**Making a diagnosis in severe cutaneous drug hypersensitivity reactions**

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**Abstract**

Purpose of review:

Severe cutaneous adverse reactions (SCAR) are relatively uncommon but can be life threatening. This review focuses on the non-anaphylactic (non-IgE mediated) phenotypes of drug hypersensitivity, with specific reference to diagnosis and management of acute generalised exanthematous pustulosis (AGEP), drug reaction with systemic symptoms (DRESS), Stevens- Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Recent findings:

Here, we review recent guidelines on optimal supportive care as well as publications of interventional treatment for SJS/TEN, including anti-TNF therapy, and management strategies for severe ocular disease with the use of amniotic membrane transplantation. In DRESS, long term autoimmune sequelae are increasingly recognised and modify strategies for treatment of the acute episode. If the causative drug is not apparent from careful inspection of the drug exposure history, in vitro diagnostics, HLA testing and skin testing before drug challenge testing may be considered and we present an algorithm for investigation of complex cases.

Summary:

Careful phenotypic analysis of the increasingly complex recognised patterns of SCAR facilitates the enhancement in our understanding of T cell mediated drug hypersensitivity and allows the improvement of in vitro diagnostic testing to minimise patient exposure to test substances in all but a very limited number of cases, thereby enhancing safety.

**Key words/Phrases:**

Diagnostic testing

Acute generalised exanthematous pustulosis

Drug reaction with eosinophilia and systemic symptoms

Stevens-Johnson syndrome

Toxic epidermal necrolysis

**Abbreviations:**

AGEP: Acute generalised exanthematous pustulosis

DRESS: Drug reaction with eosinophilia and systemic symptoms

FDE: Fixed drug eruption

GBFDE: Generalised bullous fixed drug eruption

MPE: Maculopapular exanthema

SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema

SJS: Stevens-Johnson syndrome

TEN: Toxic epidermal necrolysis

**Introduction**

Severe cutaneous adverse reactions (SCAR) are those adverse skin reactions which pose a significant morbidity or mortality and are caused by an immunologically mediated inflammatory reaction with a prominent phenotype in the skin. Although this definition is well established, fulfilling all the relevant criteria to make the diagnosis of SCAR remains a challenge in clinical practice. The clinician requires a comprehensive knowledge of the spectrum of skin reactions caused by medications (including non-immunologically mediated causes), a review of which is beyond the scope of this manuscript and we refer readers to important recent publications (1). When causality is confirmed due to drug exposure SCAR may be termed severe cutaneous drug hypersensitivity (CDH) reactions (1). However, it is important to note that it is increasingly recognised that significant numbers of SCAR may also be induced by other factors including infection (discussed below). Whilst they are concerning for the patient, benign CDH show no significant risk of morbidity/mortality and no signs of significant internal organ involvement (Table 1). Whereas SCAR typically show systemic manifestations, with involvement beyond the skin.

**How to recognise SCAR**

Severe cutaneous adverse reactions present with a rash, this may evolve over days to become widespread. The spectrum of anaphylaxis syndrome can be rapidly excluded because of the characteristic features of urticaria and angioedema due to mast cell degranulation. However, some cases present with widespread flushing. Drug exposure of a sensitised patient will typically lead to symptoms within minutes of drug exposure and almost always within one hour (2), and death is reported in 1.1% of cases (3). Similar patterns of skin involvement are seen in non-IgE mediated mast cell degranulation as with non-steroidal anti-inflammatory drug (NSAID) and opiate induced urticaria, as well as red man syndrome (flushing and itching; e.g. with Vancomycin). Infection and other triggers can also induce urticaria. Therefore, the main challenge is to establish that the reaction is genuinely due to immunological hypersensitivity. The management of anaphylaxis is well established (4). If confirmation of the cause is required, a variety of guidelines from various European institutions offer guidance on confirmatory testing (5) (6). The drug hypersensitivity syndrome of urticaria, angioedema and anaphylaxis, is generally well recognised amongst clinicians because of the characteristic rash, itch and close temporal association to the drug exposure, therefore with this review we will focus on SCAR excluding anaphylaxis. Unfortunately non-IgE mediated SCAR reactions are less well recognised, less easily treated and more complicated to manage.

