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Más Allá del Daño Cutáneo: Inmunopatogenia, Reconocimiento Temprano y Desafíos Terapéuticos en DRESS y Síndrome de Stevens-Johnson/Necrólisis Epidérmica Tóxica

Beyond Cutaneous Injury: Immunopathogenesis, Early Recognition, and Therapeutic Challenges in DRESS and Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

Ana Camila Subia Sandoval
Independiente
anacamilasubia@gmail.com
https://orcid.org/0009-0004-9184-8214

Alberto Escamilla Huerta
Benemérita Universidad Autónoma de Puebla
escamilla.civ42292@gmail.com
https://orcid.org/0009-0007-4545-2595

Oscar Emmanuel Garcia Moreno
Universidad Juárez del Estado de Durango
emmanuel_932@hotmail.com
https://orcid.org/0009-0003-5987-4992

Javier Emanuel Camacho-Patiño.
Independiente
jav.camacho.p@gmail.com
https://orcid.org/0009-0001-6427-3484

Velbeth Elizabeth Recinos Martínez
Universidad de San Carlos de Guatemala
velbethrecinos@gmail.com
https://orcid.org/0009-0009-8602-708X

Omar Abdel Orellana Arévalo
CENTRO DE ESPECIALIDADES MÉDICAS URGENMED
OMARORELLANA105@GMAIL.COM
https://orcid.org/0009-0000-8025-0170

Guillermo Andres Díaz León
Universidad FUCS
guillerdiaz97@outlook.es
https://orcid.org/0009-0001-2023-2306

José Rodrigo Roca Alvarez
Universidad de San Carlos de Guatemala
rodrigorocamedi@gmail.com
https://orcid.org/0009-0004-8183-8266

Alvaro Enrique Marroquin Murcia
Clínica Infantil Colsubsido
Enriquemurcia5@gmail.com
https://orcid.org/0000-0001-5478-6465

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***Autor de correspondencia:** anacamilasubia@gmail.com

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RESUMEN

Las reacciones cutáneas adversas graves a medicamentos representan un importante desafío clínico debido a sus complejos mecanismos inmunológicos, manifestaciones heterogéneas y capacidad para producir complicaciones sistémicas potencialmente mortales. Esta revisión narrativa analiza la inmunopatogenia, el reconocimiento temprano, la evaluación diagnóstica y el tratamiento de la reacción a medicamentos con eosinofilia y síntomas sistémicos (DRESS) y del síndrome de Stevens-Johnson/necrólisis epidérmica tóxica (SJS/TEN). Se examinaron 20 publicaciones científicas, incluyendo investigaciones clínicas, revisiones sistemáticas y consensos internacionales, mediante una síntesis cualitativa que incorporó contribuciones latinoamericanas. Los hallazgos identificaron mecanismos diferenciados de lesión inmunomediada, caracterizados por inflamación sistémica, activación de linfocitos T y posible reactivación de herpesvirus en DRESS, en contraste con la destrucción citotóxica de queratinocitos mediada por granulisina y otras vías inflamatorias en SJS/TEN. La evidencia destacó la importancia de suspender tempranamente el medicamento sospechoso, realizar una valoración multidisciplinaria y utilizar herramientas estandarizadas como RegiSCAR, ALDEN y SCORTEN. Las investigaciones terapéuticas mostraron resultados potencialmente favorables con determinadas intervenciones inmunomoduladoras, incluidos corticosteroides sistémicos, ciclosporina e inhibidores del factor de necrosis tumoral alfa; sin embargo, la heterogeneidad metodológica y la limitada evidencia de ensayos aleatorizados impiden establecer conclusiones definitivas sobre su eficacia comparativa. Las contribuciones latinoamericanas resaltaron la relevancia de las guías regionales y del acceso a atención especializada. Se concluye que integrar el conocimiento inmunológico con la evaluación clínica estructurada y el tratamiento basado en evidencia puede favorecer el reconocimiento oportuno y una atención individualizada. Se requieren investigaciones multicéntricas que esclarezcan la eficacia terapéutica, identifiquen biomarcadores confiables y mejoren los resultados a largo plazo.

PALABRAS CLAVE

Reacciones cutáneas adversas graves, síndrome DRESS, síndrome de Stevens-Johnson, necrólisis epidérmica tóxica, hipersensibilidad farmacológica, inmunopatogenia, diagnóstico temprano, tratamiento inmunomodulador, farmacovigilancia

ABSTRACT

Severe cutaneous adverse drug reactions represent a major clinical challenge due to their complex immunological mechanisms, heterogeneous manifestations, and potential to cause life-threatening systemic complications. This narrative review examines the immunopathogenesis, early recognition, diagnostic assessment, and therapeutic management of drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Twenty scientific publications, including clinical investigations, systematic reviews, and international consensus recommendations, were analyzed through a qualitative synthesis incorporating contributions from Latin America. The findings revealed distinct patterns of immune-mediated injury, characterized by systemic inflammation, T-cell activation, and potential herpesvirus reactivation in DRESS, compared with cytotoxic keratinocyte destruction mediated by granulysin and other inflammatory pathways in SJS/TEN. Clinical evidence emphasized the relevance of early drug withdrawal, multidisciplinary assessment, and standardized instruments, including RegiSCAR, ALDEN, and SCORTEN. Therapeutic investigations identified potentially favorable outcomes associated with selected immunomodulatory interventions, including systemic corticosteroids, cyclosporine, and tumor necrosis factor-alpha inhibitors; however, methodological heterogeneity and limited randomized evidence restrict definitive conclusions regarding comparative effectiveness. Latin American contributions highlighted the importance of regional clinical guidelines and improved access to specialized care. Overall, integrating immunological knowledge with structured clinical assessment and evidence-based management may contribute to earlier recognition and more individualized care. Further multicenter investigations are required to clarify therapeutic effectiveness, identify reliable biomarkers, and improve long-term outcomes.

KEYWORDS

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Severe cutaneous adverse reactions, DRESS syndrome, Stevens–Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity, immunopathogenesis, early diagnosis, immunomodulatory therapy, pharmacovigilance

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INTRODUCCIÓN

Severe cutaneous adverse reactions (SCARs) represent one of the most challenging complications of pharmacological treatment because of their unpredictable onset, complex immunological mechanisms, and potential to progress rapidly toward life-threatening systemic injury. Although most drug-induced skin eruptions are self-limited and resolve after discontinuation of the responsible medication, a small proportion develop into severe hypersensitivity syndromes characterized by extensive cutaneous inflammation, internal organ dysfunction, mucosal destruction, and prolonged recovery. Among these conditions, drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome (SJS), including its more extensive manifestation, toxic epidermal necrolysis (TEN), deserve particular attention due to their substantial morbidity, mortality, and diagnostic complexity. These disorders illustrate how an initially localized dermatological manifestation may reflect a much broader disturbance of immune regulation, requiring timely intervention from dermatology, infectious diseases, clinical immunology, internal medicine, and critical care specialists (Awad et al., 2023; Hama et al., 2022; Hama et al., 2025).

The clinical relevance of DRESS and SJS/TEN extends beyond their relatively low incidence. Their importance lies in the disproportionate severity of their consequences, the uncertainty surrounding early diagnosis, and the difficulty of identifying the medication responsible when several drugs have been administered simultaneously. In contemporary clinical practice, patients are frequently exposed to complex therapeutic regimens involving antibiotics, anticonvulsants, anti-inflammatory agents, immunomodulators, and medications used for chronic metabolic or cardiovascular conditions. Such exposure complicates pharmacological attribution and may delay recognition of serious adverse reactions, particularly when manifestations resemble infectious, autoimmune, or other inflammatory diseases. This situation becomes especially problematic in hospitalized patients, where fever, laboratory abnormalities, and progressive organ dysfunction may initially be interpreted as complications of the underlying disease rather than manifestations of drug hypersensitivity. Consequently, understanding the biological and clinical characteristics of SCARs has become an essential component of patient safety, rational prescribing, and pharmacovigilance (Cabañas et al., 2020; Brüggen et al., 2024; Murillo-Casas et al., 2025).

Historically, the classification of severe drug-induced mucocutaneous reactions has undergone substantial refinement as clinical observations have revealed important differences between individual syndromes. The work of Bastuji-Garin et al. (1993) contributed to establishing a standardized classification of SJS, SJS/TEN overlap, and TEN according to the extent of epidermal detachment and the characteristics of associated lesions. This distinction remains fundamental because the severity and clinical course of epidermal necrolysis are closely associated with the degree of skin involvement and systemic deterioration. In parallel, the recognition of DRESS as a distinct delayed hypersensitivity syndrome emphasized the importance of hematological abnormalities, prolonged latency following drug exposure, and multiorgan inflammatory injury. Nevertheless, considerable variability in its presentation has complicated the establishment of universally applicable diagnostic criteria, as discussed by Kardaun et al. (2007). Although both disorders belong to the broader category of severe delayed drug hypersensitivity reactions, their biological behavior and therapeutic requirements are not interchangeable.

DRESS is characterized by a heterogeneous combination of extensive cutaneous eruption, fever, facial edema, lymphadenopathy, hematological abnormalities, and involvement of one or more internal organs. Clinical manifestations usually develop several weeks after the introduction of the causative medication, although latency can vary according to the drug, previous sensitization, and individual susceptibility. Eosinophilia, despite being incorporated into the syndrome's name, is neither universally present nor necessarily detectable during the earliest stages of illness. This variability creates opportunities for diagnostic delay when clinicians rely excessively on isolated laboratory findings rather than the evolving clinical picture. Hepatic involvement is among the most frequently reported systemic manifestations, while renal inflammation, pneumonitis, myocarditis, and neurological complications

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may determine prognosis in particularly severe cases. The possibility of progressive organ dysfunction despite initial drug withdrawal further distinguishes DRESS from uncomplicated exanthematous reactions and reinforces the need for repeated clinical and biochemical assessment (Avancini et al., 2015; Awad et al., 2023; Criado et al., 2025).

The immunopathogenesis of DRESS is increasingly understood as a complex interaction among drug-specific immune activation, host genetic susceptibility, altered immunoregulatory responses, and reactivation of latent viral infections. Rather than resulting from a single inflammatory pathway, DRESS appears to develop through multiple immunological processes in which drug exposure triggers aberrant T-cell responses capable of producing widespread tissue inflammation. The participation of antigen-presenting cells, activated lymphocytes, cytokine signaling, and inflammatory cell recruitment contributes to cutaneous and systemic manifestations. Genetic variation, particularly within pathways involved in antigen presentation and drug recognition, may influence individual susceptibility, although the clinical relevance of specific genetic markers depends on the medication and population studied. These mechanisms suggest that the intensity and distribution of tissue injury depend not only on exposure to a particular compound but also on the interaction between drug-related characteristics and the host immune environment (Hama et al., 2022; Criado et al., 2025).

