patient	89
	2	1% and 10% Phlojel base	One patient also reacted to phenobarbital (culprit drug?); PT reactions were negative to phenytoin 1% and 10% pet.; Phlojel ® Ultra is an organic gel made from lecithin	93
	2	CP pulverized in 30 μL saline	Two positives in a group of seven tested	22
	1	CP 10% pet.[c]		58

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	CP 10% pet.[c]	Also positive patch tests to cefoxitin (with cross-reactions to other cephalosporins) and vancomycin; these drugs had been used during the phenytoin-induced episode of DRESS; repeated PT after 2-5 y with phenytoin was negative	58
	1	Data not available	Previously, the patient had suffered from AGEP caused by carbamazepine and on a separate occasion from DRESS caused by valproic acid; she had positive patch tests to all three medicaments	209
	1	5% and 10% pet.	Also positive PT to culprit drug carbamazepine	52
	1	Not specified		210
	1	1% and 10% pet.; 10% water (neg. to 1% water)	Caused flare-up of carbamazepine-induced DRESS	102
	1	1% and 5% pet.	Also pos. PT to phenobarbital (probably not culprit)	211
	1	Not specified		83
Piperacillin	1	CP 10%–30% pet.		27,30
	1	10% and 20% pet.; piperacillin-tazobactam CP as is	The patient had been treated with piperacillin-tazobactam; distant erythematous and oedematous lesion during patch testing with strongly positive test; doubtful case of DRESS	212
	1	Not specified	Pediatric case	213
Piperacillin-tazobactam	3	Not specified	Growing number of DRESS cases due to this drug	214,215
	1	CP 30% pet.		216
	1	Not specified	Also positive PT reactions to amoxicillin-clavulanic acid and meropenem; not stated which of these had caused DRESS and whether the other positive PTs were beta-lactam cross-reactions	69
	1	5% pet.		139
	1	Not specified		38
	1	Not specified	Also positive patch test reactions to culprit drugs ciprofloxacin and vancomycin	38
	1	Not specified		59
	1	Not specified		217
	?	Not specified	French pharmacovigilance database: there were eight positive reactions to delayed intradermal tests *or* patch tests; tazobactam was not tested	218
Potassium *p*-amino-benzoate	1	CP 50% pet.		219
Pristinamycin	3	CP 30% or 10% pet. (ns)	One patient also had a positive PT to vancomycin[a]	50
	1	CP 30% pet.		220

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
Proguanil	1	CP 30% pet.	The patient had used the combination tablet proguanil-atovaquone; patch tests were positive to this combination and to proguanil, but negative to atovaquone (all tested as CP 30% pet.)	221
Propylthiouracil	1	CP 10% pet.		222
Pyrazinamide	1	CP 3% pet.	Also positive patch tests to the culprit drugs ethambutol and isoniazid	160
	1	1% pet.	Also positive patch tests to culprit drugs ethambutol, pyridoxine, isoniazid and rifampicin	165
Pyridoxine	1	10% pet.	Also positive patch tests to culprit drugs pyrazinamide, ethambutol, isoniazid and rifampicin	165
Pyrimethamine	1	CP 30% pet.		50
Ranitidine	1	CP 30% pet.	Cross-reaction to cimetidine[223]; 3 y later,[224] the patient (also presented in ref.[62]) was again patch tested, both on normal and tape-stripped skin; the reactions were strongly positive and resulted in reactivation of previous positive patch tests, facial oedema, lymphopenia and lymphadenopathy[224]	62,223,224
Rifampicin	7	CP 30% water and olive oil	Great risk of generalized reactions after patch testing antituberculosis drugs in HIV-infected patients, albeit the least with rifampicin	154
	1	Not specified		155
	1	CP 50% pet.	Also tested with ethambutol and isoniazid which the patient had also used (multidrug therapy); at day 2 there was diffuse erythema around all patches; the authors admitted these may have been irritant reactions; apparently no PT readings done after day 2	156
	1	CP 30% pet.	Also positive patch test to culprit drug vancomycin; multiple other drug hypersensitivities, which may have contributed to DRESS and later developing TEN	140
	1	CP 30% a.i. water and pet.	Patch tests induced generalized pruritus and rash, facial oedema, hepatitis, and eosinophilia; quite curiously, the result of the patch tests with rifampicin and other antituberculosis agents was not mentioned	225
	1	i.v. solution	Also positive patch tests to culprit drugs pyrazinamide, pyridoxine, isoniazid, and ethambutol	165
Spironolactone	2	CP 30% pet.	Both patients also had pos. PTs to carbamazepine[a]	50
	1	See right column	CP 25, 5, 2.5 and 0.25 mg/mL and 50%, 20%, 10% and 1% pet.; oral provocation test positive (before PT)	226