The possibility of drug hypersensitivity as a cause of any new cutaneous eruption, especially where the diagnosis does not fit other common eruption patterns should be considered. However, additional suspicion should be raised if the timeline for drug ingestion and onset of the rash fit recognised parameters. As a general rule, the immune system requires one week to prime a new T cell mediated reaction, therefore at least 1 week of drug exposure is required before the onset of any hypersensitivity reaction (7). However, this time line may be complicated if prior exposure has arisen for one week and the drug exposure stopped before any prominent features of hypersensitivity arise (e.g. typical course of antibiotics), then at subsequent exposure the sensitised patient will react more quickly, typically between 24-48 hours (7).

The group of SCAR can show varying typical timelines for onset of symptoms after beginning of drug use with the longest typically seen in DRESS (2-8 weeks) and the shortest in AGEP and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) 1-12 days and <7 days respectively. Whereas SJS/TEN cases have been noted typically 4-28 days after onset of exposure (1).

Additionally, increased suspicion of a drug cause should be countenanced if the clinical features fit the characteristic signs associated with known CDHR reaction patterns.

The skin rash of DRESS (Fig. 1 a, b) may be identical to that of a typical benign maculopapular eruption with the distinction between the two conditions being made predominantly by the systemic features (8) (9) (Table 2). However, in addition to the more delayed onset, DRESS usually shows a more florid and extensive eruption and there may be associated facial swelling. Subtypes of DRESS skin rash have been proposed: Erythema multiforme-like (associated with highest risk of severe liver disease); erythroderma; morbilliform erythema; urticated exanthem (10). The mortality of DRESS is derived from catastrophic organ failure (usually liver) which happens in few patients (mortality 2-6% (8) (9)). However, morbidity beyond the acute episode can arise as a consequence of viral reactivation (HHV6/7; EBV; CMV) (11) or induction of autoimmune phenomena (12).

The identification of a non-follicular pustular eruption as a major feature of the presenting syndrome of SCAR, should point the clinician to AGEP (13) (Fig. 1 c, d; Table 3). However, it is to be noted that numerous often follicular micropustules may be seen in DRESS, and occasional pustules in other reaction types. AGEP typically presents as a rapidly arising erythema with overlying pustules, more commonly localised to the head, neck and upper torso and /or predominantly in the body folds, but widespread cases can arise. In AGEP, there is also associated fever and neutrophilia. Pustular psoriasis is the main differential diagnosis.

Blisters (epidermal detachment) within a skin eruption of CDHR are a key indicator of SJS/TEN (14), but generalised bullous fixed drug eruption GBFDE should also be considered (15). Whilst drug causality of SJS/TEN must be given central consideration, approximately 25% of adult SJS/TEN-cases (50% in children) are not drug induced. SJS and TEN are a spectrum of the same condition (less epidermal detachment vs. more respectively) and show rapid progression associated with pain, but TEN shows the higher mortality (16) (Table 1). However, both SJS and TEN give rise to associated severe haemorrhagic mucositis (typically lips and oral mucosa and eyes, but may also include genitals; Fig 1e). Although GBFDE also induces full thickness epidermal necrosis histologically, the margins of involvement are much more clearly defined than SJS/TEN (detachment can be induced by trauma in SJS/TEN – Nikolsky sign; Fig 1f) and mucosal involvement is limited. Additionally it is important to recognise that mild mucositis can arise in DRESS and AGEP, with or without superficial desquamation clinically resembling epidermal detachment. Severe mucositis can typically arise with infections such as Mycoplasma pneumoniae, (typically well demarcated, and of the external vermillion of the lips) and may be associated with severe eye and lung involvement. Herpes simplex virus induction of acral targets and modest mucositis (erythema multiforme majus) typically arises in adults. A more widespread pattern of distribution of atypical targets is more common in children, with a high prevalence of association with M. pneumonia.

**Initial investigations of SCAR**

Following careful consideration to suggest a SCAR, followed by classification of the phenotype (above), baseline investigations are recommended. To assess internal organ involvement and comorbidity status: Full blood count (FBC), urea and electrolytes (U&E) including magnesium / phosphate / bicarbonate, liver function tests (LFT), coagulation studies, glucose, Chest X-ray, HIV, ESR, CRP.