An especially important component of DRESS pathophysiology is the relationship between immune dysregulation and the reactivation of herpesviruses, including human herpesvirus 6, Epstein–Barr virus, and cytomegalovirus. Viral reactivation has been associated with the complex and occasionally relapsing course of the syndrome, although the causal contribution of each virus remains incompletely defined. These observations challenge the traditional interpretation of DRESS as an exclusively drug-dependent inflammatory event and support a broader model in which infectious and immunological processes interact throughout disease progression. Viral activity may coincide with renewed clinical manifestations, persistent laboratory abnormalities, or additional complications after the initial hypersensitivity episode. Moreover, the development of delayed autoimmune conditions after apparent recovery suggests that immune dysfunction may persist beyond the resolution of visible skin lesions. Recent studies have therefore emphasized the importance of considering viral reactivation, postacute complications, and long-term immunological consequences when assessing patients with DRESS (Hama et al., 2022; Criado et al., 2025; Mizukawa & Shiohara, 2025).

In contrast, SJS and TEN are predominantly characterized by extensive keratinocyte injury leading to epidermal necrosis, detachment, and severe mucosal involvement. Their clinical presentation often begins with nonspecific constitutional symptoms, including fever, malaise, and discomfort, followed by the appearance of painful erythematous or purpuric lesions that may evolve into blistering and epidermal separation. Ocular, oral, and genital mucosal surfaces are commonly affected, and their involvement may generate functional impairment extending well beyond the acute inflammatory period. The conventional distinction between SJS, SJS/TEN overlap, and TEN is based on epidermal detachment involving less than 10%, 10%–30%, and more than 30% of the body surface area, respectively. However, the clinical significance of these conditions cannot be reduced to the percentage of affected skin, since hemodynamic instability, respiratory complications, infection, ocular injury, and other systemic manifestations may substantially influence outcomes (Bastuji-Garin et al., 1993; Hama et al., 2025; Watanabe et al., 2026).

The mechanisms responsible for epidermal destruction in SJS/TEN differ in important respects from those commonly associated with DRESS. Drug-specific cytotoxic T lymphocytes and natural killer cells participate in the development of epidermal injury through the release of inflammatory and cytotoxic mediators. Among these, granulysin has been identified as a major contributor to disseminated keratinocyte death, providing an important mechanistic explanation for the rapid progression of epidermal necrolysis. The investigation conducted by Chung et al. (2008) represented a significant advance by identifying granulysin as a key mediator of tissue destruction in SJS/TEN. Subsequent work has expanded this understanding by examining additional inflammatory pathways, including tumor necrosis factor-alpha signaling, cytotoxic granule-associated proteins, and regulated cell-death mechanisms. These findings have generated considerable interest in therapeutic interventions directed toward specific molecular targets rather than relying exclusively on broad immunosuppression (Chung et al., 2008; Wang et al., 2018; Hama et al., 2025).

Despite these advances, the relationship between immune activation and clinical severity remains incompletely understood. Not every individual exposed to a potentially high-risk medication develops a severe reaction, and the same pharmacological agent may produce substantially different clinical manifestations among susceptible patients.

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Variations in human leukocyte antigen expression, drug metabolism, immune-cell recognition, and inflammatory regulation may contribute to this heterogeneity. The involvement of particular genetic susceptibility markers also varies among populations, creating important implications for pharmacogenomic screening and individualized prevention. Nevertheless, genetic predisposition alone does not fully explain disease onset, and the interaction between genetic background, pharmacological exposure, and immune activation requires further investigation. A more precise understanding of these mechanisms could support the identification of vulnerable populations and the development of more reliable predictive strategies (Hama et al., 2022; Hama et al., 2025).

One of the principal difficulties in managing DRESS and SJS/TEN is recognizing these conditions before irreversible organ injury or extensive epidermal destruction occurs. Early symptoms frequently overlap with those of more common disorders, including viral exanthems, bacterial infections, autoimmune diseases, and other inflammatory dermatoses. In DRESS, the delayed appearance of eosinophilia or organ involvement may complicate initial assessment, whereas in SJS/TEN, early skin findings may precede the characteristic epidermal detachment. Consequently, diagnostic evaluation requires consideration of recent medication exposure, symptom chronology, cutaneous morphology, mucosal involvement, laboratory abnormalities, and the progression of systemic manifestations. This multidimensional approach is particularly important in emergency departments and general medical services, where the first clinical assessment may determine whether the offending medication is discontinued and whether specialized care is obtained in time (Cabañas et al., 2020; Brüggen et al., 2024; Murillo-Casas et al., 2025).

Several diagnostic and prognostic instruments have been developed to improve clinical standardization. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria provide a structured framework for assessing the probability of DRESS through a combination of clinical and laboratory characteristics. In SJS/TEN, the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) offers a systematic method for evaluating the likelihood that a particular medication was responsible for the reaction. Separately, the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) was developed to estimate mortality risk on the basis of selected clinical and biochemical variables. The contributions of Bastuji-Garin et al. (2000) and Sassolas et al. (2010) established important foundations for prognostic assessment and pharmacological causality evaluation. Nevertheless, these instruments serve different purposes and should not be interpreted as interchangeable diagnostic tests. Their usefulness depends on appropriate application, accurate documentation, and integration with clinical judgment.

The identification and immediate discontinuation of the suspected medication remain central principles in the management of severe cutaneous adverse drug reactions. However, drug withdrawal alone may be insufficient when inflammatory activity persists or extensive tissue injury has already developed. In DRESS, therapeutic decisions must account for the degree of cutaneous inflammation, hematological abnormalities, and the presence and severity of organ involvement. Topical corticosteroids and supportive measures may be appropriate in selected milder presentations, whereas systemic corticosteroids are commonly recommended for severe disease, particularly when major internal organs are affected. International consensus recommendations have sought to standardize clinical assessment, treatment intensity, and postacute follow-up, while acknowledging the limitations of the available comparative evidence. The Delphi-based consensus developed by Brüggen et al. (2024), together with earlier recommendations by Cabañas et al. (2020), provides a framework for severity-adapted treatment and multidisciplinary evaluation.

Nevertheless, several questions remain unresolved regarding the optimal management of DRESS. The selection of corticosteroid dose, treatment duration, tapering schedule, and alternative immunomodulatory agents continues to depend on disease severity and clinical evolution. Relapse during treatment reduction, persistent organ inflammation, and the possibility of viral reactivation create additional difficulties in balancing inflammatory control against treatment-related immunosuppression. Cyclosporine, intravenous immunoglobulin, and selected targeted therapies have been explored in particular clinical circumstances, but their roles require more robust comparative evaluation. Likewise, the identification of patients at increased risk of delayed complications remains a major research priority. Recent investigations have emphasized the importance of distinguishing transient clinical improvement from sustained disease resolution, especially when subsequent autoimmune or infectious complications may emerge after the acute episode (Brüggen et al., 2024; Lee & Peter, 2025; Mizukawa & Shiohara, 2025).

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The therapeutic approach to SJS/TEN presents a different set of challenges because extensive epidermal injury can rapidly compromise fluid balance, temperature regulation, nutritional status, and protection against infection. High-quality supportive care therefore constitutes a fundamental component of management, including meticulous wound care, fluid and electrolyte assessment, appropriate nutritional support, pain control, infection surveillance, and early evaluation of mucosal complications. Depending on disease severity and institutional resources, patients may require admission to specialized dermatological units, intensive care departments, or experienced burn centers. Ophthalmological assessment is especially important because acute ocular inflammation may progress toward severe and potentially permanent visual complications. The need for coordinated multidisciplinary care reflects the systemic nature of epidermal necrolysis and the importance of managing both immediate complications and long-term functional consequences (Murillo-Casas et al., 2025; Martinez Villarreal et al., 2025; Watanabe et al., 2026).

Beyond supportive treatment, the use of systemic immunomodulating therapies in SJS/TEN remains an active area of investigation. Corticosteroids, cyclosporine, intravenous immunoglobulin, and tumor necrosis factor-alpha inhibitors have been employed with variable results across clinical settings. Evidence from systematic reviews and meta-analyses suggests that some interventions may provide benefits under specific circumstances, but important limitations remain because of heterogeneity in disease severity, treatment initiation, study design, and concomitant supportive measures. Zimmermann et al. (2017) identified potentially favorable outcomes associated with selected immunomodulatory approaches while emphasizing the limitations of the evidence. Subsequently, Wang et al. (2018) investigated etanercept in a randomized clinical trial, contributing evidence for targeted inhibition of tumor necrosis factor-alpha. Nevertheless, the network meta-analysis performed by Tsai et al. (2021) highlighted continuing uncertainty regarding comparative mortality benefits, demonstrating that promising individual findings do not necessarily establish the superiority of a particular intervention across all patients.

The emergence of biologically targeted treatments has also introduced new questions regarding the relationship between molecular mechanisms and therapeutic response. If keratinocyte destruction depends on specific cytotoxic and inflammatory pathways, interventions capable of modifying these processes might reduce tissue injury when administered during the appropriate stage of disease. However, therapeutic response is likely influenced by the timing of intervention, the extent of epidermal injury, the patient's physiological condition, and concurrent complications. Recent reviews have explored these mechanistic approaches while recognizing the absence of universally accepted pharmacological protocols. Current evidence therefore supports a cautious interpretation of emerging therapies, with particular attention to the distinction between biological plausibility, improvement in intermediate clinical outcomes, and demonstrated reductions in mortality or long-term disability (Hama et al., 2025; Martinez Villarreal et al., 2025; Watanabe et al., 2026).

Another important dimension of severe drug hypersensitivity is the burden of complications that persist after apparent resolution of the acute reaction. Patients recovering from DRESS may experience prolonged organ dysfunction, recurrent inflammatory episodes, or delayed autoimmune manifestations, requiring follow-up that extends beyond normalization of the initial cutaneous findings. Similarly, survivors of SJS/TEN may develop chronic ocular surface disease, cutaneous abnormalities, mucosal scarring, and persistent functional limitations. The psychological burden associated with severe illness, hospitalization, pain, and uncertainty regarding future medication exposure also deserves clinical attention. Consequently, the evaluation of successful treatment should not be limited to short-term survival or disappearance of the rash. Long-term organ function, quality of life, medication safety, rehabilitation needs, and prevention of re-exposure should be considered relevant outcomes in both clinical practice and future research (Hama et al., 2022; Mizukawa & Shiohara, 2025; Murillo-Casas et al., 2025).

