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TOXIC EPIDERMAL NECROLYSIS (LYELL SYNDROME): CURRENT INSIGHTS INTO PATHOGENESIS, CLINICAL FEATURES, AND MANAGEMENT STRATEGIES

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ABSTRACT

Introduction and objectives: Toxic epidermal necrolysis (TEN) is a rare, life-threatening disease of the skin and mucous membranes. It is characterised by extensive desquamation of the epidermis, severe systemic involvement and a high mortality rate. Despite its rarity, it poses a significant clinical challenge due to its rapid progression and the risk of serious complications. The aim of this study was to present the current state of knowledge regarding the etiology, pathogenesis, clinical presentation and treatment strategies for TEN.
Methods: A narrative review was conducted using PubMed and Google Scholar databases. Publications from 2010 to 2026 were included.
Key findings: TEN is most often drug-induced and affects the skin and mucous membranes, with a high risk of mortality. Current evidence points to a key role for cytotoxic immune responses, particularly CD8+ T cells and granzyme B, in the pathogenesis of this disease. The cornerstone of treatment remains rapid discontinuation of the causative agent and intensive supportive care. However, immunomodulatory therapies are increasingly recognized as adjunctive treatment options.
Conclusions: Despite advances in understanding the pathogenesis of TEN, this disease is still associated with high mortality and risk of severe complications. Early diagnosis, prompt discontinuation of the causative agent, and supportive care are crucial to improving prognosis. Further research into targeted therapies and the development of uniform standards for clinical management remain essential.

KEYWORDS

Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, Drug Hypersensitivity, SCORTEN, Keratinocyte Apoptosis, Supportive Care

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1. Introduction

Toxic epidermal necrolysis (TEN), also known as Lyell's Syndrome, is a rare, life-threatening disorder characterized by widespread destruction of the epidermis and mucous membranes. Clinically, it manifests as extensive sheet-like detachment of the skin accompanied by severe mucosal involvement, most commonly triggered by drug exposure (Abtahi-Naeini et al., 2024). TEN is closely related to Stevens-Johnson syndrome (SJS). This classification is based on the extent of body surface area (BSA) detachment: SJS involves less than 10%, SJS/TEN overlap involves 10–30%, and TEN involves more than 30% (Justice et al., 2025). TEN is a rare condition, with an estimated incidence of about 1–2 cases per million individuals each year (Canhão et al., 2022). Females are affected more frequently than males, with an approximate ratio of 1.5:1 (Frantz et al., 2021). The associated mortality remains significant, ranging between approximately 25% and 35% (Canhão et al., 2022). Despite its rarity, TEN is a severe and potentially life-threatening condition that may arise following exposure to widely used medications, often in an unpredictable manner. The aim of this review is to summarize the current knowledge about this disorder, with particular emphasis on its etiology, clinical features, immunopathogenesis, and current treatment strategies and their outcomes.

2. Methodology

A narrative literature review was conducted using PubMed and Google Scholar. Publications published from 2010 to early 2026 were considered. The search was performed using combinations of the following keywords: "toxic epidermal necrolysis," "Stevens-Johnson syndrome," "drug hypersensitivity," "granulysin," "SCORTEN," "ALDEN," "keratinocyte apoptosis," and "treatment of TEN." Original articles, systematic reviews, meta-analyses, clinical guidelines, and selected case series published in English were included.

Although publications from 2010 to 2026 were included in the review, particular emphasis was placed on studies published between 2016 and 2026 due to significant advances in understanding the immunopathogenesis of TEN, genetic susceptibility, and emerging research on new therapeutic strategies during this period. The publication selection process included reviewing titles and abstracts to exclude works not directly related to the topic of toxic epidermal necrolysis. Subsequently, the full texts of eligible articles were assessed for their substantive value, current data, and clinical relevance to the etiology, pathogenesis, and treatment of TEN. Following the final evaluation process, 43 publications were included in the review.

3. Etiology

3.1 Drug Hypersensitivity as the Main Etiological Factor in TEN

The vast majority of cases, exceeding 80%, are linked to prior drug exposure, most commonly involving antimicrobial agents (such as sulfonamides), antiepileptic drugs, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Shah et al., 2024). Additionally, immune checkpoint inhibitors (ICIs), which enhance T-cell activity in a non-specific manner, are recognized as potential triggers of TEN (Hung et al., 2024). Table 1 summarizes examples of drugs associated with toxic epidermal necrolysis reported in the literature.