To confirm the diagnosis and exclude differential diagnoses, send an infectious screen e.g. samples for Mycoplasma serology, take swabs from lesional skin for virology and bacteriology, when appropriate. Additionally undertake a skin biopsy (lesional skin or just adjacent to a blister) for routine histopathology and direct immunofluorescence to exclude an immunobullous disorder.

Furthermore, photographs of the skin to show the specific features of the rash and extent of involvement are recommended.

**Management of SCAR**

The priority in the management of all sCDH is to stop exposure to the culprit medication. The prognosis has been shown to correlate with the time to drug cessation in SJS/TEN (17).

1. AGEP (Figure 1c,d)

Differential diagnosis primarily consists of pustular psoriasis, but other conditions such as subcorneal pustular dermatosis should be considered and may occasionally be difficult to distinguish. Although systemic features of fever and neutrophilia are evident, and literature suggests a mortality comparable with DRESS, most cases of AGEP, resolve very well on withdrawal of the culprit drug. Topical or oral corticosteroids may be considered in the acute stage, especially for inflamed or itchy areas of skin. Desquamation usually follows pustule formation and emollients are beneficial at this stage. Internal involvement reflected by transient elevation of liver enzymes and kidney parameters has been reported to occur in up to 20% of mainly elderly patients (18)

1. DRESS (Figure 1a,b)

Supportive management of DRESS should respond to the clinical requirements of the case. Liaison with specialists in the appropriate field will be required for organ failure and some individuals may require intensive care support. One of the main advantages of diagnosing DRESS is that there is general consensus amongst experts that the condition responds well to corticosteroid therapy. In mild cases this can be delivered topically with daily application of a potent corticosteroid cream to the affected areas (19). In most cases oral or intravenous corticosteroids are required e.g. prednisolone 1mg/kg/day. During the acute period, there is good evidence that many cases suffer reactivation of HHV6/7 (also EBV/CMV), although the precise implication of the viral reactivation in disease pathogenesis has yet to be fully elucidated. However, viral reactivation seems to indicate a prolonged course of the disease with potential flare-ups. Chronic sequelae from DRESS include autoimmune conditions such as systemic thyroid dysfunction (most common), lupus, haemolytic anaemia, arthritis, alopecia areata, vitiligo, diabetes, pernicious anaemia (20) (21). Some reports have suggested that although the introduction of corticosteroids reduces the risk of autoimmune sequelae (12), it is also associated with an increased risk of infection in the acute episode (22). For treatment resistant cases, ciclosporin (23) and other immunosuppressants have been reported. IVIg has been proposed but shown mixed results with some groups reporting lack of benefit (24).

1. SJS/TEN (Figure 1 e,f)

This condition can rapidly progress and shows the highest mortality of all SCAR. Mortality correlates approximately with area of skin detachment and age of the patient, but a useful measurement of prognosis when is SCORTEN (25) (Table 5). SCORTEN is usually measured within 24 hours of admission, but an analysis of daily scores over the first five days revealed that prognostic correlation was best on day 3 (26). Individuals with extensive surface area detachment should be managed in an intensive care environment (ICU; or burns unit), but the precise threshold will be dependent upon local practice. UK guidelines suggest that ICU transfer is appropriate at >10% (27), whereas in Germany the assessment is based on evaluation of the overall medical status, and may not be required until BSA detachment >30%. Warmed environments with increased humidity and pressure relieving mattresses are recommended. It is important to minimise trauma to affected skin, therefore cannulas should be sited away from active areas and a catheter should be inserted if significant urogenital involvement is noted. Fluid replacement, nutrition and analgesia should also be started early and follow disease specific guidelines (27).

Management of skin detachment can either be conservative (regular cleansing of erosions, application of 50% white soft paraffin with 50% liquid paraffin, plus antimicrobial applications if sloughy, and complete covering with non-adherent dressings) or surgical (removal of necrotic or loose skin and wounds cleansed under general anaesthetic, surgical debridement, and closure with biocomposite or skin graft). The most common complication of SJS/TEN is sepsis secondary to skin failure or line infection. However, to avoid unnecessary therapy, prophylactic antibiotics are not recommended. Instead, regular microbiological swabbing from multiple sites on the skin can identify potential pathogenic bacterial organisms, which can then be rapidly treated in a targeted manner at the first signs of sepsis.

