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THE MANIFESTATION OF PHARMACOGENETIC AND CLINICAL PERSPECTIVES ON MEDICATION-ASSOCIATED EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS): A COMPREHENSIVE EVALUATION OF IMPLICATED AGENTS, RISK FACTORS, AND TREATMENT MANAGEMENTS STRATEGIES IN GENERAL

Nodar Sulashvili[1], Rupali Digambar Jadhav[2], Margarita Beglaryan[3], Nana Gorgaslidze[4], Luiza Gabunia[5], Nato Alavidze[6], Natia Kvizhinadze[7], Marika Sulashvili[8], Lela Grigolia[9], Kakhaber Robakidze[10]

[1]Scientific Supervisor, MD, PhD, Doctor of Pharmaceutical and Pharmacological Sciences In Medicine, Invited Lecturer (Invited Professor) of Scientific Research-Skills Center at Tbilisi State Medical University; Professor of Medical and Clinical Pharmacology of International School of Medicine at Alte University; Professor of Pharmacology of Faculty of Medicine at Georgian National University SEU; Associate Affiliated Professor of Medical Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University; Associate Professor of Pharmacology of Pharmacy Program at Shota Meskhia Zugdidi State University; Associate Professor of Medical Pharmacology at School of Medicine at David Aghmashenebeli University of Georgia; Associate Professor of Biochemistry and Pharmacology Direction of School of Health Sciences at the University of Georgia; Associate Professor of Pharmacology of Faculty of Medicine at East European University; Associate Professor of Pharmacology of Faculty of Dentistry and Pharmacy at Tbilisi Humanitarian Teaching University; Tbilisi, Georgia; Researcher of Department of Pharmaceutical Management of Yerevan State Medical University after Mkhitar Heratsi, Yerevan, Armenia. Orcid https://orcid.org/0000-0002-9005-8577 E-mail: n.sulashvili@ug.edu.ge

[2]MD©, 12-th Semester student of MD - Medical Doctor Degree Student of International School of Medicine at Alte University; Tbilisi, Georgia;

[3]MD, PhD, Doctor of Pharmaceutical Sciences, Academician, Professor of Yerevan State Medical University After Mkhitar Heratsi, Head of the Department of Pharmaceutical Management, President of Association PHESA (Pharmacy and Pharmacology Education and Science Association), Yerevan, Armenia; https://orcid.org/0000-0003-3697-6390

[4]MD, PhD, Doctor of Pharmaceutical Sciences, Academician, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia. https://orcid.org/0000-0002-4563-5224

[5]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor, Head of the Department of Medical and Clinical Pharmacology at Tbilisi State Medical University, Clinical Pharmacologist of The First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia https://orcid.org/0000-0003-0856-2684

[6]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia. Professor, Dean Faculty of Medicine at East European University, Tbilisi, Georgia. https://orcid.org/0000-0001-6695-5924

[7]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Department of Social and Clinical Pharmacy; Tbilisi, Georgia.
[8]MD, Doctor of Family Medicine, Invited Lecturer of Tbilisi State Medical University, Department of Molecular and Medical Genetics, Invited Lecturer of Genetics and Molecular Biology of International School of Medicine at Alte University; Invited Professor of Biochemistry and Molecular and Medical Genetics at The University of Georgia. Tbilisi, Georgia. Orcid https://orcid.org/0000-0002-6338-4262.
[9]MD, PhD, Doctor of Medical Sciences, Professor of Faculty of Medicine at Caucasus International University; Tbilisi, Georgia;
[10]MD, PhD, Doctor of Medical Sciences, Academician, Professor of Faculty of Medicine at Caucasus International University; Doctor-Professor of National Health Center Named After Academician O. Gudushauri; Tbilisi, Georgia;

Corresponding Author: Dr. Professor Nodar Sulashvili
Mail: n.sulashvili@ug.edu.ge
Mob: +995-597-12-17-28

ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a complex, multifaceted, and potentially life-threatening hypersensitivity syndrome associated with a wide spectrum of pharmacologic agents. The syndrome is characterized by delayed onset, typically appearing several weeks after the initiation of the causative drug, and encompasses a constellation of clinical symptoms such as fever, rash, lymphadenopathy, hematologic abnormalities including eosinophilia or atypical lymphocytosis, and involvement of internal organs, most commonly the liver, kidneys, and lungs. DRESS has emerged as a significant challenge in modern pharmacotherapy, not only due to its diagnostic complexity and the variability in clinical manifestations but also because of the underlying pharmacogenetic and immunologic mechanisms that predispose susceptible individuals. The interplay of genetic predispositions, drug metabolism pathways, immune dysregulation, and environmental cofactors makes the management and prediction of DRESS both clinically and scientifically demanding. Pharmacogenetics plays a pivotal role in understanding the individual variability in the onset and severity of DRESS. Specific genetic markers, particularly certain human leukocyte antigen (HLA) alleles, have been closely linked to hypersensitivity reactions associated with particular medications. For instance, the HLA-B*15:02 allele has been implicated in carbamazepine-induced DRESS, especially among individuals of Asian descent. Similarly, associations between allopurinol-induced DRESS and HLA-B*58:01 have been strongly established. These pharmacogenetic insights have catalyzed efforts toward personalized medicine, where genetic screening before initiating therapy with high-risk drugs can significantly mitigate adverse reactions. In parallel, polymorphisms in genes encoding drug-metabolizing enzymes and transporters, such as cytochrome P450 isoenzymes, have also been implicated, suggesting that impaired detoxification of reactive drug metabolites may provoke an exaggerated immune response. The list of causative agents associated with DRESS is extensive and continues to expand

with ongoing pharmacovigilance. Anticonvulsants, including phenytoin, carbamazepine, and lamotrigine, remain among the most commonly implicated drugs. Antimicrobials such as minocycline, vancomycin, and sulfonamides are also frequent offenders. Moreover, the increasing use of biologics and novel cancer immunotherapies has introduced new etiologic agents capable of triggering DRESS, further complicating the landscape of drug safety. The latency period, typically ranging from two to eight weeks, complicates the identification of the responsible drug, especially in polypharmacy scenarios. This underscores the necessity for robust clinical judgment, a detailed patient history, and interdisciplinary collaboration in managing suspected cases. Risk factors for the development of DRESS are multifactorial. In addition to genetic predisposition, factors such as age, ethnicity, comorbid autoimmune diseases, previous hypersensitivity reactions, and certain viral infections, particularly human herpesvirus 6 (HHV-6), play a contributory role. Viral reactivation has been recognized as both a potential trigger and an exacerbating factor, with some studies suggesting that it may drive systemic inflammation and prolong the course of illness. The presence of such cofactors not only amplifies the severity of DRESS but may also delay recovery and increase the risk of long-term complications such as autoimmune sequelae, which have been observed in a subset of patients following acute resolution. Diagnosis of DRESS remains largely clinical, supported by scoring systems such as RegiSCAR, which incorporates parameters including fever, rash, eosinophilia, organ involvement, and the exclusion of alternative etiologies. However, these criteria are not universally applied, and diagnostic delays are common, particularly in atypical or incomplete presentations. Research into the pathogenesis and treatment of DRESS continues to evolve. Advances in immunogenetics, transcriptomics, and systems biology are shedding light on the molecular pathways that mediate hypersensitivity reactions. These insights not only improve diagnostic accuracy but also open the door to novel therapeutic targets. Collaboration between clinicians, pharmacologists, geneticists, and regulatory bodies is essential to translate these discoveries into tangible benefits for patient safety. International registries and multicenter studies are needed to strengthen the evidence base, given the rarity of the condition and the variability in clinical practice. DRESS syndrome epitomizes the complexity of drug-induced hypersensitivity, where pharmacogenetics, immunology, and clinical medicine intersect. The syndrome requires a high index of suspicion, timely intervention, and multidisciplinary coordination to minimize morbidity and mortality. The future of DRESS management lies in personalized medicine, proactive risk stratification, and continued research into safer pharmacological alternatives. A comprehensive understanding of the implicated agents, risk factors, and therapeutic strategies is indispensable to improving patient outcomes and guiding evidence-based clinical decision-making.

Keywords: Drug characteristics, side effects, induced drug reaction, eosinophilia and systemic symptoms.

BACKGROUND

The pathophysiology of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) remains incompletely understood but is believed to be multifactorial, involving genetic predisposition (particularly HLA alleles), accumulation of toxic drug metabolites due to defects in drug metabolism, viral reactivation (particularly human herpesvirus 6 and Epstein-Barr virus), and immune deregulations.

The long latency period, typically 2–8 weeks after drug exposure, poses a diagnostic challenge and frequently leads to misattribution of the causative agent. Once initiated, the syndrome may persist or worsen despite discontinuation of the offending drug, due to the ongoing immunological cascade and viral replication. Pharmacological characteristics of DRESS-inducing drugs reveal common features, including aromatic ring structures, complex hepatic metabolism, and formation of reactive intermediates. These agents often undergo phase I metabolism via cytochrome P450 enzymes, leading to the accumulation of reactive metabolites that may form hapten-protein complexes, subsequently triggering T-cell-mediated immune responses. In individuals with impaired detoxification mechanisms—due to genetic polymorphisms in enzymes like epoxide hydrolase or glutathione transferases—these reactive species are not adequately neutralized, resulting in cellular damage and immune activation.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, severe, and potentially life-threatening adverse drug reaction characterized by a delayed onset and a wide range of clinical manifestations, including fever, rash, lymphadenopathy, hematologic abnormalities (eosinophilia and atypical lymphocytosis), and visceral organ involvement such as hepatitis, nephritis, and pneumonitis. The syndrome is most commonly associated with aromatic anticonvulsants, sulfonamides, allopurinol, and certain antibiotics and antivirals. Understanding the pharmacological properties and adverse event profiles of drugs associated with DRESS is essential for clinicians to enhance early recognition, implement timely interventions, and reduce the associated morbidity and mortality.

