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Diagnosis, Investigation and Management of Non-immediate (Type IV) Cutaneous Adverse Drug Reactions

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ABSTRACT
Pathophysiologically, drug hypersensitive reactions (DHRs) are classified into four types: type I, immediate reactions, and types II, III, and IV, non-immediate reactions. They are further categorized as severe or non-severe based on clinical severity. Genetic predisposition and viral reactivation are cofactors of severe DHR type IV. Rapid identification, cessation, and future avoidance of offending and cross-reactive drugs are the cornerstone of treatment. The diagnosis is established based on the history, physical examination, and subsequent *in vivo, in vitro*, and drug provocation testing, which are selected based on the severity of DHR. In non-severe DHRs, desensitization to the offending drug is possible.

KEY WORDS: drug hypersensitive reactions, non-immediate cutaneous adverse reactions, type IV hypersensitivity, diagnosis and management, drug provocation testing

INTRODUCTION

Adverse drug reactions are classified into type A and type B. The predictable pharmacological activity of the drug causes the A-type reaction, and B-type is the drug hypersensitivity reaction (DHR) (1,2) that affects more than 7% population (3). Cutaneous DHRs are classified as immediate IgE-mediated reactions, occurring nearly always within the first hour, with non-immediate exanthema occurring more than six hours later, usually twenty-four hours after drug administration (4).

PATHOPHYSIOLOGY/MECHANISM AND PHENOTYPES

In contrast to high molecular weight proteins easily recognised by our immune system, drugs or their metabolite products are predominantly of low molecular weight and must be covalently bound to protein in a process known as haptenisation to elicit an immune response (5). There are currently three models of T-cell activation. The first is through drug/metabolite processing in antigen-presenting cells (APC) and presentation on their human leukocyte antigen (HLA) molecules to the corresponding T-cell receptor (5). The other two are caused by direct non-covalent binding to HLA molecules and/or T-cell receptors. This leads to either direct activation of T-cells in the pharmacological-interaction (p-i) model (6) or altering the repertoire of self-peptide ligands, resulting in the presentation of novel peptide ligands that are recognized as foreign and elicit immune response in the altered peptide repertoire model (7). These two new models may help to explain why some drugs cause drug reactions after initial exposure (8).

Furthermore, the finding that severe cutaneous adverse reactions (SCAR) to abacavir are associated with HLA class I led to the discovery of genetic pre-

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disposition to DHR and to pre-prescription screening strategies (9). In Taiwan, personalized medicine has been employed to identify individuals at high risk of SCARs using biomarkers such as HLA-B*15:02 for carbamazepine and HLA-B*58:01 for allopurinol, effectively reducing serious cutaneous adverse drug reactions. However, these biomarkers have only been established for a limited number of drugs, indicating the need for further progress through nationwide or even international patient sampling to discover genetic markers that can predict high-risk patients based on ethnicity and the specific medication involved (9).

The most well-known viral-drug reactions are ampicillin rash, associated with EBV infection (10), and DRESS, associated with herpes virus infection, primarily HHV6 (11,12). However, the role of immune system stimulation caused by infectious agents and secondary cutaneous drug reactions is still unknown (8,13,14) and it is thought that they serve as a co-factor (15).

Hypersensitivity is a comprehensive phrase that refers to an exaggerated and potentially harmful immune response to either outside substances (such as drugs) or the body's own antigens. Gell and Coombs were the pioneers in classifying hypersensitivity responses into four kinds based on their underlying pathophysiology.; immediate (type I), cytotoxic (type II), immune complex-mediated (type III), and delayed hypersensitivity (type IV) reactions (16).

Many non-immediate type IV cutaneous adverse drug reactions are mediated by T-cells (17), occurring later than type I reactions. In some cases, these reactions may even occur after the discontinuation of the causative drug for some time. This delay is due to the recruitment and expansion of drug-reactive T-cells, which typically takes several days to weeks (4). Leukocytes such as macrophages, neutrophils, and eosinophils can be activated by helper T-cells, leading to tissue damage due to the production and release of reactive oxygen species, lysosomal enzymes, and inflammatory cytokines (18). According to the type of cells activated, type IV DHRs are classified into four subtypes (5).