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	CP 10%, 20% and 30% pet. and saline	In a second PT session positive reactions to pure spironolactone 1% and 10% pet.	227
Streptomycin	1	Not specified	Also positive patch test to culprit drug isoniazid	185
Sulfamethoxazole	1	CP 10%–30% pet. (ns)	Also positive patch test to vancomycin, which was given during the DRESS episode caused by sulfamethoxazole and induced a "relapse"[b] of DRESS	27,30
	1	CP 10%–30% pet. (ns)	Later, diclofenac caused a maculopapular eruption and showed a positive patch test	27,30
Sulfamethoxazole-trimethoprim	1	10% pet.	Sulfamethoxazole-trimethoprim = cotrimoxazole	60
	1	CP 30% pet.; pure (?) drug 1% pet.	Pediatric case	228
Sulfasalazine			Sulfasalazine is a well-known and frequent cause of DRESS, but patch tests are always negative	50,229
	1	Sulfanilamide 1% photopatch test	The patient had a photoallergic eczematous drug eruption with fever, hepatomegaly, leukocytosis, eosinophilia, elevated liver enzymes and proteinuria; photopatch tests with UVA were positive to sulfanilamide 1% pet., but negative to sulfasalazine 1% pet.; because a metabolite of sulfasalazine (2-pyridylsulfamoyl radical) is structurally very similar to sulfanilamide, the patient was diagnosed with drug hypersensitivity syndrome with involvement of photoallergy to sulfasalazine	230
Teicoplanin	1	4% water (possibly too low)	The patient had an episode of DRESS from vancomycin; teicoplanin caused a flare-up, probably from cross-reactivity between vancomycin and teicoplanin	231
Tenoxicam	1	Not specified	No cross-reaction to piroxicam or meloxicam	52
Tetrazepam	1	CP 30% pet.		50
	1	CP 1% and 10% pet.	Doubtful whether this was actually DRESS	232
Tixocortol	1	Pivalate, 0.1% pet.		50
Topiramate	1	CP 10% pet.[c]		58
	1	CP 30% water and pet.		52
Tribenoside	1	Not specified		233
Valaciclovir	3	See right column	PT CP 30% (n = 1); CP 10% pet. (n = 1); CP 5% and 30% pet. (n = 1); cross-reactions to acyclovir in 2/2 tested	234
Valproic acid	1	CP 20% water	Also positive patch test to culprit drug ethosuximide; reintroduction of skin rash on the arms, legs, and face after positive patch test to sodium	168

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
			valproate (in the DRESS episode described as pruritic morbilliform skin eruption with vesicular and target lesions)	
	1	Data not available	Previously, the patient had suffered from AGEP caused by carbamazepine and on a separate occasion from DRESS caused by phenytoin; she had positive patch tests to all three medicaments	209
	1	Data not available		235
	1	CP undiluted and 30% water		236
	1	CP 10%–30% pet. (ns)	Valproic acid caused a "relapse"[b] of DRESS after having suffered an episode of DRESS caused by amoxicillin and carbamazepine; the time period between DRESS and the relapse was not mentioned	27,30
	1	CP 10% pet.	The drug caused an exacerbation during an episode of DRESS caused by phenobarbital	91
	1	Not specified		237
	1	5% pet.	Also pos. PT to culprit drug carbamazepine	89
	1	Not specified	Secondary reaction immediately after DRESS from carbamazepine	103
	1	CP 10% pet.	Secondary non-DRESS hypersensitivity reaction (maculopapular eruption) after DRESS from carbamazepine with positive patch test	91
Vancomycin	4	CP 30% or 10% pet. (ns)	One patient also had pos. PT to imipenem-cilastatin, one to pantoprazole and one to pristinamycin[a]	50
	1	Not specified	Also positive PT to culprit drug meropenem; same patient as in refs.[27] and [30] with conflicting data: PT positive in ref.[192] and negative in refs.[27] and [30]	192
	1	10% pet.	Vancomycin caused a "relapse"[b] of DRESS after having suffered an episode of DRESS caused by sulfamethoxazole; the time period between DRESS and the relapse was not mentioned	27,30
	1	i.v. powder 10% pet.	Vancomycin was given during an episode of DRESS caused by phenytoin; unknown how it contributed to the clinical manifestations	58
	1	CP 15% and 30% pet.	Also positive patch test to culprit drug rifampicin; multiple other drug hypersensitivities, which may have contributed to DRESS and later developing TEN	140

(Continues)

TABLE 2 (Continued)

Drug	Number of patients positive	Patch test concentration and vehicle	Comments/additional information	Ref.
	1	4% water (possibly too low)	Flare-up after administration of the related teicoplanin, probably from cross-reactivity	231
	1	Not specified	Also positive patch test reactions to culprit drugs piperacillin-tazobactam and ciprofloxacin	38
	1	Not specified	Also positive PT to culprit drug meropenem	195
Zolpidem	1	Not specified		238
Zonisamide	1	Not specified		239
	1	Data not available	The skin eruption resembled TEN	240

Abbreviations: acet., acetone; AHS, anticonvulsant hypersensitivity syndrome; a.i., active ingredients; CP, commercial preparation (medication used by the patient or same drug in other application form); DHS, drug hypersensitivity syndrome; DiHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; Nr. pat., number of patients; ns, not specified; PBS, phosphate-buffered saline; PT, patch test; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]Probably also causing or contributing to DRESS.

[b]A "relapse" was defined as a transient re-occurrence of clinical symptoms and/or laboratory signs during or following the initial episode of DRESS (such as exanthema, recurrent eosinophilia, elevation of liver enzymes).

[c]Unclear whether the commercial drug was diluted at 10% pet. or whether it was diluted to achieve 10% active ingredients.

The classes of drugs causing the highest number of reactions are antiepileptic/anticonvulsant drugs with 208 positive patch tests (39% of the total of 536, 145/208 caused by carbamazepine, a total of 10 anticonvulsant drugs), beta-lactam antibiotics with 107 positive patch tests (20% of the total, 34/107 caused by amoxicillin, a total of 20 drugs), antituberculosis agents with 58 positive patch tests (11% of total, six drugs), non-beta-lactam antibiotics with 31 positive patch tests (6% of total, 10 or 11 drugs [data unclear]), and iodinated contrast media with 28 positive patch tests (5% of total, eight drugs).

3.2 | Sensitivity of patch testing in patients with DRESS

Data found on the sensitivity (percentage of positive reactions) of patch testing in DRESS are shown in Table 4.