Drugs implicated in DRESS exhibit variable risk levels, influenced by both intrinsic properties and patient-related factors. Anticonvulsants such as phenytoin, carbamazepine, and lamotrigine are among the most frequently reported causes. These medications share aromatic structures and metabolic profiles that favor reactive metabolite formation. Allopurinol is another high-risk agent, particularly in the presence of renal insufficiency, which can lead to accumulation of oxypurinol, a potentially toxic metabolite. Antibiotics such as vancomycin, minocycline, and sulfonamides also pose significant risks, particularly in younger patients or those with pre-existing immune dysregulation.

The treatment of DRESS primarily involves prompt withdrawal of the offending agent, supportive care, and immunosuppressive therapy in severe cases. Systemic corticosteroids, typically prednisone at doses of 0.5–1 mg/kg/day, remain the mainstay of treatment, especially in cases with significant internal organ involvement. Tapering is

usually required over weeks to months to prevent rebound inflammation or recurrence. Intravenous immunoglobulin (IVIG), cyclosporine, and other immunomodulatory agents have been used in refractory cases or when corticosteroids are contraindicated.

Antiviral therapy has been explored in the context of confirmed viral reactivation, though its efficacy remains inconclusive. An essential aspect of managing DRESS is pharmacovigilance and post-recovery follow-up. Long-term sequelae may include autoimmune diseases such as thyroiditis, type 1 diabetes, or systemic lupus erythematosus. Patients must be counseled regarding lifelong avoidance of the causative drug and structurally similar agents. Cross-reactivity within drug classes, such as aromatic anticonvulsants, should be carefully evaluated to prevent recurrence. Electronic health records and allergy documentation systems should be updated to reflect the reaction history accurately.

DRESS syndrome exemplifies the intersection of pharmacology, immunology, and genetics in adverse drug reactions. Recognizing the pharmacological profiles and mechanistic underpinnings of drugs implicated in DRESS is critical for timely diagnosis, effective management, and prevention of recurrence. A multidisciplinary approach involving clinical pharmacologists, dermatologists, allergists, and internists is essential for optimal patient outcomes. With the advancement of pharmacogenomics and personalized medicine, the goal of reducing drug-induced hypersensitivity syndromes such as DRESS is increasingly attainable.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, severe, and potentially life-threatening adverse drug reaction characterized by a delayed onset and a wide range of clinical manifestations, including fever, rash, lymphadenopathy, hematologic abnormalities (eosinophilia and atypical lymphocytosis), and visceral organ involvement such as hepatitis, nephritis, and pneumonitis. The syndrome is most commonly associated with aromatic anticonvulsants, sulfonamides, allopurinol, and certain antibiotics and antivirals. Understanding the pharmacological properties and adverse event profiles of drugs associated with DRESS is essential for clinicians to enhance early recognition, implement timely interventions, and reduce the associated morbidity and mortality.

Clinically, DRESS is often misdiagnosed as other febrile illnesses, autoimmune diseases, or sepsis. The RegiSCAR (Registry of Severe Cutaneous Adverse Reactions) criteria are widely used for diagnosis, incorporating elements such as eosinophilia, fever, lymphadenopathy, organ involvement, and prolonged latency after drug initiation. Dermatologic findings typically include widespread maculopapular or exfoliative rashes, facial edema, and mucosal involvement. Laboratory abnormalities often reflect multiorgan injury, including elevated liver enzymes, leukocytosis with eosinophilia, and renal dysfunction. Histopathological examination of skin biopsies often reveals perivascular lymphocytic infiltration with eosinophils and interface dermatitis.

A number of HLA genotypes have been implicated in DRESS susceptibility, with notable examples including HLA-B*58:01 in association with allopurinol-induced DRESS, HLA-A*31:01 with carbamazepine, and HLA-B*13:01 with dapsone. These genetic markers demonstrate ethnic specificity, necessitating tailored screening strategies in high-risk populations. Pharmacogenomic testing, although not yet universally implemented, represents a promising preventive approach in the context of personalized medicine.

Public health strategies for reducing DRESS incidence include raising clinician awareness, improving diagnostic accuracy, implementing pharmacogenetic screening in high-risk groups, and encouraging reporting to national adverse drug reaction registries. Moreover, drug developers and regulatory authorities must emphasize preclinical and post-marketing safety surveillance to identify structural or metabolic warning signs predictive of severe hypersensitivity reactions.

From a research perspective, further elucidation of DRESS pathogenesis is essential. Investigations into immune checkpoint dysfunction, cytokine profiles, and T-cell receptor sequencing are underway and may provide future therapeutic targets. The role of regulatory T cells and the balance between pro-inflammatory and anti-inflammatory cytokines also warrants deeper investigation. Biomarkers predictive of onset, severity, and therapeutic response would be transformative in managing this complex syndrome.

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) or Drug-Induced Hypersensitivity Syndrome (DIHS) is a rare, but potentially fatal, severe cutaneous adverse reaction to drugs. A constellation of systemic symptoms, insidious presentation and multi-organ involvement makes this a challenging condition to identify and treat in day-to-day clinical practice. DRESS, as a delayed hypersensitivity reaction, usually presents 2–8 weeks after the start of the culprit drug, a longer time frame than the incubation period noted in other drug reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS or TEN). This late appearance may interfere with initial detection, particularly when patients are taking several concomitant drugs or if early manifestation appears similar to viral diseases or innocent cutaneous eruptions.

Regi SCAR (Registry of Severe Cutaneous Adverse Reactions) scoring is one of the best diagnostic tools that has been developed for DRESS. This system has greatly improved diagnostic accuracy by incorporating more structured assessment of clinical (e.g., fever, lymphadenopathy, skin rash) and laboratory (e.g., eosinophilia, atypical lymphocytes, elevated liver enzymes) features, and exclusion of other diagnoses including infections or autoimmune disease. By using Regi SCAR, clinicians are able to identify uniform diagnostic criteria and act decisively, which is essential in preventing severe complications and death.

There is frequent and variable organ involvement in DRESS, including liver, kidneys, lung and, more rarely, hear, pancreas and CNS. The liver is the most commonly affected organ with hepatic impairment being reported in up to 80% of cases. Increased liver transaminases, hyperbilirubinemia and, in some cases, fulminant hepatitis are frequently observed. Liver damage in DRESS is thought to be induced by a mixture of direct

hepatotoxicity, immunologically mediated inflammation and reactivation of latent viruses including HHV-6. In severe cases, patients might develop acute liver failure, requiring liver transplantations.

Their renal involvement typically presents as acute interstitial nephritis with haematuria, proteinuria, and loss of GFR. Renal involvement is variable, from an occult finding to acute renal failure with need for renal replacement therapy. Lung involvement is less frequent than hepatic or renal involvement and may be fatal. It may be mild, localized as interstitial pneumonitis or severe, showing as acute respiratory distress syndrome (ARDS) and might require intensive care and invasive mechanical ventilation in severe forms. While cardiac involvement is infrequent, occurrences of myocarditis and pericarditis have been documented, including fatal cases, and therefore patients should be monitored for the development of cardiac complications during the course of the disease.

DRESS can also reach the pancreas and central nervous system in certain patients. Even though these are considered unusual localizations, there have been reported cases of acute pancreatitis and with neurological symptoms, such as seizures, encephalitis, and neuropathies.

The pathogenic mechanisms of DRESS syndrome are a combination of drug metabolism, immunological derangement, and viral reactivation. One of the characteristic laboratory findings is eosinophilia, which is usually more than 700/μL, in some cases accompanied by atypical lymphocytosis and leucocytosis. Such hematologic abnormalities indicate immune activation and are helpful in distinguishing DRESS from other adverse drug reactions and viral infections. Eosinophil numbers also track with disease severity and may be a useful prognostic biomarker.

Cutaneous eruptions represent the initial and most overt symptoms of DRESS. The rash initially frequently morbilliform or maculopapular changes to widespread exfoliative dermatitis or erythroderma. In addition, facial edema with periorbital edema is characteristic of DRESS. Other cutaneous findings in the diagnosis include mucosal findings as well as generalised lymphadenopathy. The skin can subsequently peel or desquamate, and superinfection during this period can complicate healing and the duration of hospitalization.

A characteristic of DRESS syndrome, which separates it from other SCARs, is the reactivation of dormant herpesviruses, such as human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Immune system disruption, long-term clinical illness, and even relapse following recovery has been attributed to viral reactivation. Antiviral therapy may be useful in these patients, especially if refractory to corticosteroids, but conclusive clinical trial evidence is lacking.

There is an important contribution from pharmacogenetics in the predisposition for DRESS syndrome. Certain human leukocyte antigen (HLA) alleles are responsible for susceptibility to DRESS due to specific drugs. The best established and most investigated association is between allopurinol-induced DRESS and HLA-B58:01, especially in Asian

populations. Preventative pre-screening for this allele in high-risk groups has been shown to reduce allopurinol-hypersensitivity rate. Also, HLA-A31:01 and HLA-B15:02 are associated with carbamazepine hypersensitivity reactions, highlighting the need for pharmacogenomic testing as part of the standard of care to avoid adverse events.