In type IVa, Th1 cells activate macrophages, causing them to secrete cytokines such as interferon y and TNF alfa, resulting in allergic contact dermatitis/eczema. Type IVb is mediated by Th2 cells, which produce IL-4, IL-5, and IL-13 and induce eosinophilic inflammation, resulting in drug reactions with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) with eosinophilia. Type IVc is mediated by cytotoxic CD8+T-cells, which directly kill targeted cells via various mediators such as perforin, granulysin, and granzyme B, inducing keratinocyte apoptosis and/or necrosis, resulting in MPE, Steven Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN), bullous exanthema, and fixed drug eruption (FDE). Damage to tissues is caused by type IVd reactions in which T-cell-derived CXCL-8 attracts neutrophils into tissues, causing sterile neutrophilic inflammation and the clinical picture of acute generalized exanthematous pustulosis (AGEP) (4,8,19).

DIAGNOSIS

The first step in correctly diagnosing DHR is acquiring a complete medical history. The patient's medical history must include details on the medication (preparation, dosages, route, and duration of administration) and the nature, duration, and resolution of symptoms. To validate the reaction and the responsible drug, medical records, charts, pictures, and eyewitness reports must be gathered (4). Drug causation can be determined using the Naranjo score (20). Prior medical history, pharmacological responses, and additional allergies must be considered. A thorough physical examination to identify rash and the affected body surface area can assist in identifying the processes potentially underlying the reaction and

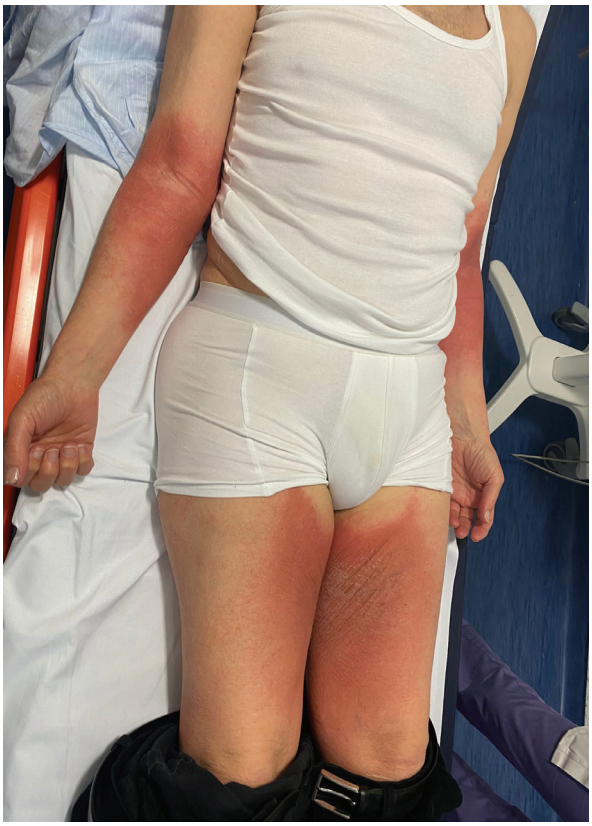

Figure 1. Exanthema in the flexural aspects of proximal extremities in a patient treated with clindamycin.

Table 1. The most common major phenotypes of non-immediate (type IV) cutaneous adverse drug reactions and their most distinctive features (4,15,18,21,22)