From an international perspective, the study of SCARs must also consider geographical differences in medication availability, prescribing patterns, genetic background, diagnostic resources, and healthcare organization. Although important advances have originated from European, Asian, and North American research networks, the applicability of their findings to other populations cannot always be assumed. Latin America provides a particularly relevant context because of its substantial population diversity, differences in access to specialized care, and the coexistence of healthcare systems with variable capacities for pharmacovigilance and intensive management. Research conducted in Brazil has contributed to the characterization of DRESS, including its clinical heterogeneity and the role of systemic inflammatory involvement. The clinical series reported by Avancini et al. (2015), together with the

immunopathological review developed by Criado et al. (2025), illustrates the scientific contributions of Latin American investigators to this field.

More recently, the publication of Latin American guidelines for the diagnosis and treatment of SJS/TEN represented an important step toward adapting international evidence to regional clinical practice. The multidisciplinary recommendations developed by Murillo-Casas et al. (2025) incorporated expertise from several Latin American countries and addressed diagnostic evaluation, identification of causative medications, therapeutic management, and prevention of complications. Likewise, the international collaboration reflected in the work of Martinez Villarreal et al. (2025), which includes participation from Mexican institutions, demonstrates the increasing contribution of Latin American researchers to discussions concerning innovative therapies. Nevertheless, region-specific data remain necessary to clarify patterns of drug exposure, diagnostic delays, treatment accessibility, clinical outcomes, and long-term complications. Greater participation from Latin American institutions could strengthen international comparisons while contributing to recommendations applicable across different healthcare environments.

Despite the substantial body of literature addressing DRESS and SJS/TEN individually, significant opportunities remain for analyses integrating their immunological foundations with practical diagnostic and therapeutic decision-making. Many investigations concentrate on a specific pathogenic pathway, clinical classification, or therapeutic intervention without fully examining how these dimensions interact during disease progression. Furthermore, differences in diagnostic definitions, causality assessment, patient selection, and outcome reporting complicate comparisons between studies. As a result, clinicians may encounter extensive scientific information without a sufficiently unified framework connecting early warning signs, underlying mechanisms, risk stratification, and treatment selection. A multidisciplinary synthesis is therefore warranted to identify established knowledge, distinguish it from emerging hypotheses, and clarify which findings have immediate clinical relevance (Awad et al., 2023; Lee & Peter, 2025; Hama et al., 2025).

The central premise of the present review is that understanding the distinct but partially overlapping immune mechanisms of DRESS and SJS/TEN, together with the appropriate use of structured clinical assessment tools, may support earlier recognition, more accurate identification of causative medications, and better-informed therapeutic decisions. From this premise, several questions emerge: Which immunological pathways contribute most directly to systemic inflammation in DRESS and epidermal destruction in SJS/TEN? Which early clinical and laboratory findings are most useful for distinguishing these conditions from other inflammatory and infectious disorders? How should available diagnostic, causality, and prognostic instruments be incorporated into clinical decision-making? What is the current strength of evidence supporting systemic corticosteroids, conventional immunomodulators, and targeted biological therapies? Finally, what limitations in the available literature are particularly relevant to clinical practice in Latin America and other settings with heterogeneous healthcare resources?

To address these questions, the present article adopts a clinically oriented narrative review design, drawing on peer-reviewed international literature, foundational investigations, systematic reviews, clinical studies, and expert consensus documents. The literature synthesis is organized around publications indexed in major biomedical databases, particularly PubMed, using concepts related to severe cutaneous adverse drug reactions, DRESS, drug-induced hypersensitivity syndrome, Stevens–Johnson syndrome, toxic epidermal necrolysis, immunopathogenesis, viral reactivation, early diagnosis, drug causality, prognostic assessment, and therapeutic interventions. Particular consideration is given to studies addressing immune-mediated tissue injury, diagnostic tools such as RegiSCAR, ALDEN, and SCORTEN, and the comparative evidence underlying currently employed treatments. Foundational contributions are considered alongside recent international recommendations published through 2026, while scientific contributions from Latin America are incorporated to broaden the geographical relevance of the analysis. Because the purpose is to develop an integrated clinical and mechanistic interpretation rather than calculate a pooled treatment effect, the review follows a qualitative synthesis approach without presenting itself as a systematic review or meta-analysis.

This design permits the examination of evidence across complementary domains that would be difficult to interpret independently. Studies addressing immunological mechanisms provide the biological basis for understanding clinical manifestations, while observational investigations and diagnostic recommendations contribute information concerning recognition and risk assessment. Randomized trials, systematic reviews, and therapeutic consensus statements are

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considered in relation to their methodological strengths and limitations, with attention to differences in patient populations, interventions, and reported outcomes. Regional studies and guidelines are examined to identify issues of transferability and contextual relevance. By integrating these perspectives, the review seeks to avoid interpreting preliminary therapeutic findings as definitive evidence and to distinguish established clinical practices from strategies that remain under investigation.

Accordingly, the objective of this review is to critically examine the immunopathogenesis, early clinical recognition, diagnostic evaluation, and therapeutic management of DRESS and SJS/TEN through an integrated dermatological, infectious disease, and immunological perspective. Particular emphasis is placed on identifying mechanisms that explain differences in clinical presentation and disease progression, evaluating the practical utility of diagnostic and prognostic instruments, and assessing the current evidence supporting conventional and emerging therapies. By incorporating international research and Latin American scientific contributions, this review aims to establish a comprehensive foundation for clinical understanding, medical education, and future investigations directed toward improving medication safety, reducing preventable complications, and supporting individualized care in patients affected by severe cutaneous adverse drug reactions.

DESARROLLO

1. Clinical and Epidemiological Characteristics of Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs) constitute a heterogeneous group of immune-mediated disorders associated with considerable clinical consequences despite their relatively low incidence. Drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are among the most clinically significant manifestations because of their potential to produce systemic inflammation, irreversible tissue damage, and death. International estimates suggest that DRESS affects approximately 2–5 individuals per million annually, whereas SJS/TEN has an estimated incidence of approximately two cases per million individuals per year, although these figures vary across populations and epidemiological methods. Their clinical burden is amplified by prolonged hospitalization, intensive treatment requirements, and complications that may persist after the resolution of acute manifestations (Brüggen et al., 2024; Murillo-Casas et al., 2025).

Several pharmacological groups have been consistently associated with these reactions, including aromatic anticonvulsants, allopurinol, sulfonamide antibiotics, and selected nonsteroidal anti-inflammatory drugs. However, the probability of developing a specific hypersensitivity phenotype depends on multiple factors, including genetic background, previous drug exposure, metabolic pathways, and individual immune responses. Latin American data illustrate the importance of regional differences. A multicenter investigation involving five countries identified 70 severe cutaneous adverse reactions, with DRESS accounting for 60% of the reported cases and anticonvulsants representing the most frequently implicated pharmacological category. Although these findings cannot establish population-level incidence, they demonstrate the clinical relevance of drug-induced hypersensitivity across Latin American healthcare settings (Murillo-Casas et al., 2025).

2. Immunopathogenesis and Systemic Inflammation in DRESS

The pathogenesis of DRESS involves a complex interaction between drug-specific immune responses, host susceptibility, and dysregulated inflammatory mechanisms. Unlike immediate allergic reactions predominantly mediated by immunoglobulin E, DRESS is generally classified as a delayed, T-cell-mediated hypersensitivity reaction. Drug molecules or their metabolites may interact with immune recognition pathways, triggering lymphocyte activation, cytokine production, and inflammatory cell recruitment. These processes contribute to widespread cutaneous manifestations and the involvement of internal organs, particularly the liver, kidneys, and lungs. Genetic susceptibility may influence immune recognition of specific medications, although the mechanisms vary according to the responsible compound and the characteristics of the exposed population (Hama et al., 2022; Criado et al., 2025).

Viral reactivation represents another important component of the biological complexity of DRESS. Human herpesvirus 6, Epstein–Barr virus, and cytomegalovirus have been associated with disease progression, recurrent inflammatory episodes, and prolonged clinical manifestations. Nevertheless, viral reactivation should not be considered a universal finding or an independently established cause of every DRESS episode. Current evidence suggests that alterations in

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immune regulation during drug hypersensitivity may facilitate viral activity, while the resulting immune responses could further influence systemic inflammation. This interaction has important implications for the interpretation of persistent fever, worsening organ dysfunction, and clinical deterioration during treatment (Criado et al., 2025; Mizukawa & Shiohara, 2025).

An additional characteristic of DRESS is the possibility of prolonged immune dysfunction following the acute episode. Some affected individuals develop recurrent inflammatory manifestations or delayed autoimmune complications, indicating that clinical improvement does not necessarily represent complete restoration of immunological balance. Consequently, monitoring should extend beyond the disappearance of skin lesions and include assessment of the organs initially affected, thyroid function, and other relevant laboratory parameters. These observations reinforce the importance of considering DRESS a systemic immunological disorder rather than an isolated dermatological reaction (Awad et al., 2023; Brüggen et al., 2024).

3. Cytotoxic Mechanisms and Epidermal Destruction in SJS/TEN

The immunopathogenesis of SJS/TEN differs substantially from that of DRESS, particularly in the mechanisms responsible for extensive epidermal injury. Drug-specific cytotoxic T lymphocytes and natural killer cells participate in the destruction of keratinocytes through the release of cytotoxic mediators. Granulysin has been identified as an important molecular contributor to widespread epidermal damage, while additional pathways involving perforin, granzymes, inflammatory cytokines, and regulated cell death may amplify tissue injury. The findings reported by Chung et al. (2008) established granulysin as a key mediator of keratinocyte death, providing a foundation for subsequent investigations into targeted treatments.

These immunological processes contribute to the characteristic progression from painful erythematous lesions to blistering, epidermal detachment, and mucosal erosion. The extent of epidermal destruction determines the conventional clinical classification: SJS involves less than 10% of body surface area, SJS/TEN overlap involves 10%–30%, and TEN affects more than 30%. However, clinical severity also depends on systemic involvement, underlying conditions, and the development of complications such as infection, fluid imbalance, respiratory dysfunction, and ocular damage (Bastuji-Garin et al., 1993; Hama et al., 2025).

Recent immunological investigations have explored additional mechanisms, including tumor necrosis factor-alpha signaling and alternative pathways of programmed cell death. These findings suggest that epidermal necrolysis results from interconnected inflammatory processes rather than a single cytotoxic mechanism. The identification of these pathways has encouraged the investigation of biological therapies, particularly agents capable of modifying specific inflammatory responses. Nevertheless, the relationship between molecular inhibition and improved survival requires further clinical validation (Wang et al., 2018; Hama et al., 2025).