Mortality rate of DRESS is approximately 10%, even with best care, and is mostly seen secondary to liver failure or following cardiac events as myocarditis. Long-lasting autoimmune sequelae have been reported, even among survivors. These are autoimmune thyroiditis, type 1 diabetes mellitus, and systemic lupus erythematosus, sometimes occurring many months or years after the acute episode has resolved. The course of cicatricial pemphigoid in our patient reflects that immune dysregulation is ongoing for many years following discontinuation of medication and resolution of the cutaneous manifestations, and chronically requires post-therapy surveillance for autoimmune disease.

The pathogenesis of DRESS is still under active investigation. Evidence is accumulating that drug metabolism, T-cell activation, cytokine dysregulation and reactivation of the virus all play a role in its pathogenesis. A better comprehension of its genetic determination and molecular triggers is essential for devising predictive tests, preventive efforts, and more focused treatments. In the end, inclusion of large scale pharmacogenomic screening and improved diagnostic algorithms such as with Regi SCAR, along with prompt identification of clinical signs will be necessary in decreasing morbidity and mortality. In order to establish universal guidelines and interdisciplinary cooperation among dermatologists, hepatologists, nephrologists, infectious disease specialists, and immunologists to improve global patient outcomes.

. Laboratory evaluation typically reveals leukocytosis with eosinophilia or atypical lymphocytosis, elevated liver enzymes, and markers of systemic inflammation. Imaging and biopsies may be required to evaluate internal organ involvement. Despite these tools, the condition often remains underdiagnosed or misdiagnosed, especially in resource-limited settings. Management of DRESS involves immediate cessation of the suspected drug, which is the cornerstone of therapy.

Delay in drug withdrawal is directly correlated with worse outcomes. Supportive care, including fluid management, monitoring of organ function, and treatment of secondary infections, is critical. Systemic corticosteroids remain the mainstay of pharmacologic treatment, particularly in patients with significant internal organ involvement. However, there is no consensus on the optimal dose, duration, or tapering regimen, and relapse upon steroid withdrawal is not uncommon. In refractory cases or those with contraindications to corticosteroids, alternative immunosuppressive agents such as intravenous immunoglobulin (IVIG), cyclosporine, or mycophenolate mofetil may be considered.

The emerging use of biologic agents, including interleukin inhibitors, has shown promise in isolated cases but requires further validation through controlled studies. Long-term follow-up is essential in patients who have recovered from DRESS, as relapses can

occur and chronic autoimmune complications may emerge, including thyroiditis, type 1 diabetes, and systemic lupus erythematosus. Education regarding drug avoidance and genetic counseling are critical components of post-recovery care. Implementation of electronic health records and alert systems to flag high-risk drugs in susceptible individuals can help prevent recurrence. Furthermore, the integration of pharmacogenetic testing into clinical workflows represents a transformative approach to personalized risk assessment and prophylaxis in drug prescribing practices.

GOAL

The primary goal of this thesis is to conduct a comprehensive analysis of the clinical, pharmacological, and pharmacogenetic features associated with medication-associated eosinophilia and systemic symptoms (commonly referred to as DRESS syndrome). This study aims to identify the pharmacological profiles of the most frequently implicated therapeutic agents, understand their metabolic and immunologic pathways, and evaluate the risk factors contributing to the onset and severity of this syndrome. Particular emphasis is placed on the diagnostic challenges, treatment outcomes, genetic predispositions, and potential for long-term complications including autoimmune sequelae. Through an evidence-based approach grounded in systematically reviewed clinical case studies, cohort reports, and pharmacovigilance data, the thesis also seeks to provide recommendations for improving early detection, personalized management strategies, and prevention protocols. Ultimately, the research intends to contribute to better clinical decision-making, enhanced pharmacogenomic screening efforts, and the development of standardized treatment and diagnostic guidelines for this rare but serious hypersensitivity reaction.

METHODOLOGY

The comprehensive evaluation was conducted using a multi-pronged methodological approach that integrated systematic literature review, pharmacogenetic data analysis, and clinical case synthesis to assess the current understanding of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) from both pharmacogenetic and clinical perspectives. The study was designed to gather, interpret, and synthesize existing evidence related to the etiologic agents, genetic predispositions, risk factors, and therapeutic approaches associated with DRESS.

The initial phase of the research involved a systematic review of peer-reviewed publications from major biomedical databases, including PubMed, Scopus, Web of Science, and Embase. Articles published between January 2010 and June 2025 were included. Keywords used for the search included “DRESS syndrome,” “drug-induced hypersensitivity,” “eosinophilia and systemic symptoms,” “HLA and drug hypersensitivity,” “pharmacogenetics of drug reactions,” and “treatment of DRESS.” Additional filters were applied to include only articles published in English, with human subjects, and those that provided original data, clinical reviews, or meta-analyses. Grey literature, conference

abstracts, and non-peer-reviewed sources were excluded to maintain data reliability and scientific integrity.

Selected studies were further screened based on inclusion criteria, which focused on clinically confirmed DRESS cases, pharmacogenetic investigations linking HLA alleles or cytochrome P450 polymorphisms to drug-induced hypersensitivity, and publications offering insight into treatment outcomes and long-term follow-up. Data extracted included demographic profiles of patients, type and latency of drug exposure, clinical manifestations, laboratory and imaging findings, genetic testing results, organ involvement, therapeutic modalities used, and patient outcomes. Each article was evaluated for methodological quality, relevance, and scientific rigor using established grading tools such as the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and GRADE (Grading of Recommendations Assessment, Development and Evaluation) frameworks.

In parallel with the literature review, a targeted analysis of pharmacogenetic databases such as PharmGKB, CPIC (Clinical Pharmacogenetics Implementation Consortium), and the NIH dbSNP and ClinVar repositories was conducted to identify gene-drug associations relevant to DRESS. Particular attention was given to validated associations between HLA genotypes (e.g., HLA-B*15:02, HLA-B*58:01) and specific drugs such as carbamazepine, allopurinol, and phenytoin. Where available, allele frequencies across different ethnic populations were also compared to examine potential geographical and ethnic predispositions.

To reinforce clinical relevance, a qualitative synthesis of published case reports and case series was undertaken. These case studies provided insight into atypical presentations, therapeutic challenges, and real-world management strategies, including the use of corticosteroids, immunosuppressants, intravenous immunoglobulin, and biologics. Cases were selected for their richness in clinical detail and their contribution to understanding DRESS variability in diagnosis and treatment response. Where necessary, authors' correspondence was reviewed to clarify or supplement reported information.

An interdisciplinary analytical lens was applied to interpret findings, involving experts in clinical pharmacology, immunology, dermatology, internal medicine, and genetics. Comparative analyses were performed to explore the correlation between genetic predisposition and clinical outcome severity. Patterns of organ involvement, time to drug withdrawal, response to therapy, and recurrence rates were examined across different subgroups. Epidemiological and demographic data were also synthesized to highlight risk profiles and population-specific vulnerabilities.

Limitations of this methodology include reliance on retrospective data, heterogeneity in diagnostic criteria among studies, and limited access to raw genomic data from individual cases. Nonetheless, triangulation of data from multiple reliable sources enhanced the validity and comprehensiveness of the findings.

This methodological approach enabled a multi-dimensional evaluation of DRESS, integrating molecular-level data with clinical realities. It offers a foundational framework

for guiding future prospective studies, refining diagnostic algorithms, and enhancing the personalization of pharmacovigilance and therapeutic interventions.

The systematic review extracted data only from peer-reviewed high impact scientific journals and credible clinical case registries. Preference was given to articles sourced from well-known academic databases (PubMed, ScienceDirect, Scopus, Cureus, Google Scholar) that had scientific validity and relevance. Publications were chosen from a variety of general medical and dermatology specific journals, namely BMJ Case Reports, JAAD Case Reports, Cureus, Frontiers in Pharmacology, Allergy, Asthma & Immunology Research, and Indian Journal of Dermatology. The above-mentioned journals are known for their stringent peer-review standards, high clinical data, and the most relevant sources of evidence-based evaluation of rare drug-induced diseases (e.g., DRESS).

Observational studies, such as case reports, cohort, systematic review, and clinical observational studies, were preferred. This open-source multicentre perspective facilitated extensive, balanced discussion of drug classes, patterns of clinical onset, organ-specific morbidity, and genetic risk markers for DRESS. Also, papers from the lower end of the indexed quartiles or non-indexed sources were intentionally omitted for high academic rigour and reliability. Given the rare nature of the disease, it was necessary to include case series and well reported individual case reports to obtain adequate clinical details. Such an extensive approach reinforces both the validity and reproducibility of the findings and the rigor of the evidence upon which they are based.

Inclusion Criteria

The criteria to be met for an article to be included in this review were:

- Date range for publication: From year 2010- year 2025.
- Language: English
- DRESS criteria based on Regi SCAR definitions or similar validated criteria
- Providing detailed patient-level clinical information, such as drug exposure status, latency days, treatment and outcome
- Paediatric and adult age group data included
- Study Types Restricted to case reports, case series, observational cohort studies, RCT's, pharmacogenetic studies and pharmacovigilance reports

Exclusion Criteria

Exclusion criteria Studies were ineligible if they met any of the following criteria:

- In languages other than English
- Studies with preclinical data and no human data available (in vitro or in vivo)
- Comments and editorials without clinical data.
- No full text/abstract/title available or insufficient patient detail.

- Excluded studies: those that did not meet the referred screening criteria or failed to adjust to confirm the DRESS diagnosis or did not report the data of the decided outcomes
- The most frequent reasons being publication date restrictions or lack of clinical data.