Table 1. Examples of drugs associated with toxic epidermal necrolysis (TEN)
(Shah et al., 2024; Obed et al., 2025)

Group	Representative drugs
Antibiotics	Piperacillin/Tazobactam Trimethoprim/Sulfamethoxazole Amoxicillin Doxycycline Ciprofloxacin Vancomycin
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital Phenytoin
Antiretroviral	Nevirapine
Other drugs	Allopurinol NSAIDs (Isoxicam, Piroxicam) Immune checkpoint inhibitors (Pembrolizumab)

Drug metabolites can induce a cytotoxic immune response mediated by CD8+ T lymphocytes and natural killer cells, leading to keratinocyte apoptosis (Obed et al., 2025). Symptoms typically develop within 4 to 28 days after initiation of the offending medication. However, latency varies, with rare cases of delayed onset occurring up to several months after drug exposure, particularly with lamotrigine. Conversely, rapid-onset reactions develop within a few days, for example in association with acetaminophen and penicillin (Shah et al., 2024). The ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis) scoring system is widely used to determine the probability of drug causality in TEN, especially in cases involving polypharmacy (Lee et al., 2023). This algorithm evaluates six key criteria to determine the most probable causative drug when multiple drugs are suspected. These include: (1) the time interval between initial drug exposure and onset of the reaction (index day); (2) the presence of the drug in the body at the index day; (3) previous exposure or rechallenge; (4) drug withdrawal (dechallenge); (5) the known association of the drug with TEN (notoriety); and (6) other causes (de Bustros et al., 2022). The ALDEN score should be calculated for each drug taken by the patient, with total scores ranging from −12 to +10. Based on the final score, drugs are classified into five categories: very probable (≥6), probable (4–5), possible (2–3), unlikely (0–1), and very unlikely (<0) (Canhão et al., 2022).

3.2 Genetic Susceptibility

Genetic predisposition also plays a significant role in susceptibility to TEN. Specific human leukocyte antigen (HLA) alleles have been strongly associated with an increased risk of drug-induced reactions. In particular, HLA-B*15:02 and HLA-B*15:11 are linked to a higher risk of TEN in patients treated with carbamazepine (Abulatan et al., 2023). In their study, Rika Yuliwulandari et al. demonstrated that the HLA-B*15:02 allele was identified in 66.7% of patients with carbamazepine-induced TEN (Yuliwulandari et al., 2017). Similarly, HLA-B*58:01 is strongly associated with allopurinol-induced TEN. Beyond HLA-associated risk, genetic polymorphisms affecting drug metabolism may also contribute to disease development. Variants in the CYP2C19 gene, which encodes a cytochrome P450 enzyme, have been associated with an increased risk of TEN in patients receiving antiepileptic drugs such as phenobarbital, phenytoin, and carbamazepine (Abulatan et al., 2023).

3.3 Infectious Triggers

Non-drug-related cases of TEN are more commonly observed in younger populations, including children, adolescents, and young adults, compared with older individuals, largely due to the greater contribution of infectious triggers in these age groups (Hung et al., 2024). Among non-drug factors, viral infections and Mycoplasma pneumoniae play a significant role in the development of SJS or TEN, especially in pediatric patients. Mycoplasma pneumoniae is considered one of the most common infectious causes, accounting for approximately 19–26% of cases (Watanabe & Hama, 2025). It may be challenging to distinguish whether symptoms such as fever, rhinorrhea, or conjunctivitis are attributable to an acute infection or represent the prodromal phase of TEN. Furthermore, patients frequently report the use of analgesic and anti-inflammatory medications to relieve these symptoms (Bordeanu-Diaconescu et al., 2024). As a result, it is often difficult to determine whether TEN was triggered by the underlying infection or by the medications used for its treatment.

