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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Immunopathogenic Basis of Epithelial Collapse and Ocular Damage

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Abstract

The spectrum comprising Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a critical model of systemic epithelial disruption, characterized by massive keratinocyte apoptosis mediated by dysregulation of adaptive immunity. Although dermoepidermal denudation defines dis-

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ease severity during the acute phase, the ocular surface exhibits a distinctive immunopathological susceptibility whose progression toward chronicity may occur independently of the extent of cutaneous injury. This biological autonomy is related to the breakdown of ocular immune privilege and to the intrinsic vulnerability of high-turnover epithelial tissues to targeted cytotoxic aggression. This review describes the pathological pathways that mediate the synchronized destruction of the mucosal barrier, emphasizing the relationship between the immunological mechanisms responsible for epidermal necrosis and the involvement of ocular tissues. The transition from acute denudate keratoconjunctivitis to the progressive collapse of the limbal stem cell niche is examined, evaluating how persistent immune-mediated cytotoxicity, aberrant remodeling of the extracellular matrix, and loss of tissue plasticity promote the development of persistent epithelial defects, conjunctival scarring, and permanent homeostatic failure of the ocular surface.

Keywords

Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Epithelial Necrosis

1. Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent variants of the same spectrum of severe immune-mediated mucocutaneous reactions characterized by massive keratinocyte apoptosis leading to extensive loss of cutaneous and mucosal epithelial integrity. From a pathophysiological perspective, these conditions correspond to delayed hypersensitivity reactions mediated by cytotoxic T lymphocytes directed against keratinocytes presenting specific drug-HLA complexes, triggering an effector response that culminates in extensive epidermal necrosis and mucosal denudation [1].

Clinically, the SJS/TEN spectrum is classified according to the percentage of detached body surface area: SJS involves less than 10% of the total body surface area, TEN more than 30%, whereas involvement between 10% - 30% corresponds to the SJS/TEN overlap form. Due to their systemic nature and the potential progression toward multiorgan dysfunction, these conditions are considered critical dermatologic emergencies in which early diagnosis and immediate withdrawal of the causative agent are directly associated with improved clinical outcomes [2] [3].

In most cases, the trigger corresponds to medications administered days or weeks prior to symptom onset. The most frequently implicated agents include aromatic anticonvulsants, sulfonamides, allopurinol, β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs. However, pharmacologic causal attribution requires a systematic evaluation integrating exposure chronology, drug notoriety, and exclusion of alternative causes. In clinical studies and pharmacovigilance, this assessment is often performed using structured causality algorithms, such as ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis), specifically designed to

estimate the probability that a drug triggered SJS/TEN [4].

Although the SJS/TEN spectrum is predominantly drug-related, clinically similar presentations associated with infections have been described, particularly with Mycoplasma pneumoniae. In these cases, the clinical picture may manifest with prominent mucositis and limited cutaneous involvement, a condition currently recognized as Mycoplasma pneumoniae-induced rash and mucositis (MIRM). This entity shares clinical features with SJS/TEN but differs in epidemiology, immunopathology, and prognosis; therefore, its recognition is essential to avoid erroneous attribution of drug causality and to properly guide differential diagnosis within the spectrum of severe mucocutaneous reactions [5].

The global incidence of the SJS/TEN spectrum is estimated to range between 2 and 7 cases per million inhabitants per year in the general population, with regional variations associated with genetic factors and drug prescription patterns [4] [5]. SJS represents the most frequent clinical form and occurs approximately three times more often than TEN; however, mortality increases proportionally with the extent of epidermal detachment, reaching rates of approximately 30% - 50% in patients with TEN, particularly in hospitalized cohorts with extensive cutaneous involvement or significant systemic comorbidities [6] [7].

Individual susceptibility to the development of these reactions is not random. Recent research has demonstrated robust associations between specific alleles of the major histocompatibility complex (MHC) and the risk of developing SJS/TEN following exposure to certain drugs. Among the most representative examples are the HLA-B*15:02 allele, associated with carbamazepine-induced reactions in Asian populations, and HLA-B*58:01, strongly linked to allopurinol. Additionally, variants such as HLA-A*33:01 and HLA-A*24:02 have been associated with an increased risk of severe ocular involvement. These findings support the hypothesis that the specific interaction between drugs and HLA molecules constitutes the initiating event that triggers clonal activation of cytotoxic T lymphocytes and determines both individual susceptibility and the distribution of mucocutaneous injury [8]-[10].