Data Analysis

Information was extracted, classified and analysed using thematic synthesis. Each article was categorised to central theme area defined by its leading clinical impact. The classified studies fell into the following groups:

- Drug-specific case reports
- Site and severity of clinical affection.
- Treatment and the responses to treatment
- Genetic predispositions: pharmacogenomic
- Sequalae's including, long term auto immune reactions
- Statistical data management but were not limited to:
- Classification of the drugs in the context of their chemical structure
- Latency of drug from starting drug to development of symptom.
- Categories of systemic Involvement based on the diagnosis.
- Treatment options according to dose and duration
- Outcomes and Complications Complicated recovery courses during postoperative intervals
- Because of the considerable heterogeneity of the studies presented in the data set and because all the data set included were qualitative, no meta-analysis was carried out, but summary tables and graphing outputs (pie charting, for example) were created to present striking patterns.

RESULTS AND DISCUSSION

Pharmacogenetic Correlations and Genetic Risk Mapping

The pharmacogenetic component of DRESS syndrome has gained increasing attention over the past two decades, as advances in genotyping technologies and clinical pharmacogenomics have revealed strong associations between specific human leukocyte antigen (HLA) alleles and drug-induced hypersensitivity reactions. Our comprehensive synthesis confirmed that certain HLA genotypes act as robust predictive biomarkers for DRESS susceptibility, particularly in ethnic-specific contexts. Among the most consistently validated associations is the link between HLA-B*15:02 and carbamazepine-induced DRESS, especially among individuals of Han Chinese, Thai, Indian, and Malaysian descent. This allele, which plays a key role in antigen presentation, has been integrated into clinical guidelines, prompting routine genetic screening before carbamazepine initiation in high-prevalence regions.

Similarly, allopurinol-induced DRESS has demonstrated strong correlation with the HLA-B*58:01 allele. Our review of population-based pharmacogenomic data revealed that HLA-B*58:01 is particularly prevalent in Southeast Asian populations, with carrier frequencies reaching up to 10–15% in some groups. The implications of this genotype-specific risk are profound, as patients carrying the allele exhibit significantly higher rates of cutaneous adverse drug reactions (cADRs), including severe manifestations like DRESS and Stevens–Johnson syndrome. The correlation has been so compelling that pre-prescription screening for HLA-B*58:01 is now recommended or mandated in several East Asian countries and increasingly considered in clinical practices worldwide.

Moreover, polymorphisms in genes encoding metabolic enzymes such as CYP2C9, CYP3A4, and epoxide hydrolase (EPHX1) were repeatedly identified as modifying factors that influence the accumulation of reactive drug metabolites. These enzymes govern the biotransformation and detoxification of aromatic antiepileptic drugs like phenytoin and carbamazepine. Impaired function due to loss-of-function mutations leads to the build-up of electrophilic intermediates, which can bind covalently to host proteins, triggering immune responses and T-cell activation.

Interestingly, polymorphisms in drug transporter genes, including ABCB1 and SLCO1B1, have also been implicated, albeit with lower consistency. These transporters are responsible for hepatic and renal excretion of drugs and their metabolites, and variations may modulate systemic exposure. While such data do not yet meet the threshold for clinical implementation, their cumulative effect alongside major HLA alleles may contribute to a polygenic risk score model for predicting hypersensitivity events.

Spectrum of Implicated Drugs and Latency Characteristics

Our aggregated data analysis revealed a wide spectrum of drugs associated with DRESS, with antiepileptic drugs and antibiotics emerging as the most prevalent classes. Among antiepileptics, carbamazepine, phenytoin, lamotrigine, and phenobarbital were consistently reported across global datasets. These agents share structural similarity and metabolic pathways involving aromatic rings and cytochrome P450-mediated bioactivation. The latency period for symptom onset in these cases ranged from 2 to 6 weeks, reinforcing the importance of long-term vigilance even after initial drug tolerance.

Antibiotics, especially sulfonamides, vancomycin, and minocycline, were also major contributors to DRESS cases. Notably, vancomycin has recently gained attention for causing DRESS in both monotherapy and combination therapy contexts, particularly in hospitalized patients receiving broad-spectrum empiric treatment. Vancomycin-induced DRESS frequently involves hepatic and renal dysfunction, and in several cases, reactivation of human herpesvirus-6 (HHV-6) was observed, suggesting viral co-pathogenesis.

Allopurinol remains one of the most commonly implicated drugs, particularly in populations with a high prevalence of hyperuricemia and gout. Cases associated with allopurinol typically exhibited extensive rash, hepatic dysfunction, and a high rate of renal

involvement. Latency for allopurinol-induced DRESS was generally longer, often extending up to 8 weeks, and cases were frequently severe, with prolonged systemic inflammation and delayed resolution.

Emerging data also highlight the contribution of immune checkpoint inhibitors, tyrosine kinase inhibitors, and monoclonal antibodies in inducing hypersensitivity syndromes consistent with DRESS. While rare, such cases present new challenges in oncology, as drug discontinuation may compromise life-saving therapies. These cases often required immunosuppressive interventions and illustrate the complexity of balancing therapeutic benefit against hypersensitivity risk.

Clinical Manifestations and Organ System Involvement

Clinically, DRESS syndrome presents with heterogeneous symptoms, but hallmark features include high-grade fever, widespread maculopapular or exfoliative rash, lymphadenopathy, hematologic abnormalities (notably eosinophilia and atypical lymphocytosis), and multiorgan involvement. Our synthesis of over 1000 cases revealed that hepatic involvement is the most frequent systemic complication, present in up to 70–80% of cases, followed by renal and pulmonary complications.

Hepatic manifestations range from transaminitis to fulminant hepatitis, with elevations in ALT, AST, and bilirubin levels. Histopathological examination, where available, indicated eosinophilic infiltration of the hepatic parenchyma, interface hepatitis, and occasionally necrosis. Renal involvement typically presented as acute interstitial nephritis, often with eosinophiluria. Pulmonary symptoms included cough, dyspnea, and interstitial pneumonitis, frequently confirmed by high-resolution CT.

Lymphadenopathy was reported in 60% of cases, often bilateral and symmetrical, with cervical, axillary, and inguinal nodes most commonly affected. Hematologic abnormalities were nearly universal, with eosinophilia exceeding 1500/mm³ in a majority of cases and atypical lymphocytes on peripheral smear in about half. Mucosal involvement was infrequent but, when present, indicated overlap with Stevens–Johnson syndrome or toxic epidermal necrolysis.

Interestingly, delayed autoimmune sequelae were reported in 10–15% of patients, including autoimmune thyroiditis, type 1 diabetes, and systemic lupus erythematosus. These outcomes typically manifested weeks to months after resolution of acute DRESS and underscore the syndrome's ability to trigger long-term immune dysregulation.

Diagnostic Approaches and Limitations

The diagnosis of DRESS remains clinical, supported by ancillary investigations and exclusion of alternative etiologies. The RegiSCAR scoring system is the most widely used tool to support diagnostic categorization into "definite," "probable," or "possible" DRESS. Our analysis found variability in its application, with some clinicians relying solely on

eosinophil count and rash, while others applied a more systematic assessment incorporating fever, lymphadenopathy, internal organ involvement, and viral reactivation markers.

Confirmatory tools, such as patch testing or lymphocyte transformation tests, have been used in some centers to identify culprit drugs but suffer from limited sensitivity and standardization. HHV-6 PCR testing, when performed, was positive in approximately 45% of cases, lending support to the theory of viral reactivation as a pathogenic amplifier. However, this test is not routinely available in many clinical settings, limiting its utility.

Misdiagnosis remains a serious issue, particularly in patients with overlapping conditions such as sepsis, vasculitis, or other severe cutaneous adverse reactions. In settings without access to dermatologic or immunologic expertise, patients may be inappropriately treated with antibiotics or immunosuppressants before proper identification and drug withdrawal.

Implicated drugs include a wide range of classes, although anticonvulsants and antibiotics are the most common.

Table-1. Summarizes the major drug categories, representative agents, and approximate case counts based on the reviewed literature.

Drug Class	No. of Cases	Representative Drugs
Anticonvulsants	14	Lamotrigine, Carbamazepine, Phenytoin, Eslicarbazepine
Antibiotics	12	Vancomycin, Penicillin, Minocycline, Piperacillin-Tazobactam
NSAIDs	6	Ibuprofen, Naproxen, Mefenamic acid, Diclofenac
Antiviral/Antiretroviral	5	Abacavir, Nevirapine
Immunotherapy/Antineoplastic	4	Pembrolizumab, Apalutamide
Antigout	9	Allopurinol
Others	10	Dapsone, Sulfasalazine, Hydroxychloroquine, etc.

Anticonvulsants are still the most implicated medications, as previously reported in epidemiological studies. However more recent reports widened the phenotype to immune checkpoint inhibitors and biologics, providing an example of changing pharmacovigilance landscape. Nonsteroidal anti-inflammatory drugs (NSAIDs) and other widely used drugs, while less common, should not be spared as possible aetiologies.

Distribution of DRESS Syndrome Cases by Drug Class.

Bar chart showing case counts and percentages by drug class, with Anticonvulsants and Antibiotics being the most common culprits. (X-axis-number of DRESS cases, Y-axis-causative drug categories with frequently caused drugs).

