

Invited Review Article

Undressing DReSS as p-i mediated disease

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Abbreviations:

AGEP, Acute generalized exanthematous pustulosis; APC, antigen presenting cell; DHR, drug hypersensitivity reaction(s); dDHR, delayed drug hypersensitivity reaction(s); DReSS, Drug Reaction with Eosinophilia and Systemic Symptoms; e instead of E, as eosinophilia can be absent in ≈10–25% of DReSS cases; GvHD, graft versus host disease; HSS, hypersensitivity syndrome; LTT/cyto-LTT, lymphocyte transformation test; cyto-LTT is based on cytokine secretion instead of measuring proliferation; MDH, multiple drug hypersensitivity; MPE, maculopapular exanthem; p-i, pharmacologic interaction with immune receptors; p-i concept, refers to the ability of drugs to elicit immune stimulation without forming an antigen, just by drug binding to immune receptors HLA and/or TCR; p-i mechanism and/or p-i stimulation, concrete mechanism of immune stimulation by p-i leading to activation of T cells; SCAR, severe cutaneous adverse reactions; SJS/TEN, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS) is a severe T cell-mediated hypersensitivity reaction. T cells in DReSS are stimulated via the p-i mechanism (pharmacological interaction with immune receptors), where the drug shows an off-target binding to immune receptors (TCR and/or HLA) leading to an unorthodox activation of T cells. P-i stimulations are particularly strong in DReSS, as the causative drugs are typically administered at high doses for prolonged durations (>7 days) and bind with relatively high affinity to a specific HLA allele and/or TCR. This mechanism results in delayed yet profound immune activation, progressing through four distinct phases.

1. Clinically Silent Phase: During the asymptomatic stage, the immune tolerance is disrupted. The precursor frequency of p-i-reactive T cells is low, requiring time for expansion (typically >2 weeks) before reaching a threshold that is sufficient to cause symptoms.
2. Acute Phase: Characterized by massive immune activation, lymphocytosis, lymphadenopathy, elevated levels of cytokines and cytotoxic molecules, fever, (facial) edema, and eosinophilia. P-i-activated CD4+ and CD8+ T cells are polyclonal, leading to widespread tissue damage via cytotoxicity, which affects the skin (exanthems), liver (hepatitis), and other organs. Despite drug withdrawal, T cells remain highly reactive, resulting in flare-up reactions (subacute phase).
3. Viraemia and autoimmunity phase: After 3–4 weeks, p-i-stimulated T cells may react with cytotoxicity to their original target peptide from viral (e.g., HHV6, CMV, and EBV) or autoantigenic origin, leading to viremia and potential autoimmunity.
4. Chronic Phase: The strong p-i stimulation leaves a long-term imprint on the immune system, resulting in sustained T cell hyperactivity and a predisposition to multiple drug hypersensitivity (MDH), where exposure to structurally unrelated drugs may trigger new hypersensitivity reactions years after the initial DReSS episode.

The p-i concept provides a unifying explanation for many puzzling aspects of DReSS and has significant implications for diagnosis, management, and prevention. Recognizing drug concentration, therapy duration, and HLA affinity as key determinants of strong p-i-mediated immune activation can improve risk assessment, early diagnosis, and intervention strategies for DReSS.

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Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS) or DiHS (drug induced hypersensitivity syndrome) is one of the most serious and potentially life-threatening drug hypersensitivity reaction (DHR).^{1–5} It is typically characterized by lymphocytosis, marked eosinophilia, systemic inflammation, organ dysfunction, and prolonged disease course. It differs from other severe cutaneous adverse reactions (SCARs) as to its delayed onset, clinical presentation, and complexity. DReSS might be elicited by multiple drugs, predominantly those administered in high doses (Table 1) and for longer time. The interindividual clinical course may vary not only as to the cutaneous, but also as to the systemic manifestations such as hepatitis, nephritis, pleuritis, carditis and colitis.⁶ Eosinophilia, a cardinal symptom in the majority of cases, is often high (>1.5G/l). However, in some instances, it may be absent.^{1–6} In contrast to more prevalent DHR, symptoms typically manifest weeks after start of therapy. Some of them persist or even develop only after cessation of treatment, which is atypical for DHR. Consequently, DReSS may not be taken into consideration early on and systemic symptoms may be misinterpreted which leads to delayed diagnosis.^{1–5}

The pathogenesis of DReSS is usually described as complex interplay between the immune system, drug metabolism, reactive intermediates, and viral infections.^{1–5} Evidence from delayed skin tests, in vitro assays and the histopathological finding of T-cell infiltration of the skin and the internal organs involved suggests that DReSS is primarily mediated by an immune response involving drug-specific T cells. However, the precise mechanisms underlying T-cell activation, the role of T-cell stimulation with regard to the clinical manifestations, and factors contributing to the prolonged sequelae of DReSS were not addressed.

This review explores the mechanism of T-cell stimulation in DReSS, highlighting the central role of pharmacological interaction with the immune receptor (p-i) mechanism in its pathogenesis.^{7–9} The p-i mechanism bypasses traditional antigen-processing pathways, and its stimulation does not require co-stimulation by dendritic cell interactions, suggesting the absence of specific immune regulatory mechanisms. P-i stimulation begins with a highly dose dependent pharmacological off-target interaction, where the drug binds directly to off-target receptors (HLA and/or TCR), which results in a T cell activation.^{7–9} The strength of this immune response depends on the affinity of the drug for these receptors as

well as the dose and duration of treatment. A strong p-i response is considered a key characteristic of DReSS.¹⁰

The objective of this review was to provide a comprehensive understanding of DReSS, emphasizing the role of the p-i mechanism, the important role of drug dose, its relation to clinical symptoms and to other DHRs, and its implications for management and prevention.

Mechanism of p-i stimulation in DReSS: understanding how drug interactions with immune receptors trigger abnormal T-cell activation

DHRs are immune and/or inflammatory reactions elicited by a drug, which can be a small molecule or peptide/protein. The immune response to small molecules depends on how and to which proteins the drug binds.^{8,11} Covalent binding can create new antigens, potentially triggering a complex immune response and leading to drug-induced allergy.¹¹ In contrast, noncovalent binding is usually ignored and does not elicit an immune response.

However, two key exceptions exist, where direct drug-protein interactions cause clinical symptoms. This occurs when a drug binds to immune receptors, such as T cell receptors (TCRs) or human leukocyte antigens (HLAs), a process termed pharmacologic interaction with immune receptors (*p-i mechanism*, short p-i). This mechanism is the primary cause of most delayed DHRs.⁹ It is an unusual off-target activity, as it leads to T cell activation even when the drug binds off-target to HLA on antigen-presenting cells (APCs).⁷ Another potential mechanism for drug hypersensitivity involves the binding of the drug to proteins that play a role in inflammatory processes, such as MasRGPRX2, ACE (angiotensin-converting enzyme), and Cox1 (cyclooxygenase). The resulting effects are complex and do not engage the specific immune system, and are collectively referred to as pseudoallergy.¹¹

Molecular basis of p-i stimulation

P-i stimulation is unusual because it does not follow classical antigen-driven immune responses.^{7–9} They occur without antigen processing, usually via noncovalent drug binding to a specific HLA allele, altering self-HLA to resemble allo-HLA.^{12–14} Alternatively, p-i stimulation can occur through direct drug binding to TCRs on CD4 and CD8 T cells.^{15–18} Binding typically occurs at the cell surface. For

Table 1

Drugs Commonly Associated with DReSS; Details for serum concentration see Ref.³⁵ and to HLA associations see Ref.³⁶

DRUG	HLA/TCR	Drug Hypersensitivity	Daily dose	Serum concentration (range)
Abacavir	B*57:01	HSS [†] /DReSS (no eosinophilia)	600 mg	≈ 0.9–3.9 µg/ml
Carbamazepine	B*15:02 A*31:01	SJS/TEN DReSS	800–1200 mg	4–12 µg/ml
Phenytoin	B*15:02 & varia	SJS/TEN DReSS	600–1800 mg	8–20 µg/ml
Lamotrigine	B*15:02 & varia	DReSS	50–600 mg	3–15 µg/ml
Sulfamethoxazole	SMX: TCR Vβ20-1°	DReSS	1600mg/320 mg	SMX: 30–60 µg/ml [†]
/Trimethoprim	HLA: varia			TRIM: 5–10 µg/ml
Salazopyrine:	SP: TCR Vβ20-1°	DReSS	1500–2000 mg	SP: 5–30 µg/ml [†]
Sulfapyridine (SP)/5-Amino-salicylic acid				
Vancomycin	A*32:01	DReSS	Ca 2000 mg	15–20 µg/ml
Dapsone	B*13:01	DReSS	100–300 mg	Ca. 2 µg/ml
Allopurinol/Oxypurinol	B*58:01	DReSS/SJS	300 mg	2–19 µg/ml
Minocycline	B*35:02	DReSS	200 mg	2.5–6.6 µg/ml
Piperacillin/Tazobactam	—	DReSS	9–13.5 g	Pip ≈ 380 µg/ml TZB ≈ 35.3 µg/ml;
Iodinated contrast media (e.g. iomeprol)	—	DReSS/SJS	20 g (50 ml à 400 mg/ml)	1–3 mg/ml (bolus) (!)

[†] HSS: hypersensitivity syndrome.

[‡] Slow acetylator ref. 15.

abacavir it has been shown that it can also bind to HLA-B*57:01 in the endoplasmic reticulum, altering peptide presentation.^{12–14,18} Dendritic cell processing is bypassed and p-i mechanisms activate naive and memory T cells, sometimes independently of CD4 or CD8 co-receptor involvement.^{13,19}

For sulfamethoxazole, it has been shown that p-i stimulation can allosterically modify TCR conformation, increasing TCR-HLA/APC interaction affinity and affecting T cell signalling.¹⁵ Some drugs bridge TCR and HLA, inducing oligoclonal T cell expansion, as observed in Stevens-Johnson syndrome (SJS)²⁰ and DReSS, where an oligoclonal T cell expansion has been detected after >3 weeks of in vitro stimulation with the causative drug (personal experience).