Management of ocular, gynaecologic, urologic, respiratory, gastrointestinal disease activity should involve the relevant specialist with expertise in management of SJS/TEN. For example there is evidence that early intervention with amniotic membrane grafting provides better outcomes following conjunctival blistering (28).

The benefit to patients with SJS/TEN from specific treatment with steroids, immunosuppressive treatment (Ciclosporin) or IVIg remains controversial with none of these modalities showing a clear benefit over the others (27). Since the systematic review undertaken for the UK guidelines (27), three further studies have been published which show a favourable outcome of treatment with ciclosporin (29-31), providing combined supporting evidence in a total of 184 SJS/TEN patients (3-5 mg/kg/day). Although, the quality of evidence is sub-optimal, largely due to the retrospective analysis design of most ciclosporin studies, the weight of evidence does seem to be tipping in favour of ciclosporin and this view has been supported by two recent meta-analyses(32, 33). One of the limitations of studies in this area is the relative rarity of the condition and lack of head to head clinical trials. Recently a randomised controlled study showed a trend to benefit of etanercept over corticosteroid therapy although this study was skewed towards mild cases and showed no statistically significant difference(34).

1. GBFDE

Management of GBFDE is essentially the same as SJS/TEN but although cases are thought to be generally less progressive with lower incidence of respiratory compromise, showing a more benign clinical course, some studies have suggested a mortality comparable to that of SJS/TEN with the same amount of skin detachment. However, GBFDE-patients who died were substantially older and many had a previous event (15).

**Diagnostic testing in SCAR**

If the culprit drug has been readily identified from examination of the ingestion history no further testing is required: the drug needs to be avoided lifelong. Current guidelines on drug allergy testing exclude the SCAR because testing protocols include intradermal or oral challenge to the patient and the possibility of inducing SCAR is realistic. Indeed, previous reports confirm the risk of recurrence and fatalities following accidental re-exposure or challenge testing (35) (36-38). Some groups have suggested algorithms based primarily on an appropriate timeline and drug imputability (39). However, such approaches are generally optimised for pharmacovigilance analyses rather than direct patient advice about future avoidance strategies. In some cases of SCAR the drug ingestion history is so complicated that it is impossible to estimate the likelihood of a drug causing the reaction. Therefore, an approach to inferring causality is required, and is best undertaken by an expert in drug reactions. One of the problems for the drug allergy specialist is that they are often involved in the case only weeks or months after the acute event. As described above, phenotypic characterisation of the acute event with detailed record keeping is critical to the analysis of the reaction pattern and assessment of causality. To address this point, national and European recommendations have suggested strategies for optimum record keeping of the acute event for general physicians to follow (1, 40) (41).

Recent work has highlighted the very strong association between various HLA alleles and risk of CDH (Table 4). Indeed, it is now mandatory to screen for HLA alleles before treating with abacavir, and in some racial groups carbamazepine. Therefore, modern approaches to diagnostic testing CDH should include gene sequencing for relevant specific HLA alleles known to be associated with risk for the drug exposure (41).

If further diagnostic work up is required, then the option of clinical and or in vitro testing needs to be considered. Application of the suspected drug directly to the skin in a patch test can elicit inflammation in the skin reflecting immunological sensitisation and the methodology has been clearly described (42) (43) (44). Although, in some groups (e.g. HIV), there appears to be a significant risk of generalized systemic reactions following patch testing (45), it is generally accepted that with appropriate dose adjustment in the patch, testing is feasible even in the most severe cases of SJS/TEN. However, this procedure is estimated to provide informative results in less than 50% of cases (46) and shows great variability between variations in population tested as well as the drugs and methodology. For example, although it has been reported that patch testing may be more informative in AGEP, and less useful in SJS/TEN (47), we have previously found 8/8 SJS/TEN patch test positive to anticonvulsants (46). Indeed, case series have suggested an overall positive yield of 32.1% of cases with DRESS, but on further analysis, 13/17 cases of carbamazepine (77%) induced DRESS were positive, whereas 0/28 were positive to allopurinol which is less lipophilic (and therefore shows poor skin penetration). Hence, allopurinol is not used in patch testing which underscores the importance of knowledge of individual drug performance when patch testing.

