**Utility and safety of skin tests in drug reaction with eosinophilia and systemic symptoms (DRESS): a systematic review**

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**Abstract**

**Background**

Determination of culprit drug in drug reaction with eosinophilia and systemic symptoms (DRESS) is crucial. Skin tests have been utilised, although it remains unclear how sensitive these are.

**Objective**

We set out to determine the value of skin tests in the assessment of drug causality in DRESS.

**Methods**

A systematic literature search was conducted for publications from 1996 onwards of skin tests (skin prick test = SPT, patch test = PT, intradermal test = IDT) performed in clearly defined DRESS cases. Outcomes of testing, drug culpability assessments and challenge test data were extracted.

**Results**

17 articles met inclusion criteria. In 290 DRESS patients, patch testing was most frequent [PT = 97.2% (n=282), IDT = 12.4% (n=36), SPT = 3.1% (n=9)]. Positive results were noted in 58.4% (n=160/282) of PT, 66.5% IDT and 25% SPT. When confidence of drug causality was high (n=73 of 194), testing did not correlate well with clinical suspicion: PT 37.6%; IDT 36.5%. Direct comparison of skin testing with provocation testing (n=12) showed 83.3% correlation. Positive IDTs were reported in 8 negative PT cases.

**Conclusion**

Skin tests, particularly PT and IDT, have been reported as tools for diagnosis of causal drugs in DRESS. Heterogeneity in methodology, results analysis and reporting of cohorts, makes meta-analysis to determine sensitivity and specificity of published literature impossible and highlights weaknesses in the field. We propose that international collaboration is essential to harmonise the methodology and reporting measures from hypersensitivity testing studies in larger cohorts.

**Highlights**:

1. What is already known about this topic?

• Drug culpability can be challenging in DRESS patients, with no validated diagnostic test available.

2. What does this article add to our knowledge?

• Significant heterogeneity in methodology and reporting is evident in current practice

• In 17 articles included for analysis, sensitivity on patch, intradermal and prick tests were 58.4%, 66.5% and 25% respectively

3. How does this study impact current management guidelines

• This systematic review shows that patch and intradermal tests are safe and can be utilised as part of diagnostic work-up in DRESS to identify culprit drug.

**Keywords**

Drug reaction with eosinophilia and systemic symptoms

Drug patch test

Intradermal test

Skin prick test

**Abbreviations**

Anticonvulsant hypersensitivity syndrome (AHS)

Confidence interval (CI)

Delayed drug hypersensitivity (DHR)

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug induced hypersensitivity syndrome (DIHS)

Drug induced delayed multiorgan hypersensitivity syndrome (DIDMOHS)

Intradermal test (IDT)

Negative predictive value (NPV)

Positive predictive value (PPV)

Patch test (PT)

Severe cutaneous adverse drug reaction (SCAR)

Standard deviation (SD)

Skin prick test (SPT)

**Introduction**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a form of severe cutaneous adverse drug reaction (SCAR). First described in 19961, awareness of this phenotype of SCAR has gradually increased, but the term drug induced hypersensitivity syndrome (DIHS) is also used in some countries2. Whilst the cutaneous presentation can be variable3-5, typical features of fever, lymphadenopathy, facial oedema, haematological abnormalities (most often eosinophilia or atypical lymphocytes) are consistently described1, 2, 4, 6.Increasingly, reactivation of viruses such as human herpes virus 6 (HHV6) and cytomegalovirus in the weeks following onset2, 7, 8 have been observed. Latency of between 2 - 8 weeks following commencement of causal drug6, 9 can result in misdiagnosis as the clinical features of DRESS can be similar to that of an infection with fever, lymphadenopathy and a rash. Of greater concern is the presence of internal organ involvement, most commonly hepatic, although renal, pulmonary, neurological, pancreatic and cardiac effects have all been reported3, 9-12. Resultant mortality is between 2-6%13 therefore, early discontinuation of the causative drug is essential. Crucially, further exposure to the culprit drug can result in a severe recurrence of the condition, with shorter time to onset2. Autoimmune sequelae can also arise years after the index episode14. Lifelong avoidance is therefore recommended but this is complicated when there are difficulties in identifying the culprit drug in those taking multiple medications.

While *in vitro* testing is available in relatively few specialised centres, *in vivo* tests such as skin tests have comparatively more widely been undertaken. The clinical utility of these remains uncertain due to variable sensitivity reported15, 16. Certain medications, in particular allopurinol and sulfamethoxazole, also seemingly give rise to false negative results on patch tests16-19. Although a challenge exposure with suspect medication remains the ‘gold standard’, this carries associated risk of re-elicitation of DRESS and is therefore often not performed16. We undertook this systematic review to critically appraise the published evidence for the utility of patch tests (PT), intradermal tests (IDT) and skin prick tests (SPT) in DRESS.