As to individual drugs, sensitivity is very high for carbamazepine, ranging from 57% to 100% (median 83%) and for amoxicillin (44% and 100%). Reactions to allopurinol and sulfasalazine (sometimes called salazopyrine, which is actually also used as a trade name for sulfasalazine are consistently negative. Because of the high sensitivity of testing carbamazepine and amoxicillin, classes of drugs having high scores of positive patch tests are antiepileptic drugs and beta-lactam antibiotics, whereas the fluoroquinolone antibiotics are rarely positive.[58] In one study, 10 out of 12 patients (83%) with DRESS from iodinated contrast media had positive patch tests, but these results may have been biased by selecting patients on the basis of a positive skin or challenge test.[61]

From these data it follows that, in groups of patients with DRESS (from various drugs), the percentage of positive reactions may be heavily influenced by the nature of the culprit drugs. In groups in which the drugs tested were specified, the sensitivity ranged from 32% to 64%. The low 32% in one study[52] may be explained by the presence of 20 patients with DRESS caused by allopurinol or sulfasalazine, which drugs always test negative. Excluding these would have increased the sensitivity to 50%.[52] In four studies in which the drugs tested were not specified, sensitivity ranged from 50% to 60%, (median 56%). In one of these (where some drug data were given), nearly all positive patch test reactions were to carbamazepine.[243]

3.3 | Optimal patch test concentrations and vehicles

There is no published study in which drugs suspected of causing DRESS have been patch tested with various test concentrations and vehicles in a considerable number of patients and with the results fully specified. The literature review does not give any indication of optimal or preferred patch test concentrations and vehicles for individual drugs.

3.4 | Safety of patch testing in DRESS

In a group of 12 patients with DRESS from antituberculosis drugs, nine of whom had HIV-infection, eight had flare-up of DRESS symptoms after patch testing (all HIV-positive).[154] Three reacted to ethambutol, four to isoniazid, and three to rifampicin; two of these had flare-ups of DRESS symptoms to both ethambutol and isoniazid in sequential patch testing. The symptoms were eosinophilia in six out of

TABLE 3 Drugs causing positive patch tests in patients with DRESS

Drug	PPT, n
Carbamazepine	145
Amoxicillin	34
Isoniazid	22
Phenytoin	21
Ethambutol	18
Fluindione	16
Phenobarbital	13
Rifampicin	12
Ceftriaxone	11[a]
Meropenem	11
Vancomycin	11
Piperacillin-tazobactam	10[b]
Valproic acid	10[a]
Iobitridol	9
Amoxicillin-clavulanic acid	8
Lamotrigine	8
Dapsone	7
Ioversol	7
Mexiletine	5
Captopril	4
Cefoxitin	4
Cloxacillin	4
Esomeprazole	4
Flucloxacillin	4[a]
Olanzapine	4
Oxcarbazepine	4
Pristinamycin	4
Spironolactone	4
Acyclovir	3
Amikacin	3
p-Aminosalicylic acid (PAS)	3
Celecoxib	3
Ciprofloxacin	3[c]
Clindamycin	3
Iohexol	3
Iomeprol	3[a]
Metamizole	3
Pantoprazole	3
Piperacillin	3
Valaciclovir	3
Acetaminophen	2[a]
Benznidazole	2
Benzylpenicillin	2
Cefadroxil	2
Cefotaxime	2
Cefuroxime	2[a]
Cyanamide	2
Diclofenac	2[a]
Enoxaparin	2
Eslicarbazepine	2
Imipenem-cilastatin	2
Iodixanol	2
Ioxitalamic acid	2
Lansoprazole	2
Oxacillin	2
Penicillin V	2
Pyrazinamide	2
Sulfamethoxazole	2
Sulfamethoxazole-trimethoprim	2
Tetrazepam	2
Topiramate	2
Zonisamide	2
Acetylsalicylic acid	1
Amitriptyline	1[a]
Ampicillin	1
Atovaquone	1
Cefonicid	1
Cephalosporins (unspecified)	1
Chloroquine	1
Citalopram	1
Clarithromycin	1
Clobazam	1
Codeine	1
Dabrafenib	1
Dicloxacillin	1
Diltiazem	1
Doxofylline	1
Erdosteine	1
Ethosuximide	1
Fluvoxamine	1
Gadobutrol	1[a]
Hydroxychloroquine	1
Iopromide	1
Ioxaglic acid	1
Levofloxacin	1
Metronidazole	1
Miconazole	1
Minodronic acid	1
Nifurtimox	1
Norfloxacin	1[d]
Omeprazole	1

(Continues)

TABLE 3 (Continued)

Drug	PPT, n
Pefloxacin	1[d]
Phenindione	1
Potassium *p*-aminobenzoate	1
Proguanil	1
Propylthiouracil	1
Pyridoxine	1
Pyrimethamine	1
Ranitidine	1
Streptomycin	1
Teicoplanin	1
Tenoxicam	1
Tixocortol	1
Tribenoside	1
Zolpidem	1

Abbreviation: PPT, positive patch tests.
[a]In one of these patients (acetaminophen both), this drug did not cause DRESS, but induced a secondary non-DRESS hypersensitivity reaction (mostly a maculopapular eruption) during an episode of DRESS caused by another drug or after complete healing of this episode (multiple drug hypersensitivity).
[b]Possibly one or more extra.
[c]Possibly two, one may have been a cross-reaction to another culprit drug (norfloxacin or pefloxacin).
[d]Uncertain, may have been a cross-reaction to a culprit drug.

10 reactions, rash (erythematous, morbilliform) in six, elevated transaminases in five, fever in four, pruritus in four, nausea and vomiting in three, oedema in two, and epidermal necrosis and mucositis in 1 of 10 reactions (details of individual patients are shown in Table 5). Four of the 10 reactions were scored as grade 1 mild, 5 as grade 2 moderate, and one as grade 3 severe, using the Common Terminology Criteria for Adverse Events of the National Cancer Institute for adverse events, version 4.03.[246] All the reactions were managed with immediate removal of the patch tests and application of topical steroids. None was severe enough to warrant the use of systemic steroids.[154]

In another study of 39 patients who had positive patch tests to drugs that had caused DRESS, eight (21%) experienced DRESS in the form of a mild skin rash developing before the 72 hours reading. In two cases, general signs were noted and in one patient eosinophilia was found, but liver and kidney assays were normal.[241] Other cases in which DRESS symptoms were reproduced by patch testing are summarized in Table 5.