4. Early Clinical Recognition and Differential Diagnosis

Early recognition remains one of the most important factors in the management of severe cutaneous adverse drug reactions. DRESS commonly develops several weeks after initiation of the responsible medication and may present with fever, diffuse maculopapular eruptions, facial edema, lymphadenopathy, and hematological abnormalities. Eosinophilia is frequently observed but may be absent during early disease stages, making isolated laboratory interpretation insufficient. Hepatitis is among the most common systemic complications, although nephritis, pneumonitis, myocarditis, and neurological involvement may also occur. Because these manifestations overlap with infectious and autoimmune disorders, diagnosis requires careful assessment of medication history, temporal relationships, laboratory abnormalities, and clinical evolution (Avancini et al., 2015; Cabañas et al., 2020).

SJS/TEN frequently begins with nonspecific systemic manifestations, followed by painful skin lesions and progressive mucosal involvement. Oral erosions, conjunctival inflammation, genital lesions, and epidermal detachment are important warning signs requiring immediate evaluation. Unlike many uncomplicated drug eruptions, skin pain and mucosal injury may precede extensive visible detachment. Differential diagnosis includes erythema multiforme major, generalized bullous fixed drug eruption, autoimmune blistering disorders, and selected infectious mucocutaneous conditions. Histopathological examination may support diagnostic assessment, particularly when clinical findings are

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atypical, but results must be interpreted within the broader clinical context (Hama et al., 2025; Murillo-Casas et al., 2025).

Structured diagnostic instruments provide additional support. RegiSCAR is commonly used to assess the likelihood of DRESS, incorporating clinical manifestations, laboratory findings, and organ involvement. ALDEN assists in determining pharmacological causality in SJS/TEN through assessment of drug exposure and temporal compatibility. SCORTEN, in contrast, is a prognostic instrument designed to estimate mortality risk in epidermal necrolysis. These tools contribute to standardized assessment but do not replace clinical judgment, particularly during early or atypical presentations (Bastuji-Garin et al., 2000; Sassolas et al., 2010; Brüggen et al., 2024).

5. Therapeutic Management and Emerging Treatment Strategies

Immediate identification and withdrawal of the suspected causative medication represent fundamental interventions in both DRESS and SJS/TEN. However, subsequent management differs according to the predominant mechanisms of tissue injury and the severity of systemic involvement.

In DRESS, treatment is primarily directed toward controlling immune-mediated inflammation and preventing progressive organ damage. Topical corticosteroids may be appropriate for selected mild presentations, whereas systemic corticosteroids are commonly recommended when significant organ involvement is present. The international Delphi consensus published by Brüggen et al. (2024) emphasized severity-based treatment, individualized assessment, and prolonged follow-up. Nevertheless, uncertainties remain regarding optimal corticosteroid regimens, treatment duration, and prevention of relapse. Cyclosporine and selected biological therapies have been investigated as alternatives in refractory cases, although the supporting evidence remains comparatively limited.

In SJS/TEN, specialized supportive care constitutes the cornerstone of treatment. Management includes fluid and electrolyte replacement, wound protection, nutritional support, pain control, infection surveillance, and early ophthalmological evaluation. The extensive loss of epidermal integrity may generate physiological disturbances resembling those observed in severe burns, making multidisciplinary care particularly important. Systemic immunomodulators, including corticosteroids, intravenous immunoglobulin, cyclosporine, and tumor necrosis factor-alpha inhibitors, have been investigated as additional therapeutic interventions, although their comparative effectiveness remains controversial (Zimmermann et al., 2017; Murillo-Casas et al., 2025).

A randomized clinical trial involving 96 patients compared etanercept with corticosteroid treatment and reported favorable results for selected clinical outcomes, supporting further investigation of tumor necrosis factor-alpha inhibition in epidermal necrolysis (Wang et al., 2018). Nevertheless, a systematic review and network meta-analysis including 67 studies and 2,079 patients found that no evaluated systemic treatment demonstrated statistically significant superiority over supportive care for mortality reduction in the network comparison. The analysis identified potentially favorable results for selected therapeutic combinations, but emphasized limitations related to study heterogeneity and the scarcity of randomized trials (Tsai et al., 2021).

These findings indicate that treatment selection should incorporate disease severity, available evidence, contraindications, and institutional expertise rather than assuming universal superiority of a particular immunomodulatory agent. The development of targeted therapies represents an important scientific advance, but larger comparative investigations remain necessary to determine their optimal indications and effects on long-term outcomes (Martinez Villarreal et al., 2025; Watanabe et al., 2026).

6. International Evidence, Latin American Perspectives, and Current Challenges

International collaboration has contributed substantially to understanding severe cutaneous adverse reactions, particularly through pharmacovigilance networks, clinical registries, immunological investigations, and therapeutic consensus initiatives. However, differences in healthcare accessibility, population genetics, medication availability, and diagnostic resources may influence the applicability of recommendations across regions.

Latin American contributions have become increasingly relevant through Brazilian investigations into DRESS immunopathogenesis and the development of regional recommendations for SJS/TEN. The guidelines published by Murillo-Casas et al. (2025) represent an important effort to integrate international evidence with the clinical realities

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of Latin American healthcare systems, including the need for early referral, standardized drug causality assessment, and prevention of complications. Nevertheless, the region continues to require larger multicenter investigations capable of evaluating epidemiological patterns, clinical outcomes, genetic susceptibility, and the accessibility of specialized treatments.

Overall, current evidence demonstrates that DRESS and SJS/TEN share a pharmacologically triggered immune-mediated origin but exhibit different mechanisms of tissue injury, clinical trajectories, and therapeutic requirements. The principal challenge is translating advances in immunopathogenesis into reliable early diagnostic strategies and interventions capable of reducing mortality and long-term disability. Greater standardization of clinical assessment, improved regional pharmacovigilance, and controlled therapeutic investigations remain essential for advancing individualized management and strengthening patient safety across different healthcare settings.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the immunopathogenesis, clinical manifestations, early diagnostic strategies, and therapeutic management of severe cutaneous adverse drug reactions, particularly drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), through an integrated review of international scientific evidence, with emphasis on improving clinical recognition, supporting evidence-based therapeutic decisions, and identifying opportunities for research and healthcare improvement in Latin America.

Specific Objectives

1. Identify and characterize the principal clinical and epidemiological features of DRESS and SJS/TEN. (Cognitive domain — Remembering and Understanding)

To describe the main pharmacological triggers, clinical manifestations, risk factors, and epidemiological characteristics associated with these conditions, establishing a conceptual foundation for understanding their relevance in contemporary medical practice.

2. Analyze the immunological and molecular mechanisms involved in severe drug hypersensitivity reactions. (Cognitive domain — Analyzing)

To examine the participation of drug-specific T lymphocytes, inflammatory cytokines, genetic susceptibility, viral reactivation, and cytotoxic mediators in the pathogenesis of DRESS and SJS/TEN, identifying the mechanisms responsible for their distinct patterns of systemic and epidermal injury.

3. Differentiate diagnostic criteria and evaluate their clinical applicability. (Cognitive domain — Applying and Evaluating)

To compare the clinical presentations of DRESS and SJS/TEN and critically assess the usefulness of RegiSCAR, ALDEN, and SCORTEN in supporting diagnostic classification, drug causality assessment, and prognostic evaluation.

4. Develop a structured approach to early clinical assessment and recognition. (Psychomotor and cognitive domains — Guided performance and Applying)

To organize the procedural steps required for medication history assessment, skin and mucosal examination, identification of warning signs, and interpretation of laboratory findings, providing a framework for practical application in clinical training and simulated patient scenarios.

5. Evaluate conventional and emerging therapeutic strategies according to available scientific evidence. (Cognitive domain — Evaluating)

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To critically examine supportive care, systemic corticosteroids, cyclosporine, intravenous immunoglobulin, and targeted biological therapies, considering their proposed mechanisms, clinical effectiveness, limitations, and implications for individualized treatment.

6. Formulate a sequential clinical management framework for severe cutaneous adverse reactions. (Psychomotor and cognitive domains — Procedural organization and Creating)

To establish an evidence-informed sequence of clinical actions, including recognition of severe manifestations, withdrawal of suspected medications, initial stabilization, multidisciplinary referral, and monitoring of complications, facilitating the development of practical decision-making skills.

7. Promote ethical responsibility, patient safety, and interdisciplinary collaboration. (Affective domain — Valuing and Organization)

To emphasize the importance of pharmacovigilance, responsible prescribing, timely communication, and respect for patient well-being, encouraging professional attitudes directed toward preventing avoidable complications and improving continuity of care.

8. Identify research gaps and formulate priorities for future investigations. (Cognitive and affective domains — Evaluating, Creating, and Valuing)

To recognize limitations in existing diagnostic and therapeutic evidence, particularly regarding long-term outcomes, genetic variability, and treatment accessibility in Latin America, and propose research priorities that support equitable healthcare practices and further scientific development.

OBJETO DE ESTUDIO

The object of study of this review comprises severe cutaneous adverse drug reactions (SCARs), specifically drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), considered from their immunopathological, clinical, diagnostic, and therapeutic dimensions. These conditions represent complex immune-mediated responses to pharmacological agents, characterized by distinct mechanisms of tissue injury, variable systemic involvement, and potentially life-threatening complications (Hama et al., 2022; Hama et al., 2025).

The study focuses on the relationship between drug-induced immune activation and the development of clinical manifestations, emphasizing the mechanisms that distinguish systemic inflammation in DRESS from extensive epidermal destruction in SJS/TEN. Particular attention is given to T-cell-mediated hypersensitivity, genetic susceptibility, viral reactivation, cytotoxic mediators, and inflammatory signaling pathways. Understanding these interactions is essential for explaining differences in disease progression, clinical severity, and responses to therapeutic interventions (Chung et al., 2008; Criado et al., 2025).

The population of interest consists of patients with suspected or confirmed DRESS or SJS/TEN, regardless of sex or geographical origin, with particular consideration of adult populations and the applicability of available findings to Latin American healthcare settings. Since this investigation is based on a narrative review of previously published studies, no patients are directly recruited, examined, or subjected to experimental interventions. Instead, the analysis considers clinical observations, epidemiological investigations, diagnostic recommendations, and therapeutic outcomes reported in the scientific literature.

The scope of the study includes the identification of frequently implicated medications, evaluation of early clinical manifestations, application of diagnostic and prognostic instruments, and assessment of conventional and emerging therapeutic strategies. Particular emphasis is placed on RegiSCAR for DRESS classification, ALDEN for drug causality assessment in SJS/TEN, and SCORTEN for prognostic evaluation. Additionally, the review examines the importance of multidisciplinary management, prevention of complications, and long-term clinical monitoring (Bastuji-Garin et al., 2000; Sassolas et al., 2010; Brüggen et al., 2024).

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Finally, the study considers international scientific evidence alongside contributions from Latin American researchers to identify differences in clinical management, healthcare accessibility, and available therapeutic resources. Its central purpose is to understand how current knowledge of immune-mediated mechanisms can inform earlier diagnosis and more individualized treatment. The investigation does not seek to establish new epidemiological estimates or demonstrate the superiority of a specific intervention; rather, it aims to integrate existing evidence, identify unresolved questions, and provide a scientific foundation for future clinical and translational research (Martinez Villarreal et al., 2025; Murillo-Casas et al., 2025).