Functional diversity of p-i stimulated T cells

T cells activated via the p-i mechanism display significant functional heterogeneity. Across all p-i-mediated reactions, cytotoxic activity is predominant, with both CD8+ and CD4+ T cells releasing granzyme B, perforin, and granulysin (key mediators of tissue damage), as well as engaging in FasL-Fas interactions, triggering apoptosis.^{21–25}

Production of various cytokines is also a major feature of p-i reactions. In DReSS, high IL-5 production is a distinguishing feature and may be linked to CD4-independent T cell activation.²⁶ IL-5 elevation leads to eosinophilia, a hallmark of DReSS, but is also found in maculopapular exanthema (MPE), and acute generalized exanthematous pustulosis (AGEP).

It is established that **i)** pharmacological interaction (p-i) stimulation engages TCR-HLA complexes of both naive and memory T cells, thereby activating them^{13,27}; **ii)** T cells and T cell clones exhibit a stronger and broader cytokine response to mitogens such as PHA, PWM, or anti-CD3 antibodies compared to antigen-

presenting cells (APC) presenting a peptide on HLA.^{28–30} The p-i stimulation appears to function similarly to such mitogenic stimuli, leading to the concurrent release of Th1 (IFN γ) and Th2 cytokines (IL-5, IL-13), as well as cytotoxic effector molecules (granzyme B, perforin) upon interaction with target cells.^{31,32} The distinctive nature of p-i stimulation, characterized by high and broad cytokine levels (IL-4, IL-5, IL-13, IFN γ , TNF α , granzyme B, etc.), renders the conventional distinction between Th1 and Th2 reactivity obsolete. DReSSs are not Th2 reactions!

The unusual T cell stimulation by p-i is probably also the reason for the high occurrence of double-positive (CD4+/CD8+) T cells and unusual HLA restrictions observed in p-i stimulated cell cultures.^{33,34}

In summary, p-i stimulation is complex, sharing traits with allor-eactivity and superantigen/mitogen responses (oligoclonal T-cell expansion, massive immune stimulation)^{7–9}. Drug-induced T-cell clones (TCCs) being cytotoxic and producing IFN γ and IL-5 challenges the Th0/Th1/Th2 distinction for these p-i reactions.

Factors influencing p-i stimulation strength in DReSS

DReSS is characterized by strong p-i stimulation, leading to polyclonal T cell expansion and cytokine storms. Several factors contribute to heightened immune activation, including high drug concentrations (>300 mg/day),³⁵ prolonged therapy durations (>7 days), and sustained T cell stimulation (Fig 1). Strong HLA-drug interactions, especially in individuals with specific HLA alleles such as B*58:01 (for allopurinol/oxypurinol) A*31:01 (carbamazepine) and many more (Table 1),³⁶ enhance drug-HLA binding stability and intensify the immune response.

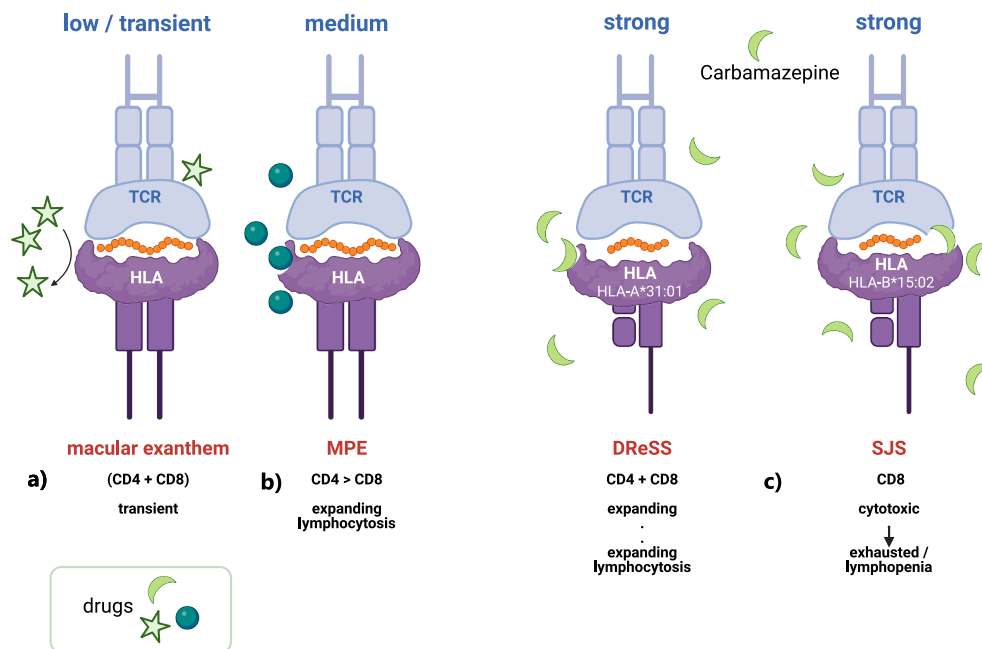


Fig. 1. P-i Stimulation Strength as a Function of Drug Affinity for Immune Receptors.

This illustrates the spectrum of p-i stimulations based on a drug's affinity for immune receptors (HLA/TCR), ranging from weak to strong interactions.

a) Low-affinity binding results in short-lived interactions with HLA or TCR, triggering cytokine release but minimal T-cell proliferation. This leads to transient macular exanthema. It is challenging to confirm a sensitization via skin or in vitro tests (LTT).

b) Moderate-affinity binding activates both CD4+ and CD8+ T cells, either locally in the skin or rarely systemically. This induces maculopapular exanthema (MPE), characterized by significant cell infiltration, predominantly CD4-mediated cytotoxicity, and typically positive skin and in vitro tests.

c) High-affinity binding strongly activates T cells, with clinical outcomes depending on the HLA and TCR binding sites. In carbamazepine hypersensitivity, binding to HLA-A*31:01 drives CD4+ and CD8+ T cell expansion, increasing DReSS risk. In contrast, binding to HLA-B*15:02 (and TCR) selectively stimulates CD8+ T cells, causing SJS/TEN via skin-specific cytotoxicity. Due to CD8+ T cell exhaustion, these cells may no longer respond when tested outside the acute phase.

Role of drug concentration and therapy duration

T-cell clone (TCC) analysis of DReSS patients confirms that p-i stimulation is the primary mechanism of immune activation.^{13,19,37–39} This is demonstrated by immediate TCC reactivity upon drug exposure, occurring without prior metabolism or antigen processing, which is required for hapten-protein interactions.^{40,41} Crystallographic, molecular modeling and competition studies using structurally related compounds^{12–18} further confirmed that these drugs bind directly to the immune receptors HLA and TCR, reinforcing the role of drug concentration, therapy duration, and drug-HLA binding affinity in triggering immune activation.⁹

DReSS-inducing drugs are typically administered at high doses (>300 mg/day) and can reach serum concentrations of up to 20 µg/mL (Table 1). In contrast, drugs with lower serum levels (<1 µg/mL) rarely induced DReSS, suggesting that a threshold concentration is required. A well-established dose-response relationship exists between high drug exposure and occurrence of SCARs,^{42–44} including DReSS. In addition, metabolism, bioactivation, tissue distribution, pharmacokinetics and intracellular processes such as liquid–liquid phase separation (LLPS) may influence the availability of drug/drug metabolites which influence p-i reactions.^{31–33,45,46}

A defining feature of DReSS is its delayed onset, which typically appears after >14 days of continuous drug exposure. This suggests that sustained high drug concentrations over time are required to maintain ongoing T-cell stimulation and drive immune response

(Fig. 2, Table 2). Epidemiological data indicate that therapy lasting more than seven days is necessary to induce DReSS or SJS/TEN. For example, valdecoxib- and imatinib-induced SJS/TEN only occurred when the drug was administered continuously for more than seven days.^{47,48} This requirement for prolonged exposure aligns with the low precursor frequency of highly drug-reactive T-cells. When just one single HLA allele is modified, only a limited number of T cells initially respond. These few drug/HLA-reactive T cells need time to expand; The asymptomatic phase lasts two or more weeks of therapy before the cells have reached a critical threshold, which then cause acute DReSS symptoms (Fig. 1, 2).

The role of drug-binding affinity for immune receptors

Another crucial factor influencing the p-i stimulation strength is the binding affinity of the drug to immune receptors. Many DReSS and SJS cases occurred in individuals expressing specific HLA alleles (Table 1). Examples include *B*57:01* in *abacavir* hypersensitivity, *A*31:01* in carbamazepine reactions, and *A*32:01* in vancomycin hypersensitivity (reviewed in 36). These risk alleles are thought to exhibit high-affinity drug binding, supporting stable TCR-drug-HLA complex formation, which serves as the basis for strong p-i stimulation. In such cases, the few T cells, which are able to react, require time for expansion, leading to delayed onset (DReSS/SJS).

In many drug therapies no risk allele is present. Sometimes the drug may still bind to multiple HLA or TCR molecules, but with low affinity, leading to mild, transient reactions: a “drug rash” appears

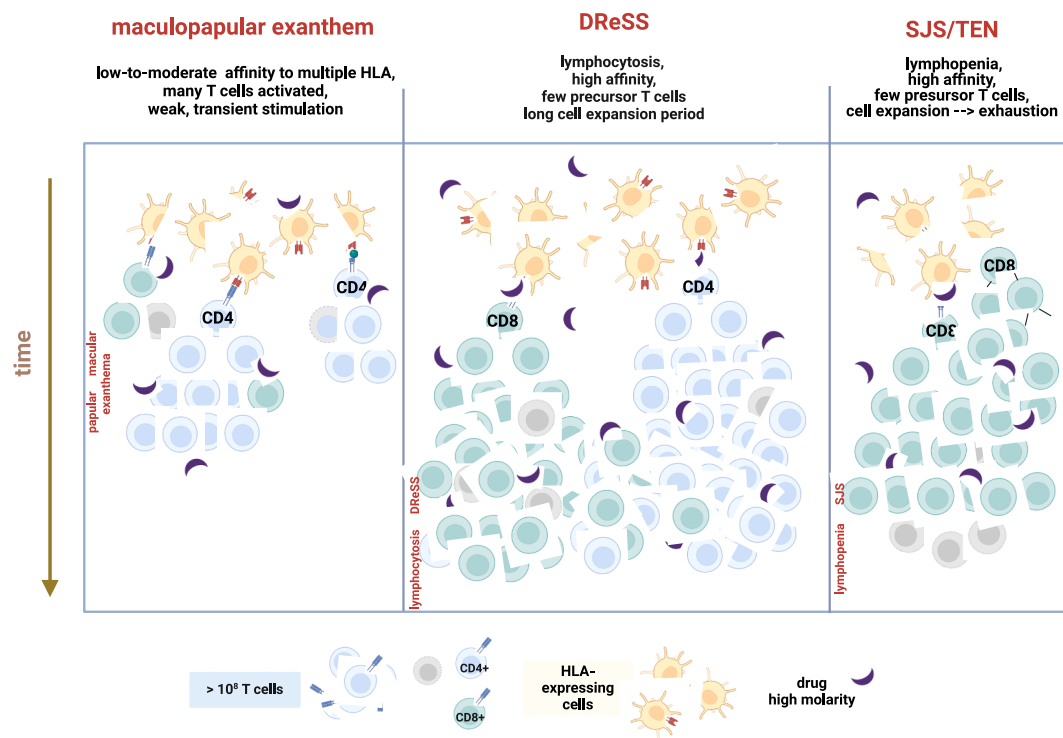


Fig. 2. Type of Drug Hypersensitivity as a Function of Drug Affinity, Precursor Frequency, and HLA Allele.