3.5 | Frequency of multiple drug hypersensitivity with positive patch tests

Few data on the subject of multiple drug hypersensitivity (MDH, also termed multiple drug hypersensitivity syndrome) in DRESS are available. In a large series of 46 patients with DRESS and positive patch tests to culprit drugs, 10 (22%) reacted to two or three unrelated drugs.[50] In a series from Portugal, 6 out of 10 (60%) patients with DRESS from an anticonvulsant (five carbamazepine, one phenytoin) developed delayed-type hypersensitivity to antibiotics (five amoxicillin, one cephalosporins and vancomycin) given during the DRESS episode.[58] In a study from Switzerland, of 46 patients with DRESS, seven (15%) had positive patch tests to two or more unrelated drugs (including the drug that initiated the DRESS episode), but only 15 of 27 patients who had clinical relapses were patch tested with the suspected drugs.[27,30]

Of the 437 patients with DRESS and a positive drug patch test found in the literature (Table 2, which include the studies mentioned above), 75 had reactions to two or more culprit drugs. In six of these, the drugs were of the same chemical/structural class and, therefore, were not considered to be MDH. In the other 69 individuals (16% of the total patient population), the drugs were of different classes, indicating MDH.[31] In this group, 56 individuals had two positive reactions, nine 3, one 4, two 5, and one 7 had positive patch tests, totalling 160 reactions. The drug classes most frequently implicated were anticonvulsants (n = 48, 30%), beta-lactam antibiotics (n = 35, 22%), antituberculosis agents (n = 29, 18%), and non-beta-lactam antibiotics (n = 18, 11%).

Individual drugs most frequently implicated in multiple drug hypersensitivity were carbamazepine (n = 26), amoxicillin (n = 13), isoniazid (n = 11), ethambutol (n = 10), vancomycin (n = 9), valproic acid (n = 8), ceftriaxone (n = 7), phenytoin (n = 5), and phenobarbital (n = 5). Of the 26 patients reacting to carbamazepine, 10 had co-reactions to other anticonvulsants and nine to antibiotics, most frequently amoxicillin (n = 6). Of the 13 patients with positive patch tests to amoxicillin, six co-reacted to carbamazepine and three to ioversol. All 11 patients who had positive patch tests to isoniazid co-reacted to other antituberculosis agents: nine to ethambutol, two to rifampicin, two to pyrazinamide, one to aminosalicylic acid, and one to streptomycin. Eight out of nine of the vancomycin-allergic patients co-reacted to one or more other antibiotics. All eight individuals sensitized to valproic acid also reacted to one or two other anticonvulsants, notably carbamazepine (n = 6). Co-reactions of two or three anticonvulsants were seen in 13 patients, to antibiotics in 12, and to antituberculosis agents in 10 individuals (all of different chemical/structural classes).

The classes of drugs and individual drugs most frequently positive in the 69 patients with MDH are largely the same as in the group of 368 individuals with DRESS who did not have MDH, but with some large differences in percentages (Table 6). Differences in the frequency of occurrence between the two disjunct subgroups of patients with vs. without MDH were compared with a Fisher's exact test, using the R statistical software package.[247] The percentages of all drug classes and all individual drugs, except carbamazepine and phenytoin, are significantly higher (*P*-value <.05) in the MDH group, the difference with phenobarbital being marginally significant.

4 | DISCUSSION

Regarding the results presented in Section 3 and the discussion in Section 4, it should be realized that (a) it is not known what proportion of patients with diagnosed DRESS has been patch tested (neither

TABLE 4 Sensitivity of patch testing in DRESS

Drugs	Nr. tested[a]	Positive patch tests n (%)	Comments	Ref.
Groups of patients				
Drugs not specified	68	39 (57)	Eight had mild flare of DRESS	241
	28	14 (50)		242
	16	9 (56)	Eight of nine reactions were caused by carbamazepine	243
	15	9 (60)		244
Drugs specified	72	46 (64)	Fourteen reactions to beta-lactams and 11 to carbamazepine	50
	56	18 (32)	The group consisted of 33 antiepileptic drugs, 19 allopurinol, and sulfasalazine, cotrimoxazole, tenoxicam, and amoxicillin, one each. 17/18 positive reactions were to antiepileptics (13 to carbamazepine) and 0 to allopurinol	52
	14	5 (36)	Children: drugs used were mostly antibiotics and anticonvulsants	67
Classes of drugs				
Antiepileptics	33	17 (52)	Thirteen caused by carbamazepine	52
	18	11 (61)	Unclear data in this article	81
	10	9 (90)	Six reactions to carbamazepine, 2 to phenytoin, one to topiramate; many co-sensitizations to antibiotics	58
Antibiotics	19	6 (32)	4/6 caused by amoxicillin	60
	17	9 (53)	Six reactions to amoxicillin and three to cephalosporins, 0/7 to fluoroquinolones (ciprofloxacin, levofloxacin); six of the nine reactors had primary DRESS to antiepileptics and three to allopurinol	58
Iodinated contrast media	12	10 (83)	The patients had been selected on the basis of a positive skin or challenge test, which may (partly) explain the high percentage of positive patch tests	61
Antibiotics, beta-lactam	10	9 (90)	Six positive reactions to amoxicillin	59
Fluoroquinolones	7	0 (0)	Five ciprofloxacin, two levofloxacin	58
Individual drugs				
Allopurinol	19	0 (0)	Allopurinol never shows positive patch tests	52
	18	0 (0)		245
	11	0 (0)	Some of these patients had AGEP or SJS/TEN	83
	7	0 (0)		58
	7	0 (0)		50
Amoxicillin	9	4 (44)		60
	6	6 (100)	Five had primary DRESS to carbamazepine and one to allopurinol	58
Carbamazepine	18	13 (72)		52
	13	11 (85)		50
	10	7 (70)		79
	7	4 (57)		85
	7	6 (86)		80
	6	6 (100)		58
	6	5 (83)		83
	6	5 (83)		82
Ciprofloxacin	5	0 (0)		58
Dapsone	16	7 (44)	Only shown in Abstract format	149
Lamotrigine	5	2 (40)		52
Phenytoin	7	2 (29)		22