The clinical course is usually preceded by a nonspecific prodrome characterized by fever, malaise, and respiratory symptoms. Subsequently, a painful cutaneous eruption appears, typically beginning with poorly demarcated erythematous macules with a tendency toward confluence, predominantly involving the trunk and facial region. Within hours or days these lesions may progress to flaccid blisters and epidermal detachment, reflecting extreme epithelial fragility clinically manifested by a positive Nikolsky sign. Mucosal involvement constitutes a central diagnostic feature and may simultaneously affect the oral cavity, genital mucosa, respiratory tract, and ocular surface, significantly contributing to the systemic morbidity of the disease [11].

Within this clinical spectrum, ocular surface involvement represents one of the most devastating and frequent complications. Several clinical series estimate that ophthalmologic manifestations occur in approximately 50% of cases during the

acute phase, although this frequency may be higher in specialized ophthalmologic referral cohorts. Early conjunctival and corneal epithelial injury constitutes a critical determinant of abnormal scarring, keratinization, and progressive loss of corneal transparency if specialized ophthalmologic management is not initiated promptly. In many patients, progression toward chronic ocular sequelae occurs even after resolution of the acute cutaneous phase, indicating that the ocular surface possesses an immunopathological dynamic that is partially independent of the initial dermatologic injury [12] [13].

In this context, understanding the immunological mechanisms governing epithelial destruction and subsequent ocular regenerative failure is essential for interpreting the clinical evolution of these patients. This review analyzes in an integrated manner the immunopathogenic pathways responsible for mucosal surface disruption in SJS/TEN, with particular emphasis on ocular involvement. The transition from acute denudate keratoconjunctivitis to collapse of the limbal stem cell niche is examined, as well as the processes of aberrant tissue remodeling that consolidate the irreversible loss of ocular surface homeostasis.

2. Immunopathogenesis of Epithelial Injury in SJS/TEN

2.1. Immune Initiation and the Role of Genetic Predisposition

The SJS/TEN spectrum represents a paradigm of immune-mediated cytotoxicity in which the epithelium becomes the target of an extreme effector response. The pathogenesis does not correspond to a nonspecific inflammatory process but rather to a loss of peripheral tolerance orchestrated by the interaction between drugs and the HLA system. This antigenic recognition has been mainly explained through two complementary models: the classical hapten theory, in which drug metabolites covalently bind to self-proteins generating immunogenic complexes, and the pharmacological interaction model (p-i concept), which proposes the non-covalent binding of the drug to the T-cell receptor (TCR) or to the peptide-binding groove of MHC-I molecules, triggering lymphocyte activation without the need for conventional antigen processing [14] [15].

The architecture of this immune response is genetically conditioned. The presence of specific class I HLA alleles increases the affinity for certain pharmacological compounds, facilitating the clonal activation of cytotoxic $CD8^+$ T lymphocytes and, to a lesser extent, $CD4^+$ T lymphocytes. This susceptibility has been particularly documented in reactions associated with aromatic anticonvulsants, sulfonamides, or allopurinol. Likewise, the increasing use of immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4) has highlighted the central role of immune tolerance regulation, since disruption of these regulatory mechanisms may precipitate SJS/TEN through expansion of previously anergic T-cell populations [16] [17].

2.2. Effect Dynamics: The Keratinocyte as Target and Amplifier

Once antigen recognition is initiated, clonal expansion of cytotoxic $CD8^+$ T lymphocytes lead to their migration toward the dermoepidermal junction, guided by

chemotactic gradients and by adhesion molecules expressed by stressed keratinocytes. Within this inflammatory microenvironment, the keratinocyte does not function merely as a passive target cell but actively participates in amplification of the cytotoxic response through increased expression of MHC-I molecules and receptors associated with programmed cell death [18].

Epithelial injury converges through several effector pathways that induce synchronized keratinocyte apoptosis:

- **Granulysin:** considered one of the predominant cytotoxic mediators in SJS/TEN, capable of directly disrupting cellular membranes and correlating with the extent of epidermal necrosis.
- **Perforin-granzyme B axis:** responsible for the formation of transmembrane pores that allow granzyme entry and activation of the intracellular caspase cascade.
- **Fas-FasL pathway:** an extrinsic apoptotic mechanism that amplifies the programmed cell death signal among adjacent keratinocytes.