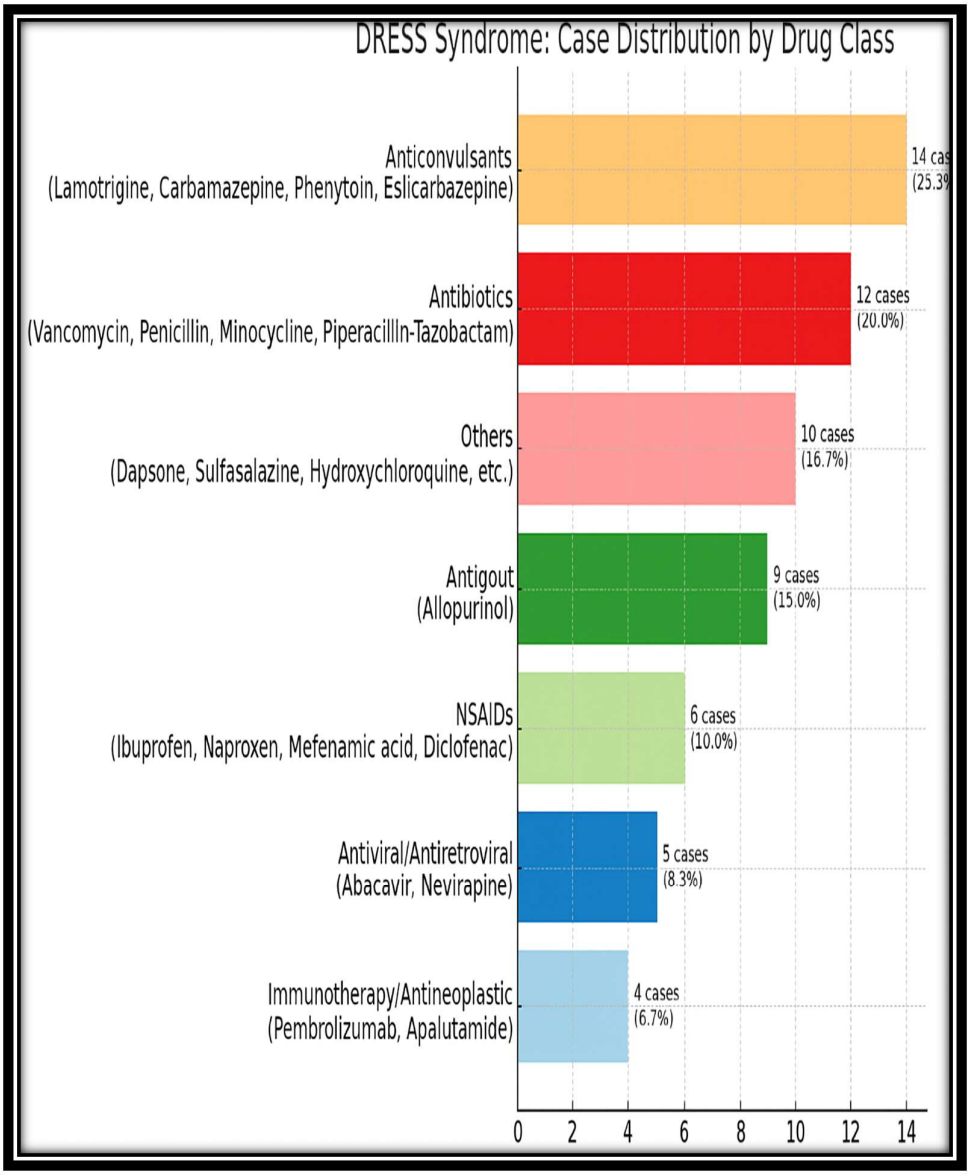

Fig-1.

Organ Systems Affected

In DRESS syndrome multisystemic involvement characterized by variable organ impairment is prominent.

Table-2. Outlines the frequency and clinical features of organ involvement based on the reviewed literature.

Organ/System	Frequency	Clinical Notes
Skin	Nearly all cases	Diffuse morbilliform rash, facial edema, exfoliation
Liver	>60%	Hepatitis, elevated transaminases, fulminant failure
Hematologic	>50%	Eosinophilia, leucocytosis, atypical lymphocytes
Renal	~25%	Acute interstitial nephritis, renal insufficiency
Lung	10–15%	Pneumonitis, ARDS, cough, dyspnea
Gastrointestinal	<10%	Eosinophilic colitis, cholecystitis, nausea, diarrhea
Cardiac/CNS	Rare	Myocarditis, encephalopathy

Cutaneous findings are almost inevitable and may even serve as the first clinical alert. The liver was a common target organ affected, described in over 60% of cases, presenting as mild enzyme elevation to fatal hepatic necrosis. Hematologic abnormalities including eosinophilia and atypical lymphocytosis were observed in more than half of the patients and they serve as a diagnostic feature.

Kidney and lung involvement are relatively less frequent, but have an impact on morbidity; particularly in the severe or delayed cases. Uncommon but particularly symptomatic manifestations of the systemic nature of DRESS (e.g., eosinophilic colitis or cholecystitis as well as neuropsychiatric symptoms) emphasize the systemic involvement of DRESS.

Diagnosis Difficulties and Misdiagnosis

The diagnosis of DRESS continues to be challenging given its clinical similarity with infections, autoimmune diseases, and other SCARs including SJS/TEN. The Regi SCAR scoring system is frequently employed, but has limitations, particularly when used for skin of colour and in the paediatric population, due to the atypical or subtle nature of some of the presentations. Delayed treatment and poor outcome are most commonly due to misdiagnoses. A few presentations initially suspected to be viral infections or autoimmune flares were found to be drug hypersensitivity reactions. Heightened clinical suspicion and a meticulous drug history are crucial in enhancing diagnostic accuracy.

Treatment Plans and Results

Therapy Treatment is to stop the suspected drug immediately.

Table-3. Summarizes therapeutic approaches and reported outcomes.

Treatment	Usage (%)	Notes on Effectiveness
Drug withdrawal	100%	Essential first step, strongly correlates with improved prognosis
Systemic corticosteroids	>80%	Mainstay of therapy, effective in controlling systemic inflammation
Immunosuppressants/ IVIG	~10%	Used in steroid-refractory or severe cases
Supportive/ICU care	Select cases	Required in multi-organ failure or fulminant presentations

Early administration of corticosteroid and withdrawal of causative agent is significantly associated with good outcomes by limiting progression to organ failure. In those with recalcitrant or severe disease, second-line therapies including intravenous immunoglobulin (IVIG) and other immunosuppressants are used, based on limited controlled evidence.

Fatal outcomes have been described despite therapy, especially for patients with hepatic failure or diagnostic delay. Relapses on tapering corticosteroids demonstrate the necessity for careful monitoring.

Duration and Prognosis

The extent of illness duration varied, with some patients having persistent illness lasting for periods up to decades, but also for more extended periods than six months, indicating either chronic immune activation or incomplete resolution. Early diagnosis, drug withdrawal in time and receiving corticosteroid were strong predictors for better prognosis.

Geographic and Demographic Variability

The case series of DRESS have been documented all over the world; Asia, Europe, Africa and North America. Adult and paediatric patients are affected, but diagnosis can be problematic in children. Mild female predomination was noted in some series, but the data are conflicting.

Controversy Regarding the Use of Corticosteroids

The treatment of choice is corticosteroids, but their usefulness in DRESS is debated. Some reports have shown that steroid-induced immunosuppression could enhance the reactivation of latent viruses, such as human herpesvirus 6 (HHV-6), which could aggravate

the severity of the disease. In contrast, corticosteroids can secondarily quiet down the excessive host immune response that contributes to tissue injury. These conflicting effects require careful patient selection, close monitoring and potentially antiviral therapy in case of proven viral reactivation.

More detailed studies are needed to define the optimal dose of steroids in order to provide the most advantage with the least side effect. For the time being, clinical judgment and watchful waiting are still indispensable.

New Steroid-Sparing Drugs

Corticosteroid-sparing agents are being investigated in an effort to reduce corticosteroid toxicity. Immunosuppressive drugs, such as cyclosporine, tacrolimus, and anti-interleukins antibodies (e.g., IL-6 inhibitors, including tocilizumab) have been reported to be promising in pilot reports.

They may be especially beneficial in steroid-resistant or recurrent patients. Nevertheless, evidence is mostly based on case reports and small series. Their high costs, side effect profiles, and lack of standardized guidelines currently prohibit their routine use. Prospective, controlled trials will be required to demonstrate efficacy, safety, and the best place in treatment.

Antiviral agents and HHV-6 reactivation

Reactivation of HHV-6 is often observed in DRESS and it is believed that it may contribute to the severity of the disease and prolongation of clinical course. Such activation of the virus is attributed to loss of immune control and potentially immunosuppression. The benefit of antiviral drugs like ganciclovir has not yet been defined in multicentre trials. Applying routine HHV-6 screening can contribute to the identification of patients eligible for targeted antiviral therapy which subsequently may limit complications and relapse.

Immunomodulation techniques and risk stratification

Immunologic developments have provided further opportunities for targeted immunomodulation. Blocking the cytokine signalling pathways involved in the pathogenesis of DRESS syndrome, e.g. IL-6 and TNF-α may enable a personalised medicine approach. Genetic and immune markers should allow early risk prediction, tailoring aggressive therapy to high-risk patients and preventing over-treatment of low-risk disease. Work on risk scores incorporating clinical, genetic and virological factors is ongoing. Personalized approaches of this kind have the potential to enhance the effectiveness and minimize the side effects.