(Continues)

TABLE 4 (Continued)

Drugs	Nr. tested[a]	Positive patch tests n (%)	Comments	Ref.
Salazopyrine[b]	7	0 (0)		245
Sulfasalazine	5	0 (0)		50

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; Nr., number; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.
[a]Minimally five patients patch tested with individual drugs.
[b]According to ChemIDPlus, salazopyrine is a combination of sulfasalazine (salazosulfapyridine) and *N*-methyl-D-glucosamine; however, it is also a Pfizer trade name for sulfasalazine tablets; the author assumes that the salazopyrine mentioned in ref.[50] is sulfasalazine.

TABLE 5 Exacerbations of DRESS symptoms after patch testing

Drug	PT concentration and vehicle	Symptoms and comments	Ref.
Amikacin	2.5 mg/mL saline	Generalized skin flare-up without other organ involvement	53
Aminosalicylic acid (PAS, *p*-aminosalicylic acid)	Sodium aminosalicylate 5% water	Generalized maculopapular eruption; the patient also had a positive patch test reaction to the culprit drug isoniazid; the patch test was performed far too soon after the episode of DRESS	56
Carbamazepine	No data available	Widespread erythema after patch testing on two occasions	131
	CP 5% pet.	Generalized skin rash	89
Esomeprazole	1%–10% "solution"	Mild erythroderma with facial oedema and desquamation	153
Ethambutol	CP 30% water and olive oil	Eosinophilia, elevated transaminases, nausea, vomiting; also erythematous rash and pruritus from patch testing isoniazid; patient with HIV infection	154
	CP 30% water and olive oil	Erythematous rash, oedema, pruritus; also erythematous rash from patch testing isoniazid; patient with HIV infection	154
	CP 30% water and olive oil	Eosinophilia, elevated transaminases, nausea, vomiting; patient with HIV-infection	154
Isoniazid	CP 30% water and olive oil	Fever, eosinophilia, elevated transaminases, morbilliform rash, nausea, vomiting; patient with HIV-infection	154,181
	CP 30% water and olive oil	Erythematous rash, pruritus; also eosinophilia, elevated transaminases, nausea and vomiting from patch testing ethambutol; patient with HIV-infection	154,181
	CP 30% water and olive oil	Erythematous rash; also erythematous rash, oedema and pruritus from patch testing ethambutol; patient with HIV-infection	154,181
	CP 30% water and olive oil	Fever, eosinophilia, erythematous rash	154,181
	CP powder, moistened	Generalized maculopapular eruption; the patient also had a positive patch test reaction to the culprit drug (*p*-) aminosalicylic acid (PAS); the patch test was performed far too soon after the episode of DRESS	56
Ranitidine	CP 30% pet.	Reactivation of previous positive patch tests, facial oedema, lymphopenia, and lymphadenopathy; patch tests were performed both on normal and on tape stripped skin	224
Rifampicin	CP 30% water and olive oil	Fever, eosinophilia, elevated transaminases, oedema; patient with HIV-infection	154
	CP 30% water and olive oil	Fever, morbilliform rash, pruritus; patient with HIV-infection	154

TABLE 5 (Continued)

Drug	PT concentration and vehicle	Symptoms and comments	Ref.
	CP 30% water and olive oil	Eosinophilia, elevated transaminases, epidermal necrosis, mucositis, pruritus; patient with HIV-infection	154
	CP 30% a.i. water and pet.	Generalized pruritus and rash, facial oedema, hepatitis, and eosinophilia; it was not mentioned whether the patch test with rifampicin was positive	225
Valproic acid	CP 20% water	Reintroduction of skin rash on the arms, legs, and face (in the DRESS episode described as pruritic morbilliform skin eruption with vesicular and target lesions)	168

Abbreviations: a.i., active ingredients; conc., concentration; CP, commercial preparation; pet., petrolatum; PT, patch test.

TABLE 6 Culprit drugs in patients with MDH vs those without MDH

Drugs	MDH group (n = 69) Positive reactions, n (%)	Non-MDH group (n = 368) Positive reactions, n (%)	*P*-value[a]
Classes of drugs			
Anticonvulsants	48 (69.6)	160 (43.5)	.029
Beta-lactam antibiotics	35 (50.7)	72 (19.6)	<.001
Antituberculosis agents	29 (42.0)	29 (7.9)	<.001
Non-beta-lactam antibiotics	18 (26.1)	13 (3.5)	<.001
Individual drugs			
Carbamazepine	26 (37.6)	119 (32.3)	.6
Amoxicillin	13 (18.8)	21 (5.7)	.0034
Isoniazid	11 (15.9)	11 (3.0)	<.001
Ethambutol	10 (14.5)	8 (2.2)	<.001
Vancomycin	9 (13.0)	2 (0.5)	<.001
Valproic acid	8 (11.6)	2 (0.5)	<.001
Ceftriaxone	7 (10.1)	4 (1.1)	<.001
Phenytoin	5 (7.2)	16 (4.3)	.36
Phenobarbital	5 (7.2)	8 (2.2)	.046

[a]Fisher's exact test.

the percentage nor culprit drugs); (b) selection may have influenced the available data (eg, investigating only patients treated with anticonvulsants or antituberculosis drugs); (c) clinical data were sometimes and patch data frequently incomplete, unclear or even absent; (d) patch tests have not infrequently been read after 24 or 48 hours only (which can lead to both false-negative and false-positive results); and (e) geographically, most patch testing has been practiced in a limited number of countries, which may influence results (e.g. the large number of positive patch test reactions to fluindione, which is widely used in France, where many studies of patch testing in DRESS and other SCARs have been performed).