METODOLOGÍA

Study Design

This study was structured as a descriptive and analytical narrative literature review based on the scientific method and a qualitative synthesis of published biomedical evidence. The methodological approach was selected to examine the immunopathogenesis, clinical recognition, diagnostic evaluation, and therapeutic management of drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Unlike experimental investigations, this review does not involve direct patient participation or clinical interventions. Its purpose is to integrate existing scientific knowledge, compare relevant findings, and identify areas requiring further investigation.

Literature Search Strategy

The bibliographic framework consisted of 20 selected scientific publications addressing severe cutaneous adverse drug reactions, including original investigations, clinical trials, systematic reviews, international guidelines, and expert consensus documents. The principal bibliographic source was PubMed/MEDLINE, with consideration of biomedical literature indexed in Scopus.

To facilitate reproducibility, the search strategy was defined using combinations of the following terms: “severe cutaneous adverse reactions,” “DRESS syndrome,” “drug-induced hypersensitivity syndrome,” “Stevens–Johnson syndrome,” “toxic epidermal necrolysis,” “immunopathogenesis,” “viral reactivation,” “early diagnosis,” “drug causality,” and “therapeutic management.” Boolean operators AND and OR were used to organize the search concepts. The strategy allows identification of studies related to immunological mechanisms, diagnostic instruments, pharmacological triggers, and therapeutic outcomes.

The literature framework included publications available through October 2026, without a restrictive initial publication date, allowing the incorporation of foundational investigations alongside recent scientific evidence. English-language studies were prioritized, while relevant publications from Latin American research groups were considered to strengthen the international perspective.

Eligibility and Selection Criteria

Scientific publications were considered relevant when they directly addressed the clinical manifestations, immunological mechanisms, diagnostic classification, prognostic evaluation, or treatment of DRESS and SJS/TEN. Priority was given to peer-reviewed studies with clearly described methodologies, recognized clinical guidelines, and investigations providing evidence applicable to medical practice.

Publications focused exclusively on uncomplicated drug eruptions, unrelated dermatological conditions, or insufficiently documented clinical observations were not prioritized. Foundational studies describing diagnostic classification, immunological mechanisms, and prognostic instruments were retained when their contributions remained relevant to contemporary clinical practice.

Data Organization and Critical Analysis

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Information from the selected publications was organized into five analytical categories: epidemiological and clinical characteristics, immunopathogenic mechanisms, early diagnostic recognition, therapeutic interventions, and international healthcare perspectives.

The comparative analysis considered study design, population characteristics, principal findings, reported clinical outcomes, and methodological limitations. Particular attention was given to the interpretation of diagnostic instruments such as RegiSCAR, ALDEN, and SCORTEN, as well as the therapeutic evidence derived from clinical trials, systematic reviews, and international consensus recommendations (Sassolas et al., 2010; Wang et al., 2018; Tsai et al., 2021).

Findings were interpreted according to the strength and consistency of the available evidence, distinguishing established clinical recommendations from emerging therapeutic approaches. International consensus documents and Latin American guidelines were incorporated to evaluate the applicability of current knowledge across different healthcare environments (Brüggen et al., 2024; Murillo-Casas et al., 2025).

Methodological Framework and Scientific Synthesis

The scientific method provided the organizational framework for the investigation through the identification of the clinical problem, formulation of research questions, examination of published evidence, critical comparison of findings, and development of evidence-based interpretations.

A thematic synthesis approach was employed to integrate immunological mechanisms with clinical manifestations and therapeutic decisions. The analysis emphasized similarities and differences between DRESS and SJS/TEN, particularly regarding systemic inflammation, epidermal injury, diagnostic challenges, and treatment selection.

Because the investigation was designed as a narrative review, no meta-analysis, statistical pooling, or quantitative estimation of treatment effects was undertaken. The interpretation was therefore based on qualitative comparison, methodological relevance, and consistency of the scientific literature. The review was intended to provide an integrated clinical perspective rather than establish definitive causal relationships or demonstrate the superiority of a particular therapeutic intervention.

Ethical Considerations

This investigation was based exclusively on previously published scientific literature and did not involve the recruitment of patients, collection of identifiable clinical information, or implementation of experimental procedures. Consequently, no direct risks to human participants were introduced. Scientific integrity was supported through appropriate bibliographic attribution, critical interpretation of published findings, and differentiation between established evidence and unresolved clinical questions.

FASES DEL DESARROLLO

Phase 1. Identification and Definition of the Research Problem

The initial phase focused on defining the clinical and scientific challenges associated with severe drug-induced hypersensitivity reactions. DRESS and SJS/TEN were selected because of their complex immune-mediated mechanisms, heterogeneous clinical manifestations, and potential to cause severe systemic complications. Particular attention was directed toward diagnostic delays, difficulties in identifying responsible medications, and uncertainty surrounding optimal therapeutic strategies. These considerations established the need for an integrated analysis connecting immunological mechanisms with clinical decision-making (Hama et al., 2022; Awad et al., 2023).

Phase 2. Formulation of Research Questions and Analytical Premises

Based on the identified problem, the review was structured around questions concerning the immunological differences between DRESS and SJS/TEN, the clinical indicators supporting early diagnosis, and the available evidence regarding therapeutic interventions. The principal analytical premise was that understanding disease-specific inflammatory

pathways, combined with structured clinical assessment, may contribute to more appropriate diagnostic and therapeutic decisions. This premise served as a framework for interpreting the literature rather than as a hypothesis subjected to experimental testing.

Phase 3. Identification and Selection of Scientific Literature

The bibliographic phase centered on a reference framework of 20 publications relevant to severe cutaneous adverse reactions. The search framework prioritized biomedical literature accessible through PubMed/MEDLINE, considering clinical investigations, systematic reviews, foundational studies, and international consensus recommendations.

The thematic search concepts included DRESS, SJS/TEN, immune-mediated drug hypersensitivity, viral reactivation, cytotoxic mechanisms, diagnostic criteria, and therapeutic management. Scientific relevance, methodological clarity, and direct applicability to the research questions guided the selection of publications. Foundational investigations were considered alongside recent contributions, including international therapeutic recommendations and Latin American clinical guidelines (Brüggen et al., 2024; Murillo-Casas et al., 2025).

Phase 4. Classification and Critical Evaluation of Evidence

The selected literature was organized into five principal categories: clinical and epidemiological characteristics, immunopathogenesis, diagnostic assessment, therapeutic interventions, and regional healthcare considerations. This classification facilitated comparisons between DRESS and SJS/TEN while preserving their distinct biological and clinical characteristics.

Critical evaluation focused on the design of each publication, the relevance of its findings, and limitations affecting clinical interpretation. Particular consideration was given to the distinction between observational evidence, randomized clinical trials, systematic reviews, and expert recommendations. Diagnostic instruments such as RegiSCAR, ALDEN, and SCORTEN were examined according to their intended applications rather than treated as equivalent assessment methods (Bastuji-Garin et al., 2000; Sassolas et al., 2010).

Phase 5. Comparative Analysis and Integration of Findings

The fifth phase involved integrating the available evidence to identify similarities, differences, and unresolved questions concerning DRESS and SJS/TEN. Immunological findings were examined in relation to clinical manifestations, including the contribution of viral reactivation and systemic inflammation in DRESS and cytotoxic keratinocyte injury in SJS/TEN.

Therapeutic evidence was compared to distinguish established management principles from emerging interventions. Immediate withdrawal of the suspected medication, supportive care, systemic corticosteroids, conventional immunomodulators, and targeted biological therapies were considered in relation to disease severity and available clinical evidence. Particular attention was given to the limitations of comparative treatment studies and the uncertainty surrounding the effectiveness of specific immunomodulatory regimens (Zimmermann et al., 2017; Wang et al., 2018; Tsai et al., 2021).

Phase 6. Scientific Interpretation and Identification of Research Priorities

The final phase focused on developing an integrated interpretation of the reviewed evidence and identifying areas requiring further investigation. The analysis emphasized the importance of early clinical recognition, appropriate drug causality assessment, multidisciplinary treatment, and long-term monitoring of complications.

Research priorities included the identification of reliable early biomarkers, clarification of immune-mediated injury pathways, evaluation of targeted therapies, and investigation of long-term clinical outcomes. The relevance of Latin American scientific contributions was also considered, particularly regarding differences in healthcare resources, regional pharmacovigilance, and the need for multicenter clinical investigations.

The conclusions derived from this process were restricted to the available published evidence. Given the narrative design, no quantitative pooling or experimental validation was performed. The resulting synthesis provides a structured

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scientific foundation for understanding DRESS and SJS/TEN, highlighting both established clinical principles and areas in which further research is necessary (Criado et al., 2025; Murillo-Casas et al., 2025; Watanabe et al., 2026).

RESULTADOS Y DISCUSIÓN

Figure 1.

Clinical manifestations and organ involvement in patients with DRESS syndrome

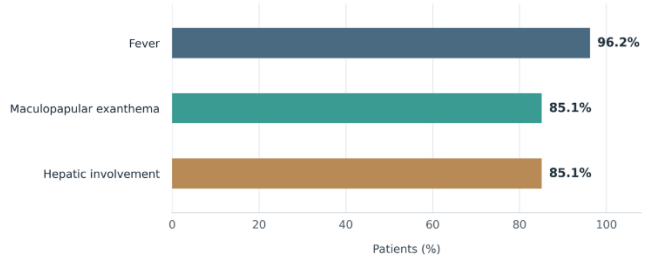


Figure 1 presents the distribution of the principal clinical and systemic manifestations documented in a retrospective cohort of patients diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) at a tertiary healthcare institution in Brazil. The investigation conducted by Avancini et al. (2015) initially evaluated 60 patients with suspected DRESS, of whom 27 fulfilled the established diagnostic criteria. The findings demonstrated a high frequency of systemic manifestations, with fever representing the most commonly reported clinical feature, followed by maculopapular exanthema and hepatic involvement.

Fever was documented in 96.2% of the confirmed cases, representing the highest proportion among the three evaluated manifestations. This finding indicates that an elevated body temperature was present in nearly the entire study population and constituted a prominent component of the observed clinical presentation. The frequency of fever exceeded that of both maculopapular exanthema and hepatic involvement by 11.1 percentage points. Its predominance is consistent with the systemic inflammatory characteristics of DRESS described in international investigations, in which constitutional manifestations frequently accompany dermatological abnormalities and may occur during the early stages of the reaction (Avancini et al., 2015; Hama et al., 2022).