**Methods**

Systematic review of the bibliographic databases (Medline, Embase, and Web of Science) was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the search protocol detailed and registered on PROSPERO (CRD42019136977). In brief, publications were searched using the terms ‘DRESS’, ‘DIHS’, ‘drug reaction with eosinophilia and systemic symptoms’, ‘drug induced hypersensitivity syndrome’, ‘drug induced delayed multi-organ hypersensitivity syndrome’, ‘anticonvulsant hypersensitivity syndrome’, or ‘severe cutaneous adverse drug reaction’. Results were combined (‘AND’) with a search report using ‘skin tests’, ‘intradermal tests’, ‘prick tests’, or ‘patch tests’. Inclusion and exclusion criteria are as listed in **Table 1**.

Search results from 1996 onwards (when DRESS was first reported as a clinical entity)1 were reviewed by 2 independent reviewers (YT, MAJ). Following independent abstract screening by both reviewers based on pre-specified inclusion/exclusion criteria, full text articles were assessed for inclusion. Disagreements were resolved by discussion. Publications with at least 3 DRESS (or synonymous term) cases which reported skin testing results were included, to ensure that cases included were diagnosed by clinicians with adequate experience in identification of DRESS and consideration of likely culprit medications. Retrospective studies and publications where DRESS subjects were tested as part of a larger cohort were included. Careful attention was made to include the same patient cohort only once. Where unclear or data was not included in publication, corresponding authors were emailed to request further information.

The data extracted from each report included: first author, publication year, type of study, number of DRESS patients, target population characteristics, time interval to testing, test intervention (PT, SPT, IDT), and other interventions performed such as challenge test. For those reports comparing a skin test result with a clinical assessment of causality we assigned a pre-test clinical confidence in culpability of the tested drug as probable, possible, or not mentioned. ‘Probable’ was assigned if this was clearly stated in the manuscript, ‘possible’ if multiple drugs were assessed when not in the context of testing for cross-reactivity and ‘not mentioned’ if it was not possible to determine if the drug tested was thought to be a suspect drug or performed as part of exploratory research. Reports of skin test results in cases who were exposed to the culprit drug by inadvertent reintroduction were included in the challenge tested group. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system20 was used for grading quality of included publications and against the Standards for Reporting of Diagnostic Accuracy Studies (STARD)21 by two authors (YT, MAJ). Publications were scored high, low or uncertain based on risk of bias to patient selection, testing (blinded or unblinded performance and detection, taking into consideration that blinding to testing would not be possible in skin testing), result reporting and high, intermediate or low to quality of study as assessed based on skin testing utility in DRESS. The subject cohort was considered a ‘unique cohort’ if only DRESS subjects were included in the study. Due to absence of ‘gold standard’ reference test for DRESS, this criterion was not included.

Where individual ages for patients were published, average age by publication and subsequently median age for all included articles were calculated. Narrative synthesis of findings of tested population demographics, type and outcome of testing and any identifiable drug culpability assessment prior to testing and subsequent challenge was performed. Where skin tests were performed to explore cross-reactivity, data was analysed separately.

**Results**

**Search results**

797 abstracts were identified from database search, of which 49 were duplicates and therefore removed. 699 of the 748 remaining abstracts were screened on relevance to topic of interest (**Figure 1**), with 97.9% (48/49) agreement between reviewers. There were 49 articles fully assessed. Corresponding authors were contacted via email for clarification if type of skin test performed and/or total number of DRESS subjects were not stated. Review of publications related to skin tests in delayed drug hypersensitivity during drafting if this manuscript identified two further publications, which were included for analysis..

A total of 17 articles met inclusion criteria (**Table 2**). Of the 34 publications excluded, 16 were found not to include any DRESS cases, 5 did not specify clearly the phenotype of subjects, 8 did not contain primary data on cases not previously published and 5 publications reported outcomes in two or fewer subjects. Of the studies included, 9 were performed retrospectively, 6 prospectively and 2 were case series. 8 of these examined DRESS cases exclusively whilst the rest of the articles assessed DRESS subjects alongside other cutaneous adverse drug reactions as well. Of the 3 types of skin testing reported, PT was the most frequently performed, [PT = 97.2% (n=282 patients), IDT = 12.4% (n=36), SPT = 3.1% (n=9)].

**Risk of bias**

Individual publications were assessed for bias based on several parameters as shown in **Figure 2**. In general, the risk of selection bias was high due to: i) the nature of the condition studied being of low incidence requiring retrospective analysis; ii) participants being pre-selected based on previous testing outcomes; iii) high confidence in single tested culprit drug; iv) and non-blinded assessments. In 4 of the included manuscripts, the main objective of the reported work was not the diagnostic utility of skin testing (utility of extemporaneous PT, comparison of testing in different delayed reaction phenotypes, reporting of cases due to drugs not previously implicated as causative of DRESS, genetic polymorphism in DRESS).