Intradermal testing is routinely used for skin prick test negative investigation of IgE mediated drug allergy and has been recommended for use in mild CDH (48). However, despite the small doses applied, severe and even fatal reactions have arisen (49 , 50). Therefore, application of intradermal testing in SCAR needs to be considered with caution. A review of the published literature for this manuscript identified only six confirmed reports of intradermal testing in SCAR (51-56) (57) (58). In these small case series, 23/40 (58%) cases of SCAR showed positive delayed reactions on intradermal test, and no systemic reactions were reported. Whilst these and other unpublished data suggest that in certain circumstances intradermal testing of DRESS can be undertaken (usually starting at a 10-100 fold lower concentration than for IgE mediated allergy), the number of reported cases of SJS/TEN tested in such a manner is very low (n=6) and it is generally accepted that intradermal testing is only used in exceptional circumstances for investigation of SJS/TEN.

In vitro diagnostic testing for investigation of SCAR is an ideal approach to allergy work-up because there is zero risk to the patient. However, the risk attached to this procedure lies in the clinical interpretation of the results. Although false positive test results will lead to unnecessary avoidance, false negative test results raise the possibility of re-exposure to a causal drug and subsequent repeated SCAR. Therefore, clinico-pathological interpretation of the in vitro test is paramount. We and others have published series of children and adults demonstrating the utility of both the lymphocyte proliferation assay (LPA; syn. lymphocyte transformation test, LTT) and drug induced cytokine assays (59-61). Cumulative published data has demonstrated good evidence for the utility of both LPA and IFN-γ ELISpot assay. A recent review of the literature calculated the specificity of the assays in DRESS to be 0.99 and 0.96 respectively, but the sensitivity was lower: 0.67 and 0.52 respectively (61). In SJS/TEN one group has also shown some evidence for measurement of drug induced granulysin and IL-4 (62) (60). The same review also suggested that the specificity of in vitro assays in SJS/TEN is also high (0.94-1.00) but that the sensitivity is lower where LPA sensitivity was calculated at 0.37(61). We have also reported similar poor utility for LPA in SJS/TEN (63). However, the IFN-γ ELISpot appears to retain some greater utility with a sensitivity of 0.71 in SJS/TEN. A recent study comparing intradermal skin tests and IFN-γ ELISpot in a variety of SCARs showed concordance between the two assays in 12/17 cases (76%) (51). Assays of granulysin and granzyme B may also prove useful in this condition (granulysin assay sensitivity 0.86, specificity 0.91) but so far the numbers of reported cases where this assay has been employed remains low (64). As yet, these assays are not widely available, because they require specialist equipment and expertise beyond the scope of most routine diagnostic laboratories.

Some groups have attempted to enhance the sensitivity of in vitro assays by depleting regulatory T cells from the conditions (65). These cells would be expected to inhibit the elicitation of drug-specific responses and their depletion thus ‘unmasking’ the drug-specific responses (66). However, the fine balance between pro-inflammatory and regulatory responses is likely to be central to initiation of hypersensitivity reactions in vivo, therefore by uncoupling part of the system to reveal higher frequencies of drug specific responses to increase sensitivity in vitro, may at the same time reduce specificity. This area needs further investigation before Treg depletion can be recommended in testing algorithms.

We propose the following algorithm for diagnostic work up of CDHR (Fig. 2.)

**Conclusion**

In conclusion, diagnosis of CDH is a complex process and relies critically on the clinical description of the acute episode, with the appropriate investigations. Management of severe CDH requires to acknowledge the different phenotypes of CDH as well as the differential diagnoses (non-CDH). Clinicians should recognise the different evidence levels to support interventions in CDH phenotypes and how these may affect prognosis. Diagnostic testing is complicated by the potential fatal outcome of drug re-exposure and the lack of consensus on the optimal acute therapy if a severe reaction is elicited.

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**Conflicts of interest**

None

**Key Bullet Points:**

1. T cell mediated drug hypersensitivity reactions present in the skin as distinct phenotypes which require the clinician to recognise the differences in presentation and prognosis.