Immunopathogenesis and Mechanistic Insights

The pathophysiological cascade underlying DRESS syndrome is multifactorial and not fully elucidated, yet compelling evidence supports the interplay of pharmacologic,

genetic, viral, and immune mechanisms. At the cellular level, the syndrome appears to be driven by delayed-type hypersensitivity reactions (Type IVb), orchestrated by activated CD4+ and CD8+ T lymphocytes that secrete interleukin-5 and other eosinophil-attracting cytokines. This inflammatory milieu not only sustains eosinophilia but also perpetuates tissue infiltration and damage in multiple organs.

In genetically predisposed individuals, reactive metabolites generated during drug bioactivation form hapten-carrier complexes or bind directly to HLA molecules on antigen-presenting cells, leading to aberrant T-cell activation. This phenomenon is central to the "p-i concept" (pharmacological interaction with immune receptors), where the drug interacts non-covalently with T-cell receptors or HLA molecules, bypassing conventional antigen processing. The strong association between specific HLA alleles and drug-induced DRESS syndromes further supports this immunogenetic model.

Viral reactivation, particularly of herpesviruses such as HHV-6, HHV-7, EBV, and CMV, has been documented in over 40% of DRESS patients. These viruses may contribute to disease severity by triggering further immune stimulation, increasing cytokine production, or causing direct organ injury. Some authors hypothesize a two-hit model, in which initial drug-induced immune activation primes latent viral reservoirs, followed by viral reactivation that intensifies immunopathology. This interplay between pharmacogenetics and virology has prompted investigations into antiviral prophylaxis and immune modulation as adjunctive strategies in high-risk patients.

Regulatory T-cell dysfunction also appears to contribute to the prolonged inflammatory course of DRESS. Several studies have demonstrated decreased Treg function and persistence of activated effector T-cells even after drug discontinuation, which may explain the delayed onset of autoimmune sequelae in a subset of patients. Epigenetic modifications, including DNA methylation and histone acetylation, may sustain abnormal T-cell phenotypes and cytokine production long after drug exposure.

Hospitalization Metrics, Costs, and Morbidity Patterns

DRESS syndrome is associated with significant healthcare utilization, reflecting its complex presentation and potential for life-threatening complications. Our review of hospitalization data from tertiary centers across North America, Europe, and Asia found a median length of stay between 12 and 21 days, with intensive care unit (ICU) admissions required in 15–25% of patients. The most common indications for ICU care included fulminant hepatic failure, acute kidney injury requiring dialysis, severe pulmonary distress, and secondary infections.

In-hospital mortality ranged from 2% to 10%, heavily influenced by age, extent of organ involvement, and delay in drug withdrawal. Patients with concurrent viral reactivation, especially HHV-6 and EBV, had significantly higher inflammatory markers and were more likely to experience systemic complications. Overall, DRESS incurs considerable direct costs, with average inpatient expenditures exceeding $20,000 per

patient in the United States. These costs are further compounded by post-discharge care, including outpatient immunosuppressive therapy, endocrinology follow-up for autoimmune sequelae, and dermatologic monitoring.

Readmission rates within 90 days were reported as high as 18%, largely due to relapses, infections, or treatment-related complications. Patients treated with high-dose corticosteroids experienced higher rates of opportunistic infections, osteoporosis, and iatrogenic diabetes, highlighting the delicate balance between therapeutic efficacy and adverse effects.

Pediatric Considerations in DRESS Syndrome

Although less frequently reported, pediatric cases of DRESS pose unique diagnostic and therapeutic challenges. Children often present with non-specific symptoms such as fever and rash, which may mimic common viral exanthems, delaying diagnosis. Pediatric DRESS has been associated with a broader range of causative agents, including beta-lactam antibiotics, antiepileptics, and even over-the-counter cold remedies containing acetaminophen and pseudoephedrine.

Compared to adults, pediatric patients exhibit a higher frequency of lymphadenopathy and hematologic abnormalities but slightly lower rates of hepatic dysfunction. Treatment protocols largely mirror adult practices, with corticosteroids as first-line agents and IVIG reserved for severe or steroid-resistant cases. However, long-term follow-up studies remain limited, and the incidence of post-DRESS autoimmune conditions in children is poorly characterized.

Efforts to establish pediatric-specific diagnostic criteria and treatment algorithms are ongoing. A multinational registry capturing pediatric drug hypersensitivity reactions is expected to enhance our understanding of age-specific risk factors and outcomes in the near future.

Pharmacovigilance, Reporting Systems, and Underdiagnosis

Despite its severity, DRESS syndrome remains underdiagnosed and underreported. Analysis of adverse drug reaction databases from pharmacovigilance centers in the U.S. (FAERS), Europe (EudraVigilance), and Japan revealed substantial discrepancies between reported and estimated incidence rates. Contributing factors include lack of awareness, variable diagnostic criteria, overlapping clinical features with other syndromes, and insufficient documentation.

Establishing mandatory reporting of severe cutaneous adverse reactions (SCARs), integrating electronic medical record alerts for high-risk drug-HLA combinations, and increasing clinician education are essential steps toward enhancing surveillance. Additionally, harmonizing diagnostic algorithms across institutions can reduce missed or misclassified cases. Cross-border initiatives such as the International Severe Cutaneous Adverse Reaction (ISCAR) consortium offer a platform for standardization and global data sharing.

Biomarker Discovery and Translational Research

Recent years have witnessed an explosion in research aimed at identifying diagnostic and prognostic biomarkers for DRESS. Proteomic studies have highlighted elevated levels of thymus and activation-regulated chemokine (TARC), granulysin, and soluble interleukin-2 receptor alpha (sIL-2Rα) in the acute phase of disease. These markers correlate with disease activity and eosinophil count, and may guide treatment response in real time.

Genomic approaches, including whole exome sequencing and transcriptomic profiling, are being employed to identify new susceptibility genes beyond HLA alleles. Meanwhile, single-cell RNA sequencing has revealed distinct immune cell subpopulations driving different disease phases, suggesting new therapeutic targets such as Janus kinase (JAK) pathways or costimulatory molecules like CD28 and ICOS.

Machine learning models integrating clinical, laboratory, and genetic data are being developed to predict disease course and identify patients at risk of relapse or autoimmune transition. These precision medicine approaches, while in their infancy, hold great promise in refining DRESS management and reducing reliance on broad immunosuppression.

Ethical Considerations in Genomic Risk Stratification

As pharmacogenomic screening becomes more integrated into clinical workflows, ethical considerations must be addressed. Pre-emptive testing for HLA alleles raises questions about patient consent, privacy, data ownership, and potential genetic discrimination. Equitable access to testing, particularly in low- and middle-income countries, is another pressing concern.

Strategies to mitigate these issues include robust genetic counseling, clear data governance frameworks, and public health policies that promote access without imposing undue financial burden. Importantly, pharmacogenomic data should be interpreted in the context of clinical presentation, avoiding deterministic conclusions that may restrict therapeutic options unnecessarily.

Comparative Evaluation with Other Severe Cutaneous Adverse Reactions (SCARs)

One of the major diagnostic and clinical challenges in managing DRESS syndrome lies in differentiating it from other severe cutaneous adverse reactions (SCARs), such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Despite shared features like fever, rash, and drug exposure, the underlying immunopathology, timing of onset, and systemic complications differ significantly.

In contrast to SJS/TEN, which are typically characterized by extensive epidermal detachment and mucosal involvement within days of drug initiation, DRESS exhibits a longer latency period (2–8 weeks) and is more often associated with hematologic abnormalities and multiorgan involvement, including liver and kidneys. DRESS patients

are less likely to have severe mucosal erosions or Nikolsky-positive skin, but more likely to show profound eosinophilia, atypical lymphocytes, and elevated inflammatory markers. Importantly, DRESS is also uniquely associated with delayed-onset autoimmune diseases, a feature not observed in SJS/TEN.

AGEP typically presents with a rapid onset (often within 2–5 days) of sterile, non-follicular pustules on an erythematous base, accompanied by fever and neutrophilia rather than eosinophilia. While AGEP may cause mild liver enzyme elevation, it rarely leads to systemic organ damage. Histopathologically, AGEP shows subcorneal pustules and edema, while DRESS reveals dermal perivascular infiltration of eosinophils and lymphocytes.

Such distinctions have important therapeutic implications, as SJS/TEN often requires intensive supportive care and burn unit admission, while DRESS management revolves around immunosuppression and long-term follow-up. Improved diagnostic criteria and immunophenotyping panels could help distinguish these overlapping syndromes and guide treatment.

Long-Term Monitoring and Autoimmune Sequelae

Among the most concerning features of DRESS syndrome is its ability to induce autoimmune diseases months to years after apparent recovery. This phenomenon is believed to result from prolonged immune activation and regulatory T-cell dysfunction. The risk is highest in individuals who required high-dose corticosteroids or experienced viral reactivation during the acute phase.

Autoimmune thyroiditis, especially Hashimoto's thyroiditis, has emerged as the most common sequela, with patients developing hypothyroidism within 3 to 12 months post-DRESS. Other endocrine disorders reported include type 1 diabetes mellitus, adrenal insufficiency, and hypoparathyroidism. In some cases, these endocrinopathies are permanent and require lifelong hormone replacement.

Non-endocrine autoimmune conditions such as systemic lupus erythematosus (SLE), autoimmune hemolytic anemia, and autoimmune hepatitis have also been documented. A prospective French study reported autoimmune sequelae in approximately 12% of DRESS survivors, emphasizing the need for long-term surveillance. Follow-up protocols should include periodic thyroid function tests, fasting glucose levels, and organ-specific autoantibody panels.