**Cohort demographics and diagnostic protocols**

A total of 335 DRESS cases were identified cumulatively from all 17 publications, of which 290 underwent skin testing. Demographics of the 335 cases are as follows: mean age 58 years (SD 7.6, range 17-93 years; data available in 11 publications); 1.2:1 males: females (data available in 13 publications). None of the manuscripts clearly described whether reported patient ages were at DRESS onset or at time of testing. An important immunological variable is the timepoint after DRESS at which testing is performed. No mention was made on time from index reaction to testing in 4 publications, whilst others reported testing between 4 weeks to 6 months from resolution or discontinuation of corticosteroid use (**Table 2**). No publications reported the exact time duration between DRESS onset and skin testing performed for every subject.

Test protocol was stated for patch testing or intradermal testing as ‘in accordance with’ the European Society of Contact Dermatitis for PT or European Network on Drug Allergy/ European Academy of Allergy and Clinical Immunology for IDT (respectively) (22, 23) recommendations in 64.7% (n=11) of manuscripts. Delayed reading of up to 7 days following testing was performed in 25% (n=4) studies. In all positive PT, a reaction was present by day 2.

**Safety**

Risk of systemic reactivation or safety was mentioned as a consideration in drug skin testing in 7 publications. In all, 1 patient developed a maculopapular exanthem attributable to skin testing provocation. No differences were noted between SPT, PT and IDT, in terms of proportion of systemic reactions, but numbers precluded a reliable analysis.

**Results by individual patient**

13 publications reported results according to the drug tested and not by individual patient. Results of testing in individual patients were reported in 293 cases18, 24-36, with some patients having more than 1 form of skin testing. Absolute number of drugs and the individual drugs tested in every patient was not able to be determined based on the published data. On a per patient basis (regardless of the drug), PT, IDT or SPT were positive in 56.7% (n=160/282), 50.0% (n=18/36) and 22.2% (n=2/9) of cases respectively. To examine the potential bias in reporting, we examined the distribution of positive rates per publication. On a per manuscript basis, the per patient percentage of positive test results varied significantly, with overall mean 62.2% (SD 30.1%), and for individual testing modalities: PT mean 58.4% (range 0-100%, SD 31.1); IDT mean 66.5% (range 28.6-100%, SD 25); SPT mean 25% (range 0-50%, SD 23.9).

12 patients had skin testing and challenge testing (accidental re-introduction or to drug negative on skin testing) to a suspected causal drug (**Table 3**). No patients with positive IDT received a challenge. Skin tests correlated with challenge reaction in 83.3% (n=10) of cases. Two cases with negative skin tests had a positive challenge test (both to allopurinol). Overall, 54.5% (n=6) of challenges were positive: 3 recurrences of DRESS, 1 maculopapular exanthem, 2 not specified. Test concentrations where published are listed in **Supplemental Tables E1 and E2**, no information on skin prick test concentrations were available.

**Results by medication in individual patients**

Four papers reported individual patients undergoing testing of more than one medication and detailed results by medication (18, 30, 31, 37). 62 different medications (inclusive of PT, IDT and SPT) were tested. Antibiotics and anti-epileptics were the most commonly tested (test performed: PT: antibiotics = 72, anti-epileptics = 56; IDT: antibiotics = 42; SPT: antibiotics = 5). No IDT or SPT were performed for anti-epileptic drugs. The proportion of positive results to antibiotics were: PT 48.6% (n=35), IDT 50.0% (n=21), SPT 40% (n=2), whilst to beta-lactams specifically: PT 51.8% (n=29 of 56), IDT 52.9% (n=18 of 34), SPT 100% (n=2 of 2) (**Table 4**).

**Results by type of skin test**

Data extracted was then examined for the number of positive results per test performed, regardless of whether an individual patient underwent multiple tests. Although PT were performed in 282 patients, it was only possible to determine total numbers of individual patients tested per medication in 217 cases, of which 43.8% (n=95) were positive. Of 52 IDT performed, 40.4% (n=21) elicited a positive reaction. 28.6% (n=2) of 7 SPT were positive (**Table 5**).

To examine the accuracy of skin tests, we sought to compare the correlation between positive results for the different skin test modalities against outcome of challenge testing. Because there were very few reports comparing skin testing to challenge testing, we applied clinical confidence (‘probable’ or ‘possible’, see methods for definition) as a pseudo-gold standard to compare skin testing to (**Supplemental Table E3**). Skin testing was consistent with clinical attribution of drug culpability in 37.4% (n= 74 of 198) [‘probable’ in 29.8% (n = 59 of 198) and ‘possible’ in 7.5% (n=15 of 198)] of PT and 36.5% (n=19 of 52) of IDT [‘possible’ in 25% (n=13 of 52) and ‘probable’ in 11.5% (n=6 of 52)]. It was not possible to determine level of confidence in drugs tested by SPT. In those tested with both PT and IDT (n=21), 9 cases (42.9%) were reported with negative PT and positive IDT. One case showed negative IDT and positive PT, and following accidental re-exposure to the same drug, developed an exanthem and liver blood test derangement. Clinical confidence in drug imputability was ‘probable’ in 59 PT performed to 9 different drugs (allopurinol, carbamazepine, cobimetinib, fluoindione, hydantoin, piperacillin-tazobactam, phenobarbital, phenytoin, topiramate, vemurafenib). Of these, only 33.9% (n=20) showed a corresponding positive PT result.