Hypersensitivity reaction	Time interval from intake to a drug reaction	Clinical manifesations	Laboratory findings	Course and outcome	Common causative drugs
Maculopapular exanthema (MPE)	4-14 days, less if repeated reaction	Erythematous macules and infiltrated papules Pruritus Desquamation in the later clearing phase Systemically well, occasionally low-grade fever	Eosinophilia	Widespread exanthems may generalize, become confluent and develop into erythroderma In early phases typically no scaling occurs, desquamation is common in the later clearing phase There have been no known cases of fatality.	Antibiotics Antiepileptics Allopurinol NSAIDs
Fixed drug eruption (FDE)/Generalized bullous FDE (GBFDE)	30 min - 8 hours after readiministration The drug was tolerated before, and milder episodes are often reported	Violaceous oval-shaped lesion Erythematous macule(s), plaque(s), bullae Single or multilocular (FDE) or generalized lesion(s) (GBFDE) Fade to lightly pigmented lesions No systemic symptoms	There is often little systemic involvement and laboratory findings are usually unaltered.	The lesion characteristically resolves with residual hyperpigmentation. Multisite bullous FDEs may occur Severity increase in recurrent events Substantial death rate from GBFDE in elderly patients (up to 22%)	Antibacterial sulfonamides Barbiturates Tetracyclines Carbamazepine Metamizole
Drug reaction with eosinophilia and symptoms (DRESS)	2-8(12) weeks	Maculopapular rash >50% body surface area Tissue (facial) oedema Fever >38.5 C Lymphadenopathy > 2 sites Systemic involvement: hepatitis, myocarditis, interstitial pneumonitis, nephritis, thyroiditis, arthritis	Eosinophilia Agranulocytosis and anemia may occur Atypical lymphocytes Abnormal liver transaminases, Elevated levels of urea and creatinine Proteinuria Abnormal ECG findings X-ray showing involvement of the interstitial tissue Elevated levels of thyroid hormones High levels of C-reactive protein and sedimentation rate.	Prolonged course, flare-ups due to reactivation of herpes viruses Mortality has been variably reported, usually related to liver failure, but was 2% in a large series of strictly validated cases of DRESS – in other studies mortality rates were up to 10%	Antiepileptics Allopurinol Dapsone Antibacterial sulfonamides
Steven-Johnson syndrome (SJS) / toxic epidermal necrosis (TEN)	4-28 days	Prodromal flu-like illness: fever, upper respiratory tract symptoms Dusky red macule and flat atypical target lesions with a blister on top Sheet-like skin loss (TEN) Nikolsky sign Blistering The area of confluent bullae leading to detachment of the skin (as calculated in burns) of the total body surface is <10% in SJS, 10%-30% in SJS/TEN overlap and >30% in TEN. Mucosal involvement Systemic symptoms	Leucoopenia, thrombopenia Abnormal liver transaminases, Elevated levels of urea and creatinine. Higher levels of C-reactive protein and sedimentation rate	Mortality rates 9% SJS, 29% SJS/TEN, 48% TEN	Allopurinol Antiepileptics Antibacterial suphonamides Nevirapine Oxicams-NSAID
Acute generalized exanthematous pustulosis (AGEP)	1-2 days for antibiotics up to 11 days for other drugs	Pustules on edematous erythema Begins on the face or intertriginous area, dissemination with hours Fever, malaise Transient renal failure	Leukocytosis, neutrophilia elevated levels of urea and creatinine.	Mortality 4% in the elderly	Beta-lactam antibiotics Macrolides Diltiazem Terbinafine Hydroxychloroquine
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	up to 7 days	Sharply delineated erythema Flexural and intertriginous areas No systematical involvement	There is often little systemic involvement and laboratory findings are usually unaltered.	Postexanthematous desquamation is often observed The symptoms often resolve spontaneously over time, and there have been no known cases of fatality.	Beta-lactam antibiotics

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Table 2. Dangerous symptoms and signs of severe cutaneous adverse reactions (SCAR) (4,21-24)

