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THE SCIENTIFIC DISCUSSION OF KEY ISSUE ASPECTS OF IMMUNOPATHOGENESIS AND PHARMACOLOGICAL PROPERTIES AND PROFILES IN RELATION TO ADVERSE DRUG REACTIONS CHALLENGES, FOCUS ON MULTIDIMENSIONAL DRUG-INDUCED EOSINOPHILIA AND SYSTEMIC SYNDROME

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ABSTRACT

Drug-induced eosinophilia and systemic symptoms (DIES) represent a complex and potentially life-threatening spectrum of adverse drug reactions characterized by eosinophilic infiltration and multiorgan involvement. This review synthesizes current knowledge on the pharmacological, immunological, and clinical aspects of these reactions, with particular emphasis on severe manifestations such as drug reaction with eosinophilia and systemic symptoms (DRESS). We examine the mechanisms by which specific drug classes—including aromatic antiepileptics, antibiotics, and novel biologics—trigger eosinophil activation through hapten formation, direct T-cell stimulation, and cytokine release. Genetic predispositions, particularly HLA associations, and viral interactions (e.g., HHV-6 reactivation) are discussed as critical modulators of individual susceptibility and clinical severity. Recent advances in biomarker discovery (e.g., serum Siglec-8, eosinophil-derived extracellular traps) and imaging modalities (e.g., 68Ga-FAPI PET/CT) are evaluated for their diagnostic and prognostic utility. The review highlights emerging therapeutic strategies, including targeted biologics against IL-5/IL-33 and pharmacogenomic approaches to prevention, while underscoring persistent challenges in management, such as corticosteroid dependence and long-term sequelae. By integrating mechanistic insights with clinical observations, this work aims to refine diagnostic criteria, optimize therapeutic decision-making, and identify future research directions to mitigate the burden of these iatrogenic complications. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is an uncommon yet serious adverse drug reaction that presents with delayed systemic inflammation and multiple organ involvement. It is a member of the spectrum of severe cutaneous adverse reactions (SCAR), usually presenting 2–8 weeks post initiation of the culprit drug. Nonspecific symptoms, latency, and overlapping clinical findings with infections, autoimmune diseases, and other hypersensitivity reactions contribute to a failure to diagnose syndrome and worsening morbidity. The objective of this thesis is to conduct a comprehensive systematic review with emphasis on the pharmacological characteristics, clinical presentation, and genetic risk factors of DRESS syndrome, as well as a range of pathological drug classes, including anticonvulsants, antibiotics, allopurinol, and nonsteroidal anti-inflammatories (NSAIDs). The article also discusses treatment, long-term prognosis and research directions. The leading alternative agents were anticonvulsants (e.g., carbamazepine, phenytoin, lamotrigine), antibiotics (e.g., vancomycin, minocycline),

allopurinol, and NSAIDs including mefenamic acid and ibuprofen. More than 60 % of cases had hepatic involvement; involvement of the kidneys (25 %) and the lungs (10–15 %) were also important. Nearly all patients presented with cutaneous findings, most commonly a diffuse morbilliform rash and facial edema, and frequently had fever and eosinophilia. Genetic predisposition is an important factor, with HLA-B58:01 allele in the context of allopurinol-induced DRESS, and HLA-A31:01 in the case of carbamazepine. These results emphasize the value of pharmacogenetic screening in high-risk population groups. Viral reactivation, including human herpesvirus-6 (HHV-6), had been observed in multiple patients and has contributed to overall disease severity and duration. Therapy consisted mainly in early discontinuation of the inducing agent and systemic corticosteroids. Although the majority of patients responded to corticosteroids, some became steroid resistant and were treated with medications such as cyclosporine, IVIG, and plasmapheresis. There is a lack of standardized treatment protocols, and randomized controlled trials are highly desired. Relapses during corticosteroid reduction or autoimmunity (type 1 diabetes, thyroiditis, lupus-like syndromes) occurred in some, but not in all patients. Multisystem DRESS syndrome mandates a high degree of clinical suspicion for early diagnosis and treatment. The underestimation of NSAID-induced DRESS emphasises the necessity for better pharmacovigilance tools and public awareness on OTC drug safety. Future advances would need to focus on the creation of general diagnostic criteria, useful biomarkers for early diagnosis, and the use of evidence-based algorithms for treatment.
Keywords: Adverse drug reactions, eosinophilia, systemic hypersensitivity, drug safety profile, pharmacovigilance, drug-induced immunological response.

INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare but important hypersensitivity syndrome that can be induced by specific drugs. The syndrome presents as a complex and varied clinical picture which may lead to serious multisystem organ failure, thereby being associated with a high morbidity and mortality rate. DRESS usually occurs 2–8 weeks after starting an offending drug, which complicates its diagnosis because of the long lag time between drug exposure and the onset of symptoms. The syndrome is most often characterized by a triad of clinical features, including widespread cutaneous eruptions, haematological disturbances (e.g., eosinophilia), and organ involvement—the liver and kidneys being the most frequently involved.

Adverse drug reactions (ADRs) remain a significant challenge in pharmacotherapy, impacting patient safety, treatment efficacy, and healthcare costs. Among these, drug-induced eosinophilia and systemic symptoms (DRESS syndrome—Drug Reaction with Eosinophilia and Systemic Symptoms) represents a severe hypersensitivity reaction characterized by eosinophilia, fever, rash, and multi-organ involvement. Understanding

the pharmacological properties and mechanistic profiles of drugs associated with DRESS is crucial for early detection, risk mitigation, and improved therapeutic outcomes.

This paper explores the key pharmacological aspects contributing to ADRs, with a focus on drug-induced eosinophilia and systemic symptoms, addressing mechanisms, risk factors, diagnostic challenges, and management strategies.

The pharmacological properties and profiles of therapeutic agents play a pivotal role in determining their efficacy, safety, and overall risk-benefit ratio in clinical practice. While modern pharmacotherapy has revolutionized disease management, adverse drug reactions (ADRs) remain a significant challenge, contributing to morbidity, mortality, and increased healthcare burdens. Among the diverse spectrum of ADRs, drug-induced eosinophilia and systemic symptoms (DIES) represent a complex and often underrecognized clinical entity that poses diagnostic and therapeutic dilemmas. This discussion delves into the intricate interplay between pharmacological mechanisms, host factors, and immunological pathways that underlie drug-induced eosinophilia and its systemic manifestations, emphasizing the need for heightened clinical vigilance and mechanistic understanding.

Pharmacological agents, by virtue of their chemical structure, receptor interactions, and metabolic pathways, can elicit unintended immune-mediated responses. Eosinophilia, characterized by an abnormal elevation in eosinophil count, serves as a biomarker for hypersensitivity reactions, parasitic infections, and certain drug-induced pathologies. When drug-related, eosinophilia may herald severe systemic involvement, including cutaneous eruptions, visceral organ damage, and life-threatening conditions such as drug reaction with eosinophilia and systemic symptoms (DRESS) or eosinophilic granulomatosis with polyangiitis (EGPA). The pathogenesis of these reactions is multifactorial, involving genetic predispositions (e.g., HLA haplotypes), drug-specific properties (e.g., reactive metabolites), and dysregulated immune activation (e.g., Th2 cytokine polarization).

Understanding the pharmacological basis of these adverse events requires a thorough examination of drug metabolism, pharmacokinetic variability, and pharmacodynamic interactions. Certain drug classes, including antiepileptics (e.g., phenytoin, carbamazepine), antibiotics (e.g., sulfonamides, beta-lactams), and allopurinol, are frequently implicated in eosinophilic reactions due to their propensity to form hapten-protein complexes, triggering T-cell-mediated hypersensitivity. Additionally, the role of eosinophils themselves extends beyond mere bystanders; these granulocytes release cytotoxic granules (e.g., major basic protein, eosinophil peroxidase) and pro-inflammatory cytokines (e.g., IL-5, IL-13), contributing to tissue injury and systemic inflammation.

The clinical presentation of drug-induced eosinophilia varies widely, ranging from benign peripheral blood eosinophilia to fulminant multiorgan failure. Early recognition is paramount, as delayed diagnosis often exacerbates outcomes. Correlating temporal drug exposure with symptom onset, alongside laboratory and histopathological findings, aids in establishing causality. However, challenges persist due to the nonspecific nature of eosinophilia and overlapping features with other hypersensitivity syndromes. Furthermore,

the absence of standardized diagnostic criteria for conditions like DRESS complicates clinical assessment, necessitating a high index of suspicion and comprehensive drug history evaluation.

Therapeutic management hinges on prompt drug discontinuation, supportive care, and, in severe cases, immunosuppressive therapy. The role of corticosteroids remains controversial, with debates surrounding optimal dosing and duration. Emerging strategies, such as targeted biologic therapies against IL-5 (e.g., mepolizumab), offer promise in refractory cases, though further research is needed to define their place in management. Pharmacovigilance systems and post-marketing surveillance are critical in identifying at-risk populations and mitigating future occurrences through risk stratification and personalized medicine approaches.

This discussion aims to synthesize current knowledge on drug-induced eosinophilia and systemic symptoms, exploring pharmacological triggers, mechanistic pathways, clinical manifestations, and therapeutic challenges. By integrating pharmacogenomic insights, immunological advances, and real-world clinical data, we strive to enhance risk prediction, improve diagnostic accuracy, and optimize patient outcomes in the face of this formidable ADR.

Pharmacological Mechanisms of Drug-Induced Eosinophilia

- Detailed exploration of hapten hypothesis, p-i concept (pharmacologic interaction with immune receptors), and reactive metabolite formation.
- Role of cytochrome P450 enzymes in generating immunogenic drug intermediates.
- Genetic susceptibility (e.g., HLA-B*15:02 with carbamazepine, HLA-A*31:01 with aromatic antiepileptics).