**Cross-reactivity**

Cross-reactivity was reported in 8 manuscripts (18, 24, 28, 29, 34, 35, 38), and was most frequently reported for anti-epileptic medications, in particular carbamazepine with oxcarbazapine. Reports showed evidence of cross-reactivity in DRESS by both PT (34/92, 37.0% positive) and IDT (21/52, 40.3% positive). In 8 cases, skin test result (PT or IDT) were compared to challenge testing and in all such cases, skin testing (PT or IDT) correlated with challenge outcome (**Table 6**).

**Discussion**

Skin tests are relatively straightforward, inexpensive and easy to perform, and are used routinely for the investigation of allergic contact dermatitis and type I IgE mediated hypersensitivities. In this systematic review of the published literature, we set out to examine the evidence for diagnostic accuracy of skin testing modalities in the investigation of DRESS. As expected by established mechanistic understanding, SPT was used less, which is to be expected based on knowledge of pathophysiology of DRESS. However, the sample size was too small to definitely conclude that it is less useful as compared to IDT or PT. It was notable that, in addition to other limitations, test methodology was variable across the published reports, including time to testing, concentrations used, testing to panels inclusive of drugs not clinically suspected, and duration of reviews increased the risk of bias. In addition, we identified that overall, the risk of selection bias in the reported cohorts was very high. Principally this arose because few studies were prospective. Therefore, although we report that proportions of positive responses in patch test and intradermal tests were similar (56.7% vs 50%), the clinical interpretation needs significant caution because of potential bias resulting from differences in the tested populations, including smaller number of patients IDT tested and to medications available in injectable formulations. Only a select number of patients from the same centres had IDT performed and in such cases, IDT may have been performed subsequent to PT, whereby duplicate testing modalities may not have been performed as positive results had already been excluded on PT. This would therefore reduce the apparent sensitivity of IDT. Such differences were highlighted most strongly by the wide distribution of percentage positive assays in different manuscripts, where the range varied from 0-100% for PT and 28.6-100% for IDT.

The frequent poor clinical characterisation of the index reaction is important as it is accepted that the pathomechanisms involved in SCAR phenotypes vary (39), suggesting that investigational approaches will show differing pre-test probabilities. Therefore, detailed clinical information is critical for each patient: classification of index reaction, time between index reaction and test date, comorbidities (especially immune dysfunction or cancer), concurrent medications (especially immunosuppressant / immunomodulators) and prior allergic history. In comparing across classes, it is important to be mindful of inevitable selection bias. For example, of the 56 cases of DRESS who had PT to anti-epileptics, 37 (66%) were carbamazepine tests, whereas all other anti-epileptics made up only 5-11% of the data, which demonstrates the risk of bias by analysis of drug classes caused by skewed frequencies of testing. Furthermore, even though anti-epileptic hypersensitivity accounts for a significant proportion of DRESS cases, there were no IDT to compare with PT. This likely reflects the limited availability of intravenous formulations. Potential cross-reactivity between different tested substances is an important issue clinically, and is essential to account for in a metanalysis approach to the data to prevent overestimation of positive detection caused by multiple positive tests from cross-reacting drugs, but while cross-reactivity was recorded in 8 publications and showed similar utility for PT and IDT (37% vs. 40%), reporting of assessments at a patient level is not routine and hence there is a risk of bias from multiple testing to structurally related compounds in the same individual. Therefore, as earlier, the cross-reactive investigation data should be interpreted with caution.

These results need to be interpreted with caution because of the inclusion of drugs that are unlikely to show positive results with skin tests. Patch testing cohorts of known allergic individuals demonstrates that some drugs, for example carbamazepine, show a strong correlation between patch testing results and clinically determined causality30, 40, whereas others such as salazosulfapyridine41, macrolides (except spiramycin)42, salazopyrin16, and allopurinol4, 18 are almost always negative even in ‘known allergics’. In comparison, sensitivity between 57-100% has been reported with carbamazepine and 44-100% with amoxicillin, as two of the most frequently tested medications, as reported in a recent publication encompassing PT in different medication classes17. The precise reasons for these phenomena need to be fully evaluated to clarify how different drugs rank in their suitability to patch testing. It may be that modifications to the standard technique, such as increasing concentrations, using different vehicles, testing drug metabolites, or disruption of the stratum corneum permeability barrier by tape stripping will facilitate PT for drugs where penetration is limiting. However, even with multiple approaches, some reports have shown that this is not always possible18.