4. Immunopathogenesis of TEN

4.1 Fas–FasL Pathway in Keratinocyte Apoptosis

The Fas–Fas ligand (FasL) pathway represents one of the key mechanisms involved in keratinocyte apoptosis in TEN. FasL, produced by cytotoxic CD8+ T lymphocytes and natural killer (NK) cells, binds to Fas receptors on target cells, thereby activating the caspase cascade and inducing apoptosis. Under physiological conditions, Fas is expressed on the cell surface, whereas FasL is primarily localized intracellularly. Upon activation of apoptotic signaling pathways, FasL is translocated to the cell surface (Hasegawa & Abe, 2024). Increased serum levels of soluble Fas ligand (sFasL) have been noted in patients with SJS/TEN (Justice et al., 2025), which may be associated with disease activity.

4.2 Granulysin- and Granzyme B–Mediated Cytotoxicity in TEN

Granulysin and granzyme B are key mediators of skin injury in TEN. During the acute phase of the disease, these molecules are present at elevated levels in both serum and blister fluid, reflecting drug-induced immune activation (Srinoulprasert et al., 2026). CD8+ T lymphocytes and NK cells exert their cytotoxic effects through the release of perforin and granzyme B. Perforin forms pores in the target cell membrane, thereby facilitating the entry of granzyme B. Once inside, granzyme B, a serine protease, induces apoptosis by activating key executioner caspases, particularly caspase-3 and caspase-7 (Justice et al., 2025).

Granulysin interacts with cell membranes, disrupting their integrity and leading to mitochondrial damage and ultimately cell death. Its expression is upregulated following activation of T cells and NK cells. Notably, granulysin expression in blister-derived cells from SJS/TEN patients is 10–20 times higher than in peripheral blood mononuclear cells (PBMCs). In comparison, the increase in other cytotoxic mediators is less pronounced, including granzyme B (8-fold), perforin (3-fold), and Fas ligand (2-fold), suggesting that granulysin plays a dominant role in mediating keratinocyte apoptosis in SJS/TEN (Justice et al., 2025).

5. Clinical Presentation

TEN typically begins with a short prodromal phase (1–3 days) marked by high fever and influenza-like symptoms, followed by rapidly progressive mucocutaneous involvement (Singh & Phillips, 2022). Involvement of mucosal surfaces is observed in the vast majority of cases (>90%), most frequently affecting the ocular, oral, and genital regions, where it presents as conjunctival inflammation, painful oral erosions, and genital ulcerations (Breidung et al., 2025). Cutaneous manifestations are typically characterized by abrupt onset of a painful, burning macular exanthema. Lesions initially appear symmetrically on the face, proximal extremities, and upper trunk, often sparing the scalp, before rapidly disseminating. The eruption often reaches maximal extent within four days, although in severe cases progression may occur within hours (Bordeanu-Diaconescu et al., 2024). Severe cases are characterized by widespread epidermal detachment with sheet-like desquamation (positive Nikolsky sign) (Naik, 2022). In addition to cutaneous manifestations, TEN is characterized by early systemic involvement affecting the respiratory tract, gastrointestinal mucosa, and kidneys, with gastrointestinal involvement presenting as severe diarrhea and renal involvement potentially leading to acute tubular necrosis and acute kidney injury (Surowiecka et al., 2023).

6. Management of Toxic Epidermal Necrolysis

The management of TEN begins with the immediate identification and withdrawal of the causative agent. The ALDEN scale and the Liverpool Adverse Drug Reaction Causality Assessment Tool (ADR CAT) have been shown to be effective in identifying the suspected offending drug (Gallagher et al., 2011; Sassolas et al., 2010). Prognostic evaluation is commonly performed using the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN), which remains the most extensively validated tool to date (Dobry et al., 2022; Gallagher et al., 2011). It has demonstrated superior predictive accuracy compared with alternative scoring systems, including the ABCD-10 algorithm developed by Noe et al. (2019). These prognostic models may support clinical decision-making, including the need for intensive care unit admission or transfer to a specialized burn center (Frantz et al., 2021).

6.1 Supportive care

Management is difficult due to the rarity of the disease and the lack of high-quality randomized controlled trials. The basis of treatment remains supportive care, including airway protection, pain control, fluid and electrolyte management, nutritional support, and prophylaxis of stress ulcers and deep vein thrombosis. Multidisciplinary involvement is essential, including specialists in dermatology, intensive care, ophthalmology, oral medicine, and urology (Shah et al., 2024).