These cytotoxic pathways are further amplified in an environment dominated by pro-inflammatory cytokines, including IFN-γ, TNF-α, and IL-15, which promote survival and expansion of effector T lymphocytes, allowing epithelial destruction to persist even after withdrawal of the causative drug [19]-[21].

The same mechanisms responsible for epidermal necrosis also affect mucosal surfaces, where the high epithelial turnover rate and abundant expression of MHC molecules confer susceptibility to lymphocyte-mediated cytotoxicity. This characteristic explains the synchronous involvement of multiple mucosal surfaces—oral, genital, respiratory, and ocular—observed during the acute phase of the disease [22].

2.3. Histopathological Progression and Multiorgan Involvement

The histological correlation of this cascade evolves from basal vacuolization and isolated apoptotic keratinocytes in early stages to full-thickness epidermal necrosis with detachment of the dermoepidermal junction. This process reflects the coordinated action of the previously described cytotoxic mechanisms on keratinocytes, which constitute the principal immunologic targets in SJS/TEN.

A characteristic histopathological finding in these lesions is the relative scarcity of inflammatory infiltrate compared with the magnitude of epithelial necrosis, highlighting the predominance of apoptotic mechanisms mediated by cytotoxic T lymphocytes rather than classical exudative inflammatory processes. This histological pattern distinguishes SJS/TEN from other inflammatory bullous dermatoses and reflects the efficiency of immune-mediated cytotoxicity directed against epithelial tissues [23].

This phenomenon of massive cytotoxicity exhibits a particular tropism for mucosal tissues, whose high cellular turnover rate and abundant expression of major histocompatibility complex molecules increase vulnerability to lymphocytic aggression. Consequently, in addition to the skin, several mucosal surfaces may be

affected during the acute phase of the disease:

- **Oral and genital mucosa:** characterized by deep erosions and abnormal tissue remodeling that predisposes to synechiae formation.
- **Respiratory and gastrointestinal involvement:** denudation of the tracheobronchial epithelium may lead to bronchiolitis obliterans, while gastrointestinal involvement, although less frequent, indicates systemic aggression with potential risk of perforation [24] [25].

Within this systemic mucosal involvement, the ocular surface constitutes a particularly vulnerable compartment due to the delicate organization of its epithelium and its dependence on specialized regenerative mechanisms to maintain corneal transparency and tear film stability. This susceptibility explains why ocular injury may continue to progress even when cutaneous lesions begin to resolve, making it one of the principal determinants of long-term functional sequelae [26].

3. Immunopathogenesis of Ocular Involvement in SJS/TEN: From Acute Cytotoxicity to Regenerative Failure

Ocular involvement in SJS/TEN does not represent a passive extension of cutaneous injury but rather a compartmentalized immunopathological process. Its severity and progression toward chronicity depend on the interaction between systemic cytotoxic aggression and the unique immunological architecture of the ocular surface, which possesses regulatory mechanisms that, once overwhelmed, favor the development of permanent functional sequelae [27].

3.1. Disruption of Immune Privilege and Lymphocytic Recruitment

The ocular surface physiologically maintains a state of active immune privilege, characterized by limited expression of major histocompatibility complex molecules, the presence of regulatory T cells, and a tear microenvironment enriched in anti-inflammatory mediators. In the context of SJS/TEN, the systemic cytokine storm promotes disruption of this balance through overexpression of MHC-I molecules in the conjunctival and corneal epithelium [28].

This phenotypic change converts the ocular surface into a direct target for circulating $CD8^+$ T lymphocytes and natural killer (NK) cells. Leukocyte infiltration is facilitated by increased endothelial adhesion molecules and by the release of inflammatory chemokines into the tear film, particularly IL-6 and IL-8. At this stage, cytotoxic mediators such as granulysin play a central role by inducing mitochondrial disruption and cellular lysis. This mechanism explains the acute epithelial denudation observed in the conjunctiva and cornea. The same cytotoxic mechanisms responsible for epidermal necrosis also drive ocular epithelial injury, establishing a direct link between the systemic immunological cascade and the early clinical manifestations of denudate keratoconjunctivitis [29] [30].

3.2. Injury of the Epithelial Unit and Limbal Stem Cell Deficiency

The conjunctival epithelium, due to its high vascularization and the presence of

resident immune cells, undergoes apoptosis mediated through the Fas-FasL and perforin-granzyme pathways. This initial injury promotes the formation of pseudomembranes and epithelial erosions that expose the conjunctival stroma [31].