Other factors may contribute to differences in PT sensitivity including irritant concentration (which may be a more critical issue for IDT), requirement for skin metabolism to generate the drug antigen, formulation of drug used for testing, and differing thresholds for positive test classification15, 22, 43. Concentration used should ideally be one which does not cause a reaction in controls but can elicit a response in allergic subjects. However, an aspect for consideration is that the reactiveness of an individual DRESS patient is likely to correlate with the degree to which they are sensitised. However, because pre-test determination of optimal test dose in an individual patient is unlikely to be feasible, a fixed concentration approach for testing will result in some false negative responses. Commencing at a low concentration, such as 0.1-1% and step-wise dose increments would be desirable until the highest non-irritant dose is achieved. Such dose-titration measures can complicate the testing process. Final drug concentrations in prepared PT reagents have been observed to be variable, reported to be between 0.05% to 30% in one study44. Commercially prepared patches are available for a limited number of drugs from Chemotechnique Diagnostics (Vellinge, Sweden), but for a comprehensive approach investigating centres typically require the support of pharmacy services to prepare PT, which limits widespread availability. However, Assier et al.37 performed conventional patch testing alongside extemporaneous testing of crushed, patient-provided medication, and showed that crushed tablets are a valid tool for PT.

Additionally, without inter-center agreement as to maximum non-irritant dose for testing of individual drugs, cumulative comparison of results per drug is impossible. The optimal duration of testing is an area of interest but there remains insufficient information with regards this. Whilst generally skin tests are avoided during the acute and resolution phase, it would be of interest to determine if tests performed at the six week mark post resolution or even six weeks after onset of symptoms differs from that performed six months after. As more global broad-ranging timeframes are reported in published data, it was not possible to determine if there would be signification variability in test results or intensity of reaction with longer interval from index reaction. A promising aspect of the data reported here shows that skin responsiveness appears to be long-lasting, up to 11 years16, suggesting that testing can be undertaken even if there has been an interval after the acute event. Limitations in interpretation of IDT are highlighted by the fact that there are far fewer reports of IDT used in DRESS compared to PT (total IDT performed equivalent to 12.7% of all PT reports). Even in cases where there was reported a high clinical confidence on drug culpability, only 1/3 of skin tests were positive on IDT to these medications. Whether this poor concordance is due to incorrect diagnosis, lack of skin metabolism of the medications, absence of critical co-factors (e.g. concurrent viral infection) during the testing process, or poor choice of tested medications remains unclear. Safety concerns regarding the possibility of re-elicitation also results in limited centres performing skin tests in DRESS. Importantly, whilst recurrence of rash can occur45, serious adverse events are very uncommon. Of the 290 patients who underwent skin tests in the publications reviewed, a single subject was noted by Barbaud et al. to have a flare on IDT16. We have previously reported a case with systemic symptoms (lymphopaenia, facial swelling, lymphadenopathy) on PT several years after index reaction, which resolved within 72 hours without resultant sequelae46. Generalised systemic reactions have been primarily reported following PT to anti-tuberculous drugs in HIV patients47. In contrast, abacavir PT has been widely performed in HIV without similar issues48-50. A further consideration is the pathway for allergy testing. Although, from a safety perspective it may make sense to consider PT safer than IDT, there is little evidence to support this assertion.

In conclusion, the principal conclusion from this systematic review is that the quality of published evidence for the role of skin testing in DRESS is low. This is mainly because of test protocol and reporting heterogeneity. This work underscores the importance for the allergy community to harmonising test protocols. In addition, it is clear that there are differences between the suitability of different drugs for different test modalities, therefore reports need to be made on a per drug basis. Here, we demonstrate the limitations of the current published literature on DRESS. Importantly, skin test utility is likely to be modified by the hypersensitivity phenotype so it is critical that studies compare across tightly defined phenotypes eg. DRESS. Many journals now subscribe to the Standards for Reporting Diagnostic Accuracy Studies (STARD)21, and we support their application to drug hypersensitivity. A critical next step will be international collaboration to define a drug hypersensitivity testing protocol, thereby allowing meta-analysis of data between reports. To address these shortfalls in our understanding of the appropriateness of individual drugs for skin tests, it is essential that centres with special interest in drug hypersensitivity test and publish their experience, inclusive of negative results as this provides invaluable guidance to other centres. Overall evidence would suggest skin tests may have a role in determination of drug culpability when performed in cases where drugs in questions are essential for patient treatment, particularly when antiepileptics and beta-lactam antibiotics are suspected. Where intravenous formulations as available, IDT could be performed in place of PT. Testing should be performed by clinicians with experience in interpretation of test results in context of clinical history to avoid overinterpretation of results.

**Figure Legends**

**Figure 1.** Flow diagram of study selection.

**Figure 2.** Evaluation of included studies against relevant items of Standards for Reporting Diagnostic accuracy studies (STARD) and risk of bias.