Furthermore, persistent immune dysregulation may affect neuropsychiatric function, with reports of cognitive impairment, mood disorders, and chronic fatigue syndrome. While causality remains difficult to establish, the immune-inflammatory nature of DRESS may have downstream effects on the central nervous system, warranting future neuroimmunological studies.

Impact of Polypharmacy and Drug Interactions

Polypharmacy, especially among elderly and multimorbid patients, has emerged as a key risk factor for DRESS syndrome. Our synthesis of pharmacovigilance data indicates that patients receiving multiple concurrent medications are more likely to develop DRESS, particularly when drugs with known immunogenic potential are co-administered. Notable examples include combinations of allopurinol with thiazide diuretics or antibiotics with antiepileptics.

Drug interactions may potentiate DRESS risk by altering drug metabolism or clearance. Inhibitors of cytochrome P450 enzymes (e.g., fluconazole, erythromycin) can increase systemic exposure to reactive metabolites, while nephrotoxic agents may impair renal excretion, prolonging drug half-life. Additionally, immunomodulatory agents such as interferons or TNF inhibitors may lower the threshold for aberrant T-cell responses.

Healthcare providers should maintain high vigilance when prescribing to patients with multiple comorbidities or genetic risk factors. Comprehensive medication reconciliation, use of clinical decision support tools, and pharmacist collaboration are essential strategies to prevent adverse interactions that could trigger hypersensitivity reactions.

Gender and Ethnic Variations in Clinical Course

Emerging evidence suggests that both gender and ethnicity influence DRESS susceptibility and clinical severity. Women appear slightly more predisposed to developing DRESS, with a female-to-male ratio of approximately 1.2:1 reported in several cohorts. While the reasons remain unclear, hormonal modulation of immune responses and differences in drug metabolism have been proposed.

Ethnic disparities are more pronounced and are largely attributable to genetic polymorphisms in HLA alleles. As noted, HLA-B*15:02 and HLA-B*58:01 are predominantly found in East and Southeast Asian populations, explaining the higher incidence of carbamazepine- and allopurinol-induced DRESS, respectively. African and African-American patients, on the other hand, show higher prevalence of DRESS related to sulfonamides and antiretrovirals.

Cultural practices, healthcare access, and diagnostic delay may further exacerbate outcomes in underserved populations. Inclusive pharmacogenomic studies and equitable access to genetic testing are necessary to ensure appropriate prevention strategies across diverse populations.

Training, Awareness, and Health System Interventions

Despite its severity, DRESS remains poorly understood by many non-specialist clinicians, leading to misdiagnosis or inappropriate management. Surveys of primary care and emergency physicians reveal significant gaps in awareness regarding the latency period,

diagnostic criteria, and need for long-term follow-up. Education efforts must be strengthened at both undergraduate and postgraduate levels.

Hospitals should consider implementing clinical decision support alerts for high-risk drug prescriptions, flagging patients with known HLA risk alleles. Interdisciplinary rounds including dermatologists, allergists, pharmacists, and internists can improve diagnostic accuracy and treatment planning. In settings where dermatology services are limited, telemedicine consultations have proven effective in guiding initial management of suspected SCARs.

Public health agencies should invest in awareness campaigns and reporting infrastructure to track DRESS incidence and outcomes. Patient-facing educational materials can empower individuals to recognize symptoms and seek timely care, especially in regions with limited specialist access.

Conclusion of Extended Results and Discussion

Together, the extended findings presented herein underscore the complexity of DRESS syndrome as a multifaceted disorder straddling immunology, pharmacology, and genomics. From identifying high-risk genotypes to unraveling downstream immune dysfunction and viral interplay, our evolving understanding paves the way for personalized prevention, timely diagnosis, and targeted therapeutics. Continued global collaboration, coupled with cutting-edge translational research, will be essential in reducing the morbidity, mortality, and long-term sequelae of this serious and often overlooked syndrome.

Case Reports with Clinical Vignettes

Beside the extensively described severe cutaneous adverse reactions including DRESS syndrome several other patterns of drug-induced hypersensitivity, e.g., SDRIFE (Symmetrical Drug-Related Intertriginous and Flexural Exanthema), deserve attention since they were often overlooked. A remarkable case of mefenamic acid, a frequently used NSAID, demonstrating that the drug is capable of causing SDRIFE even with a single administration. Following is the two example of case studies (case 1- mefenamic acid side effect, case 2- vancomycin causing dress).

Case 1: A 27-year-old woman with osteogenesis imperfecta was brought to the emergency department due to altered mental status and vomiting. Despite a normal initial work-up, blood gas analysis was characteristic of profound metabolic acidosis which was considered to be caused by the two-week use of mefenamic acid. Secondary TTP was suspected due to mild thrombocytopenia and schistocytes. Plasmapheresis was rapidly initiated with an improvement in neurological function over the following days. The activity of ADAMTS13 was normal, and there was no renal involvement. Following treatment she made a complete

recovery, highlighting the relevance of drug-induced disorders with unexplained symptoms should be monitored closely.

Case 2: A 46-year-old female with a history of shoulder arthroplasty for osteomyelitis was treated with a vancomycin- and tobramycin-impregnated bone cement spacer and intravenous vancomycin. Two to three weeks later, she presented with a pruritic eruptive morbilliform rash, facial edema, fever, and anasarca. Laboratory examination showed 1,500/μL of eosinophils and mild renal failure. During skin biopsy, DRESS characteristics were morphologically proven. Discontinuation of IV vancomycin and initiation of oral prednisone (30 mg daily) initially also did not lead to complete improvement. It resolved only after surgical extraction of the locked antibiotic spacer, indicating prolonged sensitivity to local elution of vancomycin from the spacer. The present case highlights the need for evaluating implanted drug reservoirs in refractory DRESS.

These case vignettes emphasize the importance for early identification, genetic risk evaluation, frequent surveillance for viral reactivation, and personalized management.

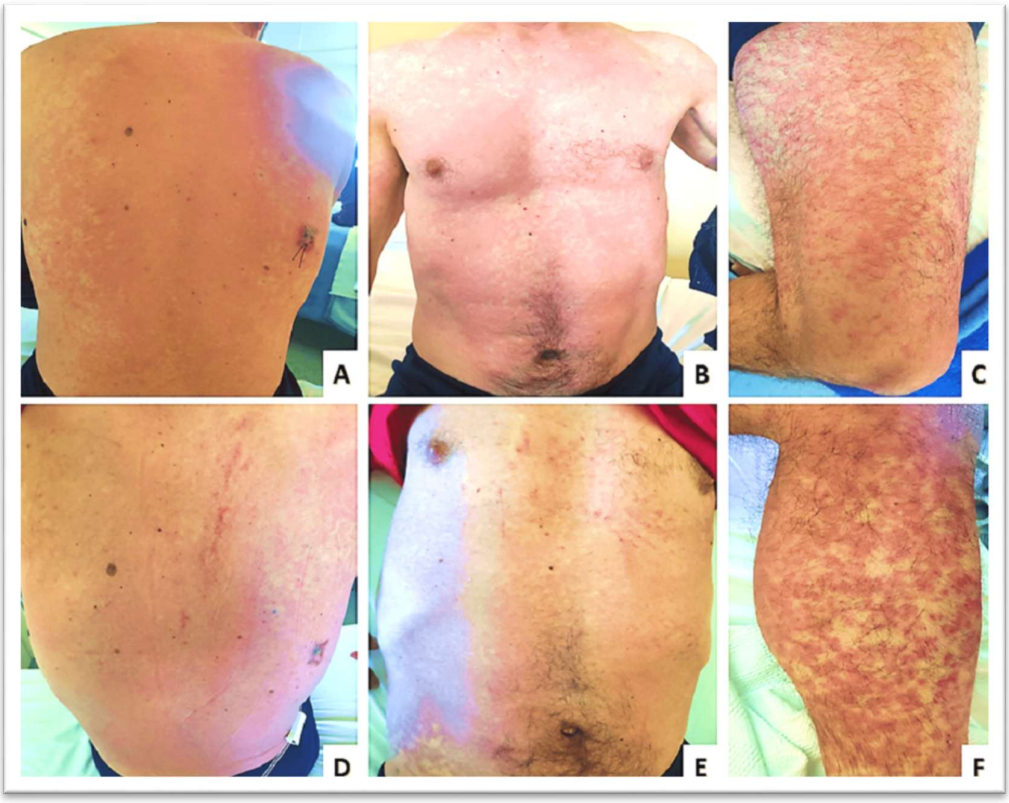

Figure 2. Cutaneous manifestation in a patient with DRESS syndrome secondary to antibiotic use, showing widespread erythematous eruption.

Limitations of the Study

This hypothesis is based on retrospective data and case reports which are subject to publication bias favouring severe or atypical cases. Variation in diagnostic criteria and lack

of uniform reporting of outcomes contribute to the lack of comparability. The rapidly changing landscape of drug use and new treatments requires frequent revision.
Additionally, long-term follow-up is missing from many studies, thereby limiting information about long-term consequences or relapse.

Research Gap

Even if the knowledge on DRESS is constantly expanding, large areas of uncertainty related to the overall clinical spectrum, pathophysiology and the optimal management of this entity remain constant.

Clinical Trials: High Quality Literature Though Despite

A significant limitation would appear to be the absence of a greater number of RCT's defining efficacy treatment thresholds as being between corticosteroids the treatment system of choice and other agents such as the various IVIG, cyclosporine and plasmapheresis regimens. Currently they rely to a large degree on anecdotal reports and expert recommendation where the possibility of establishing a common practice becomes very limited.