4.1 | Drugs causing DRESS and showing positive patch tests

According to this literature review, 105 drugs that have caused DRESS also induced a positive patch test reaction, with a total of 536 positive patch tests. Over 40% of the 105 pharmaceuticals caused a single case only. More than 80% of the 536 patch test reactions were caused by drugs belonging to one of five drug classes: anticonvulsants (40% of total, of which nearly 70% was carbamazepine), beta-lactam antibiotics (20%, amoxicillin in 32%), antituberculosis agents (11%), non-beta-lactam antibiotics (6%, 35% vancomycin), and iodinated contrast media (5%, 32% iobitridol) (see Section 3.1). Fifteen individual drugs caused two-thirds of all reported DRESS cases with positive patch test reactions (Table 3): carbamazepine, amoxicillin, isoniazid, phenytoin, ethambutol, fluindione, phenobarbital, rifampicin, ceftriaxone, meropenem, vancomycin, piperacillin-tazobactam, valproic acid, iobitridol, and amoxicillin-clavulanic acid. These data generally correspond well to the data in review articles on DRESS not selected for positive patch testing, where it is often stated that DRESS is caused by a "limited number of drugs" and where the same drug classes and individual drugs are usually also mentioned as culprit drugs for DRESS (Table 1). However, there are also some major differences: allopurinol, sulfasalazine and dapsone are always mentioned as

(frequent) culprit drugs in DRESS, but allopurinol and sulfasalazine have never caused positive patch tests and dapsone has done so in only one study.[149]

In the studies found in this review, allopurinol has been patch tested in 62 patients with zero positive results.[50,52,58,83,245] There is no definite explanation for these (false-) negative results, but there may be several possible causes: (a) the final responsible agent is a drug metabolite that is not formed in the skin during patch testing; (b) there is no immune mechanism involved; (c) concomitant factors that are responsible in inducing transient drug intolerance, such as viral infection, are not present at the time of testing; and (d) wrong choice of vehicle (limited skin penetration), drug concentration, or exposure time.[52] When administered orally, allopurinol is rapidly converted into its oxidative metabolite 8-oxypurinol,[52] which may be the culprit in drug hypersensitivity to allopurinol, as these reactions appear to be primarily mediated by an oxypurinol-specific T cell response.[52,248] In spite of this, patch tests with oxypurinol 5% and 10% pet. have also been consistently negative in patients with allopurinol-induced DRESS.[52,249] A recent hypothesis is that oxypurinol is rapidly bound in the peptide-binding groove of the HLAB*5801 molecule without requiring peptide processing. The net result is a novel drug peptide-HLA complex that drives the immunological reaction resulting in allopurinol-related SCARs.[250]

Sulfasalazine, a drug used for the treatment of Crohn's disease and rheumatoid arthritis, is a well-known cause of DRESS, but patch tests have never been positive.[50,52,229,245,251] A possible relationship between allergy to sulfasalazine, and especially its active metabolite mesalamine (mesalazine) and *p*-phenylenediamine (PPD), has been suggested.[251-253] However, mesalamine is 5-aminosalicylic acid and, therefore, not a para-compound. Nevertheless, the clinical data were not unconvincing. Also, it was found that mesalamine contains traces (≤0.01%) of *p*-aminophenol (which nearly always cross-reacts to PPD) and that *p*-aminophenol can also be produced by decarboxylation of mesalamine.[253]

Dapsone is used mainly for the treatment of leprosy and dermatitis herpetiformis. Although this drug is frequently mentioned as a cause of DRESS (better known as dapsone hypersensitivity syndrome), only one report of seven positive patch test reactions was found.[149] Possibly, in countries with many leprosy patients, patch tests are infrequently performed.

4.2 | Sensitivity of patch testing in patients with DRESS

The usefulness of patch testing in DRESS depends on its sensitivity (ie, the percentage of positive patch tests). High yields have been observed with testing anticonvulsants (especially carbamazepine), beta-lactam antibiotics (especially amoxicillin), and iodinated contrast media, but in the latter case, the patients had been selected on the basis of a positive patch or challenge test (Table 4). Patch testing dapsone may also be sensitive, although only one study is available, apparently only in Abstract form.[149] Patch testing allopurinol and sulfasalazine does not seem to be useful (always negative, Table 4), but when other drugs may also be involved in the DRESS episode, this diagnostic test should certainly be considered. For most other drugs, insufficient data are available to establish the patch testing sensitivity. In four groups of patients with DRESS from unspecified drugs, patch tests were positive in >50% of cases.[241-244] Despite the lack of data, considering the fact that delayed-type hypersensitivity is involved in DRESS, routine patch testing of all drugs used by the patients with DRESS (>6 months after complete healing) seems appropriate.

4.3 | Optimal patch test concentrations and vehicles

As shown in Table 2, a large range of concentrations has been used for drug patch tests in patients with DRESS. In most cases, the commercial preparations taken by the patients (often tablets) have been pulverized and the powder used for patch testing. Formerly, a concentration of 30% pet. and/or water for commercialized drugs has been recommended for patch testing in delayed drug eruptions including DRESS),[254] and this concentration has indeed frequently been used (Table 2). Pure drugs were tested in a minority of cases (especially amoxicillin), probably due to difficulties in obtaining these. From the studies presented thus far, no evidence for the optimal patch test concentration and vehicle for any drug has emerged and, therefore, some practical recommendations are given here, which also apply to other delayed-type drug hypersensitivity reactions.[4,255-257]

In the author's opinion, patch testing should be the first diagnostic method in the search for the drug(s) that are responsible for cutaneous adverse drug reactions, with the possible exception of cases where patients with DRESS had used only allopurinol or sulfasalazine. Preferably, the pure drugs, not the commercialized tablets, used by the patients, should be tested to obtain well-defined test materials and to avoid false-positive results (ie, not indicating hypersensitivity to the active drug material) due to hidden additives in the drug formulations, degradation products, or impurities. Over 80 drugs for systemic use are commercially available from Chemotechnique Diagnostics (www.chemotechnique.se), SmartPractice Canada (www.smartpracticecanada.com), and SmartPractice Europe (www.smartpracticeeurope.com) (Table 7).