This illustrates how drug affinity for immune receptors (HLA/TCR), the precursor frequency of reactive T cells, and HLA allele specificity influence the type and timing of drug hypersensitivity (DH) reactions.

A low-affinity drug (X) binds weakly to multiple HLA alleles and TCRs, forming numerous but unstable TCR-drug-HLA complexes. This leads to weak, transient p-i stimulation, with symptoms appearing early (2–7 days) as mild macular to maculopapular exanthems.

In contrast, a high-affinity drug (Y) binds strongly to a single risk-associated HLA allele, forming a stable TCR-drug-HLA complex that elicits a robust immune response. Due to the low precursor frequency of highly reactive T cells, expansion requires sustained drug exposure (>10 days), leading to delayed but severe reactions such as DReSS.

In SJS/TEN, early stimulation strongly activates cytotoxic CD8+ T cells, causing tissue damage. However, these cells undergo terminal differentiation and exhaustion, becoming refractory to further stimulation, which may explain their reduced detectability outside the acute phase.

Table 2

Influence of Risk Alleles, Strength, and Type of p-i Stimulation on Clinical Manifestations of Drug Hypersensitivity Reactions (DHRs).

Presence of Risk Allele	The drug's ability to bind immune receptors (HLA/TCR) is influenced by the structure of these molecules. Some HLA alleles have a high affinity for specific drugs, increasing the risk of DHR. Examples include dapsone (HLA-B*13:01), Vancomycin (HLA-A *32:01) and many more.
Strength of p-i Stimulation	Determined by drug affinity for immune receptors, dose, and therapy duration. The strength correlates with T-cell expansion and tissue infiltration, leading to varying degrees of damage. - High: SJS/TEN (localized to the skin, but reactive CD8+ T cells undergo exhaustion), DReSS (affecting skin and other organs). - Moderate: MPE - Low: Mild MPE, often requiring viral cofactors (increase of avidity).
Types and Complexity of p-i Stimulation	- Cytotoxicity: Found in all dDHRs, mediated by p-i-induced CD4+ T cells (MPE, DReSS, AGEP) and CD8+ T cells (SJS/TEN, but also DReSS, AGEP) via granzyme B, perforin, granulysin, and Fas/FasL-mediated apoptosis. - IL-5 production and eosinophilia: Frequent in DReSS, MPE, AGEP. - IL-8, GM-CSF, IL-36 γ with neutrophil recruitment: Common in AGEP, occasionally observed in DReSS, MPE.

(Fig. 1). This low-affinity binding results in minimal T-cell proliferation; however, initially, a larger number of T cells can react transiently. Clinically, these patients present with macular rather than maculopapular exanthems, minimal cytokine release, and limited cellular infiltration. Since multiple T cells are involved, symptoms appear earlier (within 1–6 days), but remain transient. Clinically, skin tests and in vitro assays for drug-specific T cells often yield negative results. Consequently, this early, transient binding may explain the weak T-cell stimulation observed with lower cytokine levels and limited expansion compared to DReSS (Fig. 1,2).

As discussed recently, also the avidity (sum of affinities) of drugs for immune receptors can be influenced: Virus infections increase IFN γ levels, which enhances the density of the immune receptors HLA and TCR on the cell surface.⁴⁹ This offers more binding sites for drugs, and thus may make a weak p-i reaction to a

stronger one (higher avidity): a subclinical p-i stimulation may become a mild exanthema. This may be the explanation for drug related exanthema in childhood, where virus infections and drug therapy coincide, causing a transient drug hypersensitivity reaction, which is later no more demonstrable, as the cofactor is missing (Fig. 3).

Quantitative data on the affinity of noncovalent drug binding to HLA/TCR with functional consequences are limited but estimated in the range of Kd: 10^{-7} – 10^{-6} M. Indirect data suggest that some drugs stimulate T cells only in the presence of risk alleles (e.g., abacavir), while others show a preference for more alleles (e.g. oxypurinol: B*58:01, A*33:02), and some have no or only a weak preference (Table 1). Exceptions to the principle of <drug dose-duration-affinity> include β -lactams, such as piperacillin/tazobactam, and iodinated contrast media (RCM).^{50,51} These drugs can induce DReSS, with symptoms manifesting earlier than the typical

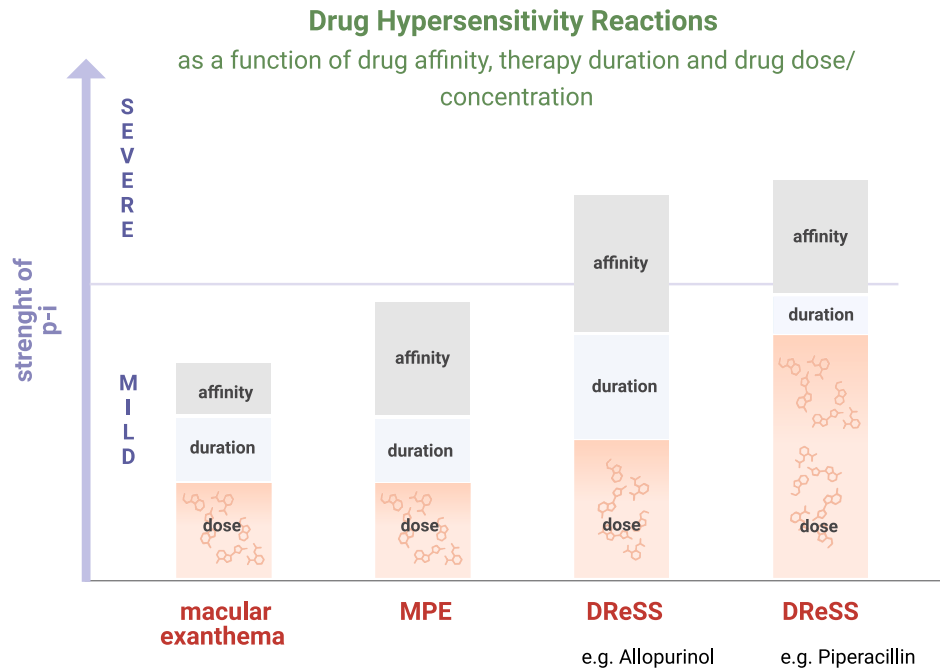


Fig. 3. This illustrates how drug affinity for immune receptors (HLA/TCR), drug concentration, and therapy duration influence the strength of p-i stimulation and the manifestation of drug-induced hypersensitivity reactions (dDHRs).

Mild-maculopapular reaction: Some p-i reactions may remain unnoticed or are just a mild exanthema. It would become clinically more manifest, if a concomitant virus infection increases immune receptor expression ($\uparrow$ IFN γ), thereby increasing the sum of drug-immune receptor affinities (avidity) $\rightarrow$ then the patient has an MPE, cotriggered by virus infection.⁵²

Severe reaction: In E.g., allopurinol/oxypurinol-induced DReSS is strongly influenced by the presence of the HLA-B*58:01 risk allele (affinity $\uparrow$) and elevated drug concentrations, such as in patients with renal insufficiency, leading to a high-intensity p-i response and increased risk of DReSS.

In contrast, piperacillin-induced DReSS appears to be driven by high drug doses and resulting high tissue concentrations, despite the absence of a known risk allele. This suggests that massive drug exposure alone can facilitate strong p-i stimulation, emphasizing the importance of dose-dependent effects in DReSS pathogenesis.

14-day threshold. RCM is given as a bolus in extremely high doses, and piperacillin/tazobactam is administered in very high concentrations to achieve substantial tissue penetration (Table 1,^{51–53}). This suggests that high drug doses can compensate for the short exposure duration and lower affinity, leading to sufficiently stable p-i stimulation and the development of DReSS (Fig. 3).

In summary, p-i stimulation can result in either numerous but weak stimulations, leading to rapidly appearing but transient exanthems (“drug rashes”), intermediate reactions (MPE) and severe reactions (severe MPE, DReSS, SJS/TEN), which mostly rely on fewer, but stronger stimulations restricted to a single/a few HLA alleles. The few reactive T cells require time for T-cell expansion, which explains the late appearance of symptoms in DReSS and SJS/TEN.

Strength of p-i stimulation in DReSS

Understanding the complexity of TCR-HLA interactions in p-i stimulation further clarifies why DReSS presents with a severe hypersensitivity reaction.

Comparison between p-i stimulation and hapten-peptide stimulations

A fundamental distinction between p-i stimulation and hapten-peptide stimulation is the nature and extent of immune activation. When TCCs from the same individual exhibited p-i and hapten peptide responses, the p-i response was stronger and more complex.^{54,55} In hapten-peptide mechanisms, hapten-modified peptides undergo antigen processing and are presented by specific – but not all – HLA-alleles. Self-peptides can compete for binding within the peptide-binding groove, limiting the number of activated T-cells. Consequently, hapten mechanisms activate a small subset of T cells. In contrast, in p-i stimulations e.g. all B*58:01 alleles may be modified and make them to potential targets of an immune reaction.