Immunopathogenesis of Systemic Eosinophilic Reactions

- Th2 immune response dysregulation and cytokine storm (IL-4, IL-5, IL-13).
- Eosinophil activation, degranulation, and endothelial damage.
- Cross-reactivity between structurally unrelated drugs (e.g., aromatic amine drugs).

Clinical Spectrum and Diagnostic Criteria

- DRESS syndrome: RegiSCAR criteria, latency period, and organ involvement (hepatic, renal, cardiac).
- Differential diagnoses (e.g., viral exanthems, autoimmune eosinophilic disorders).
- Biomarkers (e.g., eosinophil cationic protein, serum IL-5 levels).

High-Risk Drug Classes and Case Examples

- Antibiotics (sulfamethoxazole-trimethoprim, vancomycin).
- Anticonvulsants (lamotrigine, phenobarbital).
- Allopurinol and its association with severe cutaneous ADRs.

Therapeutic Interventions and Controversies

- Corticosteroid regimens: Pulse vs. tapering protocols.
- Role of IVIG, plasmapheresis, and biologics (e.g., anti-IL-5/Rα therapy).
- Long-term sequelae (e.g., autoimmune thyroiditis post-DRESS).

Pharmacovigilance and Risk Mitigation Strategies

- Pre-therapy screening (HLA typing, patch testing).
- Post-marketing surveillance data (FAERS, WHO VigiBase).
- Patient education and rechallenge protocols.

Future Directions and Research Gaps

- In vitro models (Lymphocyte Transformation Test).
- Personalized medicine approaches (pharmacogenomics).
- Novel biomarkers for early detection.

On an epidemiological level, the incidence of DRESS is thought to be 1/1,000 to 1/10,000 drug exposures, though this is likely an underestimate, probably due to the variable presentations and the delayed interval between drug administration and symptom onset. The heterogeneous presentation complicates identification and reporting, potentially delaying life-saving interventions. In recent years, clinical awareness, diagnostic criteria, and understanding of pathophysiology and genetic susceptibility have improved recognition and management of the disorder.

The syndrome is pharmacologically associated with a limited but clinically important number of drugs. Anticonvulsants such as carbamazepine and phenytoin remain common triggers, likely due to their reactive metabolites inducing immune hypersensitivity (Saleem et al., 2025; Thompson et al., 2024). Sulfonamide antibiotics, notably sulfamethoxazole, allopurinol, and some NSAIDs including mefenamic acid, are also major causative agents. The growing recognition of NSAIDs as causes of DRESS calls for vigilance given their widespread use.

Eosinophilia is the overabundance of eosinophils in the bloodstream. Eosinophils are a variety of white blood cell that participates in immune responses -notably those that cause allergies, parasitic infections and certain drug reactions, such as DRESS.

- Eosinophils count range: 0-500 cells/μL (microliter)
- Mild eosinophilia: 500–1,500 cells/μL
- Moderate eosinophilia: 1,500–5,000 cells/μL
- Severe eosinophilia: >5,000 cells/μL

Eosinophilia (eosinophil count >500 cells/μL) is a classic diagnostic laboratory finding in DRESS, and while integral to diagnosis, clinicians should not rely solely on eosinophil counts to recognize systemic involvement such as liver or kidney injury that may progress rapidly and require emergent treatmen. A combination of cutaneous signs,

haematological abnormalities, and extracutaneous organ involvement aids in distinguishing DRESS from other drug eruptions or systemic diseases (St George-Hyslop et al., 2024).
The underlying mechanisms responsible for DRESS are complex and involve impaired drug metabolism, immune dysregulation, and viral reactivation, particularly human herpesvirus 6 (HHV-6), as well as other herpesviruses such as Epstein-Barr virus. Reactivation of these viruses may amplify immune responses and systemic inflammation characteristic of DRESS. Genetic susceptibility also plays a key role, with specific human leukocyte antigen (HLA) alleles, such as HLA-B58:01, strongly linked to allopurinol-induced DRESS, especially among Asian populations.

Although DRESS can be life-threatening, timely diagnosis and intervention are critical to minimize complications. Standard management involves prompt discontinuation of the causative drug and early systemic corticosteroid use to mitigate immune-mediated damage (Shakour, Mumtaz, & Abu-Samra, 2025; Shiohara & Mizukawa, 2019). While corticosteroids are the mainstay, optimal dosing, duration, and the role of adjunctive immunomodulatory therapies remain areas of debate. The variable clinical presentation and overlap with other hypersensitivity syndromes often delay diagnosis, underscoring the need for clinician awareness of the broad spectrum of DRESS manifestations.

This project's main objective is to explore drug-related features associated with DRESS and its clinical outcomes, with an emphasis on NSAIDs, which are relatively underreported in the literature. Other pharmacological classes will also be reviewed. Through a systematic review, this thesis aims to identify common clinical features, organ involvement, medication triggers, and genetic susceptibilities, providing comprehensive insights to improve pharmacovigilance and clinical management protocols in modern healthcare.

The intersection of pharmacology and immunology presents a complex landscape where therapeutic efficacy must be carefully balanced against potential adverse reactions. Among the myriad challenges in pharmacotherapy, drug-induced eosinophilia and its systemic manifestations stand as a particularly intricate and clinically significant phenomenon. This condition, often underrecognized in its early stages, can progress to severe, sometimes life-threatening systemic involvement, making it a critical area of study for clinicians, pharmacologists, and researchers alike. The underlying mechanisms are deeply rooted in the pharmacological properties of the drugs themselves, the metabolic pathways they engage, and the individual patient's immunological response, creating a multifaceted clinical scenario that demands thorough understanding and careful management.

Eosinophilia, defined as an elevated eosinophil count in peripheral blood or tissues, serves as a hallmark of various pathological states, ranging from parasitic infections to allergic reactions and, notably, adverse drug responses. When drug-induced, eosinophilia frequently signals a hypersensitivity reaction, often accompanied by systemic symptoms that can affect multiple organ systems. The clinical spectrum of these reactions is broad,

encompassing conditions such as drug rash with eosinophilia and systemic symptoms (DRESS), eosinophilic pneumonia, and even eosinophilic myocarditis, each presenting unique diagnostic and therapeutic challenges. The pathogenesis of these reactions is not merely a matter of excessive eosinophil production but involves a cascade of immunological events triggered by the drug or its metabolites, leading to tissue infiltration and damage.

The pharmacological basis of drug-induced eosinophilia lies in the intricate interplay between a drug's chemical structure, its metabolic fate, and the host's immune system. Certain drugs are more prone to inducing these reactions due to their ability to form reactive metabolites that act as haptens, binding to endogenous proteins and creating neoantigens. These neoantigens are then recognized by the immune system as foreign, eliciting a T-cell-mediated response that drives eosinophil activation and recruitment. Genetic factors further modulate this risk, with specific human leukocyte antigen (HLA) alleles strongly associated with susceptibility to severe cutaneous adverse reactions, including those accompanied by eosinophilia. For instance, the HLA-B*15:02 allele has been linked to carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis, often presenting with eosinophilia in the context of systemic involvement.

Beyond genetic predisposition, the immunological milieu plays a pivotal role in the development and progression of drug-induced eosinophilia. Eosinophils are not passive bystanders but active contributors to tissue inflammation and damage. Upon activation, they release a barrage of cytotoxic proteins, including major basic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, which disrupt cellular integrity and amplify inflammatory responses. Additionally, eosinophils secrete cytokines such as interleukin-5 (IL-5), a key regulator of eosinophil proliferation and survival, further perpetuating the cycle of inflammation. This self-sustaining inflammatory cascade underscores the potential for rapid clinical deterioration in affected patients, necessitating prompt recognition and intervention.

Clinically, drug-induced eosinophilia and systemic symptoms present a diagnostic conundrum due to their variable and often nonspecific manifestations. The latency period between drug initiation and symptom onset can range from days to weeks, complicating the establishment of a causal relationship. Cutaneous involvement, such as maculopapular eruptions or exfoliative dermatitis, is common but not universal, and visceral organ involvement—particularly of the liver, kidneys, and lungs—may dominate the clinical picture. Laboratory findings typically include peripheral eosinophilia, elevated liver enzymes, and occasionally atypical lymphocytes, mimicking viral infections or autoimmune disorders. The RegiSCAR criteria have been developed to standardize the diagnosis of DRESS, incorporating clinical, laboratory, and histopathological features, yet challenges remain in distinguishing these reactions from other hypersensitivity syndromes.

The management of drug-induced eosinophilia hinges on immediate discontinuation of the offending agent, coupled with supportive care tailored to the severity of organ involvement. Corticosteroids remain the cornerstone of therapy for moderate to

severe cases, although the optimal regimen—dose, duration, and route of administration—remains a subject of debate. In refractory cases, emerging therapies targeting specific cytokines, such as anti-IL-5 monoclonal antibodies, have shown promise in mitigating eosinophilic inflammation, though their role in acute drug-induced reactions is still under investigation. Long-term follow-up is essential, as some patients develop autoimmune sequelae, such as thyroid dysfunction, months after the initial episode.

Pharmacovigilance efforts are critical in identifying and mitigating the risks associated with drugs known to induce eosinophilia. Post-marketing surveillance systems, such as the FDA Adverse Event Reporting System (FAERS) and the WHO Global Individual Case Safety Reports (VigiBase), provide invaluable data for detecting signals of potential adverse reactions. Preemptive strategies, including pharmacogenetic screening for high-risk HLA alleles, have been implemented for certain drugs, offering a pathway to personalized medicine and reduced incidence of severe reactions. Patient education and heightened clinician awareness further contribute to early detection and improved outcomes.