Most (other) pure systemic drugs can be tested at 10% pet. When the pure chemical is not available, the test material can best be prepared from intravenous powder, the content of capsules or – when also not available – from powdered tablets, to achieve a final concentration of the active drug of 10% pet. wt/wt.[4,255,256,257] When the content of the active drug is too low in the patient's drug to achieve a 10% concentration, the whole powder should be diluted in 30% pet., which is non-irritant for nearly all commercial medications.[258] When possible, the excipients of the pharmaceutical should also be patch tested. Alternatively, combined commercial drug and pure drug testing may point at either excipients or the active drug being the sensitizer,[255] but excipients are probably rarely responsible for DRESS. Heparins/heparinoids, local anaesthetics, and iodinated contrast media can be tested as commercial preparations, undiluted.[42] Positive patch test results obtained with in-house preparations should

TABLE 7 Drugs used systemically that are commercially available for patch testing[a]

Acetaminophen (paracetamol)	Dexketoprofen	Norfloxacin
Acetylsalicylic acid	Diclofenac	Nystatin
Acyclovir	Diclofenac sodium salt	Oxytetracycline
Aminophenazone	Dicloxacillin sodium salt hydrate	Paracetamol (acetaminophen)
Amoxicillin trihydrate	Diltiazem hydrochloride	Penicillamine
Ampicillin	Diphenhydramine hydrochloride	Phenacetin
Articaine hydrochloride	Doxycycline monohydrate	Phenazone
Betamethasone dipropionate[b]	Erythromycin	Phenylbutazone
Captopril	Fenofibrate	Phenylephrine hydrochloride
Carbamazepine	Fusidic acid sodium salt	Piperazine
Cefalexin	Gentamicin sulphate	Piroxicam
Cefixime trihydrate	Hydrochlorothiazide	Polidocanol
Cefotaxim sodium salt	Hydrocortisone	Polymyxin B sulphate
Cefpodoxime proxetil	Hydrocortisone acetate	Potassium clavulanate
Cefradine	Hydroxyzine hydrochloride	Prednisolone
Cefuroxime sodium	Ibuprofen	Prilocaine hydrochloride
Chloramphenicol	Indomethacin	Procaine hydrochloride
Chlorpheniramine maleate	Kanamycin sulphate	Promethazine hydrochloride
Chlorpromazine hydrochloride	Ketoprofen	Propranolol hydrochloride
Chlortetracycline hydrochloride	Lamotrigine	Propyphenazone
Ciprofloxacin hydrochloride	Lidocaine	Quinine sulphate
Clarithromycin	Lidocaine hydrochloride	Spiramycin
Clavulanate potassium	Mepivacaine hydrochloride	Streptomycin sulphate
Clindamycin phosphate	Metamizole	Sulfamethoxazole-trimethoprim
Clioquinol	Methylprednisolone aceponate	Tetracycline hydrochloride
Cotrimoxazole	Metronidazole	Tixocortol pivalate[c]
Dexamethasone	Naproxen	Tobramycin
Dexamethasone-21-phosphate (disodium salt)	Neomycin sulphate	Triamcinolone acetonide
	Nitrofurazone	Vancomycin hydrochloride

[a]Adapted from ref.[255] For oral or parenteral (intravenous, intramuscular, subcutaneous injections) administration or as enema.
[b]Available for patch testing in cases of suspected betamethasone allergy (the dipropionate ester is not used systemically itself).
[c]Available for patch testing in cases of suspected tixocortol allergy (the pivalate ester is not used systemically itself).

always be validated with controls to exclude irritancy of the patch test material.[256]

In the case of DRESS (in which viruses often play a role), it is advised to wait 6 months after disappearance of the skin exanthema and other sequelae, in order to avoid any virus reactivation.[36,40] The patch test materials should be removed after 2 days and the reactions read 30 minutes later; a second reading at day (D) 3 or D4[259] is necessary and a later reading at D7 (or D8–D10) is strongly recommended, the latter especially for corticosteroids (due to the anti-inflammatory effect of the molecule),[260] iodinated contrast media, heparins, and aminoglycoside antibiotics.[255]

Test reading is usually performed according to the ESCD guidelines for conducting patch tests (at least in Europe)[256]; the system used by the German Contact Allergy Group is virtually identical.[261] The relevance of any positive drug patch test should be carefully assessed.[262,263] A positive patch test result can help to confirm a possible culprit drug and mostly abolishes the need for further diagnostic testing. However, it must be stressed that a negative patch test result does not exclude the drug tested as the or one of the chemicals responsible for the observed DRESS hypersensitivity reaction. With negative patch test results, further diagnostic tests are necessary, the second step usually being an IDT with delayed readings[255] (see also Section 2.6.2).

4.4 | Safety of patch testing in DRESS

Generally, performing patch tests in DRESS is considered to be a safe procedure.[2,10,11,20,21,255] Indeed, few studies have reported a flare-up of DRESS symptoms resulting from patch testing and none has

threatened patients' health (Section 3.4 and Table 5). Yet, the finding of eight patients with skin rashes from patch testing in 39 patients with DRESS and positive patch tests (albeit apparently only presented in Abstract form)[241] and a series of eight patients in another investigation[154] suggests that such reactions may not be rare. Most flare-ups from patch testing appear to be (largely) limited to the skin. For systemic reactions (fever, eosinophilia, elevated transaminases), HIV infection, and possibly treatment with antituberculosis drugs appear to be risk factors.[154,181] In such patients, starting with patch testing at a dose lower than 10% active ingredients may be considered, possibly enhancing the safety of the procedure.