Measuring the strength of p-i stimulation in DReSS

P-i stimulation leads to polyclonal expansion with diverse functional consequences, including cytotoxicity and eosinophilia. The severity of tissue damage in DReSS is likely related to the strength of the p-i stimulation. To assess the p-i stimulation strength, cytokine and cytotoxic mediator release were measured

as markers using in vitro stimulation assays (Cyto-LTT).^{10,56} The results of 48 patients with positive cyto-LTT are shown in Figure 4; they demonstrated that T cells from DReSS patients (n = 22) exhibited the strongest response, secreting substantial levels of all five cytokines and mediators. IL-5 and IL-13 levels were approximately 100-fold higher in DReSS than in controls. High IFN γ and granzyme B levels were observed in both DReSS and MPE (n = 20). In contrast, granulysin levels were the highest in SJS/TEN (n = 6), while other cytokines remained low. A more complete picture on >6000 cyto-LTT evaluations and its ability to define strong p-i reactions is provided in Peyer T et al., 2025.¹⁰

In conclusion, p-i stimulation in DReSS is characterized by diverse TCR-HLA interactions, atypical co-receptor usage, and strong cytokine responses. The intensity of this response, namely the high cytokine values, correlates with eosinophilia and systemic inflammation, which are the key clinical features of DReSS. Understanding these mechanisms provides insights into the distinct clinical presentation of DReSS and its potential diagnostic and therapeutic strategies (Table 2).

Clinical presentation of acute DReSS as a consequence of massive p-i triggered immune stimulation

Patients with DReSS present with a clinical picture typical of massive immune stimulation (Fig. 4).^{1–5,57} The following characteristics occur:

- Lymphocytosis and Lymph Node Swelling:** Marked lymphocytosis (>4 G/L) due to CD4+ and CD8+ T-cell expansion, often accompanied by lymphadenopathy, which occurs in 75–100 % of cases^{1–5};
- Cytokine Storm and Systemic Inflammation:** Elevated levels of multiple cytokines, including IL-2, IL-2R, IFN γ , TNF α , perforin, granzyme B, granulysin, IL-5, IL-10, IL-13, and TARC/CCL17.⁵⁸ The cytokine profile resembles superantigen-like or anti-CD28/anti-CD3 antibody-mediated immune activation.⁵⁹ High levels of IL-2, TNF α , and IFN γ correlate with fever, malaise, and vascular leak syndrome, which manifests clinically as generalized edema or pulmonary edema, a phenomenon also observed in patients undergoing high-dose IL-2 therapy.⁶⁰ Facial swelling, occurring in approximately 30 % of patients, is likely linked to cytokine-induced vascular permeability⁶¹;
- Organ Damage** driven by cytotoxic CD4+ and CD8+ T-cell activation. These T cells release granzyme B, perforin, and granulysin, which leads to direct tissue destruction.^{20–23,62}

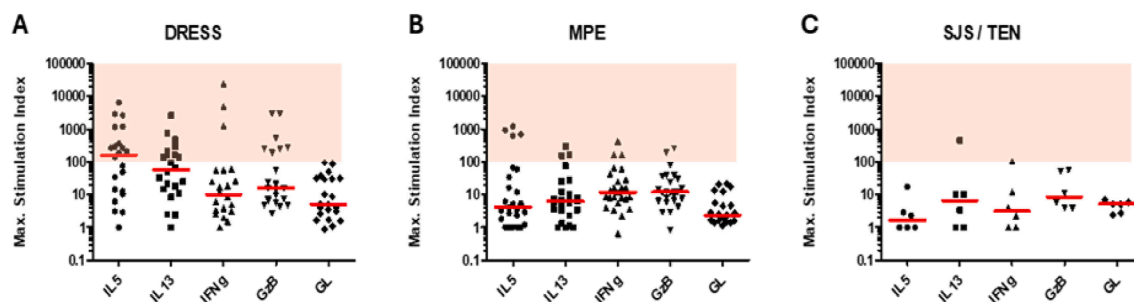


Fig. 4. Cytokine Secretion Profiles in MPE, DReSS, and SJS/TEN. This illustrates cytokine and cytotoxic mediator secretion in patients diagnosed with DReSS (n = 22), maculopapular exanthema (MPE, n = 20), and SJS/TEN (n = 6), analyzed using cyto-LTT at 4–50 weeks after the acute drug hypersensitivity reaction.

Patient T cells were cultured with the implicated drug at three concentrations for six–seven days, and the secretion of IL-5, IL-13, IFN γ , granzyme B, and granulysin was measured using bead-based assays (details see ref 10). Tested drugs included amoxicillin, piperacillin, sulfamethoxazole, trimethoprim, carbamazepine, lamotrigine, sulfapyrin, and vancomycin. Only the highest cytokine levels observed across the tested concentrations are depicted.

Healthy controls (n = 15) exposed to these drugs showed no significant cytokine release (SI < 3), confirming the specificity of the response.

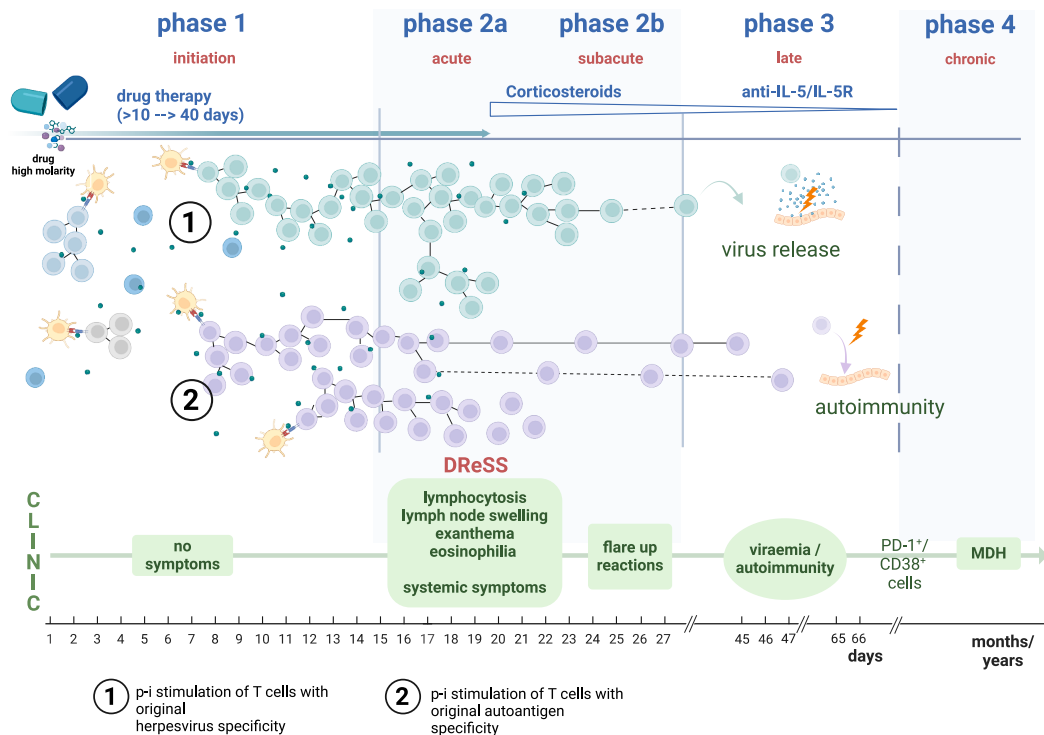


Fig. 5. Four Phases of DReSS. See text.

Skin involvement typically presents as *morbilliform eruptions* (80 %), sometimes with targetoid lesions, blisters, or pustules, progressing to erythroderma or exfoliative dermatitis in 10 % of cases.³ Drug-induced liver injury (DILI) is common, with cholestatic and hepatocellular involvement, and in some cases nephritis, colitis, pancreatitis and carditis may occur. It is essential to actively exclude myocarditis in the case of suspected cardiac involvement.⁶³ The mechanism directing organ-specific T-cell infiltration remains unclear, but drug-specific targeting of organs has been suggested.⁶

A further rare complication of DRESS is drug induced hemophagocytic lymphohistiocytosis/macrophage activation syndrome.⁶⁴ Thus, rapid examination and treatment is mandatory if signs of additional macrophage activation are present.

- D) **Eosinophilia and IL-5 Dominance:** Massive eosinophilia (>1.5 G/L) occurs in >75 % of DReSS cases. Many drug-reactive T cells in DReSS are stimulated via p-i mechanisms that lack CD4/CD8 co-receptor involvement.^{26,33,34} This co-receptor-independent TCR-drug-HLA interaction alters Lck signaling, potentially enhancing IL-5 production and contributing to eosinophilia.²⁶ The role of eosinophils in tissue damage remains debated, but IL-5/IL-5R blockade has shown clinical benefit by reducing eosinophilia and improving the disease course⁶⁵;
- D) **Neutrophilic Involvement:** The recruitment and activation of neutrophilic leukocytes is another feature of some dDHRs, particularly acute generalized exanthematous pustulosis (AGEP) and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE).⁶⁶ Approximately 15 % of patients with DReSS exhibit neutrophilic infiltration in skin lesions,⁶⁷ and 10 % initially present with pustular exanthem resembling AGEP, later progressing to systemic DReSS.^{68,6}

The precise mechanisms remain unclear but may involve IL-8, GM-CSF, IL-5, and IL-36γ.⁶⁹ The role of IL-17 is controversial. Recent data suggest a connection between AGEP and generalized pustular psoriasis.⁷⁰

Acute DReSS is driven by massive p-i stimulation, leading to lymphocytosis with lymphadenopathy, cytokine storm causing fever, malaise, edema, eosinophilia, various exanthema types, and organ damage due to cytotoxic T-cell activity.

Four phases of DReSS (see Fig. 5)

DReSS progresses through four distinct phases, characterized by changes in T cell activation, immune response, and clinical presentation. These phases are influenced by the presence or absence of the drug, allo-like immune stimulation (p-i), peptide-specific immune responses to self-HLA, and long-term hyper-reactivity to further p-i stimulation (multiple drug hypersensitivity, MDH) (Fig. 1,3).