Maculopapular exanthema was identified in 85.1% of patients, confirming its predominance as a characteristic cutaneous manifestation in the evaluated cohort. The frequency of this morphological pattern reflects the prominent dermatological component of DRESS, although its absence in a proportion of cases demonstrates that the syndrome is not invariably associated with a single type of skin eruption. The clinical spectrum may include additional morphological patterns, such as diffuse erythema, facial edema, exfoliative changes, and other inflammatory lesions. These variations have been documented in previous clinical investigations and contribute to the heterogeneity observed among patients meeting diagnostic criteria for DRESS (Avancini et al., 2015; Awad et al., 2023; Criado et al., 2025).

Hepatic involvement was reported in 85.1% of the study population, demonstrating a frequency identical to that of maculopapular exanthema. This result identifies the liver as a major site of extracutaneous involvement in the Brazilian cohort. The original investigation also reported a statistically significant association between the presence of atypical lymphocytes and higher alanine aminotransferase concentrations ($p < 0.001$), documenting a relationship between hematological abnormalities and biochemical indicators of hepatic injury. However, this association does not establish a causal relationship between the two findings. The frequency of hepatic abnormalities is consistent with the broader scientific literature, which describes liver involvement as one of the most common visceral manifestations of DRESS (Avancini et al., 2015; Cabañas et al., 2020; Criado et al., 2025).

The distribution of these manifestations demonstrates that cutaneous and extracutaneous abnormalities were both frequent within the same study population. Fever was the predominant finding, while maculopapular exanthema and hepatic involvement exhibited equivalent proportions. Nevertheless, these percentages represent the individual

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frequency of each manifestation and do not establish the proportion of patients who simultaneously experienced all three findings. The available aggregate results therefore describe the clinical profile of the cohort without determining the precise combinations of manifestations observed at the individual patient level.

Regarding pharmacological exposure, the original study identified anticonvulsants as the most frequently implicated drug category, accounting for 77.7% of the cases. Phenytoin and carbamazepine were particularly prominent, representing 44.4% and 29.6% of the confirmed cases, respectively. These findings characterize the medication exposure profile of the analyzed population and provide additional context for the distribution of clinical manifestations. However, the percentages represent the implicated medications among patients already diagnosed with DRESS and should not be interpreted as estimates of the risk of developing the syndrome among all individuals receiving these drugs (Avancini et al., 2015).

Figure 2.

Classification of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis According to Epidermal Detachment

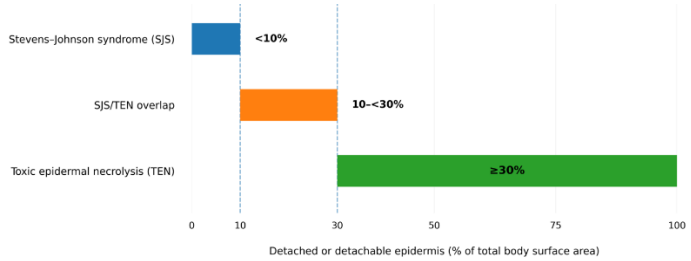


Figure 2 illustrates the distribution of epidermal detachment thresholds used to classify Stevens–Johnson syndrome (SJS), Stevens–Johnson syndrome/toxic epidermal necrolysis overlap (SJS/TEN), and toxic epidermal necrolysis (TEN). The classification is based on the percentage of total body surface area presenting epidermal detachment or clinically detachable epidermis. Three principal categories are represented, corresponding to progressively greater anatomical involvement. The classification framework originates from the clinical criteria established by Bastuji-Garin et al. (1993) and remains incorporated into contemporary recommendations, including the Latin American guidelines published by Murillo-Casas et al. (2025).

The first category corresponds to Stevens–Johnson syndrome, characterized by epidermal detachment involving less than 10% of the total body surface area. Within this interval, patients may exhibit widespread erythematous or purpuric macules, atypical target lesions, epidermal blistering, and mucosal involvement. The limited percentage of detached epidermis does not necessarily correspond to a limited distribution of inflammatory lesions, since areas of erythema without epidermal detachment are evaluated separately. Consequently, the classification is determined by the extent of actual or potential epidermal separation rather than the total surface occupied by visible cutaneous abnormalities (Bastuji-Garin et al., 1993; Hama et al., 2025).

The second category, SJS/TEN overlap, encompasses epidermal detachment involving at least 10% but less than 30% of the total body surface area. This intermediate interval represents a distinct anatomical classification within the spectrum of epidermal necrolysis. The graphical representation demonstrates that the overlap category occupies the range between the two principal classification thresholds, reflecting a greater extent of epidermal separation than SJS without reaching the criterion used for TEN. Clinical descriptions of this category include confluent epidermal blistering, erosions, mucosal involvement, and variable systemic manifestations. The extent of detachment constitutes the defining measurement for categorization, although individual presentations may differ in lesion morphology and extracutaneous involvement (Bastuji-Garin et al., 1993; Murillo-Casas et al., 2025).

The third category corresponds to toxic epidermal necrolysis, represented by epidermal detachment involving 30% or more of the total body surface area according to the thresholds adopted in the Latin American recommendations. This

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category encompasses the most extensive range of epidermal involvement within the conventional three-category framework. Clinical manifestations may include large areas of epidermal necrosis, widespread detachment, severe mucosal erosions, and extensive loss of cutaneous integrity. The magnitude of skin involvement is accompanied by considerable variability in physiological abnormalities and associated organ dysfunction. Therefore, the anatomical classification describes the extent of epidermal injury without independently quantifying the severity of individual systemic complications (Murillo-Casas et al., 2025; Watanabe et al., 2026).

The horizontal representation highlights two classification boundaries: 10% and 30% of total body surface area. The first distinguishes SJS from the overlap category, whereas the second separates overlap from TEN. These values are diagnostic classification thresholds rather than measurements of incidence, mortality, or treatment response. Accordingly, the different lengths of the graphical segments represent the numerical intervals assigned to each category and should not be interpreted as differences in the number of patients or the relative frequency of each condition.

An additional component of the classification involves the distinction between detached or detachable epidermis and inflammatory lesions that remain intact. Macular erythema, purpuric lesions, and atypical targets may extend beyond areas of epidermal separation, creating differences between the total visible eruption and the surface area incorporated into the detachment measurement. The Latin American guidelines describe the use of standardized body surface area estimation methods, including Wallace's rule of nines and the Lund–Browder method, for documenting epidermal involvement. These methods provide a quantitative framework for estimating the affected surface area and facilitate the classification of cases according to the established thresholds (Murillo-Casas et al., 2025).

The reviewed literature also identifies differences between the traditional classification and alternative approaches proposed in more recent investigations. Although the three-category system remains widely used, Hama et al. (2025) described evidence supporting a simplified classification distinguishing SJS with less than 10% epidermal detachment from TEN with 10% or greater involvement. This proposal was based on analyses of clinical outcomes associated with epidermal detachment thresholds. Nevertheless, the conventional distinction between SJS, SJS/TEN overlap, and TEN continues to appear in international clinical publications and regional recommendations. These approaches therefore represent differences in the classification frameworks reported in the contemporary literature.

It is also relevant that the original classification described by Bastuji-Garin et al. (1993) incorporated lesion morphology and distribution in addition to epidermal detachment. In particular, distinctions were made between presentations with widespread macules or atypical targets and those characterized by large sheets of epidermal detachment without such lesions. Figure 2 summarizes the commonly used three-category classification according to body surface area, rather than reproducing every morphological subtype contained in the original system.

Figure 3.

Comparative Assessment of RegiSCAR, ALDEN, and SCORTEN in Severe Cutaneous Adverse Reactions



Figure 3 presents a comparative analysis of the principal clinical and laboratory domains incorporated into three established instruments used in the assessment of severe cutaneous adverse drug reactions: RegiSCAR, the Algorithm

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of Drug Causality for Epidermal Necrolysis (ALDEN), and the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN). The comparative matrix identifies substantial differences in the variables evaluated by each instrument, reflecting their distinct purposes within the clinical assessment of drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). RegiSCAR primarily evaluates diagnostic probability, ALDEN examines the likelihood of a causal relationship between medication exposure and epidermal necrolysis, and SCORTEN estimates mortality risk through selected clinical and biochemical variables (Kardaun et al., 2007; Bastuji-Garin et al., 2000; Sassolas et al., 2010).

The RegiSCAR framework demonstrated the broadest distribution of inflammatory and multisystem clinical domains represented in the comparison. Its assessment includes fever, lymphadenopathy, eosinophilia, atypical lymphocytes, cutaneous characteristics, internal organ involvement, disease duration, and the exclusion of alternative diagnoses. Cutaneous assessment considers both the extent and morphology of the eruption, while systemic evaluation incorporates abnormalities affecting organs such as the liver, kidneys, lungs, and heart. The combination of these parameters allows cases to be classified according to increasing levels of diagnostic probability, ranging from an excluded diagnosis to possible, probable, or definite DRESS. The instrument therefore integrates several clinical dimensions rather than depending on an isolated dermatological or hematological finding (Kardaun et al., 2007; Cabañas et al., 2020).

Among the domains included in RegiSCAR, hematological abnormalities constitute a particularly distinctive component. Eosinophilia and atypical lymphocytosis are incorporated into the diagnostic assessment alongside fever and lymphadenopathy. However, the scoring framework does not require every characteristic to be present simultaneously. This feature corresponds to the heterogeneous clinical presentation documented in published DRESS investigations, in which laboratory abnormalities and organ involvement may develop at different stages of the disease. Similarly, the inclusion of investigations for alternative causes demonstrates that diagnostic classification incorporates both positive clinical findings and the exclusion of competing explanations for systemic inflammation (Kardaun et al., 2007; Awad et al., 2023; Brüggen et al., 2024).

In contrast, ALDEN demonstrated a predominantly pharmacological and chronological assessment profile. Its principal components include the interval between medication initiation and symptom onset, the probability that the suspected medication remained present in the body at the index date, previous exposure or reactions to the medication, the consequences of continued exposure, the established association between the drug and epidermal necrolysis, and the presence of alternative etiologies. Unlike RegiSCAR, ALDEN does not primarily classify the syndrome according to inflammatory manifestations or the extent of organ involvement. Instead, it evaluates the plausibility of individual medications as causative agents after the clinical identification of SJS/TEN (Sassolas et al., 2010).

The original evaluation of ALDEN included a comparison involving 100 cases of epidermal necrolysis. The algorithm classified the implicated medications as having probable or very probable causality in 69 cases, compared with 23 cases using the French pharmacovigilance method. Furthermore, the investigators reported a strong correlation between ALDEN causality assessments and the drug associations established through the EuroSCAR case-control investigation, with a correlation coefficient of 0.90. These findings describe the discriminatory characteristics observed during the original evaluation of the instrument and its ability to differentiate between medications with varying degrees of causal plausibility (Sassolas et al., 2010).