**Tables**

**Table 1.** Inclusion and exclusion criteria of screened articles

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| * Clear diagnosis of DRESS/DIHS/anticonvulsant hypersensitivity
* Skin testing (prick, intradermal, patch) performed
* Publications after 1996 (when DRESS first reported as a clinical entity)
* Agreement by both reviewers article appropriate for inclusion
 | * Case reports or series with 1-2 DRESS cases
* Conference abstracts
* Review article or guidelines without new DRESS cases tested
* Results of entire DRESS cohort not reported
* Unclear phenotype of tested subject
 |

**Table 2:** Tests performed in included publications

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Publication** | **Cases** | **Mean age (range)** | **Sex (M:F)** | **Medication class** | **Duration to testing** | **Skin prick test** **n (positive; %)** | **Patch test****n (positive; %)** | **Intradermal test****n (positive; %)** | **Correlation skin test with oral challenge****n (positive; %)** |
| Assier et al. 2017 | 9 | UNK | UNK | Various | 6 months | NP | 9 (1; 11.1%) | NP  |  |
| Barbaud et al. 2012 | 72 | 51.2 (17-76) | 26:46 | Various | 12 months- 11 years | 4(2; 50%) | 72 (46; 63.9%) | 4 (3; 75%) |  |
| Ben Mahmoud et al. 2017 | 5 | UNK | UNK | AED | UNK† | NP | 5 (5; 100%) | NP |  |
| Ben-Said et al. 2015 | 10 | UNK | 5:5 | Antibiotics | 4 weeks after resolution | NP | 10 (9; 90%) | NP | 1 (1; 100%) |
| Brégeon et al. 2019 | 11 | 62.7 (34-81) | 3:8 | Chemotherapy | UNK | NP | 3 (0; 0%) | NP |  |
| Cabañas et al. 2014 | 8 | 62.7(39-83) | 5:3 | Antibiotics | 4 weeks after resolution | UNKΔ | 4(1; 25%) | 4(3; 75%) | 1(1; 100%) |
| Daveluy et al. 2011‡ | 36 | 65 (28-95) | 19:17 | Vitamin K antagonist | UNK | NP | 10 (9; 90%) | 1 (1; 100%) |  |
| Ingen-Housz-Oro et al. 2018 | 3 | UNK | 1:2 | Various | 3-6 months | NP | 3 (3; 100%) | NP | 2 (2; 100%) |
| Lin et al 2013  | 10 | 55.4 (25-84) | 3:7 | AED | 1-6 months | NP | 10 (7; 70%) | NP |  |
| Ohtoshi et al. 2013 | 16 | UNK | UNK | Various | 2 weeks – 4 months post onset | NP | 16 (9; 56.3%) | NP |  |
| Pinho et al. 2016 | 19 | UNK | UNK | Various | 6 weeks – 6 months post onset | NP | 19 (6; 31.6%) | NP |  |
| Pinho et al. 2017 | 3 | 75 (61-82) | 1:2 | Various | UNK | NP | 3 (2; 66.7%) | NP | 2(2; 100%) |
| Santiago et al. 2010 | 56 | 52.9 (12-93) | 18:38 | Various | 6 weeks – 6 months post resolution | NP | 56 (18; 32.1%) | NP | 2 (0; 0%) |
| Santiago et al. 2020 | 17 | 47.4 (10-89) | 9:8 | Various | 6 weeks – 6 months§ | NP | 17 (17; 100%) | NP |  |
| Soria et al. 2019 | 14 | 58 (35-89) | 9:5 | Various | 1 – 53 months post resolution | 5 (0; 0%) | 14 (7; 50%) | 14 (4; 28.5%) |  |
| Tanno et al. 2015 | 32 | 49.7¶ | 26:6 | AED | 6 weeks – 6 months | NP | 25 (18; 72%) | NP |  |
| Trubiano et al. 2018 | 14 | 60.2 (38-75) | 9:5 | Antibiotics | ≥6 weeks | NP | 6 (2; 33.3%) | 13 (7; 53.8%) | 4 (4; 100%) |

AED = anti-epileptic drugs; UNK = unknown, details not included in manuscript; †= duration reported from drug exposure but not in relation to resolution or symptom onset; ‡ = other skin tests performed not specified; § = repeat testing performed 2-5 years after initial test; ¶= age range not published; Δ = skin prick test results not reported

**Table 3.** Cases investigated with challenge test

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **n** | **Challenge outcome** | **Medication** | **Drug imputability pre-challenge\*** | **PT result** | **IDT result** |
| Ben Said et al. 2015 | 1 | Tolerated | Cefixim | Possible | Negative | NP |
| Cabañas et al. 2014 | 1 | DRESS | Piperacillin-tazobactam | Probable | Positive | Negative |
| Ingen-Housz-Oro et al. 2018 | 2 | DRESS | Valaciclovir | Possible | Positive | NP |
| DRESS | Valaciclovir | Possible | Positive | NP |
| Pinho et al. 2017 | 2 | Positive, reaction not reported | Metamizole | Possible | Positive | NP |
| Metamizole | Possible | Positive | NP |
| Santiago et al. 2010 | 2 | DRESS | Allopurinol  | Possible | Negative | NP |
| Exanthem | Allopurinol | Possible | Negative | NP |
| Trubiano et al. 2018 | 4 | Tolerant (challenged to negative on skin tests) | Vancomycin | Possible | NP | Negative |
| Piperacillin-tazocin, Meropenem | Possible | NP | Negative |
| Amoxicillin-clavulanate | Possible | NP | Negative |
| Ampicillin | Possible | NP | Negative |