2. Skin biopsy for histology and immunofluorescence is critical in the diagnostic work up of cutaneous drug hypersensitivity reactions, especially for blistering phenotypes.

3. Supportive care for SJS/TEN remains critical but increasing evidence lends support for ciclosporin and potentially anti-TNF inhibitors as interventional therapy.

4. Early intervention in ocular involvement of SJS/TEN with amniotic membrane grafting holds promise for prevention of severe chronic eye sequelae.

5. Therapy of DRESS with systemic corticosteroids increases the risk of infection, but reduces the risk of later development of autoimmune disease.

6. Diagnostic evaluation of drug induced SCAR is important for patients. Whilst in vitro testing is safe, some risk is encountered with skin testing and should be undertaken by those with experience in this area.

**Legends**

**Tables.**

Table 1. Benign CDHR and SCAR.

Table 2 (On line only). RegiSCAR validation criteria for DRESS.

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

a After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

\*“Yes” for liver involvement only, if liver enzymes are elevated 2-times above the normal value on two different dates

\*\*“Yes” for kidney involvement only, if renal parameters elevated 1.5-times above the normal value of the patient

Adapted from (67)

Table 3 (On line only). Diagnostic criteria of AGEP. Adapted from (68)

Table 4. HLA Associations with CDHR. Adapted from (69, 70)

Table 5 (On line only). SCORTEN predicted mortality in SJS/TEN. Adapted from (25)

**Figures.**

Fig. 1.

a, b. Examples of infiltrated erythema on the torso typical of DRESS. c, Sheets of superficial 1-3mm pustules typical of AGEP. d, Superficial desquamation seen in later stages of AGEP. e, Haemorrhagic mucosal blistering typical of SJS/TEN. f, extensive cutaneous blistering and epidermal detachment typical of SJS/TEN.

Fig. 2.

Diagnostic algorithm for drug allergy testing in CDHR

Cases of CDHR must be classified from the clinical features as to whether the condition was likely to be T cell mediated (see text). Mild CDHR, can be managed on the typical pathway for drug allergy testing. However, severe CDHR require more careful consideration because of the concern that if the disease is elicited by allergy testing, the treatment and recovery is much more uncertain and potentially fatal. For individuals where the culprit drug is known (through clinical interpretation of the exposure timeline) or if avoidance is feasible, the safest approach is to avoid the drug. In centres where HLA testing/ in vitro diagnostics are available, the safety of these tests supports their use in SCAR. Subsequent skin testing to confirm negativity (not to confirm allergenicity) may then be appropriate in certain cases if blood tests are negative. Intradermal testing is of greater risk and careful consideration needs to be undertaken before testing SCAR. Finally, the gold standard, as in all allergy testing is a challenge test, where the drug exposure is repeated (at low dose initially). This needs to be undertaken with extreme caution in SCAR and only in selected cases.

+, See text for details of clinical features to help distinguish T cell mediated from other types of hypersensitivity. \*, see text for list of SCAR and the associated clinical phenotypes. #, HLA testing and or in vitro diagnostics may be appropriate in some circumstances and not in others, the clinician also needs to consider the evidence for the test proposed and the evidence for its usefulness in the particular CDHR phenotype and drug in question. &, Intradermal testing needs to be undertaken with extreme caution in SCAR. ^, challenge testing is only undertaken in rare situations in severe CDHR and the risk needs to be carefully assessed on a case by case basis.

HLA, Human Leukocyte Antigen; CDHR, Cutaneous drug hypersensitivity reaction.

Reference recommendations:

1. \*\* This manuscript offers a comprehensive guide to how to assess skin reactions due to drugs and how to classify them.

34. \* This paper offers an important contribution to the evidence base in management of SJS/TEN. Despite limitations, as discussed, it reports a randomised control trial of anti-TNF therapy versus oral corticosteroids

58. \* This paper reports a case series of DRESS cases and demonstrates safe evaluation of DRESS by skin testing with intradermal and patch testing.

69. \* This paper undertakes a very useful review of the mechanisms of delayed type drug hypersensitivity reactions.

70. \* This paper reports a new HLA association for DRESS reactions to Vancomycin

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