Initiation phase (1) - asymptomatic preclinical stage

The initiation phase begins with drug exposure and remains clinically silent until symptoms suggestive of hypersensitivity emerge. DReSS develops slowly (Fig. 1) because of the low precursor frequency of T cells that are reactive to HLA-drug complexes. This phase typically lasts 2–6 weeks. Despite the presence of risk alleles and drug exposure, most individuals do not develop DReSS owing to robust immune tolerance mechanisms (T reg cells,^{71,72}). The precise triggers for breaking tolerance and initiating T cell expansion are unclear. The increased incidence of severe DH in patients undergoing therapy with checkpoint inhibitors suggest that these inhibitory mechanism do also play a role in tolerance mechanism to drugs.^{73–76}

Increased drug concentrations due to higher doses or impaired metabolism may play a role. For example, elevated vancomycin trough levels correlate with a higher risk of vancomycin-induced DReSS⁷⁷ and renal impairment has been linked to allopurinol-related DReSS.⁷⁸ Viral infections and increased immune receptor expression may also contribute.⁴⁹ This phase ends with prodromal symptoms, including low-grade fever, malaise, sore throat, dysphagia, pruritus, and burning skin sensations, marking the transition to the acute phase.³

Acute phase (2) - systemic immune activation

The acute phase is characterized by generalized immune activation, presenting with fever, malaise, pleomorphic cutaneous eruptions (erythematous, urticarial, eczematous, lichenoid, exfoliative, targetoid, purpuric, vesicular, and pustular), and facial/periorbital edema. Lymphadenopathy is a key feature observed in most patients in the RegiSCAR study.¹ Mild liver involvement may be an early finding, with other organ manifestations developing later, or alongside liver dysfunction.^{1–5}

The initial symptoms manifest in the presence of the drug (2a). At this stage, p-i-stimulated T cells are expanded, leading to lymphocytosis, lymphadenopathy, and tissue infiltration (skin, liver, etc.). They form {TCR-drug-HLA} complexes in target organs, triggering cytotoxicity and systemic inflammation. In this phase lasting several days, the patient is sick.

In most cases, discontinuation of the drug and initiation of systemic corticosteroid treatment will not lead to immediate resolution of symptoms. Some manifestations may persist or worsen following drug withdrawal (2b). P-i-activated T cells remain reactive, continue to release cytokines, and exert cytotoxic effects for days to weeks, even in the absence of the drug. Some allo-like T cells may cross-react with self-HLA molecules on tissue cells, causing flare-up reactions,⁷⁹ such as recurrent eosinophilia, elevated liver enzymes, and transient organ dysfunction. These flare up reactions can be exacerbated by minor external triggers, including viral infections, new medications (e.g., paracetamol), or even dietary components (spices, personal experience). The sub-acute phase (2b) can last for several days to weeks.

Late complications (3) - immune reprogramming and autoimmunity

Late complications typically arise approximately 3–4 weeks after drug withdrawal.⁸⁰ T-cell hyperactivation and eosinophilia gradually decrease with immunosuppressive therapy (systemic corticosteroids, anti-IL-5 therapy). During this period, T cells transition from an *allo*-like hyperreactive state back to a *self*-HLA/peptide-specific response.

A substantial portion of p-i-stimulated T cells are originally specific for viral (HHV-6, CMV, EBV) or autoantigen-derived peptides (Fig. 5).⁸¹ Prior to p-i stimulation, these T cells primarily function as IFN- γ -secreting controllers of viral infections.⁸¹ However, intermittent p-i stimulation may affect their function and convert them into cytotoxic effector T-cells.^{82,83} Virus reactivation may lead to enhanced expression of virus-related⁸⁴ or self-peptides on self-HLA, to which these T cells react with cytotoxic immune responses, attacking virus infected or autoimmune cells.⁸⁵ Herpes virus reactivation is a frequent complication in this phase, with viremia observed in HHV-6, CMV, and EBV infections.⁸⁰ This may result from direct cytotoxic T cell attacks on infected cells,⁸⁵ enhanced viral replication,^{80,84,86} or a combination of both. New-onset autoimmune diseases primarily target

endocrine organs in approximately 20 % of patients with DReSS,⁸⁰ and may occur also in the chronic phase.

Chronic phase (4) – persistent T-cell hyperreactivity and multiple drug hypersensitivity (MDH)

Following severe p-i stimulation, long-term immune alterations persist, resembling chronic graft-versus-host disease (GvHD).⁹ Hyperreactive T cells expressing CD38+ and PD-1+ persist in peripheral blood for years.⁸⁷ Up to 25 % of DReSS patients develop multiple drug hypersensitivity (MDH) upon exposure to structurally unrelated drugs.^{87–89}

MDH may emerge at different stages, including: *a) initiation phase*: reactivity to both or more components of combination therapies (e.g., sulfamethoxazole/trimethoprim); *b) acute or late phases*: additional drug hypersensitivity reactions to newly introduced drugs; *c) months to years* after the first p-i stimulation: Delayed MDH development.

To mitigate MDH risk, it might be advisable to avoid high-dosed drugs that reach serum concentrations >1–2 $\mu\text{g/mL}$. Though the chronic phase is asymptomatic, clinicians should be aware of the fact that a history of DReSS is associated with an elevated risk to develop future drug hypersensitivity reactions.⁸⁹

DReSS vs. SJS/TEN: T-cell expansion vs. exhaustion and the role of HLA and drug in fine-tuning p-i stimulations

Differences in immune mechanisms: expansion vs. exhaustion

All major forms of delayed drug hypersensitivity reactions (dDHRs), including MPE, AGEP, DReSS, and SJS/TEN, appear to be mediated by p-i stimulation.⁹ These reactions manifest as distinct clinical presentations, often in response to the same drug. The strength and type of p-i stimulation determines the disease phenotype, as exemplified by the contrast between DReSS and SJS/TEN.

DReSS is characterized by lymphocytosis and robust T-cell expansion involving reactive CD4+ and CD8+ T cells, extensive cytokine production, and cytotoxic effects on multiple organs. The immune response persists even after drug withdrawal and often leads to late immune-mediated complications. In vitro analyses confirm strong, drug-inducible T cell expansion, and skin tests are often positive (1–5, Fig. 4).

SJS/TEN is a severe reaction of skin and mucosal surfaces characterized by p-i-stimulated, often oligoclonal, highly cytotoxic CD8+ T cells found in blister fluids. These cells do – at time of investigation (>3 weeks after start) – exhibit often only minimal proliferation upon drug exposure, which was interpreted as being due to terminal differentiation.²⁰ This refractoriness to restimulation is evident in vitro, as cyto-LTT of SJS patients is often negative when tested in remission^{90,91} or cytokine levels in cytokine based LTT remain low (Fig. 4). The exhaustion of originally hyperactivated CD8+ T cells likely explains this phenomenon.²⁰

IFN γ production can still be detected in some SJS/TEN patients, originating from CD4+ T cells rather than exhausted CD8+ T cells, the primary effectors of SJS/TEN.⁹¹ This suggests that terminal differentiation primarily affects CD8+ T cells, and since only a limited number of CD4+ T cells respond, cyto-LTT results remain low despite initial strong p-i stimulation. Unlike DReSS, SJS/TEN patients exhibit lymphopenia, lack significant eosinophilia, and suffer primarily from degenerative complications, such as mucosal scarring and increased risk of malignancies, potentially due to immune deficiency due to T-cell exhaustion.^{92,93} Unlike DReSS,

multiple drug hypersensitivity (MDH) is not a late consequence of SJS/TEN.⁸⁹

The role of HLA: fine-tuning p-i stimulation and disease phenotype

Epidemiological studies suggest that a decisive factor for developing either DReSS or SJS to the same drug can be the drug's interaction with the HLA-allele: Some of the strong p-i stimulators like allopurinol/oxypurinol, phenytoin, carbamazepine cause either DReSS or SJS/TEN, whereby carbamazepine data suggest that this depends on the HLA background, which is “fine tuning” the p-i stimulation^{94–96}; the same drug may bind to a distinct binding site on the HLA-allele A*31:01 or on B*15:02: This is schematically illustrated for CBZ in Figure 1: CBZ is able to elicit either a p-i stimulation involving CD4 (+CD8) cell expansion and cytotoxicity with high IL-5 production (DReSS, A*31:01), or a mainly cytotoxic, often oligoclonal CD8/NK-cell reaction with involvement of certain TCR-Vβ (SJS/TEN, B*15:02), which is soon exhausted and refractory to further stimulation.^{20,90,91}

The role of drug-specific factors

Epidemiological data demonstrate the influence of the drug on the clinical presentation of DReSS.⁶ For instance, lamotrigine-related DReSS often presents without eosinophilia; allopurinol/oxypurinol-triggered DReSS frequently exhibits involvement of the kidneys, and minocycline often displays marked lymphadenopathy, among others.^{96–98} Abacavir induced DHR were usually not categorized as DReSS, as eosinophilia, lymphadenopathy, and liver involvement is rare or absent, while the lung and kidney are often affected.⁹⁹ These findings suggest that homing of activated T cells to the tissue may be influenced by the drug involved in DHR/DReSS. However, the mechanism underlying this phenomenon remains unclear.

The analysis of cyto-LTT data in recent years also suggests that the type of drug has an influence on DReSS development. The cytokine patterns of drugs having elicited DReSS differed, as the aromatic sulfonamides (sulfamethoxazole and sulfapyrin) induced a different pattern of cytokine secretion in vitro than vancomycin or amoxicillin: DReSS ≠ DReSS (Peyer T *et al.*, in preparation).

A compelling example of the impact of drug type on the clinical manifestation of DH is the case of a female patient who, during sequential treatment with rifampicin, gabapentin, levofloxacin, meropenem, and colistin, developed a MPE, followed by DReSS, AGEP, and ultimately TEN, which proved fatal.¹⁰⁰

In summary, strong p-i stimulation can manifest as DReSS, which is characterized by a cell-expanding immune response with lymphocytosis, or as SJS/TEN, which exhibits a cytotoxic and exhausted T cell profile (lymphopenia). Although CD8+ T cell stimulation in SJS/TEN is initially strong, these cells rapidly become exhausted. The type (DReSS vs SJS) and clinical manifestation of DReSS (e.g. eosinophilia, liver involvement etc.) are influenced by the HLA allele or the type of drug.