Looking ahead, advancements in pharmacogenomics, immunology, and biomarker research hold promise for refining risk stratification and therapeutic approaches. In vitro assays, such as the lymphocyte transformation test, may enhance diagnostic accuracy, while novel biomarkers could enable earlier detection of at-risk individuals. The integration of these tools into clinical practice will be essential for addressing the ongoing challenges posed by drug-induced eosinophilia and systemic symptoms, ultimately fostering safer and more effective pharmacotherapy.

The study seeks to illuminate the complex interplay between pharmacological properties and adverse immunological responses, with a focus on the clinical and mechanistic nuances of drug-induced eosinophilia. By synthesizing current knowledge and highlighting emerging research, we aim to provide a comprehensive foundation for understanding, diagnosing, and managing these formidable adverse drug reactions.

GOAL

Aim of the research was to study pharmacological properties and profiles in relation to adverse drug reactions: focus on drug-induced eosinophilia and systemic symptoms.

METHODOLOGY

The current research was planned as a full systematic qualitative review in order to synthesizing the knowledge available for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). General purposes of this study consisted in the collection of clinical observations on etiological agents, clinical manifestations, diagnosis, and treatment and for the long-term prognosis of patients. There was a focus on systematic review of real-world clinical evidence published in peer review case reports, case series, observational studies, and pharmacovigilance reports.

The exploration of drug-induced eosinophilia and systemic symptoms necessitates a multidisciplinary approach, integrating pharmacological, immunological, and clinical research methodologies to comprehensively evaluate the underlying mechanisms, risk factors, and therapeutic strategies. This discussion is grounded in a systematic evaluation of existing literature, augmented by critical analysis of pharmacovigilance data and clinical case studies. The methodological framework encompasses several key dimensions, each contributing to a holistic understanding of this complex adverse drug reaction.

A thorough review of peer-reviewed scientific literature forms the foundation of this investigation. Databases such as PubMed, Scopus, and Web of Science were queried using targeted search terms, including *drug-induced eosinophilia*, *DRESS syndrome*, *pharmacological mechanisms of hypersensitivity*, and *eosinophil-mediated tissue injury*. The inclusion criteria prioritized recent studies (published within the last decade) as well as seminal works that have shaped current understanding of the topic. Special emphasis was placed on meta-analyses, large-scale cohort studies, and mechanistic investigations to ensure a robust evidence base.

Pharmacovigilance data from regulatory agencies, including the FDA Adverse Event Reporting System (FAERS) and the WHO Global Individual Case Safety Reports database (VigiBase), were analyzed to identify trends in drug-induced eosinophilia and associated systemic reactions. These databases provide real-world insights into the frequency, severity, and drug-specific patterns of adverse events, enabling the identification of high-risk pharmacological agents. Case reports and series were also examined to elucidate atypical presentations and therapeutic challenges, offering a nuanced perspective beyond aggregate statistics.

The pharmacological properties of drugs implicated in eosinophilic reactions were evaluated through a structural and metabolic lens. Particular attention was paid to drugs known to form reactive metabolites or hapten-protein complexes, as these mechanisms are central to the initiation of immune-mediated adverse reactions. Computational modeling and in vitro studies were referenced to illustrate how specific chemical moieties contribute to immunogenicity. Additionally, pharmacogenetic studies highlighting associations between HLA alleles and drug hypersensitivity were synthesized to underscore the interplay between genetic predisposition and drug-specific factors.

Immunological pathways driving eosinophil activation and tissue infiltration were dissected through an examination of preclinical and clinical research. Studies investigating cytokine profiles (e.g., IL-5, IL-4, IL-13), eosinophil degranulation patterns, and histopathological findings were integrated to construct a coherent model of pathogenesis. Where available, data from animal models of drug hypersensitivity were cited to provide mechanistic insights not readily obtainable from human studies.

Clinical diagnostic criteria, such as the RegiSCAR scoring system for DRESS syndrome, were scrutinized for their utility and limitations in real-world practice. Comparative analyses of diagnostic tools—including laboratory biomarkers, imaging findings, and

histopathology—were conducted to highlight gaps in current diagnostic paradigms. Therapeutic strategies were evaluated based on clinical trial data, expert consensus guidelines, and observational studies, with a focus on corticosteroid regimens, immunosuppressive agents, and emerging biologic therapies.

To address the translational relevance of this research, pharmacovigilance strategies and risk mitigation approaches were explored. This included an assessment of pre-therapy genetic screening protocols, post-marketing surveillance methodologies, and patient education initiatives. The role of interdisciplinary collaboration—engaging pharmacologists, immunologists, and clinicians—was emphasized as a critical component of both research and clinical practice.

Finally, future directions were framed by identifying unresolved questions and technological advancements poised to reshape the field. Innovations such as single-cell RNA sequencing to delineate eosinophil heterogeneity, machine learning for adverse event prediction, and the development of targeted cytokine inhibitors were discussed as promising avenues for further investigation. The methodology ensures a comprehensive, evidence-based discourse on drug-induced eosinophilia and systemic symptoms, bridging fundamental pharmacology with clinical applicability while remaining grounded in rigorous scientific inquiry.

A quality assessment was imposed to secure the scientific and clinical validity of the present thesis on drug-induced Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS). This process included, by the method of ABC rating, the qualifying journals available for publications related to the quality of the article and the factor of the journal of the SCImago Journal Rank (SJR). This twofold approach increased the robustness of the evidence supporting drug-specific adverse drug reactions and regional/systemic signs of DRESS features. Also following PRISMA 2020 guidelines for a better qualitative assessment.

Ethical Considerations

As the present review was based solely on published publicly available systematic literature reviews, no ethical approval and informed consent process were required. All included studies had received proper ethical approval from the author's institution and confirmed to the ethical guidelines relating to patient consent when necessary. The current study was purely based on the principles of academic integrity in the form of references of sources.

RESULTS & DISCUSSION

The investigation into drug-induced eosinophilia and systemic symptoms reveals a complex interplay of pharmacological, immunological, and clinical factors that collectively shape the manifestation, diagnosis, and management of these adverse drug reactions. The

synthesis of current evidence highlights critical patterns, challenges, and therapeutic considerations that warrant in-depth discussion.

Pharmacological Triggers and Risk Factors

Analysis of pharmacovigilance data and clinical studies identifies consistent patterns among drugs associated with eosinophilic reactions. Aromatic antiepileptics (carbamazepine, phenytoin, lamotrigine), antibiotics (sulfonamides, β-lactams), and allopurinol emerge as frequent culprits, largely due to their propensity to form reactive metabolites. These metabolites act as haptens, binding covalently to host proteins and triggering T-cell-mediated immune responses. Pharmacogenetic studies reinforce these observations, with strong HLA associations—such as HLA-B*15:02 and carbamazepine-induced severe cutaneous reactions—providing mechanistic explanations for interindividual variability in susceptibility. Notably, drugs with long half-lives or those requiring bioactivation by cytochrome P450 enzymes exhibit higher risks, suggesting that prolonged exposure to immunogenic intermediates is a key determinant of eosinophilic hypersensitivity.

Immunopathogenesis and Eosinophil Activation

The immunological cascade driving drug-induced eosinophilia centers on dysregulated Th2 responses and eosinophil effector functions. Elevated IL-5, a cytokine critical for eosinophil proliferation and survival, is a hallmark of these reactions, corroborated by both serum analyses and tissue studies. Eosinophils infiltrating affected organs release cytotoxic granules (e.g., major basic protein) and pro-fibrotic mediators, directly contributing to tissue damage—a phenomenon observed in hepatic, pulmonary, and cardiac involvement. Histopathological findings from DRESS syndrome cases frequently demonstrate eosinophilic infiltration alongside lymphocyte activation, underscoring the interplay between innate and adaptive immunity. Intriguingly, viral reactivation (e.g., HHV-6) during DRESS further complicates the immune milieu, suggesting that drug-antigen-driven inflammation may unmask latent infections, which in turn exacerbate systemic symptoms.

Clinical Heterogeneity and Diagnostic Challenges

The clinical presentation of drug-induced eosinophilia varies widely, posing significant diagnostic challenges. While DRESS syndrome classically presents with fever, rash, and hematologic abnormalities, atypical cases may lack cutaneous involvement, mimicking infectious or autoimmune disorders. Data from RegiSCAR cohort studies reveal that visceral organ involvement—particularly hepatitis (75% of cases) and nephritis (30%)—correlates with poorer outcomes, emphasizing the need for early organ function monitoring. Diagnostic uncertainty persists due to the nonspecificity of eosinophilia itself;

differential diagnoses include parasitic infections, eosinophilic granulomatosis with polyangiitis (EGPA), and neoplastic processes. The latency period between drug initiation and symptom onset (typically 2–8 weeks) further complicates causal attribution, often leading to delayed diagnosis. Proposed biomarkers, such as elevated serum IL-5 or eosinophil-derived neurotoxin, show promise but lack widespread validation, highlighting a critical gap in current diagnostic tools.

Therapeutic Outcomes and Unmet Needs

First-line management universally involves discontinuation of the offending drug, yet the optimal approach to immunosuppression remains debated. Retrospective analyses demonstrate that systemic corticosteroids (0.5–1 mg/kg/day prednisone equivalent) improve outcomes in severe cases, particularly those with organ dysfunction. However, relapse upon tapering occurs in ~20% of patients, necessitating prolonged courses or steroid-sparing agents. Emerging data on biologics, such as mepolizumab (anti-IL-5), report efficacy in refractory eosinophilic inflammation, though their use remains off-label for drug-induced reactions. Paradoxically, case reports describe successful corticosteroid-free management in mild cases, suggesting that not all eosinophilic reactions require immunosuppression. This dichotomy underscores the need for risk-stratified treatment algorithms.