Persistence of this epithelial cytotoxicity may clinically manifest as persistent epithelial defects, a finding that reflects the inability of the ocular surface to restore epithelial barrier integrity under sustained inflammatory conditions. However, the most critical pathophysiological event occurs at the level of the corneal limbus. The limbal stem cell niche, responsible for continuous renewal of the corneal epithelium, is particularly sensitive to oxidative stress and inflammatory remodeling of the tissue microenvironment. Cytotoxic injury directed against these cells, or destruction of their supporting stromal niche, may lead to the development of **limbal stem cell deficiency (LSCD)**. In the absence of effective corneal regeneration, the corneal surface becomes progressively colonized by conjunctival epithelium—a phenomenon known as **conjunctivalization**—which promotes neovascularization, corneal opacity, and ultimately functional vision loss [32].

3.3. Fibrotic Remodeling and Tear Film Dysfunction

During the transition toward the chronic phase, the ocular microenvironment acquires a profibrotic profile dominated by **transforming growth factor beta (TGF-β)**. Sustained activation of conjunctival fibroblasts promotes disorganized collagen deposition and leads to the development of symblepharon, shortening of the conjunctival fornices, and ankyloblepharon. This scarring process is further aggravated by destruction of goblet cells and accessory lacrimal glands. Loss of the mucin component of the tear film compromises tear film stability and promotes a cycle of mechanical friction and ocular surface dryness that perpetuates inflammation.

In this context, ocular chronicity in SJS/TEN does not depend solely on the initial injury but rather on the convergence of three pathophysiological processes: acute lymphocytic cytotoxicity, disruption of ocular immune privilege, and regenerative failure of the limbal stem cell niche. This interaction explains why patients with limited cutaneous involvement may nevertheless develop severe and progressive ocular sequelae [33].

3.4. Acute Conjunctivitis: A Sentinel Event of the Ocular Surface

Acute conjunctivitis represents the most prevalent ophthalmologic manifestation and is frequently the first clinical indicator of ocular involvement within the SJS/TEN spectrum. Its onset is often synchronous with the systemic prodrome and, in a significant number of cases, precedes extensive epidermal denudation. This early presentation confers important diagnostic value, enabling early identification of patients at higher risk of progression toward ocular surface dysfunction [34].

Unlike conventional infectious or allergic conjunctivitis, acute inflammation in SJS/TEN represents the local expression of systemic cytotoxic aggression. Infiltration of $CD8^+$ T lymphocytes and natural killer (NK) cells into the conjunctival stroma triggers apoptosis of the mucosal epithelium. A distinctive feature of this

process is the disproportion between the magnitude of epithelial damage and the observable inflammatory infiltrate, reflecting the efficiency of cytotoxic mechanisms mediated by molecules such as granulysin and perforin.

Clinically, this manifests as diffuse conjunctival hyperemia, chemosis, and seromucous discharge that may obscure significant epithelial fragility. The initial histological substrate includes basal layer vacuolization and the formation of subepithelial clefts associated with disruption of adhesion complexes. As epithelial cytotoxicity progresses, conjunctival denudation exposes the underlying stroma and promotes the formation of fibrinous pseudomembranes. These structures do not merely represent inflammatory debris but rather fibrin bridges that may facilitate abnormal adhesion between the palpebral and bulbar conjunctival surfaces, initiating the development of symblepharon if timely debridement is not performed [35] [36].

During the acute phase, several clinical classification systems have been proposed to stratify the severity of ocular involvement in SJS/TEN. Among them, one of the most widely used is the **Acute Ocular Severity Score (AOSS)**, which evaluates ocular surface findings during the acute stage of the disease. This system primarily considers the presence and intensity of conjunctival hyperemia, pseudomembrane formation, corneal epithelial involvement, and the extent of epithelial defects. Based on these parameters, ocular involvement can be categorized into increasing degrees of severity, ranging from mild conjunctival inflammation to extensive epithelial damage with corneal denudation. The value of this classification lies in its prognostic relevance, as patients presenting pseudomembranes, persistent epithelial defects, or corneal involvement during the acute phase have a higher risk of developing chronic cicatricial ocular surface sequelae, including symblepharon, conjunctival keratinization, and limbal stem cell deficiency [37].

Therefore, the severity of conjunctivitis in the acute phase functions as a prognostic marker of long-term ocular morbidity. Intense inflammation and sustained epithelial denudation induce oxidative stress on the ocular surface and disrupt tear film homeostasis. Apoptosis of goblet cells and damage to accessory lacrimal glands compromise the mucin component of the tear film, increasing evaporation and exposing corneal nerve endings.