Mixed clinical presentations

DReSS, SJS/TEN, AGEP, and MPE represent distinct clinical manifestations of dDHR, each associated with differences in p-i stimulation strength, drug interaction sites within the TCR–HLA complex, and T-cell activation type. Certain drugs, such as carbamazepine, oxypurinol, and phenytoin, can trigger either an expansive or a cytotoxic/exhaustive T-cell response. However, overlapping symptoms in some cases of dDHR suggest that the

severity of immune activation may exist along a continuum, where moderate immune responses may escalate, or expansive and cytotoxic/exhaustive T-cell stimulations may coexist.¹⁰¹

MPE-DReSS overlap

MPE and DReSS are generally considered to represent distinct diseases. But it is less clear whether they differ just in intensity or also mechanism. MPE and classical skin lesions in DReSS may not be distinguished using biopsy as the histopathological features are not pathognomonic. Their exanthems are heterogeneous, varying in the extent of skin cell infiltration and presence of eosinophilia.¹⁰²

A recent study suggested that skin-resident memory T cells are the primary effector cells in MPE.¹⁰³ However, in a prospective study of severe MPE, approximately 25 % of patients exhibited moderate liver involvement (elevated ALAT/ASAT, although <500 IU), and lymphadenopathy and lymphocytosis were frequently observed.¹⁰⁴ While these systemic immune manifestations are less pronounced in MPE than in DReSS, they indicate that severe MPE can go along with extracutaneous immunological manifestations. Additionally, approximately 50 % of MPE patients exhibit significant eosinophilia, though rarely exceeding 1.5 G/L.¹⁰² This suggests that some severe cases of MPE and mild cases of DReSS may differ more in intensity than mechanism, with MPE being primarily skin-focused and severe MPE exhibiting systemic involvement. Pinto-Couveia *et al.* attempted to define the criteria for an overlapping MPE-DReSS syndrome, highlighting this continuum.¹⁰⁵

AGEP-DReSS overlap

The exact mechanism of AGEP remains unclear, but the rapid symptom onset and lack of strong HLA associations suggest that AGEP results from early, weak/moderate p-i stimulation that promotes neutrophil recruitment.⁶⁶ In addition, various studies have established a significant association between IL36RN variants and AGEP, emphasizing the IL-1/IL-36-chemokine-neutrophil axis as a common pathogenic mechanism.¹⁰⁶ Interestingly, up to 10 % of DReSS cases initially present with pustular reactions within the first seven days, resembling AGEP, before progressing to full DReSS.⁵⁷ This could be due to an initial broad p-i stimulation involving multiple HLA alleles (Fig. 1), with later expansion of T cells responding to stronger, high-affinity p-i stimulations, ultimately shifting the disease phenotype toward DReSS.

SJS-DReSS overlap

The primary immune response in DReSS is characterized by T cell expansion whereas SJS/TEN is dominated by cytotoxicity, leading to the rapid exhaustion of activated CD8+ T cells (lymphopenia). However, some patients with DReSS also present with blistering skin reactions, likely due to robust CD8+ T-cell activation. In rare cases, patients may meet the diagnostic criteria for both DReSS and SJS/TEN with overlapping immune responses leading to a combined clinical phenotype. Such overlapping syndromes account for approximately 3 % of DReSS cases.^{90,98} This phenomenon may result from the simultaneous activation of different p-i stimulation pathways resulting in a mixed clinical presentation.

Summary and clinical implications

DReSS is a key example for a p-i mediated dDHR. It is a clinically perplexing disease with some similarity to acute and chronic allo-like immune reactions (GvHD), while some aspects are

reminiscent of superantigen stimulations. Its clinic is peculiar, as it is based on an *immunologically unorthodox* T cell stimulation:

- Not an antigen, but a drug, which is *acting as drug - and not as antigen*, elicits massive immune stimulations with sometimes prolonged immunological effects. In p-i, pharmacology not only intersects with immunology but also fundamentally alters the patient's immune system for good!
- DReSS is not a drug-specific disease. The immunity is not directed towards the drug (as it is in hapten reactions). DReSS is a drug-triggered disease, with strongly positive skin and in vitro tests: T cells are predominantly activated in a manner that is independent of their peptide specificity, as observed in cases of superantigen or numerous allo-antigen stimulations.⁹
- P-i stimulations, akin to mitogens or anti-CD3, concurrently induce the production of IFN- γ /Th1, IL-5, IL-13/Th2 cytokines, and cytotoxic mediators such as perforin, granzyme B, and granulysin in T cells. The classification into Th1 or Th2 subsets and the associated cytokine patterns is *not* applicable to p-i stimulations.
- The course of DReSS is clinically variable (Fig. 5), as is the immune stimulation: it begins with an allo-like reaction (ca. 2–6 weeks of asymptomatic cell expansion), followed by 1–3 weeks of acute and subacute symptoms. Despite drug withdrawal, strong hyperreactivity continues for ca. 3–4 weeks (flare-up reactions). After >4 weeks and corticosteroid therapy, the immune reaction returns to self-HLA restriction with viral and auto-immune peptide specificity, potentially leading to viraemia and autoimmunity.
- Similar to chronic GvHD,⁹ DReSS appears to leave a permanent imprint on patient immunity with long-lasting consequences, as MDH syndrome and occasionally autoimmunity may develop years after acute DReSS.
- The clinical manifestation of dDHR is determined by the drug type, its binding affinity to immune receptors, dose, concentration, and therapy duration. These parameters can be influenced: dose may increase, other drugs may interfere with metabolism, or therapy duration may change; alternatively, a viral infection may increase drug avidity to HLA/TCR.⁴⁹ As replicating these conditions in drug provocation tests is difficult, the significance of a negative challenge may be questioned.
- Checkpoint inhibitors, as potent immune stimulators, must be considered for SCAR induction like DRESS or SJS, as potential boosters for new drug sensitization, or as culprit drugs themselves. HLA-genetic testing is strongly advisable for patients receiving checkpoint inhibitors and drugs with increased risk of HLA-linked DRESS.^{73–75}

Clinical impact of the p-i mechanism

The recognition of p-i stimulation as a fundamental mechanism in DReSS has important clinical implications.

- Role of Drug Concentration: In contrast to the traditional conviction that idiosyncratic reactions are dose-independent,¹⁰⁷ there is evidence that *drug concentration is critical* in DReSS pathogenesis (and actually all dDHR). Because p-i stimulation begins as an off-target pharmacological interaction, a threshold concentration is required for sufficient immune activation. This explains why adjusting drug doses can modulate disease severity.
- Diagnosis: DReSS should be suspected in patients who were exposed to a high-risk drug for more than seven days showing

eosinophilia and systemic symptoms. These main features reflect the underlying immunopathology and align with the disease nomenclature.

- Grading p-i Stimulation Strength: dDHRs vary in severity based on the strength of the p-i stimulation. Measuring cytokine and cytotoxic mediator release after in vitro drug stimulation may help distinguish mild, moderate, and strong p-i reactions (Table 2, Fig. 4).¹⁰ Strong p-i stimulations are associated with long-term immune complications, including MDH.
- Early testing in SJS/TEN: Because CD8+ T-cell exhaustion occurs rapidly in SJS/TEN, in vitro assays performed after clinical remission may underestimate the initial immune response. Testing for drug reactivity during the acute phase, as recommended by Kano *et al.*⁹⁰ may improve diagnostic sensitivity.

Future directions and preventive strategies

Placing greater emphasis on signal-transmitting, functional p-i interactions during preclinical drug evaluation may improve drug safety. A comprehensive understanding of drug affinity for immune receptors and the establishment of affinity thresholds for p-i stimulation could facilitate the prediction of adverse reactions and inform risk stratification.^{107,108} Although precise affinity measurements of p-i interactions are currently unavailable, further research could enhance our capacity to assess risk and potentially exclude high-risk individuals from therapy through HLA screening.³⁶

DReSS as well as GvHD results in long-term immune modifications, leading to chronic conditions, such as MDH. This highlights the need to view dDHRs not only as acute events, but also as potential drivers of persistent immune dysregulation. The observation that CD8+ T-cell exhaustion in SJS/TEN limits long-term immune alterations further emphasizes the need to understand how different p-i stimulations shape immune trajectories.

Beyond adverse drug reactions: therapeutic potential of p-i mechanisms

While the p-i mechanism is currently viewed as a driver of severe adverse drug reactions, its potential to modulate immune responses can be utilized therapeutically. Controlled p-i interactions may provide novel strategies to influence T-cell responses in autoimmune diseases, transplant medicine, vaccinations. The understanding of how non-covalent drug binding to immune receptors can selectively activate or suppress immune pathways may open new possibilities for immunomodulatory therapies.

Conclusion

DReSS represents a strong p-i-mediated immune reaction, with significant clinical implications. It is a complex disease in which drug-induced modifications of the TCR-HLA axis trigger an allo-like immune response, leading to severe acute symptoms and long-term immune alterations. Recognizing the pivotal role of drug concentration and immune receptor affinity may allow for better understanding disease progression, optimizing treatment strategies, and ultimately, preventing severe drug hypersensitivity reactions. The lessons learned from DReSS are a reminder of the powerful and sometimes unpredictable consequences of pharmacological therapies, especially when they happen to interact with the immune system.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

WJP was responsible for scientific background, formulation of the research question, conceptual manuscript design, figure development, and drafting of the manuscript inclusive reference management.

LT and DY contributed to figure conceptualization and manuscript editing and revision. TP, OH, YM, ML, LJ, and TH were involved in patient recruitment and data collection, as well as manuscript editing and revision. KM was responsible for figure design and adaptation, manuscript drafting, editing, and revision.