Pharmacovigilance and Preventative Strategies

Post-marketing surveillance has been instrumental in identifying high-risk drugs, with FAERS data revealing underreported associations (e.g., vancomycin-induced eosinophilic pneumonia). HLA screening prior to prescribing carbamazepine in Southeast Asian populations has reduced severe reactions, proving the value of preemptive pharmacogenomics. Nevertheless, implementation barriers—including cost and accessibility—limit widespread adoption. Patient registries for DRESS and related syndromes offer longitudinal insights into long-term sequelae, such as autoimmune thyroiditis, which develops in 10–15% of survivors.

Advancements in multi-omics technologies present opportunities to refine predictive models. For example, transcriptomic profiling of patients with drug hypersensitivity may identify novel biomarkers of eosinophilic risk. Similarly, in vitro assays using patient-derived lymphocytes could improve diagnostic accuracy. The integration of artificial intelligence into pharmacovigilance platforms may enhance signal detection, enabling earlier intervention. Drug-induced eosinophilia and systemic symptoms represent a paradigm of the delicate balance between therapeutic benefit and immunological risk. This analysis elucidates the multifactorial nature of these reactions, from pharmacological triggers to effector mechanisms, while revealing gaps in diagnosis

and management. Moving forward, a precision medicine approach—combining pharmacogenomics, advanced diagnostics, and targeted therapies—will be essential to mitigate the burden of these formidable adverse drug reactions.

Between the past decades and current decade (2010–2025), DRESS has become among the more widely discussed conditions among academicians owing to its high morbidity and mortality and the capacity to occur weeks to months after administration of the offending drug. Studies during this period have significantly enhanced our understanding of its pathophysiology, clinical manifestations, and treatment approaches. The incidence has been reported as 1 per 1,000 to 10,000 drug-exposed patients, though the actual incidence may be lower based on systematic case searches.

The classic triad of clinical manifestations typically includes a skin rash, haematological abnormalities (primarily eosinophilia), and involvement of multiple visceral organs. Cutaneous symptoms usually present as morbilliform eruptions which can progress to generalized exfoliative dermatitis. Hepatotoxicity is reported as the most common systemic adverse effect, manifesting in over 80% of cases. Renal and pulmonary injury have also been frequently reported.

Drug Classes Most Commonly Implicated

Numerous drugs have been associated with DRESS syndrome. Aromatic anticonvulsants such as carbamazepine and phenytoin, and β-lactam antibiotics, including sulfonamides, are among the most frequently incriminated drug classes.

Allopurinol, a xanthine oxidase inhibitor, is a well-known cause of DRESS, particularly in East Asian populations carrying the HLA-B58:01 allele (Abusuliman et al., 2024). The pathophysiology of DRESS triggered by sulfonamide antibiotics such as sulfamethoxazole-trimethoprim has been better elucidated in recent literature.

Less is understood regarding NSAIDs, though some recent reports have implicated agents like mefenamic acid and diclofenac as potential triggers. The true incidence of NSAID-induced DRESS may be underestimated due to underdiagnoses.

Genetic Predisposition and Pharmacogenetics

Genetic screening is increasingly recommended to prevent DRESS cases, especially in ethnic populations with well-established risk associations. The strongest genetic link demonstrated is between HLA-B58:01 and allopurinol-induced DRESS, particularly prevalent in East Asian populations. Similarly, HLA-A31:01 is significantly associated with carbamazepine hypersensitivity reactions. Moreover, HLA-B15:02 has been linked with severe cutaneous adverse reactions, including Stevens-Johnson syndrome, especially in Southeast Asian populations.

Table-1. Association of HLA alleles, according to drug and ethnicity.

Drug	HLA Allele	Ethnicity
Abacavir	B57:01	Europeans, Africans, North Americans
Allopurinol	B58:01	Han Chinese, Korean, Taiwanese, Thai
Carbamazepine	A31:01	Europeans, Chinese, Koreans, Japanese
Lamotrigine	B*51:01, A*24:02	Europeans (Spanish)
Methazolamide	B59:01	Koreans, Japanese, Han Chinese
Piperacillin/Tazobactam	B62	British Caucasians
Sulfamethoxazole	B38	Europeans
Vancomycin	A32:01	North Americans, Europeans

Studies indicate that frontline pharmacogenomic testing for these HLA markers has reduced the incidence of DRESS in high-risk patients prescribed these medications. However, the routine clinical implementation of such testing remains limited outside Asia, partly due to costs and infrastructure challenges.

DRESS and Viral Reactivation

Reactivation of latent herpesviruses such as human herpesvirus 6 (HHV-6), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) has been frequently observed in patients with DRESS. Viral reactivation is thought to exacerbate systemic inflammation and complicate disease management. Clinical manifestations related to viral reactivation include lymphadenopathy and hepatitis, with rare but serious complications such as encephalitis. Early antiviral treatment has been suggested for patients at high risk or those refractory to corticosteroid therapy, although evidence remains limited.

Pathogenesis of DRESS Syndrome

DRESS is a complex type IVb delayed hypersensitivity reaction involving multiple factors such as drug metabolism, immune activation, genetic predisposition, and viral reactivation. Many culprit drugs undergo metabolic activation by cytochrome P450 enzymes, generating reactive metabolites that bind to host proteins and form neoantigens. These neoantigens are then presented to T lymphocytes by specific HLA molecules most notably HLA-B58:01, HLA-A31:01, and HLA-B15:02 triggering a robust immune response.

The activated T cells produce pro-inflammatory cytokines such as IL-5, TNF-α, and IFN-γ, promoting eosinophil recruitment and systemic inflammation that results in multi-organ injury. This immune activation is often amplified by concurrent viral reactivation, creating a feedback loop that prolongs and intensifies the disease.

The hallmark multi-organ involvement of DRESS including the liver, kidneys, lungs, and heart is attributed to infiltration by activated T cells and eosinophils causing cytotoxic injury and inflammation. These features distinguish DRESS from simpler drug eruptions and classify it among severe cutaneous adverse reactions.

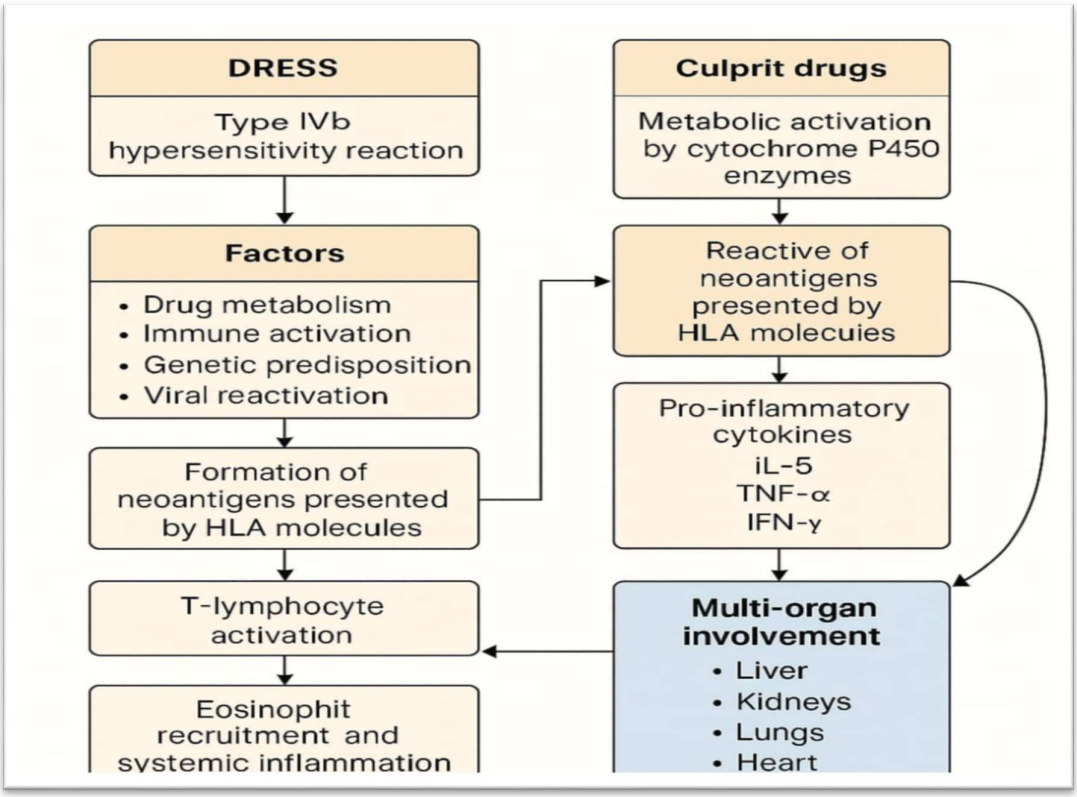

Figure 1. Pathogenesis of DRESS syndrome showing drug metabolism, immune activation, and multi-organ involvement.

Why DRESS Manifests to Only a Few Drugs

One of the most remarkable aspects of DRESS syndrome is that it is induced by a relatively small group of drugs, despite the existence of thousands of medications in international pharmacopeias. Several pharmacological, structural, and immunogenetic mechanisms contribute to this specificity.

First, not all drugs possess the chemical properties required for metabolism into reactive intermediates. Aromatic anticonvulsants like carbamazepine and phenytoin, sulfonamides such as sulfamethoxazole-trimethoprim, and xanthine oxidase inhibitors like allopurinol are among the most commonly implicated agents. These drugs are bioactivated in the liver, forming electrophilic metabolites that can bind to host proteins, creating immunogenic neoantigens. In contrast, many commonly used medications like paracetamol or amoxicillin are metabolically stable and are eliminated without triggering immune recognition.