4.5 | Frequency of multiple drug hypersensitivity with positive patch tests

Delayed-type hypersensitivity reactions in a patient with DRESS to two or more drugs from different chemical/structural classes, as shown by positive patch tests,[30,50] positive delayed IDTs, or in vitro tests, such as the lymphocyte transformation tests, are observed not infrequently in patients with DRESS. This is called MDH or "MDH syndrome."[27,28,31,58,99] MDH develops as a consequence of massive T cell stimulations and is characterized by long-lasting drug hypersensitivity reactions (DHR) to different drugs. There appear to be three subtypes of MDH: (a) simultaneous MDH, in which two or more sensitizations occur against drugs given at the same time; (b) sequential MDH, in which two or more sensitizations develop to drugs given for the same episode (subsequent symptoms overlapping with the first DRESS symptoms); and (c) distant MDH, in which symptoms of a new drug hypersensitivity reaction appear when the initial DRESS episode has already disappeared, sometimes years apart.[31,99] The reactions in sequential and distant MDH may either be DRESS or another clinical manifestation,[28,30,31,99] mostly maculopapular exanthemas.[27,30,58] Risk factors for developing MDH in DRESS appear to be certain medicaments (antiepileptics, sulphonamide antibiotics, sulfasalazine, allopurinol), high drug doses, treatment with a fixed combination therapy (eg, amoxicillin/clavulanic acid, cotrimoxazole [sulfamethoxazole/trimethoprim], piperacillin/tazobactam, two or more antituberculosis drugs, or antiepileptics), and longer-lasting (>10–20 days) treatment.[31]

It has been claimed that drug-related "flare-up reactions" of DRESS during the initial episode are not part of MDH syndrome. These reactions, which may appear 2–4 hours to 2 days after the introduction of a new drug, are characterized by transient and rapid reappearance or aggravation of identical DRESS symptoms (skin reaction, transient increase in the number of circulating eosinophils and/or liver enzymes), while the immune system is still activated from the DRESS episode. Such flare-ups do not lead to sensitization to the drug: it is given only briefly, as the drug is quickly withdrawn after the flare-up. Skin tests and in vitro tests with these drugs remain negative and the drugs will later be tolerated when the activation of T cells caused by the initial DRESS episode has resolved. However, when the treatment lasts longer, a second, true DHR directed against the alternative drug may develop, resulting in MDH.[27,31]

One of the aims of this review was to investigate the frequency of MDH in DRESS, as shown by two or more positive patch tests to chemically/structurally unrelated drugs. Patients reacting to drugs from the same class that may cross-react, for example, beta-lactam antibiotics or fluoroquinolones, are not considered as having MDH. In the literature, two or more reactions to antiepileptic drugs are often termed "cross-reactions."[81] Given the dissimilar structures of the various drugs of this therapeutic class (with the exception of carbamazepine and oxcarbazepine), this is probably incorrect and patients reacting to two or more anticonvulsants can be considered as having MDH.

Reported percentages of MDH based on positive patch tests in series of patients with DRESS have been 22,[50] 60 (only 10 patients)[58] and 15.[27,30] The aggregated literature data in Table 2 show MDH in 16% of the patch test positive DRESS patients. There is no study in which, of large groups of patients with DRESS, all individuals, including those with relapses or secondary reactions, were patch tested with every drug used. Given the infrequent occurrence of DRESS, it will be very difficult to collect such data. Therefore, it is very hard to make a substantiated estimation of the frequency of patch-test-proven MDH in DRESS. However, it is highly likely that its true prevalence is far higher than the 16% calculated in this review. This assumption is based on the following considerations: (a) most likely, only a minority of patients with DRESS are patch tested (which may, of course, also result in a lower percentage of MDH); (b) not always does patch testing include all drugs used by the patients; (c) some patch tests may be false-negative; (d) allopurinol and sulfasalazine are frequent causes of DRESS, but patch tests are always negative and are therefore not counted as MDH; (e) patients with possible MDH who were not patch tested or were patch test negative, but who did have positive delayed IDTs, in vitro tests (LTT, ELISPOT), or both (which tests also prove the existence of delayed-type hypersensitivity to the drugs) were also not counted as having MDH.

When looking at the culprit drugs in MDH, there is a statistically significant overrepresentation in the MDH patient group vs the non-MDH patients of all four major drug classes (anticonvulsants, beta-lactam antibiotics, antituberculosis agents and non-beta-lactam antibiotics) and the individual drugs amoxicillin, isoniazid, ethambutol, vancomycin, valproic acid, ceftriaxone and phenobarbital, but not carbamazepine and phenytoin. In 50% of the patients, there were co-reactions of at least two anticonvulsants, of at least two antibiotics (not of the same chemical/structural class), or of two or more antituberculosis agents. Co-reactions in the latter group is likely to be the result of first-line antituberculosis treatment with the combination of isoniazid, ethambutol, rifampicin, and pyrazinamide.[154] Antiepileptics may also be given in combination to patients and sequential administration of different drugs can occur when therapy is ineffective or when one drug is stopped because of the development of DRESS and immediately replaced with another when continued antiepileptic treatment is indicated. The overrepresentation of beta-lactam antibiotics (notably amoxicillin and ceftriaxone) may be the result of treatment with these drugs because of suspicion of a bacterial infection at the onset of DRESS (because of the high fever) or a flare-up during

the DRESS episode. Half of all reactions to non-beta-lactam antibiotics were caused by vancomycin, which is a last resort antibiotic, given only when others do not work. Possibly, this antibiotic was given to patients with DRESS when other antibiotics were perceived to fail, for example, because of persistent – non-infectious but DRESS-related – fever. Indeed, in eight of the nine cases of vancomycin allergy, co-reactions were observed to one or more other antibiotics.

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DATA AVAILABILITY STATEMENT

Research data are not shared

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