References

- Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;**169**:1071–80.
- Hama N, Abe R, Gibson A, Phillips EJ. Drug-Induced Hypersensitivity Syndrome (DIHS)/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): clinical features and pathogenesis. *J Allergy Clin Immunol Pract* 2022;**10**:1155–67.e5.
- Kroshinsky D, Cardones ARG, Blumenthal KG. Drug reaction with eosinophilia and systemic symptoms. *N Engl J Med* 2024;**391**:2242–54.
- Chen CB, Hung WK, Wang CW, Lee CC, Hung SI, Chung WH. Advances in understanding the pathogenesis and therapeutic implications of drug reaction with eosinophilia and systemic symptoms: an updated review. *Front Med (Lausanne)* 2023;**10**:1187937.
- Miyagawa F, Asada H. Current perspective regarding the immunopathogenesis of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS). *Int J Mol Sci* 2021;**22**:2147.
- Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2006;**155**:422–8.
- Pichler WJ, Adam J, Watkins S, Willemin N, Yun J, Yerly D. Drug hypersensitivity: how drugs stimulate T cells via pharmacological interaction with immune receptors. *Int Arch Allergy Immunol* 2015;**168**:13–24.
- Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. *Allergy* 2019;**74**:1457–71.
- Pichler WJ. Delayed drug hypersensitivity reactions: how p-i transforms pharmacology into immunology. *Allergol Int* 2025;**74**:33–41.
- Peyer T, Thoo L, Yerly D, Hausmann O, Pichler WJ. The Cyto-LTT: a multiplex cytokine assay to detect and assess the strength of T cell reactivity in drug hypersensitivity. *Allergol Int* 2026;**75**:200–6. <https://doi.org/10.1016/j.alit.2025.09.004>.
- Pichler WJ, Hausmann O. Classification of drug hypersensitivity into allergic, p-i, and pseudo-allergic forms. *Int Arch Allergy Immunol* 2016;**171**:166–79.
- Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature* 2012;**486**:554–8.
- Adam J, Willemin N, Watkins S, Jamin H, Eriksson K, Villiger PM, et al. Abacavir-induced T cell reactivity represents an allo-immune reaction. *PLoS One* 2014;**9**:e95339.
- Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci U S A* 2012;**109**:9959–64.
- Watkins S, Pichler WJ. Sulfamethoxazole induces a switch mechanism in T cell receptors containing TCRβ20-1, altering pHLA recognition. *PLoS One* 2013;**8**:e76211.
- Watkins S, Pichler WJ. Activating interactions of sulfanilamides with T cell receptors. *Open J Immunol* 2013;**3**:139–57.
- Ko TM, Chung WH, Wei CY, Shih HY, Chen JK, Lin CH, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2011;**128**:1266–76.e11.
- Pan RY, Chu MT, Wang CW, Lee YS, Lemonnier F, Michels AW, et al. Identification of drug-specific public TCR driving severe cutaneous adverse reactions. *Nat Commun* 2019;**10**:3569.
- Schmid DA, Depta JPH, Lüthi M, Pichler WJ. Transfection of drug specific T cell receptors into hybridoma cells: tools to monitor drug binding to TCR and to evaluate cross-reactivity to related compounds. *Mol Pharmacol* 2006;**70**:356–65.
- Villani AP, Rozieres A, Bensaid B, Eriksson KK, Mosnier A, Albert F, et al. Massive clonal expansion of polycytotoxic skin and blood CD8+ T cells in patients with toxic epidermal necrolysis. *Sci Adv* 2021;**7**:eabe0013.
- Schnyder B, Frutig K, Mauri-Hellweg D, Limat A, Yawalkar N, Pichler WJ. T-cell-mediated cytotoxicity against keratinocytes in sulfamethoxazole-induced skin reaction. *Clin Exp Allergy* 1998;**28**:1412–7.
- Yawalkar N, Egli F, Hari Y, Nievergelt H, Braathen LR, Pichler WJ. Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. *Clin Exp Allergy* 2000;**30**:847–55.
- Kuechler PC, Britschgi M, Schmid S, Hari Y, Grabscheid B, Pichler WJ. Cytotoxic mechanisms in different forms of T-cell-mediated drug allergies. *Allergy* 2004;**59**:613–22.
- Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein P, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J Allergy Clin Immunol* 2004;**114**:1209–15.
- Schlapbach C, Zawodniak A, Irla N, Adam J, Hunger RE, Yerly D, et al. NKp46+ cells express granzysin in multiple cutaneous adverse drug reactions. *Allergy* 2011;**66**:1469–76.
- Pichler WJ, Thoo L, Yerly D. Drug hypersensitivity and eosinophilia: the decisive role of p-i stimulation. *Allergy* 2023;**78**:2596–605.
- Lucas A, Lucas M, Strhyn A, Keane NM, McKinnon E, Pavlos R, et al. Abacavir-reactive memory T cells are present in drug-naïve individuals. *PLoS One* 2015;**10**:e0117160.
- Barberis M, Helikar T, Verbruggen P. Simulation of stimulation: cytokine dosage and cell cycle crosstalk driving timing-dependent T cell differentiation. *Front Physiol* 2018;**9**:879.
- Wyss-Coray T, Pichler WJ. Nonclassical antigen-presenting cells stimulate the proliferation of Th0 but not Th1/Th2 clones and modulate the cytokine pattern of T-helper clones. *Int Arch Allergy Immunol* 1992;**99**:370–2.
- Isakov N, Mally MI, Altman A. Mitogen-induced human T cell proliferation is associated with increased expression of selected PKC genes. *Mol Immunol* 1992;**29**:927–33.
- Naisbitt DJ, Britschgi M, Wong G, Farrell J, Depta JP, Chadwick DW, et al. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. *Mol Pharmacol* 2003;**63**:732–41.
- Naisbitt DJ, Farrell J, Wong G, Depta JP, Dodd CC, Hopkins JE, et al. Characterization of drug-specific T cells in lamotrigine hypersensitivity. *J Allergy Clin Immunol* 2003;**111**:1393–403.
- Wu Y, Farrell J, Pirmohamed M, Park BK, Naisbitt DJ. Generation and characterization of antigen-specific CD4+, CD8+, and CD4+CD8+ T-cell clones from patients with carbamazepine hypersensitivity. *J Allergy Clin Immunol* 2007;**119**:973–81.
- Zhao Q, Almutairi M, Taylor A, Lister A, Harper N, Line J, et al. HLA class II-restricted CD8+ T cells contribute to the promiscuous immune response in dapsone hypersensitive patients. *J Invest Dermatol* 2021;**141**:2412–25.e2.
- Schulz M, Iwersen-Bergmann S, Andresen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics. *Crit Care* 2012;**16**:R136.
- Deshpande P, Hertzman RJ, Palubinsky AM, Giles JB, Karnes JH, Gibson A, et al. Immunopharmacogenomics: mechanisms of HLA-associated drug reactions. *Clin Pharmacol Ther* 2021;**110**:607–15.
- Adam J, Eriksson KK, Schnyder B, Fontana S, Pichler WJ, Yerly D. Avidity determines T-cell reactivity in abacavir hypersensitivity. *Eur J Immunol* 2012;**42**:1–11.
- Konvinse KC, Trubiano JA, Pavlos R, James I, Shaffer CM, Bejan CA, et al. HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms. *J Allergy Clin Immunol* 2019;**144**:183–92.
- Yun J, Marcaida MJ, Eriksson KK, Jamin H, Fontana S, Pichler WJ, et al. Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01. *J Immunol* 2014;**192**:2984–93.
- Schnyder B, Mauri-Hellweg D, Zanni M, Bettens F, Pichler WJ. Direct, MHC-dependent presentation of the drug sulfamethoxazole to human alphabeta T cell clones. *J Clin Invest* 1997;**100**:136–41.
- Zanni MP, von Greysen S, Schnyder B, Brander KA, Frutig K, Hari Y, et al. HLA-restricted, processing- and metabolism-independent pathway of drug recognition by human alphabeta T lymphocytes. *J Clin Invest* 1998;**102**:1591–8.
- Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008;**58**:25–32.
- Paulmann M, Mockenhaupt M. Severe drug-induced skin reactions: clinical features, diagnosis, etiology, and therapy. *J Dtsch Dermatol Ges* 2015;**13**:625–45.
- Tehrany YA, Laffitte E, Grosgrain O, Spoerl D. Syndrome DRESS (drug reaction with eosinophilia and systemic symptoms). *Rev Med Suisse* 2016;**12**:684–90.
- Chung WH, Chang WC, Stocker SL, Juo CG, Graham GG, Lee MH, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis* 2015;**74**:2157–64.
- Favetta B, Wang H, Shi Z, Schuster BS. Amphiphilic protein surfactants reduce the interfacial tension of biomolecular condensates. *Langmuir* 2025;**41**:23827–36.
- Ziemer M, Wiesend CL, Vetter R, Weiss J, Blaschke S, Norgauer J, et al. Cutaneous adverse reactions to valdecoxib distinct from Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2007;**143**:711–6.
- Brouard M, Saurat JH. Cutaneous reactions to STI571 (Imatinib). *N Engl J Med* 2001;**345**:618–9.
- Pichler WJ, Brüggemann MC. Viral infections and drug hypersensitivity. *Allergy* 2023;**78**:60–70.
- Soria A, Bernier C, Veyrac G, Garbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: a retrospective study. *J Am Acad Dermatol* 2020;**82**:606–11.