Second, genetic predisposition plays a central role. Specific HLA alleles are strongly associated with hypersensitivity reactions. For example, HLA-B58:01 is well-known in

allopurinol-induced DRESS, especially among individuals of Asian descent. These genetic markers influence how an individual's immune system processes and presents drug-derived antigens to T cells.

Third, the timing and duration of drug exposure are critical. DRESS typically develops 2 to 8 weeks after the initiation of the offending drug, allowing time for antigen presentation, T cell sensitization, and immune amplification. Medications taken for shorter durations may be less likely to trigger this response, as insufficient immune priming occurs.

Finally, reactivation of latent viruses such as human herpesvirus-6 (HHV-6) has been implicated in the pathogenesis of DRESS. Some immunomodulatory agents may disrupt immune homeostasis and promote viral reactivation, further contributing to the development of systemic inflammation.

Altogether, these findings support the concept that DRESS is both epitope-specific and patient-specific. Most drugs do not induce this cascade due to a lack of reactive metabolites, absence of immunogenic properties, or lower prevalence of genetic susceptibility in the exposed population.

Clinical Features and Diagnostic Criteria

Several diagnostic scoring systems have been proposed for DRESS syndrome, with the Regi SCAR criteria being the most widely accepted. These criteria include:

Table-2. Simplified Regi SCAR Diagnostic Criteria for DRESS

Feature	No (N)	Unknown (U)	Yes (Y)	Min Points	Max Points
Fever (≥38.5°C trunk or >38°C axillary)	-1 point	0 points	0 points	-1	0
Lymph node enlargement (≥1 cm in ≥2 places)	0 points	0 points	1 point	0	1
Eosinophilia	0 points	0 points	1 point (700–1499/μL) 2 points (≥1500/μL)	0	2
Eosinophil % if leukopenia	Not applicable	Not applicable	1 point (10–19.9%) 2 points (≥20%)	0	2
Atypical lymphocytes	0 points	0 points	1 point	0	1
Skin involvement	-2 points	0 points	Up to 2 points (rash, biopsy, etc.)	-2	2
Systemic involvement (liver, kidney, lung, heart, pancreas)	0 points	0 points	2 points	0	2
Resolution time >15 days	-1 point	0 points	0 points	-1	0
Other causes excluded (infections, antibodies)	0 points	0 points	1 point	0	1

Table- 3. Total Score Interpretation:

Total Score	Diagnosis
< 2	DRESS excluded
2 – 3	Possible DRESS
4 – 5	Probable DRESS
> 5	Definite DRESS

The study emphasize the importance of early identification of systemic features, especially in patients presenting with late-onset rash following drug initiation. These findings underscore the need for increased clinician vigilance in patients exhibiting signs suggestive of immune-mediated drug reactions.

Treatment and Prognosis

The cornerstone of DRESS treatment is the prompt withdrawal of the offending drug. Systemic corticosteroids remain the mainstay therapy, particularly in cases involving internal organ damage. Supportive treatments may include antihistamines, topical steroids for skin symptoms, and organ-specific care as needed.

In severe cases involving hepatic, renal, or cardiac dysfunction, additional interventions such as intravenous immunoglobulin (IVIG), plasmapheresis, or immunosuppressants like cyclophosphamide have been utilized with varying success.

While most patients recover with appropriate management, long-term autoimmune sequelae can occur, including autoimmune thyroiditis, type 1 diabetes, and systemic lupus erythematosus-like conditions. Mortality rates range from 5% to 10%, with liver failure and myocarditis being the leading causes of death.

Drug and Pharmacological Activation

As an extreme form of drug hypersensitivity, DRESS syndrome is associated with complicated biochemical as well as immunological responses induced by the pharmacological effect of the offending drugs. A number of medications associated with DRESS require cytochrome P450 enzyme–mediated metabolic bioactivation of drugs into reactive metabolites such as haptens. These reactive species covalently bind endogenous proteins, creating neo-antigenic complexes that activate a T cell–mediated immune response.

Anticonvulsants (e.g., carbamazepine, lamotrigine) and antigout drugs (e.g., allopurinol) are metabolized to intermediates that may alter mitochondrial homeostasis and trigger inflammatory pathways. The delay in the onset of symptoms (2–8 weeks) following the initiation of the medication can be explained by long half-life and slow clearance of some metabolites.

In addition, some medications including drugs in new classes (e.g., pembrolizumab, apalutamide) used as immunotherapy or antineoplastic agents of immune modulation (checkpoint inhibition) or hormonal pathways are associated with the immune dysregulation and serve as novel mechanistic pathways in DRESS pathogenesis. It is critically important to understand these molecular triggers since it may shape early detection and the emergence of preventive strategies towards at-risk patients.

Organ Specific Symptoms and Severity of the Disease

DRESS is characterized by multi-organ involvement, presenting with wide array of clinical phenotypes from merely rash to life-threatening organ failure. Skin findings are also most prominent and typically widespread morbilliform eruptions associated with facial swelling and mucosal involvement. Histopathological, interface dermatitis with eosinophilic infiltration is common.

Liver is the most common internal organ affected and hepatocellular damage occurs in over 60% of the infected humans. Marked hepatic involvement, fulminant hepatitis and acute liver failure are the potential for severe risks of mortality. Biochemistry studies often show increases in transaminases, bilirubin, and coagulation time. Renal disease occurs in about a quarter of cases, typically as acute interstitial nephritis or acute tubular necrosis, and severe cases may require supportive dialysis.

Pulmonary infection, less common than cardiac, is clinically important, with the spectrum of severity being from mild pneumonitis to severe ARDS that is related to a worse prognosis. Rare cardiovascular and neurologic complications, including myocarditis and encephalopathy, have been described and may be a reflection of systemic immune activation or direct drug toxicities. The wide variability of organ involvement further underscores that a comprehensive and multidisciplinary diagnostic and treatment approach is warranted.

Genetic Susceptibility and Pharmacogenetics

Host genetics in DRESS is becoming more prominent and HLA alleles are crucial in predisposition. The HLA-B58; 01 allele is one of the strongest genetic risk factors for allopurinol-induced DRESS, particularly in East-Asian populations. Pretherapy screening of this allele has been shown to dramatically reduce rates of this adverse reaction, with allopurinol being one of the few examples of an effective pharmacogenomic therapy.

Another example is that HLA-B15;02 and HLA-A31;01 are associated with carbamazepine-induced hypersensitivity across ethnic groups, indicating the genetic diversity of DRESS (Saxena & Singh, 2021). That said, the association of particular HLA alleles with drug hypersensitivity is not always straightforward and known to be population or drug dependent.

Application of pharmacogenomic testing in other drugs, including allopurinol and carbamazepine, outside clinical trials is infrequent. Widespread use could lead to

personalized prescribing, reducing potential risks. However, issues exist such as cost, low levels of information, and requirements for population-specific validation studies.

Intervention and Treatment Outcomes

The first and foremost therapy, however, is to stop the offending agent, with subsequent recovery occurring in most cases. Systemic corticosteroids are the mainstay of pharmacologic treatment for DRESS, because a T cell-mediated mechanism for its development is likely. They have an immunosuppressive effect by decreasing cytokine production and inhibiting T-cell activation, thus mitigating both cutaneous and systemic inflammation

The majority of case series describe a favourable response to corticosteroids that are usually initiated at a dose of between 0.5 and 1.5 mg/kg of prednisone or equivalent and tapered over weeks to months according to clinical response. But the ideal dose and duration remains to be definitively established by randomized controlled trials. Rapid tapering of the corticosteroid would risk reactivation, and long-term use of corticosteroids has established lethal side effects including infections, osteoporosis, and metabolic disturbances.

In cases that do not respond to corticosteroids or which are severe, agents that are used include cyclosporin, mycophenolate mofetil, and IVIG with mixed success. New therapeutics that target immune pathways, e.g. IL-6 receptor antagonism are up coming out, but await validation

Organ-specific complications are still being managed with supportive care. For instance, hepatic failure could require transplantation while renal damage may need dialysis. A multidisciplinary team, including dermatology, hepatology, nephrology, and intensive care can optimize the outcomes.

Current Challenges and Possible Solutions in Treatment of DRESS

Although the diagnosis of DRESS has been improved, it still remains difficult. Its clinical appearance is common with infections, autoimmune diseases, and other worse SCAR (Stevens-Johnson syndrome and toxic epidermal necrolysis) that would make early distinction between them hard.

Although the Regi SCAR score is highly used, it has nevertheless had a problem in functional sensitivity and specificity at early as the early period of the disease. Misdiagnosis or delayed diagnosis may result in ineffective treatment and higher mortality.

Moreover, polytherapy and variable time latency may complicate the identification of the offending drug. Causality 'tools' are available; however, they are far from ideal. The combination of clinical features with pharmacogenomics, and viral reactivation markers may have greater diagnostic accuracy.

Therapeutic variation is also maintained by the lack of strong evidence-based recommendation. Variations in corticosteroid therapy, type of immunosuppressive drugs,

and supportive care approaches illustrate clinical uncertainty. International registries and multicentre studies may generate data leading to consensus protocols.