6.2 Wound management

Patients with TEN require wound care comparable to that used in severe burn injuries due to extensive epidermal loss. Current dermatological guidelines generally discourage early surgical intervention, favoring conservative management strategies instead (Seminario-Vidal et al., 2020). Appropriate wound care involves the use of non-adherent dressings that minimize trauma to the epidermis and reduce the risk of infection (Schneider & Cohen, 2017). Castillo et al. compared simple and advanced dressings (fiber-based, biologic, synthetic) and found modern options may support standard care, though more studies are needed to confirm their effect on healing time (Castillo et al., 2018). Regarding wound cleansing strategies, comparative studies

assessing early debridement techniques (including water-jet systems combined with synthetic dressings) versus conservative approaches have shown no definitive superiority of either method, with similar outcomes in terms of mortality and re-epithelialization time (Creamer et al., 2016).

6.3 Systemic therapy

Systemic treatment of TEN remains controversial due to limited evidence and the rarity of the condition. Therapeutic decisions are based mainly on observational studies, case series, and meta-analyses rather than on randomized controlled trials (Surowiecka et al., 2023).

Oral or intravenous corticosteroids are commonly used in the treatment of TEN. Some studies suggest that early initiation of high-dose therapy, particularly within the first 24–48 hours of symptom onset, may improve patient outcomes (Shah et al., 2024). However, the effectiveness of corticosteroid therapy remains controversial. Previous reports highlighted an increased risk of infections, including sepsis, and a lack of a clear effect on mortality, whereas more recent systematic reviews and meta-analyses suggest potential benefits of systemic corticosteroids in patients with TEN compared with supportive care (Hsieh et al., 2021).

Ciclosporin A is considered a promising therapeutic option for TEN. Multiple studies have reported improved survival outcomes compared with supportive care alone (González-Herrada et al., 2017; Lee et al., 2017; Torres-Navarro et al., 2021). However, its efficacy may be reduced in patients with significant comorbidities, particularly renal impairment, and this should be considered when selecting therapy (Noe et al., 2018).

Tumor necrosis factor-alpha (TNF-α) inhibitors, such as etanercept, represent an emerging therapeutic option in TEN, with limited but growing evidence suggesting potential benefit.

These agents represent a novel and increasingly studied therapeutic strategy. Evidence suggests that etanercept, particularly with corticosteroids, may reduce mortality and accelerate re-epithelialization. Therefore, combination therapy may be an alternative for patients with severe disease or poor response to corticosteroids. Nevertheless, further research is required to confirm these findings (Tian et al., 2022; Zhang et al., 2022). Current evidence is limited primarily to observational studies and small patient cohorts, restricting the generalizability of reported benefits.

Despite previous evidence suggesting the potential efficacy of IVIG, current data do not clearly support its clinical benefit in TEN. More recent systematic reviews and meta-analyses have not demonstrated a significant improvement in survival compared with supportive care alone, a finding also supported by retrospective studies that found no association between IVIG dose and patient outcomes. The lack of consensus and inconsistent clinical data suggest a need for further research on the efficacy of IVIG in the treatment of TEN (Charlton et al., 2020).

6.4 Special populations and emerging therapies

Special populations, such as pregnant patients and children, may require individualized treatment and dose adjustments due to altered pharmacokinetics and safety (Shah et al., 2024). Current treatment strategies primarily focus on inflammation suppression. Increasing insight into disease pathogenesis has led to the development of several novel targeted therapies, including the human monoclonal antibody PC111, formyl peptide receptor 1 (FPR1) antagonists, Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors, and daratumumab, an anti-CD38+ monoclonal antibody (Hama et al., 2024).

7. Complications and Outcomes

7.1 Infections and Sepsis

TEN is associated with a high mortality rate, estimated at 25–35%, primarily due to infectious complications and multi-organ failure (Canhão et al., 2022). Prevention of sepsis remains a critical component of management (Sunaga et al., 2022). Patient management requires ongoing clinical surveillance, including assessment of vital signs and targeted testing for infectious complications. Routine antibiotic prophylaxis is not recommended, but antimicrobial therapy should be initiated immediately after infection is confirmed (Shah et al., 2024).