SCORTEN presented a different pattern of assessed variables, concentrating on characteristics associated with mortality rather than the identification of the responsible medication or diagnostic confirmation. The instrument incorporates seven clinical and biochemical predictors: age greater than 40 years, the presence of malignancy, heart rate greater than 120 beats per minute, initial epidermal detachment involving more than 10% of total body surface area, serum urea greater than 10 mmol/L, serum glucose greater than 14 mmol/L, and serum bicarbonate below 20 mmol/L. The distribution represented in Figure 3 therefore illustrates the predominance of physiological, metabolic, and baseline clinical characteristics within the SCORTEN framework (Bastuji-Garin et al., 2000).

The original SCORTEN investigation included 165 patients in the development sample and 75 patients in the validation sample. The analysis identified seven independent predictors of mortality and demonstrated an area under the receiver operating characteristic curve of approximately 0.82. The original model also showed close agreement between

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predicted and observed mortality in the development population. These findings established the quantitative basis for using the instrument as a prognostic assessment method in epidermal necrolysis, independently of the diagnostic and causality classifications performed using other tools (Bastuji-Garin et al., 2000).

An important difference identified in the comparative matrix concerns the evaluation of cutaneous involvement. RegiSCAR incorporates skin eruption characteristics and the extent of affected body surface area as components of DRESS classification. SCORTEN, however, evaluates the percentage of epidermal detachment as one of its mortality-associated variables. Although both instruments include a cutaneous domain, the underlying measurements are not equivalent. The surface affected by a DRESS-associated eruption is not directly comparable with the detached or detachable epidermal surface evaluated in epidermal necrolysis. Likewise, ALDEN does not use the extent of epidermal detachment as an independent causality-scoring component, since its principal variables are related to drug exposure and causal probability (Kardaun et al., 2007; Sassolas et al., 2010; Bastuji-Garin et al., 2000).

The evaluation of alternative explanations was another domain shared by RegiSCAR and ALDEN, although its application differs between the two instruments. RegiSCAR incorporates investigations intended to exclude infectious, autoimmune, or other potential causes of the observed systemic manifestations. ALDEN considers alternative etiologies when determining the probability that a specific medication caused epidermal necrolysis. SCORTEN does not directly assess competing diagnostic explanations because its variables are selected for mortality prediction rather than causal attribution. This distinction is reflected in the comparative distribution of domains represented in the figure.

Figure 4.

Therapeutic Outcomes of Systemic Immunomodulatory Treatments in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

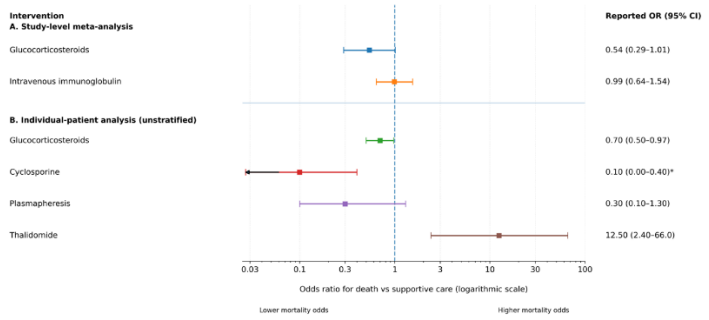


Figure 4 presents the comparative mortality estimates associated with systemic immunomodulatory therapies in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). The graphical representation is based on the systematic review and meta-analysis conducted by Zimmermann et al. (2017), which included 96 studies involving 3,248 patients. The investigation evaluated several therapeutic approaches, including systemic glucocorticosteroids, intravenous immunoglobulin, cyclosporine, plasmapheresis, and thalidomide. Treatment-associated mortality was expressed through odds ratios (ORs) and 95% confidence intervals (CIs), using supportive care as the reference condition. The figure distinguishes estimates derived from pooled study-level data from those obtained through unstratified individual-patient regression models.

In the pooled study-level analysis, systemic glucocorticosteroids were associated with an estimated mortality OR of 0.54 (95% CI: 0.29–1.01). The point estimate indicated lower odds of death among corticosteroid-treated patients compared with those receiving supportive care. However, the confidence interval extended slightly beyond the null value of 1.0, indicating that the association did not reach conventional statistical significance. This estimate was derived from 11 studies providing 12 independent comparisons, with relatively low reported statistical heterogeneity ($I^2 = 5.9\%$). The findings therefore demonstrated a favorable direction of association without establishing a statistically significant reduction in mortality within the aggregated analysis (Zimmermann et al., 2017).

The same investigation performed analyses using individual patient data from a subset of the included studies. The unstratified regression model identified an OR of 0.70 (95% CI: 0.50–0.97) for systemic glucocorticosteroids, representing a statistically significant association with lower mortality odds. Nevertheless, the corresponding analysis stratified by study produced an OR of 0.80 (95% CI: 0.40–1.30), which did not demonstrate statistical significance. These results indicate that the magnitude and statistical precision of the corticosteroid-associated effect varied according to the analytical approach. The differences between models are particularly relevant because the estimates were generated from partially overlapping patient populations and should not be interpreted as independent treatment comparisons (Zimmermann et al., 2017).

Intravenous immunoglobulin demonstrated a different distribution of mortality estimates. The pooled analysis produced an OR of 0.99 (95% CI: 0.64–1.54), with the point estimate positioned close to the null value. The confidence interval extended across both potentially favorable and unfavorable associations, and no statistically significant difference in mortality was identified relative to supportive care. This result was derived from nine studies contributing ten independent treatment comparisons. The investigators reported no detectable statistical heterogeneity in this comparison ($I^2 = 0\%$), although the absence of measurable heterogeneity did not eliminate uncertainty concerning treatment effectiveness. Individual-patient analyses similarly failed to demonstrate a consistent survival advantage associated with intravenous immunoglobulin (Zimmermann et al., 2017).

Among the therapies evaluated through individual-patient regression, cyclosporine exhibited one of the lowest reported mortality estimates. The unstratified exact logistic regression model produced an OR of 0.10 (95% CI: 0.00–0.40, with the lower bound rounded as reported in the original publication). The estimate was derived from a subgroup of 40 patients receiving cyclosporine, among whom no deaths were recorded. The graphical representation therefore places the point estimate below the null value while indicating the uncertainty associated with the lower confidence limit. Although the reported association was statistically significant, the relatively small treatment group and the characteristics of the underlying observational evidence limited the precision and generalizability of the estimate (Zimmermann et al., 2017).

Plasmapheresis was associated with an estimated mortality OR of 0.30 (95% CI: 0.10–1.30) in the unstratified individual-patient analysis. Although the point estimate indicated lower mortality odds relative to supportive care, the confidence interval included the null value, and the association was not statistically significant. The analysis involved a comparatively small subgroup of 16 patients who received plasmapheresis. The relatively broad confidence interval reflected considerable uncertainty surrounding the estimated treatment-associated effect. Consequently, the available quantitative findings described a potentially favorable direction without establishing a statistically reliable mortality difference (Zimmermann et al., 2017).

In contrast to the preceding interventions, thalidomide demonstrated an association with increased mortality. The unstratified individual-patient analysis produced an OR of 12.50 (95% CI: 2.40–66.00), indicating significantly higher mortality odds among treated patients compared with supportive care. The estimate was based on a small number of exposed patients, with much of the available information originating from a randomized trial that had previously identified unfavorable treatment outcomes. The wide confidence interval reflected substantial imprecision in the magnitude of the estimated association, although its lower limit remained above 1.0. Among the interventions represented in Figure 4, thalidomide was the only treatment whose plotted mortality estimate and confidence interval were entirely positioned on the side indicating increased mortality odds (Zimmermann et al., 2017).

The distribution of confidence intervals across the six plotted estimates demonstrated considerable differences in statistical precision and direction of association. Systemic glucocorticosteroids showed estimates below 1.0 in both represented analytical approaches, although statistical significance was observed only in the unstratified individual-patient model. Intravenous immunoglobulin produced a point estimate close to 1.0, while plasmapheresis demonstrated a lower point estimate with a confidence interval crossing the null value. Cyclosporine exhibited a statistically significant association with lower mortality odds in a relatively small patient subgroup. Thalidomide showed a statistically significant association with increased mortality. These findings describe the reported results of different analytical models rather than a direct randomized comparison between all five interventions.

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Additional evidence from the network meta-analysis conducted by Tsai et al. (2021) provides a broader quantitative assessment of systemic treatment outcomes in SJS/TEN overlap and TEN. This investigation included 67 studies involving 2,079 patients and evaluated ten treatments in its network comparison of mortality rates. No treatment demonstrated statistically significant superiority over supportive care for mortality reduction in that network analysis, whereas thalidomide was associated with significantly increased mortality (OR: 11.67; 95% CI: 1.42–95.96). A separate analysis using SCORTEN-based standardized mortality ratios identified a statistically significant result for combined corticosteroid and intravenous immunoglobulin therapy (SMR: 0.53; 95% CI: 0.31–0.93). Because standardized mortality ratios and odds ratios represent different statistical measures, the former estimate was not incorporated into the forest plot (Tsai et al., 2021).

The comparison between these investigations also revealed differences in sample size, included treatment groups, outcome assessment, and analytical methodology. Zimmermann et al. (2017) combined study-level meta-analysis with individual-patient regression, whereas Tsai et al. (2021) employed a frequentist network meta-analysis and examined both mortality odds and standardized mortality ratios. Both investigations identified limitations related to heterogeneous clinical populations and the relatively small number of randomized controlled trials. Furthermore, the distribution of disease severity, timing of therapeutic administration, and differences in accompanying supportive care varied among the original studies.

DISCUSIÓN

The findings of this narrative review highlight the considerable clinical and immunological complexity of severe cutaneous adverse drug reactions, particularly drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Although these conditions share an association with delayed drug hypersensitivity, their differences in inflammatory mechanisms, tissue injury, clinical progression, and therapeutic requirements support the need for individualized diagnostic and management strategies. The integration of clinical investigations, mechanistic studies, and international treatment recommendations demonstrates that early recognition remains essential, while important uncertainties persist regarding the prediction of disease severity and the effectiveness of systemic immunomodulatory interventions (Hama et al., 2022; Brüggen et al., 2024; Hama et al., 2025).

The clinical findings summarized in Figure 1 demonstrate the relevance of systemic manifestations in DRESS. In the Brazilian cohort reported by Avancini et al. (2015), fever was observed in 96.2% of patients, while maculopapular exanthema and hepatic involvement were each documented in 85.1%. These findings reinforce the importance of evaluating DRESS as a systemic inflammatory condition rather than an exclusively dermatological disorder. Nevertheless, the elevated frequencies should be interpreted within the context of a relatively small hospital-based population, in which referral patterns and disease severity may influence the distribution of manifestations. The substantial proportion of patients presenting hepatic abnormalities is consistent with international descriptions identifying the liver as one of the most frequently affected organs. This observation also supports the importance of integrating biochemical monitoring into clinical assessment, particularly when the cutaneous presentation appears disproportionate to the underlying systemic injury (Awad et al., 2023; Criado et al., 2025).