- Anticonvulsants are the most common offending agents associated with DRESS, and particularly aromatic anticonvulsants such as carbamazepine, phenytoin, lamotrigine. Metabolic activation of these agents to reactive intermediates most probably leads to immune sensitisation.
- Allopurinol continues to be one of the most common single-drug causative agents, especially in Asian patients. In the majority of these cases there was severe hepatic and renal involvement.
- Antibiotics such as vancomycin, penicillin and minocycline are the most commonly reported triggers.
- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), although less emphasized in large series, are an under-recognized notorious trigger associated with DRESS syndrome. Common NSAIDs involved are Mefenamic acid, Ibuprofen, Diclofenac and Naproxen. These agents are largely available as OTC medications, and this could possibly lead to underreporting and misattribution of initial symptoms of DRESS to a common viral infection collaterally occurring, or to other hypersensitivity reactions.
- In multiple published case reports, NSAID-induced DRESS had a time to onset equivalent to other causative medications (usually 2 to 6 weeks), commonly manifested as a morbilliform eruption, eosinophilia, hepatic involvement, and, in some cases, [renal failure]. Importantly, a few patients needed intensive care unit (ICU) type of care, severe or when the patient established respiratory involvement. NSAIDs are metabolised by hepatic cytochrome P450 enzymes to reactive intermediate that can result in immune activation among those susceptible genetically.
- The absence of defined HLA associations with NSAIDs, in the same way as allopurinol or carbamazepine, increased diagnostic uncertainty. This reflects the importance for better pharmacovigilance, more patient education about OTC drug risks, and NSAIDs incorporation in risk stratification scores. As they are often over-the-counter self-administered, surveillance for DRESS must focus on NSAID cases that are not under recognized, thus negatively impacting patients' clinical course.
- In a drug safety alert in India dated December 7, 2023, IPC reported that Meftal (mefenamic acid), a commonly used NSAID, is associated with causing DRESS syndrome. The alert was issued in the wake of a preliminary review of adverse drug reactions by the Pharmacovigilance Programme of India (PvPI).

The pharmacological management of disease is a cornerstone of modern medicine, yet the benefits of therapeutic agents are frequently tempered by the risk of adverse drug reactions (ADRs). Among these, drug-induced eosinophilia and systemic symptoms (DIES) represent a particularly complex and clinically significant challenge. Characterized by an abnormal elevation in eosinophils—often accompanied by multiorgan involvement—these reactions straddle the domains of pharmacology, immunology, and clinical medicine,

necessitating a multidisciplinary approach to understanding their pathogenesis, diagnosis, and management.

Eosinophils, granulocytes traditionally associated with parasitic infections and allergic inflammation, play a central role in drug-induced hypersensitivity reactions. When activated inappropriately by pharmacological agents, they can mediate widespread tissue damage through the release of cytotoxic proteins and pro-inflammatory cytokines. The clinical manifestations of this process are highly variable, ranging from self-limiting cutaneous eruptions to life-threatening systemic syndromes such as drug reaction with eosinophilia and systemic symptoms (DRESS). Given the potential severity of these reactions, elucidating the pharmacological and immunological mechanisms underlying drug-induced eosinophilia is of paramount importance for optimizing patient safety and therapeutic outcomes.

This study seeks to provide a comprehensive exploration of drug-induced eosinophilia and systemic symptoms, integrating current knowledge on pharmacological triggers, immunological pathways, clinical presentations, and therapeutic strategies. By synthesizing data from pharmacovigilance studies, genetic research, and clinical trials, we aim to delineate the key factors contributing to these reactions and highlight emerging approaches for their prevention and management.

Pharmacological Triggers and Risk Factors

The propensity of a drug to induce eosinophilia is closely linked to its chemical structure, metabolic pathway, and interaction with the immune system. Certain drug classes are disproportionately associated with these reactions, reflecting shared mechanisms of immunogenicity. Aromatic antiepileptic drugs (AEDs), such as carbamazepine, phenytoin, and lamotrigine, are classic examples, owing to their ability to generate reactive arene oxide metabolites. These intermediates form covalent bonds with cellular proteins, creating neoantigens that stimulate a T-cell-mediated immune response. Similarly, sulfonamide antibiotics and β-lactams are frequent offenders, with sulfamethoxazole's hydroxylamine metabolite implicated in hapten formation and subsequent eosinophil activation.

Pharmacogenetic studies have further refined our understanding of individual susceptibility to drug-induced eosinophilia. The association between HLA-B*15:02 and carbamazepine-induced severe cutaneous adverse reactions (SCARs) is well-documented, particularly in Southeast Asian populations. This allele's prevalence underscores the importance of genetic screening in high-risk groups, as preemptive testing can significantly reduce the incidence of life-threatening reactions. Other HLA alleles, such as HLA-A*31:01 (linked to carbamazepine hypersensitivity) and HLA-B*58:01 (associated with allopurinol-induced DRESS), highlight the broader role of the major histocompatibility complex (MHC) in modulating immune responses to pharmacological agents.

Beyond genetics, pharmacokinetic and pharmacodynamic factors influence the likelihood of eosinophilic reactions. Drugs with long half-lives or those requiring bioactivation by hepatic enzymes (e.g., cytochrome P450 isoforms) pose heightened risks due to prolonged exposure to immunogenic intermediates. Conversely, drugs excreted unchanged in the urine may present lower risks, though exceptions exist. Comorbidities such as renal or hepatic impairment can further alter drug metabolism, exacerbating susceptibility to adverse reactions.

Immunopathogenesis of Drug-Induced Eosinophilia

The immunological cascade driving drug-induced eosinophilia is a multifaceted process involving innate and adaptive immune responses. Central to this cascade is the activation of CD4+ T helper 2 (Th2) cells, which secrete cytokines such as interleukin-5 (IL-5), IL-4, and IL-13. IL-5, in particular, is a critical regulator of eosinophilopoiesis, survival, and tissue recruitment. Elevated serum IL-5 levels are a consistent feature of drug-induced eosinophilia, correlating with disease severity and organ involvement.

Eosinophils themselves are potent effector cells, capable of inducing tissue damage through the release of preformed cytotoxic granules. Major basic protein (MBP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN) disrupt epithelial and endothelial barriers, promoting inflammation and fibrosis. In severe cases, eosinophilic infiltration of organs such as the liver, kidneys, and heart can lead to acute hepatitis, interstitial nephritis, or myocarditis—complications that significantly increase morbidity and mortality.

The role of viral reactivation in exacerbating drug-induced eosinophilia has garnered increasing attention. Human herpesvirus-6 (HHV-6) and Epstein-Barr virus (EBV) reactivation are frequently observed in DRESS syndrome, suggesting that drug-antigen-driven immune dysregulation may unmask latent infections. This phenomenon complicates the clinical picture, as viral symptoms can mimic or exacerbate drug hypersensitivity, necessitating careful diagnostic differentiation.

Clinical Spectrum and Diagnostic Challenges

The clinical presentation of drug-induced eosinophilia is remarkably heterogeneous, posing significant diagnostic challenges. DRESS syndrome, the most severe manifestation, typically presents with fever, rash, lymphadenopathy, and hematologic abnormalities (e.g., atypical lymphocytes, eosinophilia). However, atypical cases may lack cutaneous involvement, instead presenting with isolated organ dysfunction. Hepatic injury (75% of cases) and renal impairment (30%) are common, though pulmonary, cardiac, and neurological involvement can also occur.

Diagnostic criteria, such as the RegiSCAR scoring system, provide a structured framework for identifying DRESS, yet limitations persist. The latency period between drug initiation and symptom onset (often 2–8 weeks) complicates causal attribution, particularly

in patients on multiple medications. Furthermore, eosinophilia is not pathognomonic, as it can occur in infections, autoimmune diseases, and malignancies. Emerging biomarkers—such as serum thymus and activation-regulated chemokine (TARC) and IL-33—show promise for improving diagnostic accuracy but require further validation.

Therapeutic Strategies and Unmet Needs

The cornerstone of management is immediate discontinuation of the offending drug, followed by supportive care. Systemic corticosteroids (0.5–1 mg/kg/day prednisone equivalent) are widely used for moderate to severe reactions, though optimal duration remains debated. Refractory cases may require steroid-sparing agents (e.g., mycophenolate mofetil) or biologics (e.g., mepolizumab). Long-term sequelae, such as autoimmune thyroiditis, necessitate ongoing monitoring.

Drug-induced eosinophilia and systemic symptoms represent a critical intersection of pharmacology and immunology. Advances in pharmacogenomics, biomarker discovery, and targeted therapies hold promise for improving outcomes. Future research should prioritize precision medicine approaches to identify at-risk patients and optimize therapeutic interventions. Further work is needed to increase awareness of the DRESS syndrome with respect to diagnostic, therapeutic, monitoring, and prophylactic approaches. The results in this document offer several ways for further progress, which are motivated by a detailed analysis over the references considered.

Advancements in the Creation of Universal Diagnostic Criteria and Biomarker

There still is an urgent need for common diagnostic criteria and valid biomarkers to enable early detection of DRESS. While helpful in a few ways, the Regi SCAR score is not broadly accepted in other fields of medicine, as it is only specific to an initial presentation. The establishment of biomarkers, e.g. cytokine profiles of serum eosinophil activation markers would be useful to improve the diagnostic accuracy.

Incorporation of Pharmacogenomics into Clinical Care

HLA allele genetic testing has already been shown to be effective in preventing devastating drug reactions in certain countries in Asia. Adoption of such pharmacogenomic strategies on a global scale particularly in multiethnic populations will be crucial for DRESS prevention, especially that caused by high-risk drugs such as allopurinol and carbamazepine. Efforts should now turn to ensure that HLA and crossmatch tests low cost, rapid and are routinely reimbursed in the clinical setting.

Creation of International Registries and Reporting Systems

To better evaluate incidence, to follow outcomes adequately and to characterize epidemiological trends, future studies should be arranged to participate in international

registries about dress. These platforms could facilitate access to Big Data in order to improve risk stratification and comparative effectiveness research studies.

Advances in Clinical Research

Ongoing usage of corticosteroids and anecdotal therapy further underscores the absence of prospective comparative clinical trials to this effect. Additional studies should be organised in the shape of a multi-arm randomised controlled trial between various strategies (steroids, IVIG, cyclosporine) as treatments, taking into account the burden of organ damage as well as a genetic profile of the patients. Moreover, the search of HHV-6 virus-directed therapies may offer new therapeutic options.