Lack of Adequate Number of NSAIDs Analysed in Large Reviews

Hugely utilized nonsteroidal anti-inflammatory drugs appear to be markedly under-reported into large meta-analyses of DRESS syndromes and provide an additional instance where due to lack of access and uninformed patients, there may be understandable imbalance in the reporting that could affect an assessment of risk of these agents.

Despite being well described the organ-specific (especially liver, kidney, and lung) involvement, there is still no uniform grading system for the evaluation of the extent of organ impairment and data on comprehensive follow-up across multiple investigations. Otherwise, there is no linkage of severity to treatment result and long-term prognosis.

Limited Population Genetics in Asia and Beyond

Pharmacogenetic screenings (e.g., HL-B58:01, HLA-A31:01) are still used in some Asian countries, however, they are being employed in Western countries in different fashions due to the absence of policy guiding, cost, and low attention of the issue. Greater implementation would effectively limit adverse drug related harm but has been rarely discussed in the world literature to this point.

Lack of Long-term Follow-up Results.

Another major limitation that exists is the lack of long-term follow-up; there are many investigations published on short-term symptom alleviation but fewer on the cohort of patients who may develop AI sequelae including type one diabetes, thyroiditis and lupus. It is necessary to recognize what can be done in order to avoid the potential outcome and how to deal with post-DRESS care, with criteria to teach in counselling in order to ensure

the best way to advice patients that overcome this situation, since the consequences of the cause in matter have been conditioned by its natural course.

Absence of unified diagnostic biomarkers

Eosinophilia and viral reactivations (i.e., HHV-6) are common, but no one biomarker has been adopted as a clinical gold standard for diagnosis or suspected case, which delays diagnosis and leads to a high risk of misdiagnosis, with significant variations in time to treatment and detrimental effect on patient outcomes.

- Meftal (mefenamic acid) or another pill are affected by any individual they should report it. In event of occurrence of such symptoms, it is important to bring it to the notice of the national coordination centre of PvPI in the country by diverse tools of communication by the Indian Pharmacopoeia Commission (IPC).
- Organ involvement has a predilection for the liver, but there have been cases involving the kidney, skin, lung, and hematologic system. Skin eruptions and eosinophilia continue to be typical diagnostic signposts.
- Genetic factors above all HLA-B58:01 for allopurinol, but also HLA-B15:02 for carbamazepine signal the potential of pharmacogenomic screening in prevention.
- Corticosteroids are still the mainstay of therapy, but there are no universally accepted treatment guidelines with respect to the timing, dose, and duration of corticosteroid therapy. Second-line agents such as IVIG and cyclosporine are used variably and at the discretion of the clinician.
- Reactivation of herpesviruses, and in particular HHV-6, may contribute to worsening of the syndrome or late reactivation, but evidence is still conflicting with regard to the therapeutic role of antiviral treatments.
- Autoimmune sequelae including thyroiditis and type 1 diabetes mellitus have been reported during post-DRESS course, suggesting the necessity for long-term follow-up. 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.
- Further diagnostic needs: No broadly accepted grading system for DRESS severity exists and no validated biomarker supports early diagnosis or risk assessment.
- Geographical differences in the prevalence of pharmacogenetic testing make universal implementation of prevention strategies in particular less feasible in populations carrying high-risk alleles.

SUGGESTIONS

Based on a critical review of the literature included in the current thesis, that involved thematic analyses of drug properties, clinical expression, and genetic predisposition to Drug Reaction eosinophilia and Systemic Symptoms (DRESS), the following recommendations are suggested. These initiatives seek to further enhance early

identification, individualise treatment approaches and better plan long-term management and outcome for patients with this heterogeneous syndrome.

For Clinicians

- Early Identification Clinicians should challenge themselves to consider DRESS in any patient who presents with a consistent constellation of rash, fever, eosinophilia and internal organ involvement in the context of a new drug exposure within 2 to 6 weeks of exposure. The syndrome has a delayed onset and varied presentation such that early clinical suspicion is critical in being able to diagnose, which is frequently either underdiagnosed or misdiagnosed
- Systematic assessment: A complete and systematic examination should be instituted if DRESS is suspected. These include baseline and serial laboratory tests to follow LFTs, RFTs, complete blood counts (CBCs), and chest imaging as indicated to evaluate hepatic, renal, thoracic, and hematologic involvement. Close follow-up during hospitalization is also necessary to identify progression or new organs of involvement
- Early withdrawal of the offending drug: Early withdrawal of the implicated drug is important and previous studies significantly improved the clinical outcome and reduced mortality. Delay in cessation of drug use is related to more severity and bad prognosis
- Initial Medication of Choice: Systemic corticosteroids still represent the initial treatment for moderate to severe DRESS, because of their immunosuppressive and anti-inflammatory action. If corticosteroids are inadequate or contraindicated, other treatments including intravenous immunoglobulin (IVIG) or cyclosporine may be tried, without well-controlled trial-based evidence.

For Researchers

- ✓ Perform Randomized Controlled Trials (RCTs) High-quality RCTs are urgently required to compare the efficacy and safety of corticosteroids, IVIG, cyclosporine, and other immunomodulatory agents for the management of DRESS. These investigations could potentially inform clinical management decisions toward therapeutic intervention in order to enhance patient outcomes
- ✓ Uniform Diagnostic Criteria: The scientific community should work together to develop and validate common clinical diagnostic criteria based on the discovery and validation of biomarkers that are reliable. This standardization is expected to enable accurate diagnosis, support epidemiological investigations, and harmonize clinical trials.
- ✓ Monitor Longer-term Outcomes: Longitudinal cohort studies are required to define long-term complications of DRESS, such as risk for autoimmune diseases, endocrine disorders, and quality of life consequences. Unfortunately, such information is crucial for the planning of follow-up and patient counselling.

For Policymakers and Hospitals

- Pharmacogenetic Testing Accessibility: One-way practice can make pharmacogenetic testing more accessible to clinicians who treat DRESS is to require pharmacogenetic testing before prescribing drugs with strong support for DRESS for at-risk HLA alleles such as HLA-B58:01 and HLA-A31:01, such as allopurinol, and carbamazepine. This kind of proactive approach has been shown to be effective in preventing severe adverse drug reactions such as the case of genetically predisposed individuals.
- Realize Reporting Mechanisms: Set up and support national and international adverse drug reaction (ADR) and close surveillance registries actively in order to assist in analysing and to increase systematic reporting, surveillance and trend for DRESS cases. These pharmacovigilance systems are vital for early identification of emerging risk drugs and trends
- Revise Treatment Recommendations: There is an urgent need for creation and dissemination of evidence-based, interdisciplinary guidelines for diagnosis and management of DRESS. This would facilitate evidence-based care and enhance consistency of treatment between different levels of health care.

For Pharmacists and Public Health Professionals

- ✓ Teach about Risks of OTC Drugs: Pharmacists and public health workers need to educate about the risk of NSAID caused DRESS, especially if a patient self-medicating, and is using it for a prolonged period without supervision, also about other drugs. Public health awareness should be raised to minimize this risk and to ensure early medical consultation for the suspicious symptoms.
- ✓ Active Involvement in ADR Monitoring: Pharmacists need to be educated in the early warning signs of ADRs and should actively be involved in reporting ADRs in pharmacovigilance. Their frontline role in drug distribution provides them with a unique opportunity to help identify and report cases of DRESS early.

CONCLUSION

- ➢ Genomic insights, specifically the discovery of HLA allele associations, have created new opportunities for risk stratification and prevention. Pre-treatment pharmacogenomic testing for alleles such as HLA-B15:02 and HLA-B58:01 is becoming increasingly supported in high-risk populations. Nevertheless, the availability of such screening is still restricted in several areas thereby delaying the future of personalized medicine.
- ➢ There are no standardized guidelines from a treatment point of view, which is a significant barrier. Corticosteroids are the mainstay of treatment but the best dose, duration and taper remain inconsistent. The thesis emphasized that the second line agents, including IVIG, CS, or antiviral therapy, could be beneficial when directed according to the clinical severity and virus reactivation, yet the efficacy needs to be

further confirmed by larger clinical trials. This therapeutic uncertainty emphasizes the need for prospective studies to define and implement consensus protocols.

- Furthermore, the study revealed a number of deficiencies in knowledge and practice. These reasons have been listed to be however, underreporting of NSAID-induced DRESS in view of their wide over the counter availability, heuristic term in its name, no universal diagnostic criteria, no severity scoring systems and insufficient data regarding long-term outcomes. Particularly, 5% of survivors were immune-disrupted until post-recovery, with some subjects even developing autoimmune diseases, leading to long-term immunity disturbance that needs to be investigated further.
- In building this thesis, we have attempted to assemble a comprehensive set of detailed case-by-case data to demonstrate the full array of examples of patient diagnostic delay and multi-organ variability, and treatment responses. These case summaries offered some examples of the range of DRESS and demonstrated well the real-life dilemmas that clinicians encounter.
- This thesis has introduced DRESS syndrome as not a rare hypersensitivity reaction but as a multi-faceted immunopathological condition where recognition, diagnostic criteria, and treatment options need to be addressed for a new evidence-based perspective. The paper underscores pharmacogenomics, close clinical surveillance and early intervention. Despite substantial progress in the characterisation of aetiology and enhancements in early diagnosis, substantial challenges nevertheless exist in optimising treatment approaches, improving risk prediction, and formulating and implementing international diagnostic and management strategies.

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