Dangerous symptoms	Dangerous signs
• Fever >38.5 ˚C • Malaise • Skin extension of MPE >50%-DRESS • Centrofacial oedema-DRESS and AGEP • Painful skin- SJS/TEN • Atypical flat target lesions-SJS/TEN • Tiny vesicles or crust, grey-violaceous or dusky colour –SJS/TEN • Erosions of mucosa (>2 mucosae membranes), especially hemorrhagic-SJS/TEN • Non-follicular pustules occur within 1-2 days after edematous erythema-AGEP	• Lymphadenopathy (>2 sites >1cm)-DRESS • Blood count • eosinophilia, atypical lymphocytes- DRESS, leucopenia, thrombocytopenia-SJS/TEN, • leukocytosis, neutrophilia-AGEP • Liver function tests (high transaminase)-DRESS • Proteinuria-DRESS • Skin blisters, bulle-SJS/TEN • Nikolsky sign-SJS/TEN • Skin detachment, < 10% SJS >10% and < 30% SJS/TEN >30% TEN • Renal function (rise of urea and creatinine)-SJS/TEN and AGEP

directing further inquiry (4). Table 1 shows the most important clinical phenotypes of type IV DHR.

MPE is the most common form of DHR, and, unlike infection-related reactive exanthema, it is usually limited to the flexural aspects of the proximal extremities (4), as shown in Figure 1.

MPE is a mild/moderate DHR presenting as maculopapular, lichenoid, urticarial, morbilliform, vesicular, pustular, and acneiform exanthema. However, SCARs in their early stages may resemble MPE, and the course of the MPE has to be regularly monitored, with repeated examination for dangerous symptoms and signs (Table 2) of SCARs (4). While patients with MPE may occasionally have a mild increase in body temperature, the presence of severe fever, general discomfort, involvement of over 50% of the skin, swelling in the central face area, and swelling of lymph nodes in more than two locations indicate the development of DRESS. Signs of SJS/TEN include painful skin with unusual skin lesions, small vesicles or crusts, and involvement of the mucous membranes. If non-follicular pustules appear within 1-2 days following edematous erythema, this is indicative of AGEP. In addition, the presence of eosinophilia and atypical lymphocytes, elevated transaminase levels, and proteinuria indicate DRESS syndrome. On the other hand, leucopenia and thrombocytopenia imply SJS/TEN. Leukocytosis and neutrophilia are associated with AGEP, and both conditions can be accompanied by an increase in urea and creatinine levels. Furthermore, other diseases that resemble DHR must be excluded using viral serology, an autoimmune panel, cultures, and, in some cases, a skin biopsy (15).

The AGEP validation score is used to estimate AGEP likelihood (21), and the RegiScar scoring system is used to estimate likelihood of DRESS (23). There is, however, no valid score for SJS/TEN likelihood. However, the ALDEN score can be used to predict drug causality (24), and the SCORTEN score can be calculated at admission in the first 24 hours to predict mortality in patients with TEN (25).

INVESTIGATIONS AND MANAGEMENT

Treatment of DHRs is based on prompt identification and discontinuation of suspected culprits. However, in individuals taking many medications, every attempt should be made to discontinue only the most suspect medication(s) and not all medications. Moreover, if the treatment is urgently required and there is no viable option for less severe DHR such as MPE, drug treatment may remain unaltered under close medical monitoring, a procedure known as "treating through" (26,27). Acute therapy varies based on the severity of DHR, as shown in Table 3.

SCARs require routine clinical, laboratory, and imaging monitoring, as well as timely consultation with different specialists (e.g., a hepatologist, nephrologist, pulmonologist, dermatologists, surgeons, infectious disease specialists, etc.) (22). The course of AGEP is often uncomplicated (39), with microbiological superinfection being the greatest risk of morbidity in an otherwise mild course (28). The acute phase of SJS/TEN is self-limiting, lasting roughly eight days from the onset of symptoms to the point of maximal skin detachment. Therefore, commencing immunomodulatory therapy outside this window is unlikely to alter disease progression (29). Moreover, there is limited evidence for the benefits of immunosuppression treatments, and none of them can be recommended with certainty (30). Systemic immunosuppression has

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Table 3. Treatment options in delayed type IV drug hypersensitivity reaction (28-38)