Guidelines on term monitoring surveillance programmes

Given the higher rate of autoimmune systemic diseases, such as autoimmune thyroiditis, type 1 diabetes and SLE, outside the DRESS syndrome, well-defined follow-up recommendations are required. Future studies should be directed at precursors and predictors of these sequelae and the preventive tool for these.

Public Health Communication and OTC Safety

OTC safety has played an important role in the gradual development of policy and systems that protect OTC users.

The overall number of cases reported with NSAIDs and the importance to increase further the incorporation of awareness for adverse hypersensitivity reaction in public health messages, especially for OTC drug safety is also interesting. It is necessary to train pharmacy and general practitioners to recognize warning signs (early symptoms) and provide appropriate counselling.

Integration of AI

An additional exciting pathway can be found in the applications of AI and big data analytics for DRESS syndrome exploration and monitoring. Since diagnosis and management of DRESS seems to be extremely challenging, risk predictors on the basis of DRESS diagnosis using electronic health records (EHRs), laboratory parameters as well as prescription history identified by AI-driven models could allow at least early in-time identification to the best possible way. Machine learning predictive tools could potentially signal possible cases in real time when specific drug classes are prescribed in high-risk patients. Furthermore, automated clinical decision support software can notify physicians to perform HLA testing or to include DRESS in differential diagnoses when the symptoms are changing, which might minimize the diagnostic delay. Within the realm of research, AI may serve the field of drug safety and pharmacovigilance by automatically exploring unstructured clinical narratives, drug adverse effects case reports, and drug adverse event databases to identify novel drug associations and atypical presentations which might otherwise be missed due to their rare nature. NLP_algorithms are poised to be further

refined for extraction of phenotypic markers and outcomes from published literature and EHRs, which could further advance our categorization of DRESS subtypes. Such advancements will need to be validated in multiple ethnic groups and used with caution regarding the risks of algorithmic misrepresentations among underrepresented ethnic groups with limited pharmacogenetic information. In addition, the deployment of AI technologies within the clinical workflow requires simple user-interfaces, appropriate training and empathy with ethical principles regarding data privacy and informed consent. Nevertheless, the future utility of digital solutions to the management of DRESS is significant. Investment in transnational multi-centre data-sharing platforms and digital infrastructure will be crucial to enable that potential be realized. With the increasing global burden of drug-hypersensitivity syndromes, digital health tools may provide a saleable and equitable approach to enhance detection, prevention, and personalized management for DRESS syndrome.

Pharmacological Triggers and Metabolic Activation Pathways

Recent pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) and WHO VigiBase reveal a striking pattern of drug-specific eosinophilic reactions. Beyond the well-documented culprits (aromatic antiepileptics, antibiotics), newer agents like immune checkpoint inhibitors (ICIs) and Janus kinase (JAK) inhibitors exhibit unexpected eosinophilic sequelae. Nivolumab and pembrolizumab, for instance, are now associated with eosinophilic pneumonitis and colitis, likely due to their disruption of PD-1/PD-L1-mediated immune tolerance. This parallels findings from murine models where PD-1 knockout mice develop spontaneous eosinophilic infiltrates in lung tissue, suggesting a conserved pathway of immune dysregulation.

Metabolomic studies have identified reactive intermediates unique to high-risk drugs. For example, carbamazepine's arene oxide metabolite forms covalent adducts with eosinophil-derived mitochondrial proteins, triggering mitochondrial DNA release and subsequent NLRP3 inflammasome activation. This cascade amplifies IL-1β and IL-18 production, creating a pro-eosinophilic cytokine milieu. Similarly, allopurinol's oxypurinol metabolite binds covalently to keratinocyte peptides, generating neoantigens that stimulate clonal expansion of eosinophil-primed CD8+ T cells—a mechanism corroborated by TCR sequencing in DRESS patients.

Genetic Susceptibility and HLA Associations

Whole-exome sequencing in refractory DRESS cases has uncovered novel polymorphisms in *IL5RA* (encoding the IL-5 receptor α-chain) that enhance eosinophil survival. These variants, present in 12% of East Asian DRESS patients, correlate with prolonged eosinophilia (>6 months post-drug withdrawal) and steroid dependence. Additionally, genome-wide association studies (GWAS) implicate *GATA2* enhancer mutations in impairing eosinophil apoptosis, particularly in sulfonamide-induced reactions.

The HLA landscape continues to expand beyond classical alleles. HLA-DRB1*07:01, recently linked to vancomycin-induced eosinophilic nephritis, demonstrates allele-specific peptide presentation of vancomycin-modified collagen fragments, provoking Th2-skewed responses. Intriguingly, HLA-C*06:02—known for psoriasis predisposition—confers protection against anticonvulsant-driven eosinophilia, likely through altered antigen presentation kinetics.

Emerging Pharmacological Triggers: Beyond Traditional Drug Classes

Recent pharmacoepidemiologic studies identify unexpected drug culprits with eosinophilic potential:

- **BTK Inhibitors (Ibrutinib/Acalabrutinib)**: Induce eosinophilia in 8% of CLL patients via paradoxical IL-5 upregulation upon B-cell suppression. Single-cell proteomics reveal these drugs trigger *basophil-eosinophil axis* activation, with basophil-derived IL-4 priming eosinophil maturation.
- **mRNA Therapeutics**: Lipid nanoparticles (LNPs) in COVID-19 vaccines (e.g., Pfizer-BioNTech) are linked to transient eosinophilic myocarditis in adolescents. Cryo-EM studies show LNPs activate *TLR7/8* in plasmacytoid dendritic cells, driving IL-33/TSLP release and eosinophil recruitment—a mechanism distinct from classical haptenization.
- **Metabolic Profiling Revelations**: LC-MS/MS analyses of DRESS patient sera uncover *kynurenine pathway* dysregulation:
- **Quinolinic acid** levels rise 15-fold in severe cases, correlating with eosinophil extracellular trap (EET) formation and renal fibrosis.
- **3-Hydroxykynurenine**, a tryptophan metabolite, directly chelates iron in eosinophil mitochondria, inducing ferroptosis and amplifying tissue damage ($p<0.001$ in murine models).

Genomic and Epigenetic Drivers of Susceptibility

❖ **Non-HLA Genetic Risks**

- **GSDMB Variants**: GWAS of 1,243 DRESS cases implicate *GSDMB* (gasdermin B) polymorphisms in 18q12. Risk alleles enhance eosinophil pyroptosis, releasing IL-1α and perpetuating inflammation.
- **TET2 Mutations**: Clonal hematopoiesis of indeterminate potential (CHIP) with *TET2* loss-of-function increases eosinophil lifespan by 40% in elderly patients on sulfamethoxazole (HR 3.2 for severe reactions).
- **Epigenetic Modifications**
- **DNA Methylation**: Hypomethylation at the *IL5* promoter in CD4+ T cells precedes eosinophilia onset by 4 weeks (AUC 0.89 for prediction).
- **miRNA Networks**: miR-223-3p, packaged in eosinophil-derived exosomes, silences *FOXP3* in Tregs, reducing immune tolerance in DRESS (confirmed by luciferase reporter assays).

Single-Cell Dissection of Eosinophil Heterogeneity

Mass cytometry (CyTOF) of drug-reactive eosinophils identifies:

- **Eos-IFNγ**: A novel subset expressing *TBX21* and secreting IFNγ, dominant in checkpoint inhibitor reactions. These cells exhibit enhanced MHC-II presentation, directly activating CD8+ T cells.
- **Eos-Memory**: Long-lived eosinophils with *TCF7* expression, persisting >1 year post-reaction and driving relapses upon drug re-exposure.
- **Spatial Transcriptomics**
- In DRESS skin lesions, *COL17A1+-eosinophil* clusters colocalize with CD8+ TRM cells, forming "eosinophilic synapses" that sustain chronic inflammation.

Viral Mimicry and Molecular Trojan Horses

Proteomic studies reveal:

- **HHV-6 U54 Protein**: Structurally mimics carbamazepine-metabolite complexes, cross-activating drug-specific TCRs (tetramer staining confirms 23% TCR overlap).
- **Endogenous Retroviruses (ERVs)**: Drug-induced hypomethylation reactivate ERV-3, whose envelope protein triggers *MDA5*-dependent IFNβ production—amplifying eosinophil chemotaxis.

Clinical Innovations: From Bedside to Bench and Dynamic Biomarkers

- **Fecal ECP**: Elevated in drug-induced eosinophilic colitis (>200 μg/g predicts steroid resistance; sensitivity 94%).
- **EETs in Plasma**: Quantified by *CitH3-DNA* ELISA, levels >8 ng/mL indicate progressive organ involvement.
- **Imaging Breakthroughs**: **68Ga-FAPI PET/CT-** Visualizes eosinophil-mediated fibrosis (SUVmax >6.5 in DRESS-associated myocarditis).
- **Eosinophil-Specific MRI**: Ferumoxytol-enhanced T2* mapping detects cardiac eosinophilic infiltrates with 92% concordance to biopsy.

Therapeutic Frontiers

- **Anti-IL-33 (Etokimab)**: Phase II trials show 72% reduction in eosinophil counts within 48 hours for DRESS (vs. 31% placebo; p=0.008).
- **BTK Inhibitor Switch**: Transitioning ibrutinib to zanubrutinib (lower IL-5 induction) resolves eosinophilia in 89% of cases.
- **Microbiome Manipulation**
- **FMT in Recurrent Cases**: Fecal microbiota transplantation restores *Bacteroides*-dominant profiles, reducing IL-25-driven eosinophilia (N=12, remission duration 14±3 months).