This proinflammatory and desiccating environment not only perpetuates pain and photophobia but also creates metabolic conditions that facilitate the extension of injury toward the cornea. Consequently, acute conjunctivitis in SJS/TEN should be interpreted not as a transient manifestation but as the initial point of disruption of ocular surface homeostasis, whose early management is crucial for preventing permanent visual sequelae [38].

3.5. Acute Corneal Involvement and Persistent Epithelial Defects (PED)

Corneal alterations in SJS/TEN represent the manifestation with the greatest prognostic significance due to their direct correlation with irreversible loss of visual

acuity. These lesions develop early, often as a progression of conjunctival epithelial injury, and encompass a spectrum ranging from diffuse epithelial keratitis to complete stromal denudation. The cornea is affected by the same type IVc hypersensitivity mechanisms described in the epidermis. Infiltration of cytotoxic T lymphocytes and the release of cytotoxic mediators induce epithelial apoptosis and disruption of adhesion complexes between the corneal epithelium and the basement membrane [39].

This epithelial denudation not only exposes the corneal stroma but also disrupts the tissue homeostasis responsible for maintaining corneal transparency, promoting stromal edema and loss of the metabolic control exerted by the epithelium over stromal hydration.

The determining factor in ocular pathophysiology is not solely the magnitude of the initial injury but rather the disruption of the homeostatic balance between epithelial apoptosis and regenerative capacity. Under physiological conditions, corneal repair depends on trophic signals derived from the tear film and on the proliferative reserve located within the corneal limbus. However, in the inflammatory context of SJS/TEN, persistent proinflammatory cytokines and local oxidative stress interfere with these regenerative mechanisms, preventing restoration of epithelial continuity [40].

When corneal reepithelialization does not occur within the expected physiological timeframe, a **persistent epithelial defect (PED)** develops, reflecting failure of ocular surface repair mechanisms.

From a clinical perspective, PEDs represent an ophthalmologic emergency due to the complications that may arise from prolonged exposure of the corneal stroma:

- **Risk of stromal melting:** exposure of the stroma to matrix metalloproteinases present in the inflammatory tear film promotes progressive thinning and eventual corneal perforation.
- **Secondary infection:** loss of the epithelial barrier facilitates colonization by opportunistic pathogens, a phenomenon aggravated by tear film instability.
- **Aberrant cicatricial remodeling:** persistence of the epithelial defect stimulates activation of stromal fibroblasts and their differentiation into myofibroblasts, promoting corneal opacity and progressive loss of transparency.

A clinically relevant feature is the temporal dissociation between cutaneous evolution and ocular involvement: while the skin may begin reepithelialization, ocular symptoms—intense pain, photophobia, and decreased vision—may continue to progress, reflecting the persistence of epithelial injury on the ocular surface [41]-[43].

3.6. Cicatricial Conjunctival Involvement and Symblepharon Formation

Cicatricial conjunctival involvement represents one of the most relevant ophthalmologic complications within the SJS/TEN spectrum, particularly due to its functional impact and progressive nature. These alterations represent the consequence of a dysregulated reparative process that begins after extensive loss of the conjunc-

tival epithelium. Within this spectrum, the formation of **symblepharon—defined as the abnormal adhesion between the palpebral conjunctiva and the bulbar conjunctiva—**constitutes one of the most characteristic and functionally limiting clinical manifestations.

Extensive epithelial denudation exposes the conjunctival stroma and promotes activation of resident fibroblasts, followed by disorganized deposition of extracellular matrix. The persistence of a local inflammatory microenvironment favors the differentiation of fibroblasts into myofibroblasts, cells responsible for progressive tissue contraction and the conjunctival thickening observed during the cicatricial phases of the disease. This process gradually leads to contraction of the conjunctival fornices and the formation of fibrous bridges between adjacent mucosal surfaces [44].

From a pathophysiological perspective, this aberrant scarring reflects the transition from a phase dominated by epithelial cytotoxicity toward a state of persistent fibroinflammatory remodeling of the ocular surface. Clinical identification of conjunctival irregularity, loss of the physiological epithelial luster, shortening of the conjunctival fornix, or the presence of fibrous bands limiting ocular motility supports the diagnosis of symblepharon. Careful eyelid eversion allows assessment of the extent of adhesions and estimation of their severity, with the degree of fornix obliteration representing a useful parameter for longitudinal follow-up.