51. Sasidharanpillai S, Ajithkumar K, Khader A, Reena Mariyath OK. Drug reaction with eosinophilia and systemic symptoms within 1 week of exposure to the drug. *J Am Acad Dermatol* 2020;**83**:e17–8.
52. Soria A, Amsler E, Bernier C, Milpied B, Tétart F, Morice C, et al. DRESS and AGEP reactions to iodinated contrast media: a French case series. *J Allergy Clin Immunol Pract* 2021;**9**:3041–50.
53. Lorusso V, Taroni P, Alvino S, Spinazzi A. Pharmacokinetics and safety of iomeprol in healthy volunteers and in patients with renal impairment or end-stage renal disease requiring hemodialysis. *Invest Radiol* 2001;**36**:309–16.
54. Wüillemin N, Ballmer-Weber B, Schlapbach C, Jörg L, Yerly D. The activation pattern of drug-reacting T cells has an impact on the clinical picture of hypersensitivity reactions. *Front Allergy* 2022;**3**:804605.
55. Wüillemin N, Adam J, Fontana S, Krähenbühl S, Pichler WJ, Yerly D. HLA haplotype determines hapten or p-i T cell reactivity to flucloxacillin. *J Immunol* 2013;**190**:4956–64.
56. Thoo L, Gschwend A, Lang C, et al. High cytokine responses and altered T cell activation in DRESS patients at risk for multiple drug hypersensitivity. *Authorea[Preprint]* 2024. <https://doi.org/10.22541/au.172466425.58562503/v1>.
57. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009;**29**:481–501.
58. Ogawa K, Morito H, Hasegawa A, Daikoku N, Miyagawa F, Okazaki A, et al. Identification of thymus and activation-regulated chemokine (TARC/CCL17) as a potential marker for early indication of disease and prediction of disease activity in drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS). *J Dermatol Sci* 2013;**69**:38–43.
59. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;**355**:1018–28.
60. Funke I, Prümmer O, Schrezenmeier H, Hardt D, Weiss M, Porzolt F, et al. Capillary leak syndrome associated with elevated IL-2 serum levels after allogeneic bone marrow transplantation. *Ann Hematol* 1994;**68**:49–52.
61. Awad A, Goh MS, Trubiano JA. Drug reaction with eosinophilia and systemic symptoms: a systematic review. *J Allergy Clin Immunol Pract* 2023;**11**:1856–68.
62. Zawodniak A, Lochmatter P, Yerly D, Kawabata T, Lerch M, Yawalkar N, et al. In vitro detection of cytotoxic T and NK cells in peripheral blood of patients with various drug-induced skin diseases. *Allergy* 2010;**65**:376–84.
63. Bourgeois GP, Cafardi JA, Groysman V, Hughey LC. A review of DRESS-associated myocarditis. *J Am Acad Dermatol* 2012;**66**:e229–36.
64. Yang JJ, Lei DK, Ravi V, Maloney NJ, Crew A, Worswick S. Overlap between hemophagocytic lymphohistiocytosis and drug reaction and eosinophilia with systemic symptoms: a review. *Int J Dermatol* 2021;**60**:925–32.
65. Gschwend A, Helbling A, Feldmeyer L, Mani-Weber U, Meincke C, Heidemeyer K, et al. Treatment with IL-5/IL-5 receptor antagonists in drug reaction with eosinophilia and systemic symptoms (DRESS). *Allergy J Int* 2023;**32**:104–11.
66. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy. *Int J Mol Sci* 2016;**17**:1214.
67. Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. *J Am Acad Dermatol* 2008;**59**:995–9.
68. Messagier AL, Salzes C, Jouary T. DRESS avec pustulose et atteinte cardiaque [DRESS syndrome with pustules and cardiac impairment]. *Ann Dermatol Venerol* 2020;**147**:451–5 (in French).
69. Meier-Schiesser B, Feldmeyer L, Jankovic D, Mellett M, Satoh TK, Yerly D, et al. Culpit drugs induce specific IL-36 overexpression in acute generalized exanthematous pustulosis. *J Invest Dermatol* 2019;**139**:848–58.
70. Benezeder T, Bordag N, Woltsche J, Falkensteiner K, Graier T, Schadelbauer E, et al. IL-36-driven pustulosis: transcriptomic signatures match between generalized pustular psoriasis (GPP) and acute generalized exanthematous pustulosis (AGEP). *J Allergy Clin Immunol* 2025;**155**:1913–27.
71. Watanabe H. Recent advances in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. *J Immunol Res* 2018;**2018**:5163129.
72. Morito H, Ogawa K, Fukumoto T, Kobayashi N, Morii T, Kasai T, et al. Increased ratio of FoxP3+ regulatory T cells/CD3+ T cells in skin lesions in drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. *Clin Exp Dermatol* 2014;**39**:284–91.
73. Hammond S, Olsson-Brown A, Gardner J, Thomson P, Ali SE, Jolly C, et al. T cell mediated hypersensitivity to previously tolerated iodinated contrast media precipitated by introduction of atezolizumab. *J Immunother Cancer* 2021;**9**:e002521.
74. Bray ER, Lin RR, Li JN, Elgart GW, Elman SA, Maderal AD. Immune checkpoint inhibitor associated epidermal necrosis, beyond SJS and TEN: a review of 98 cases. *Arch Dermatol Res* 2024;**316**:233.
75. Ai L, Gao J, Zhao S, Li Q, Cui YH, Liu Q, et al. Nivolumab-associated DRESS in a genetically susceptible individual. *J Immunother Cancer* 2021;**9**:e002879.
76. Ubukata N, Hashizume H, Nakatani E, Sasaki H, Miyachi Y. Risk factors and drugs associated with the development of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: a population-based cohort study using the Shizuoka Kokuho database. *J Am Acad Dermatol* 2024;**91**:573–5.
77. Blumenthal KG, Alvarez-Arango S, Fu X, Kroshinsky D, Choi H, Phillips E, et al. Risk factors for vancomycin drug reaction with eosinophilia and systemic symptoms syndrome. *JAMA Dermatol* 2022;**158**:1449–53.
78. Wang CW, Dao RL, Chung WH. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. *Curr Opin Allergy Clin Immunol* 2016;**16**:339–45.
79. Pichler WJ, Daubner B, Kawabata T. Drug hypersensitivity: flare-up reactions, cross-reactivity and multiple drug hypersensitivity. *J Dermatol* 2011;**38**:216–21.
80. Kano Y, Tohyama M, Aihara M, Matsukura S, Watanabe H, Sueki H, et al. Sequelae in 145 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: survey conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions (ASCAR). *J Dermatol* 2015;**42**:276–82.
81. Jergović M, Contreras NA, Nikolich-Zugich J. Impact of CMV upon immune aging: facts and fiction. *Med Microbiol Immunol* 2019;**208**:263–9.
82. Edwards ES, Smith C, Khanna R. Phenotypic and transcriptional profile correlates with functional plasticity of antigen-specific CD4+ T cells. *Immunol Cell Biol* 2014;**92**:181–90.
83. Pachnio A, Ciauriz M, Begum J, Lal N, Zuo J, Beggs A, et al. Cytomegalovirus infection leads to development of high frequencies of cytotoxic virus-specific CD4+ T cells targeted to vascular endothelium. *PLoS Pathog* 2016;**12**:e1005832.
84. Hashizume H, Fujiyama T, Kanebayashi J, Kito Y, Hata M, Yagi H. Skin recruitment of monomyeloid precursors involves human herpesvirus-6 reactivation in drug allergy. *Allergy* 2013;**68**:681–9.
85. Pichler WJ. The important role of non-covalent drug-protein interactions in drug hypersensitivity reactions. *Allergy* 2022;**77**:404–15.
86. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. *Allergol Int* 2019;**68**:301–8.
87. Daubner B, Groux-Keller M, Hausmann OV, Kawabata T, Naisbitt DJ, Park BK, et al. Multiple drug hypersensitivity: normal Treg cell function but enhanced in vivo activation of drug-specific T cells. *Allergy* 2012;**67**:58–66.
88. Jörg L, Helbling A, Yerly D, Pichler WJ. Drug-related relapses in drug reaction with eosinophilia and systemic symptoms (DRESS). *Clin Transl Allergy* 2020;**10**:52.
89. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple drug hypersensitivity. *Int Arch Allergy Immunol* 2017;**172**:129–38.
90. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy* 2007;**62**:1439–44.
91. Porebski G, Pecaric-Petkovic T, Groux-Keller M, Bosak M, Kawabata TT, Pichler WJ. In vitro drug causality assessment in Stevens-Johnson syndrome – alternatives for lymphocyte transformation test. *Clin Exp Allergy* 2013;**43**:1027–37.
92. Paulmann M, Mockenhaupt M. Severe drug hypersensitivity reactions: clinical pattern, diagnosis, etiology and therapeutic options. *Curr Pharm Des* 2016;**22**:6852–61.
93. Lee HY, Walsh SA, Creamer D. Long-term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): the spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multidisciplinary follow-up. *Br J Dermatol* 2017;**177**:924–35.
94. Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, Chang PY, et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. *Pharmacogenomics J* 2014;**14**:281–8.
95. Kim HJ, Shim JS, Park GY, Kang DY, Shin JY, Kim SM, et al. Association of HLA-B*13:01 with DRESS and HLA-A*31:01 with eosinophilia in SJS/TEN induced by carbamazepine. *J Allergy Clin Immunol Pract* 2024;**12**:3436–8.e3.
96. Fukunaga K, Tsukagoshi E, Kurata M, Mizukawa Y, Niihara H, Morita E, et al. Differential effects of HLA-B*15:11 and HLA-A*31:01 on carbamazepine-induced cutaneous adverse reactions. *J Invest Dermatol* 2024;**144**:908–11.e7.
97. Gupta D, Singh K, Dhaka A, Sengupta P. Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) masquerading as acute leukemia. *Indian J Pathol Microbiol* 2025;**68**:398–401.
98. Liu Q, Zhao S, Chen W. Clinical features, treatment outcomes and prognostic factors of allopurinol-induced DRESS in 52 patients. *J Clin Pharm Ther* 2022;**47**:1368–78.
99. Hughes CA, Foisy MM, Dewhurst N, Higgins N, Robinson L, Kelly DV, et al. Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008;**42**:387–96.
100. Chularojanamontri L, Tuchinda P, Srinoulprasert Y, Kulthanan K, Pichler WJ. Sequential appearance of four clinical delayed drug hypersensitivity reactions in the same patient. *Int J Basic Clin Pharmacol* 2016;**5**:2688–91.
101. Bouvresse S, Valeyrie-Allanore L, Ortonne N, Konstantinou MP, Kardan SH, Bagot M, et al. Toxic epidermal necrolysis, DRESS, AGEP: do overlap cases exist? *Orphanet J Rare Dis* 2012;**7**:72.
102. Yang J, Pan X, Li M. Peripheral blood eosinophil counts predict the prognosis of drug eruptions. *J Invest Allergol Clin Immunol* 2013;**23**:248–55.
103. Shah PN, Romar GA, Manukyan A, Ko WC, Hsieh PC, Velasquez GA, et al. Systemic and skin-limited delayed-type drug hypersensitivity reactions

- associate with distinct resident and recruited T cell subsets. *J Clin Invest* 2024;**134**:e178253.
104. Hari Y, Frutig-Schnyder K, Hurni M, Yawalkar N, Zanni MP, Schnyder B, et al. T cell involvement in cutaneous drug eruptions. *Clin Exp Allergy* 2001;**31**: 1398–408.
 105. Pinto Gouveia M, Gameiro A, Coutinho I, Pereira N, Cardoso JC, Gonalo M. Overlap between maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms among cutaneous adverse drug reactions in a dermatology ward. *Br J Dermatol* 2016;**175**:1274–83.
 106. Chen J, Xue X, Wang Z, Liu H, Zhang F. Genetic analysis of different subtypes of aseptic pustulosis in the Chinese population. *Clin Exp Dermatol* 2024;**49**: 1217–26.
 107. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;**356**:1255–9.
 108. Pichler WJ, Watkins S, Yerly D. Risk assessment in drug hypersensitivity: detecting small molecules which outsmart the immune system. *Front Allergy* 2022;**3**:827893.