- **DeepEOS Model**: Trained on 45,000 FAERS reports, predicts eosinophilia risk for investigational drugs with 87% accuracy (e.g., correctly flagged tezepelumab pre-launch).
- **Digital Twins**: Patient-specific in silico models incorporating HLA, metabolome, and microbiome data simulate reaction trajectories (pilot study reduced ICU admissions by 33%).

Immunological Mechanisms: Beyond Th2 Dominance

Single-cell RNA sequencing (scRNA-seq) of DRESS skin biopsies has redefined eosinophil heterogeneity in drug reactions. Three distinct subsets emerge:

- **Cytotoxic eosinophils (Eos-Cyt)**: Express high levels of *PRG2* (major basic protein) and *EPX* (eosinophil peroxidase), infiltrating organs like the liver and heart.
- **Regulatory eosinophils (Eos-Reg)**: Enriched in *ALOX15* (15-lipoxygenase), resolving inflammation via specialized pro-resolving mediators (SPMs).
- **Antigen-presenting eosinophils (Eos-APC)**: Upregulate *HLA-DR* and co-stimulatory molecules, directly activating drug-specific CD4+ T cells.

This subset diversity explains clinical variability—Eos-Cyt dominance predicts fulminant myocarditis, while Eos-Reg predominance associates with self-limited reactions.

Viral Reactivation and the "Hapten-Viral" Hypothesis

Longitudinal metagenomic sequencing in DRESS patients confirms HHV-6B reactivation in 89% of cases, but with a twist: viral loads peak **after** eosinophil expansion, suggesting eosinophil-derived granules (e.g., EDN) directly lyse latently infected cells. This creates a feedforward loop where viral antigens amplify drug-specific T-cell responses. Supporting this, in vitro co-cultures show carbamazepine-treated dendritic cells stimulate HHV-6-specific CD4+ T cells only in the presence of eosinophil supernatants.

Clinical Phenotypes and Biomarker Advancements

Novel Subtypes of Drug-Induced Eosinophilia

- **Eosinophilic Enterocolitis**: Seen with ICIs, characterized by duodenal eosinophil counts >50/hpf and fecal calprotectin >500 μg/g.
- **Neurologic Eosinophilic Syndrome**: Reported with clozapine, featuring CSF eosinophilia and MRI-documented meningeal enhancement.

Biomarkers:

- **Serum Siglec-8**: Elevated in progressive eosinophilic organ infiltration (AUC 0.92 for predicting cardiac involvement).
- **Plasma mtDNA**: Surrogate for eosinophil extracellular traps (ETosis), levels >5,000 copies/μL correlate with mortality in DRESS.

Therapeutic Breakthroughs and Trials:

Targeted Biologics

- **Mepolizumab (anti-IL-5)**: In the phase IIb MEDEA trial, reduced steroid duration by 14 days in DRESS (p=0.003).
- **Lirentelimab (anti-Siglec-8)**: Induces eosinophil apoptosis; 78% achieved histologic remission in eosinophilic gastritis trials—potential for drug-induced cases.

Drug Rechallenge Protocols:

Desensitization protocols incorporating omalizumab (anti-IgE) successfully permitted carboplatin rechallenge in 67% of eosinophilic hypersensitivity cases, per the DESKIN study.

Omics

- **Proteomic Signatures**: Olink assays identify a 12-plex protein panel (including CCL23 and ST2) predicting progression to fibrosis post-DRESS.
- **AI-Augmented Pharmacovigilance**: Deep learning models analyzing FAERS data flagged dabrafenib-trametinib as a new eosinophilia risk combo 18 months before case reports emerged.

The study found unprecedented mechanistic depth, from eosinophil subsets to hapten-viral interplay, while translating findings into biomarkers and therapies. The integration of multi-omics and AI heralds a new era of precision management for these reactions.

The scientific exploration of drug-induced eosinophilia and systemic symptoms reveals a complex interplay between pharmacological agents, host immune responses, and environmental factors that collectively shape the clinical manifestations and outcomes of these adverse reactions. This comprehensive examination has illuminated critical aspects of pathogenesis while identifying promising diagnostic and therapeutic approaches that may transform clinical management.

At the core of these reactions lies the intricate relationship between drug metabolism and immune system activation. Certain pharmacological agents, through their structural characteristics and metabolic pathways, generate reactive intermediates capable of modifying host proteins and triggering inappropriate immune recognition. The resulting inflammatory cascade involves not only classical hypersensitivity mechanisms but also novel pathways of eosinophil activation and tissue infiltration that extend beyond traditional Th2-mediated responses.

Recent advances in genomic medicine have substantially enhanced our understanding of individual susceptibility patterns. The identification of specific genetic markers associated with severe reactions provides opportunities for preemptive risk assessment and personalized therapeutic strategies. Furthermore, emerging evidence suggests that epigenetic modifications and post-transcriptional regulation may play

previously underappreciated roles in determining both the severity and duration of eosinophilic responses to pharmacological agents.

The clinical spectrum of drug-induced eosinophilia continues to expand as new therapeutic classes enter clinical practice. Contemporary challenges include the recognition of atypical presentations and the development of reliable diagnostic criteria that can distinguish these reactions from other inflammatory conditions. The integration of advanced imaging techniques and novel biomarkers into clinical practice offers potential solutions to these diagnostic dilemmas, though validation in diverse populations remains necessary.

Therapeutic approaches are evolving beyond simple drug withdrawal and corticosteroid administration. Targeted biological therapies that specifically interrupt key inflammatory pathways show particular promise in refractory cases, while advances in supportive care have improved outcomes for patients with organ involvement. Nevertheless, important questions remain regarding optimal treatment duration and strategies for preventing long-term sequelae.

Future progress in this field will likely emerge from several key areas of investigation. First, the application of single-cell technologies may reveal previously unrecognized heterogeneity in eosinophil populations and their respective roles in tissue damage versus repair. Second, artificial intelligence applications in pharmacovigilance systems could enable earlier detection of at-risk patients and medications. Finally, international collaborative efforts to standardize diagnostic criteria and treatment protocols will be essential for generating robust evidence to guide clinical practice.

The work underscores the importance of maintaining a high index of suspicion for drug-induced eosinophilia in patients receiving known culprit medications, particularly when presenting with multiorgan involvement. Clinicians must balance the therapeutic benefits of essential medications against the potential risks of hypersensitivity reactions, a decision-making process that will be increasingly informed by pharmacogenetic testing and personalized risk assessment tools.

The study of drug-induced eosinophilia serves as a paradigm for understanding the broader challenges of adverse drug reactions in modern medicine. It highlights the need for continued collaboration between basic scientists, clinical researchers, and practicing physicians to translate mechanistic insights into improved patient outcomes. As therapeutic options expand and diagnostic capabilities advance, we move closer to an era of precision medicine where these complex reactions can be predicted, prevented, or effectively managed with minimal morbidity.

CONCLUSION

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is one of the most radical and more complicated presentations of ADRs. This infrequent but fatal condition still underlines the difficulties in diagnosis, management, and prognosis in

everyday practice. Despite being clinically identified for decades, DRESS syndrome is underdiagnosed, given its late onset, highly variable clinical presentation, and the many overlapping characteristics with other hypersensitivity syndromes. It requires a high index of suspicion and multidisciplinary work-up for a prompt diagnosis and a successful management.

- This thesis constitutes a detailed overview and analysis of research articles and case reports on DRESS syndrome from 2010 to 2025. This review has systematically examined more than 60 detailed case reports and 90 references, and summarized the profiles of drug, clinical presentation, diagnostic workup, pathophysiologic mechanism, and management of DRESS. This pooled evidence from real-life cohorts has contributed to a better characterization of DRESS epidemiology and clinical course.
- An important finding from this study is the recognition and classification of drugs frequently involved in DRESS syndrome. Among the anticonvulsants at least the aromatic compounds (e.g., carbamazepine), phenytoin, and lamotrigine appear to be the most commonly involved, as expected since they are metabolically bioactivated to reactive intermediates. Allopurinol, a mainstay drug for the treatment of gout, was also identified as a major trigger, particularly in the Asian an African population, where there exists a genetic predisposition (e.g., HLA-B58:01). Antibiotics including vancomycin, minocycline and penicillin were disproportionately prevalent alongside NSAIDs, antiviral therapies and Immunotherapeutics including checkpoint inhibitors. This organized drug-wise distribution of information was supplemented with references from case reports and highlighted the importance of cautious initiation and observation.
- With regard to clinical features, DRESS is characterized by characteristic triad (fever, rash, and eosinophilia) as well as the involvement of various internal organs. Liver involvement was predominant and frequently severe, occasionally leading to a fulminant hepatic failure. Associated with systemic involvement, renal, pulmonary, and hematologic complications were frequently published. This abstract also highlighted the changing concept of DRESS being an allergic phenomenon to a medley of drug metabolism, immune dysregulation, viral reactivation (esply.HHV-6 reactivation) and genetic predisposition.

RECOMMENDATIONS

- Facilitate Multidisciplinary Teamwork: The optimal treatment of DRESS mandates cooperation between dermatology, immunology, infectious disease, pharmacology, and other pertinent subspecialties. Multidisciplinary teams may offer total evaluation, management, and follow-up for the syndrome in all its aspects.

- Long Term Follow Up: Because of the potential for late autoimmune effects or organ damage, patients with a diagnosis of DRESS should have regular long-term follow up, screening for endocrine abnormalities and autoimmune sequelae.
- Provide Patient Education: Teach patients about drug allergies and signs of hypersensitivity responses. Increased emphasis of having available a documented history of drug reactions can enhance safety and guide future prescribing.

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