From an immunological perspective, DRESS illustrates the interaction between pharmacological exposure, genetic susceptibility, immune dysregulation, and latent viral infections. The participation of drug-reactive T lymphocytes and inflammatory mediators contributes to tissue injury, while herpesvirus reactivation may accompany prolonged disease activity and recurrent manifestations. However, the precise relationship between viral replication and disease progression remains incompletely understood. Hama et al. (2022) and Criado et al. (2025) describe a complex immunological process in which viral reactivation and drug-specific immune responses may interact without necessarily following an identical sequence in all affected patients. This variability limits the interpretation of individual virological findings and emphasizes the need for investigations capable of distinguishing associated immune events from mechanisms directly responsible for organ injury.

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In contrast, the pathophysiology of SJS/TEN is characterized by extensive cytotoxic damage to epidermal cells. The identification of granulysin as a major mediator of keratinocyte death represented an important advance in understanding the biological basis of epidermal necrolysis. Chung et al. (2008) demonstrated the participation of this cytotoxic molecule in widespread epidermal destruction, while subsequent studies identified additional inflammatory pathways involving activated cytotoxic lymphocytes and tumor necrosis factor-alpha signaling. These mechanisms provide a biological rationale for investigating targeted immunomodulatory agents. However, identifying a pathway involved in disease development does not necessarily establish that inhibiting it will improve survival or prevent long-term complications. The translation of experimental mechanisms into effective clinical interventions therefore remains an important challenge (Wang et al., 2018; Hama et al., 2025).

The anatomical classification represented in Figure 2 provides a standardized framework for distinguishing SJS, SJS/TEN overlap, and TEN according to the extent of epidermal detachment. Nevertheless, the percentage of detached epidermis should not be considered an isolated representation of overall clinical severity. Patients with limited detachment may develop substantial mucosal involvement, severe ocular complications, or systemic abnormalities, while the extent of cutaneous injury may change during disease progression. The distinction between classification and prognosis is therefore clinically relevant. The criteria established by Bastuji-Garin et al. (1993) continue to provide a widely recognized framework, although recent international recommendations acknowledge variations in classification systems and emphasize the evaluation of associated complications (Murillo-Casas et al., 2025; Watanabe et al., 2026).

The comparison of RegiSCAR, ALDEN, and SCORTEN in Figure 3 further emphasizes the importance of selecting assessment instruments according to their specific clinical purposes. RegiSCAR provides a structured approach to DRESS diagnostic classification, ALDEN evaluates the probability that a particular medication caused epidermal necrolysis, and SCORTEN estimates mortality risk in SJS/TEN. These instruments address complementary but fundamentally different questions and should not be interpreted interchangeably. Their incorporation into clinical practice may improve documentation and communication among specialists, although none replaces clinical judgment or comprehensive patient evaluation. Furthermore, diagnostic scores may be influenced by the timing of assessment, since certain manifestations and laboratory abnormalities develop progressively. Repeated evaluation may therefore be necessary when the initial presentation is incomplete or atypical (Kardaun et al., 2007; Bastuji-Garin et al., 2000; Sassolas et al., 2010).

Therapeutic management represents one of the areas with the greatest remaining uncertainty. In DRESS, systemic corticosteroids continue to play a central role in patients with significant internal organ involvement, while less severe presentations may be managed through topical treatment and supportive measures. The international Delphi consensus developed by Brüggen et al. (2024) established recommendations based on disease severity and emphasized prolonged monitoring because of the possibility of relapse and delayed complications. Nevertheless, the limited availability of comparative clinical trials restricts conclusions regarding optimal corticosteroid dosing, treatment duration, and the effectiveness of alternative immunosuppressive agents. This situation demonstrates the importance of distinguishing widely accepted therapeutic practice from interventions supported by stronger comparative evidence.

In SJS/TEN, the quantitative findings presented in Figure 4 illustrate the difficulty of establishing the superiority of individual immunomodulatory treatments. Zimmermann et al. (2017) identified potentially favorable mortality associations for systemic corticosteroids and cyclosporine, whereas intravenous immunoglobulin did not demonstrate a consistent survival benefit. The interpretation of these results is complicated by differences in patient characteristics, disease severity, therapeutic timing, and statistical methodology. Additionally, observational studies may be affected by treatment-selection bias, since interventions are frequently chosen according to the patient's clinical condition. Consequently, associations between treatment exposure and mortality cannot be assumed to demonstrate a direct causal effect.

These uncertainties are further illustrated by the network meta-analysis conducted by Tsai et al. (2021), in which no evaluated systemic treatment demonstrated statistically significant superiority over supportive care in the principal network comparison of mortality. Although combined corticosteroid and intravenous immunoglobulin therapy showed a favorable association in the standardized mortality analysis, differences between outcome measures prevent direct equivalence with odds ratios from other investigations. Similarly, cyclosporine and tumor necrosis factor-alpha

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inhibitors remain promising interventions, but their precise role requires additional comparative evidence. The randomized investigation conducted by Wang et al. (2018) provided support for etanercept as a potential therapeutic option, while more recent recommendations continue to recognize limitations concerning study size, patient selection, and treatment combinations (Martinez Villarreal et al., 2025; Watanabe et al., 2026).

An important consideration emerging from these findings is that therapeutic effectiveness cannot be evaluated independently of supportive care. In SJS/TEN, fluid management, wound protection, infection surveillance, nutritional support, pain control, and early ophthalmological assessment remain fundamental components of treatment. Similarly, the management of DRESS requires monitoring of affected organs, evaluation of inflammatory activity, and prevention of medication re-exposure. The development of multidisciplinary clinical pathways may contribute to greater consistency in patient assessment and referral. However, demonstrating their impact on mortality, complications, and long-term functional outcomes will require appropriately designed clinical investigations (Cabañas et al., 2020; Murillo-Casas et al., 2025).

The international applicability of the reviewed evidence also deserves consideration. Latin American investigations have contributed to the characterization of DRESS and the development of regionally relevant recommendations for SJS/TEN. Nevertheless, differences in pharmacological availability, healthcare infrastructure, diagnostic resources, and access to specialized services may influence clinical outcomes. The Latin American guidelines published by Murillo-Casas et al. (2025) represent an important contribution by adapting available evidence and expert recommendations to regional practice. Future multicenter investigations involving Latin American populations could strengthen knowledge of regional pharmacological triggers, genetic susceptibility, diagnostic delays, and treatment accessibility. Such research would also improve the representation of populations that remain relatively underrepresented in large international clinical datasets.

Several limitations must be acknowledged. First, the narrative design and focused selection of 20 scientific publications do not provide the comprehensive coverage or formal risk-of-bias assessment characteristic of a systematic review. Second, the included investigations differ in diagnostic definitions, sample sizes, clinical populations, and reported outcomes, limiting direct comparisons. Third, the quantitative findings represented in the figures originate from previously published studies and should not be interpreted as results from a newly recruited patient population. Finally, the relatively limited number of randomized controlled trials and the predominance of retrospective evidence in certain therapeutic comparisons restrict the strength of causal conclusions. These limitations reinforce the need for standardized outcome definitions, prospective multicenter studies, and more consistent evaluation of both acute mortality and long-term complications.

Taken together, the available evidence suggests that advances in understanding the immunopathogenesis of DRESS and SJS/TEN have improved the biological interpretation of their clinical manifestations, but important gaps remain between mechanistic knowledge and definitive therapeutic recommendations. Early withdrawal of the suspected medication, structured assessment, appropriate supportive care, and multidisciplinary follow-up remain central components of management. Further research should prioritize reliable early biomarkers, improved pharmacogenomic risk assessment, well-designed comparative therapeutic trials, and long-term outcomes across diverse populations. Integrating these research priorities with international collaboration and greater Latin American participation may contribute to more consistent, individualized, and evidence-based care for patients with severe cutaneous adverse drug reactions.

CONCLUSIÓN

Severe cutaneous adverse drug reactions, particularly drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), represent complex immune-mediated disorders that require early recognition, accurate clinical assessment, and individualized therapeutic management. The evidence reviewed demonstrates that, although these conditions share an association with drug-induced hypersensitivity, their immunopathological mechanisms and patterns of tissue injury differ substantially. DRESS is predominantly characterized by systemic inflammation, immune dysregulation, and potential viral

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reactivation, whereas SJS/TEN involves extensive cytotoxic keratinocyte injury and epidermal destruction (Hama et al., 2022; Hama et al., 2025).

The findings emphasize the importance of integrating clinical manifestations, medication history, laboratory abnormalities, and standardized assessment instruments into the diagnostic process. RegiSCAR, ALDEN, and SCORTEN provide complementary approaches to diagnostic classification, pharmacological causality assessment, and mortality risk estimation, respectively. Their appropriate application may support more consistent clinical evaluation, although these instruments must be interpreted alongside the patient's evolving condition and should not replace professional judgment.

Regarding therapeutic management, immediate discontinuation of the suspected medication, supportive care, and multidisciplinary monitoring remain essential components of treatment. Systemic corticosteroids continue to be widely employed in severe DRESS, while immunomodulatory therapies such as cyclosporine and tumor necrosis factor-alpha inhibitors have shown potentially favorable outcomes in selected SJS/TEN investigations. Nevertheless, the heterogeneity of available studies and the limited number of randomized clinical trials prevent definitive conclusions regarding the superiority of individual therapeutic interventions. Treatment decisions must therefore consider disease severity, organ involvement, available clinical evidence, and patient-specific characteristics (Zimmermann et al., 2017; Brüggen et al., 2024).

The integration of international research with Latin American scientific contributions highlights the importance of developing more representative clinical evidence. Regional differences in genetic susceptibility, medication exposure, specialized healthcare access, and pharmacovigilance resources require further investigation. Future studies should prioritize prospective multicenter designs, early diagnostic biomarkers, comparative therapeutic effectiveness, and long-term functional outcomes to strengthen clinical recommendations across diverse populations (Criado et al., 2025; Murillo-Casas et al., 2025).

In conclusion, improving outcomes in DRESS and SJS/TEN requires the integration of immunological knowledge with systematic clinical evaluation and evidence-based therapeutic strategies. Although substantial advances have improved understanding of these conditions, important diagnostic and therapeutic uncertainties remain. Continued international collaboration, standardized clinical assessment, and further investigation into targeted interventions are essential for advancing personalized management, reducing preventable complications, and improving the quality and safety of care for patients affected by severe cutaneous adverse drug reactions.

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