IDT = intradermal test; MPE = maculopapular exanthem; n= number of cases; NP = not performed; PT = patch test; \* = clinical suspicion based on interpretation of published data in articles

**Table 4**. Skin testing to antibiotics in individual patients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tested drug** | **Positive PT** | **PT performed** | **Positive IDT** | **IDT performed** | **Positive SPT** | **SPT performed** |
| Amikacin |  |  |  |  |  |  |
| Amoxicillin | 19 | 29 | 2 | 2 |  |  |
| Amoxicillin clavulanate | 2 | 3 | 0 | 1 |  |  |
| Ampicillin |  |  | 1 | 2 |  |  |
| Benzylpenicillin |  |  |  |  |  |  |
| Beta lactam† |  |  | 1 | 1 |  |  |
| Cefazolin |  |  | 1 | 2 |  |  |
| Cefazoline | 0 | 1 | 0 | 1 |  |  |
| Cefixim | 0 | 1 |  |  |  |  |
| Cefotaxime | 0 | 1 |  |  |  |  |
| Cefoxitin | 2 | 2 |  |  |  |  |
| Cefpodoxime |  |  |  |  | 0 | 1 |
| Ceftazidime | 0 | 1 |  |  |  |  |
| Ceftriaxone | 3 | 3 | 0 | 1 |  |  |
| Cefuroxime | 0 | 1 | 0 | 1 |  |  |
| Cephalosporins† |  |  |  |  |  |  |
| Cloxacillin |  |  |  |  |  |  |
| Dicloxacillin |  |  |  |  |  |  |
| Doxycycline | 0 | 1 |  |  |  |  |
| Gentamycin | 0 | 1 |  |  |  |  |
| Glycopeptide antibiotics† |  |  | 1 | 1 | 0 | 1 |
| Imipenam | 0 | 1 |  |  |  |  |
| Imipenem-cilastatin |  |  | 1 | 1 |  |  |
| Levofloxacin | 0 | 4 | 0 | 1 |  |  |
| Meropenem | 1 | 1 | 1 | 2 |  |  |
| Metronidazole | 0 | 1 |  |  |  |  |
| Penicillin G |  |  | 0 | 1 |  |  |
| Penicillin V | 0 | 1 |  |  |  |  |
| Piperacillin-tazobactam | 5 | 11 | 8 | 12 |  |  |
| Pristinamycin |  |  |  |  |  |  |
| Pyrazinamide | 0 | 1 |  |  | 0 | 1 |
| Quinolones† |  |  |  |  |  |  |
| Rifampicin | 0 | 1 | 1 | 2 |  |  |
| Tazocillin |  |  | 1 | 1 | 1 | 1 |
| Trimethoprim | 1 | 1 |  |  |  |  |
| Vancomycin | 2 | 6 | 3 | 10 | 1 | 1 |
| **Total** | **35** | **72** | **21** | **42** | **2** | **5** |

IDT = intradermal test; PT= patch test; SPT = skin prick test; †= drug tested to not specified in published data