7.2 Quality of life

TEN is a severe condition with a broad spectrum of complications. Affected patients report a significantly reduced quality of life and impaired physical functioning compared to the general population, particularly among younger individuals (Chiu & Chiu, 2023). Multidisciplinary follow-up is recommended both during the acute phase and after hospital discharge. Survivors frequently experience significant psychosocial sequelae, including post-traumatic stress disorder (PTSD), depression, and anxiety. Clinicians should remain vigilant for these conditions, incorporate validated screening tools into mental health assessments, and refer patients to appropriate support groups (Hoffman et al., 2021).

7.3 Somatic complications

Beyond psychosocial sequelae, survivors are also at risk of a wide range of long-term somatic complications. They most commonly involve the skin, eyes, and oral mucosa, but may also affect the respiratory, gastrointestinal, genitourinary, and otorhinolaryngological systems (Hoffman et al., 2021). Long-term somatic complications are presented in table 2.

Table 2. Classification of long-term somatic complications of toxic epidermal necrolysis by organ system (Shah et al., 2024).

General	fatigue, malaise, sleep disturbances, chronic pain
Cutaneous	dyspigmentation, photosensitivity, abnormal sweating, scarring, nail and hair loss, post-inflammatory skin changes
Ocular	dry eye, eyelid dysfunction, symblepharon, chronic ocular surface inflammation, conjunctivalization of the cornea, keratinization, neovascularization, punctal damage and tear duct scarring, photophobia, visual impairment
Oral mucosa	dryness, dental caries, abnormal root development, hypoplasia of permanent teeth, mucosal scarring, loss of tongue papillae
Pulmonary	dyspnea, cough, wheezing, obstructive lung disease (i.e., bronchiolitis obliterans, bronchiectasis)
Gastrointestinal	intestinal ulcers, dysphagia, esophageal strictures or webs
Genitourinary	dyspareunia, vulvar and vaginal adenosis or stenosis, labial fusion, subfertility or infertility (secondary to menstrual abnormalities), urethral erosions and strictures, balanitis, phimosis

7.4 Multidisciplinary follow-up

A multidisciplinary follow-up schedule proposed by Ingen-Housz-Oro et al. recommends evaluation by a dermatologist, ophthalmologist, and psychiatrist or psychologist within 1–2 months after discharge. Additional consultations with a pulmonologist, gynecologist or urologist, and dietitian should be arranged as clinically indicated. At 6 months, reassessment by the relevant specialists is advised based on individual patient needs, along with a dental evaluation. This time point is also suitable for a comprehensive allergy work-up. After 1 year, continued dermatological follow-up is recommended to reassess patient needs and coordinate ongoing multidisciplinary care (Ingen-Housz-Oro et al., 2023).

8. Recovery and Rehabilitation

Toxic Epidermal Necrolysis leads to long-term complications affecting biological, psychological, and social functioning. Survivors frequently experience widespread pain, severe fatigue, physical changes, and a significant psychological burden, including health-related anxiety and disrupted interpersonal relationships. Post-discharge follow-up is often insufficient, contributing to reduced trust in healthcare systems and highlighting gaps in patient education, coordination of services, and access to mental health support (Martin-Pozo et al., 2026).

Early rehabilitation during hospitalization, followed by continued multidisciplinary follow-up, is essential to improve recovery and long-term outcomes. Ophthalmic complications require early treatment and visual rehabilitation, followed by ongoing specialist monitoring after discharge (Akgun et al., 2025). The same

applies to vulvovaginal changes, indicating that gynecological assessment and support should also be included in long-term management (DenAdel et al., 2022).

Overall, these findings highlight the need for coordinated care pathways and better education of healthcare professionals managing TEN survivors.

9. Conclusions

Toxic epidermal necrolysis remains a rare but severe and life-threatening drug-induced disease characterized by extensive keratinocyte apoptosis and high mortality. Current evidence suggests a key role for cytotoxic immune mechanisms, particularly CD8+ T cells and effector molecules such as granulysin and granzyme B, in the pathogenesis of the disease.

Despite advances in understanding the underlying mechanisms, supportive care and prompt drug discontinuation remain the cornerstone of treatment. New immunomodulatory therapies show potential benefits, but their effectiveness remains limited and inconsistent. The high risk of infectious complications, long-term sequelae, and impaired quality of life underscores the importance of multidisciplinary treatment and structured, long-term follow-up. Further research is needed to develop standardized, targeted treatment strategies and improve clinical outcomes in patients with TEN.

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