Non-immediate type IV cutaneous adverse drug reactions	Treatment
Mild forms (MPE, FDE, SDRIFE) without systemic symptoms Mild forms (MPE, FDE, SDRIFE) without intense pruritus	Medium- to high-potency topical corticosteroids plus systemic antihistamines
FDE and MPE with systemic symptoms Generalized FDE and MPE with intense pruritus Generalized bullous fixed drug eruption (GBFDE)	Medium to high potency topical corticosteroid plus systemic antihistamines plus a short course of moderate dosage of systemic corticosteroids.
DRESS with an elevation of liver transaminases <3 times the upper limit of normal DRESS without other organ involvement	Medium- to high-potency topical corticosteroids plus systemic antihistamines.
Severe DRESS with liver transaminases >3 times the upper limit of normal Severe DRESS with single or multiple organ involvement (excluding the liver)	Moderate to high dosage of systemic corticosteroids until symptoms are resolved, followed by gradual reduction for 8 to 12 weeks. Second-line therapies: cyclosporine, intravenous immunoglobulins, JAK inhibitors and cyclophosphamide – are used anecdotally. Antivirotics for viral reactivation and evidence of viral-induced organ damage.
AGEP	Moist dressings. Topical corticosteroids in combination with topical antibiotics to prevent superinfection.
SJS/TEN >10% Body surface area epidermal loss	A multidisciplinary team should treat patients in the intensive care unit or burn center if available. Topical therapy as for burns. Supporting fluid replacement, calorie support, analgesia, surgical debridement, topical and systemic antimicrobials. Limited evidence of benefit of systemic immunosuppressive or immunomodulating agents with no benefits after the first eight days from the onset of symptoms.

the most evidence for use in the treatment of DRESS, although a relapse is possible, necessitating careful reduction over 8-12 weeks after symptom remission (31).

To avoid false results and flare-ups of systemic reactions, evaluation and testing of DHRs are indicated 4-6 weeks after initial presentation (22).

The optimal strategy for delayed DHR is a structured algorithmic method, as described by Watts (40), which consists of *in vivo* tests such as the patch test and intradermal test (IDT) with delayed reading, and *in vitro* testing such as the lymphocyte transformation test (LTT) and INF-y release assay. The combination of tests boosts the sensitivity of the diagnostic tests (41). Unfortunately, only a few research facilities do *in vitro* studies, while *in vivo* tests, which can cause relapse, are the most commonly used (40).

The patch test has a higher specificity (42), a better safety profile (in SCARs), and a noticeable advantage when oral medication preparation is the only option (43,44). Moreover, the patch test offers additional benefits for diagnosing FDE (through lesional testing) at the eruption site. However, IDT has better sensitivity (42). HLA testing is indicated prior to giving abacavir, carbamazepine, and allopurinol to patients at risk (45) but is not routinely recommended in patients without risks (15).

If the previously mentioned tests are negative, the choice to proceed to the drug provocation test (DPT) must be carefully weighed against the benefits of testing and the risk of reactivation (8). A single dosage of drug provocation is deemed safe in cases with a demonstrated history of benign exanthema (46). However, a single dose may not be sufficient to determine the tolerance to specific doses or the entire treatment cycle, and many treatment days are required (40). However, DPT can be harmful in the context of a SCAR history, and BSACI guidelines discourage its use (15). If a suitable replacement drug is available, avoiding the offending and cross-reactive drugs is advisable. However, if this is not possible, pharmacological desensitization can be administered for non-SCARs (15), such as MPE (47) and FDE (48). Desensitization must be administered in a hospital setting by an allergy team with extensive competence (15).

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CONCLUSION

Different immunological pathomechanisms and clinical manifestations characterize the delayed type IV cutaneous reaction subgroup of DHRs. The most significant distinction is between severe and non-severe DHR. Rapid detection of DHR and drug withdrawal are the cornerstones of acute treatment, with supportive measures and multidisciplinary team participation, particularly in the case of SCAR.

A systematic, algorithmic approach, including history taking, *in vitro* and *in vivo* skin and drug provocation testing, has been demonstrated to be the most effective method for confirming DHR type IV. If the medication is essential in the case of MPE and FDE, desensitization to the offending drug has been shown to be effective and safe.

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