**Table 5.** Skin tests performed to each medication

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  **Tested drug** | **PT positive** | **PT performed** | **IDT positive** | **IDT performed** | **SPT positive** | **SPT performed** |
| Antibiotics  |
|  Amoxicillin | 19 | 29 | 2 | 2 |  |  |
|  Amoxicillin clavulanate | 2 | 3 | 0 | 1 |  |  |
|  Ampicillin |  |  | 1 | 2 |  |  |
|  Beta lactam\*\* |  |  | 1 | 1 |  |  |
|  Cefazolin |  |  | 1 | 2 |  |  |
|  Cefazoline | 0 | 1 | 0 | 1 |  |  |
|  Cefixim | 0 | 1 |  |  |  |  |
|  Cefotaxime | 0 | 1 |  |  |  |  |
|  Cefoxitin | 2 | 2 |  |  |  |  |
|  Ceftazidime | 0 | 1 |  |  |  |  |
|  Ceftriaxone | 3 | 3 | 0 | 1 |  |  |
|  Cefuroxime | 0 | 1 | 0 | 1 |  |  |
|  Ciprofloxacin | 1 | 6 |  |  |  |  |
|  Cotrimoxazole | 0 | 4 | 0 | 2 |  |  |
|  Daptomycin | 0 | 1 | 0 | 1 |  |  |
|  Doxycycline | 0 | 1 |  |  |  |  |
|  Ethambutol | 0 | 1 | 0 | 1 |  |  |
|  Gentamycin | 0 | 1 |  |  |  |  |
|  Glycopeptide antibiotics\*\* |  |  | 1 | 1 | 0 | 1 |
|  Imipenam | 0 | 1 |  |  |  |  |
|  Imipenem-cilastatin |  |  | 1 | 1 |  |  |
|  Isoniazid | 0 | 1 | 0 | 1 |  |  |
|  Levofloxacin | 0 | 4 | 0 | 1 |  |  |
|  Meropenem | 1 | 1 | 1 | 2 |  |  |
|  Metronidazole | 0 | 1 |  |  |  |  |
|  Penicillin G |  |  | 0 | 1 |  |  |
|  Penicillin V | 0 | 1 |  |  |  |  |
|  Piperacillin-tazobactam | 5 | 11 | 8 | 12 |  |  |
|  Pyrazinamide | 0 | 1 |  |  | 0 | 1 |
|  Rifampicin | 0 | 1 | 1 | 2 |  |  |
|  Spiramycin | 0 | 1 |  |  |  |  |
|  Tazocillin |  |  | 1 | 1 | 1 | 1 |
|  Trimethoprim | 1 | 1 |  |  |  |  |
|  Vancomycin | 2 | 6 | 3 | 10 | 1 | 1 |
| Anti-epileptics |
|  Carbamazepine | 29 | 37 |  |  |  |  |
|  Hydantoin | 0 | 1 |  |  |  |  |
|  Lamotrigine | 2 | 5 |  |  |  |  |
|  Phenobarbital | 3 | 6 |  |  |  |  |
|  Phenytoin | 3 | 3 |  |  |  |  |
|  Topiramate | 2 | 2 |  |  |  |  |
|  Valproic acid | 2 | 2 |  |  |  |  |
| Anti-viral |
|  Acyclovir | 0 | 1 | 0 | 1 |  |  |
|  Valaciclovir | 3 | 3 |  |  |  |  |
| Anti-fungal |  |  |  |  |  |
|  Fluconazole | 0 | 1 |  |  |  |  |
| Non-steroidal anti-inflammatory |  |  |  |
|  Diclofenac | 0 | 3 |  |  |  |  |
|  Metamizole | 2 | 3 |  |  |  |  |
|  Tenoxicam | 1 | 1 |  |  |  |  |
| Opiate analgesic |
|  Codeine | 0 | 1 |  |  | 0 | 1 |
|  Tramadol | 0 | 1 |  |  | 0 | 1 |
| Anti-coagulant |
|  Enoxaparin | 0 | 1 | 0 | 1 |  |  |
|  Fluoindione | 9 | 10 |  |  |  |  |
| Contrast media |
|  Iomeprol | 2 | 2 |  |  |  |  |
|  Ioversol | 1 | 1 |  |  |  |  |
| Protein-pump inhibitor |
|  Esomeprazole | 0 | 1 |  |  |  |  |
|  Lanzoprazole | 0 | 1 |  |  | 0 | 1 |
|  Pantoprazole | 0 | 1 | 0 | 1 |  |  |
| Chemotherapy |
|  Bendamustine | 0 | 1 |  |  |  |  |
|  Cobimetinib | 0 | 3 |  |  |  |  |
|  Lenalidomide | 0 | 1 |  |  |  |  |
|  Rituximab | 0 | 1 |  |  |  |  |
|  Vemurafenib | 0 | 3 |  |  |  |  |
| Other |
|  Allopurinol | 0 | 32 |  |  |  |  |
|  Amitriptyline | 0 | 1 |  |  |  |  |
|  Nefopam | 0 | 1 | 0 | 1 |  |  |
|  Ondansetron | 0 | 1 | 0 | 1 |   |   |
| Total | 95 | 217 | 21 | 52 | 2 | 7 |

**Table 6. Challenge test to cross-reactive reactions on skin tests**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **n** | **Challenge outcome** | **Initial culprit drug** | **Challenged drug** | **PT result** | **IDT result** |
| Cabañas et al. 2014 | 1 | Tolerated | Piperacillin-tazobactam | Meropenem | Negative | Negative |
| Lin et al. 2013 | 3 | Exanthem | Carbamazepine | Oxcarbazepine  | Positive | NP |
| Mild DRESS | Carbamazepine | Oxcarbazepine  | Positive | NP |
| Tolerated | Carbamazepine | Oxcarbazepine  | Negative | NP |
| Santiago et al. 2010 | 1 | DRESS | Carbamazepine | Phenytoin | Positive to both | NP |
| Santiago et al. 2020 | 2 | MPE | Carbamazepine | Amoxicillin | Positive | NP |
| MPE | Phenytoin | Cefotaxime | Positive | NP |
| Trubiano et al. 2018 | 1 | Tolerant  | Cefazolin, meropenem | Penicillin V, Flucloxacillin | NP | NP |

DRESS = drug reaction with eosinophilia and systemic symptoms; IDT = intradermal test; n= number of cases; NP = not performed; PT = patch test

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