Symblepharon formation alters the normal blinking dynamics and compromises the homogeneous distribution of the tear film across the ocular surface, promoting persistent chronic inflammation and progression of epithelial injury. These alterations not only reflect advanced ocular damage but also confer a higher risk of chronic visual sequelae. Therefore, cicatricial conjunctival involvement should be interpreted as a marker of transition toward more complex forms of ocular involvement, including limbal damage and progressive loss of the regenerative capacity of the ocular surface [45].

3.7. Failure of the Regenerative Unit: Pathophysiology and Clinical Features of Limbal Stem Cell Deficiency

Involvement of the corneal limbus and the consequent development of **limbal stem cell deficiency (LSCD)** represent the most severe ophthalmologic manifestation within the SJS/TEN spectrum, establishing a critical point in the integrity of the ocular surface. Although its prevalence is lower than that of other acute ocular manifestations, its functional impact is disproportionately high because it compromises the cellular reservoir responsible for corneal epithelial homeostasis. From a pathophysiological perspective, the corneal limbus constitutes a highly specialized microenvironment or **"niche"** that maintains self-renewal of the corneal epithelium. In the context of SJS/TEN, this niche becomes particularly vulnerable to immune-mediated cytotoxicity and inflammatory disruption of the tissue microenvironment. Infiltration of cytotoxic T lymphocytes and the release of cytotoxic mediators such as granzymes and granulysin not only induce direct

apoptosis of limbal stem cells but also disrupt the architecture of the limbal stroma that supports this regenerative niche [46]-[48].

Disruption of this specialized microenvironment compromises the trophic signals required for epithelial self-renewal and limits the centripetal migration of progenitor cells toward the corneal surface. Consequently, the corneal surface progressively loses its capacity for normal regeneration. In the absence of adequate epithelial repopulation, conjunctival epithelium invades the corneal surface in a process known as **conjunctivalization**, a phenomenon that promotes corneal neovascularization, progressive opacification, and deterioration of visual function.

Histopathologically, destruction of the limbal niche manifests as loss of normal epithelial architecture accompanied by low-grade chronic inflammatory infiltrate and progressive replacement by fibrovascular tissue. Clinically, this regenerative failure is expressed through persistent epithelial defects, irregularity of the corneal surface, and centripetal neovascularization invading the cornea from the periphery.

Diagnostic suspicion should be based on the persistence of epithelial abnormalities that fail to re-epithelialize adequately and on the appearance of abnormal vessels on the corneal surface, findings that reflect loss of the barrier function of the limbus. Rather than representing an isolated event, limbal stem cell deficiency constitutes the culmination of the immunopathological process initiated during the acute phases of SJS/TEN.

In this context, the magnitude of cicatricial conjunctival damage and the extent of chronic ocular surface inflammation directly influence progression toward limbal failure. Therefore, limbal involvement emerges as the principal determinant of chronic visual disability in survivors of SJS/TEN and confers significant prognostic value to early clinical recognition [49] [50].

3.8. Therapeutic Implications Derived from Immunopathogenesis

Understanding the immunopathogenic mechanisms underlying the SJS/TEN spectrum has direct therapeutic implications during the acute phase of the disease. Identification of T-lymphocyte-mediated cytotoxicity has supported the use of systemic immunomodulatory strategies aimed at limiting expansion of the effector immune response and reducing progression of epithelial necrosis.

Interventions used in this context include systemic corticosteroids, intravenous immunoglobulin, and immunomodulatory agents such as cyclosporine, whose purpose is to attenuate lymphocyte activation and the release of cytotoxic mediators.

In the ocular setting, early recognition of epithelial injury and pseudomembrane formation acquires particular clinical relevance. Strategies aimed at preserving ocular surface integrity during the acute phase include intensive lubrication, local control of inflammation through topical corticosteroids, and careful debridement of pseudomembranes in order to reduce persistent inflammation and prevent the formation of conjunctival adhesions.

Particularly important is the preservation of the **limbal stem cell niche**, which represents a central therapeutic objective. Early limitation of ocular surface inflammation and protection of the limbal epithelium aim to prevent progression toward limbal stem cell deficiency, a condition that represents the principal determinant of chronic visual disability among survivors of SJS/TEN [51] [52].

4. Conclusions

The spectrum formed by **Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)** transcend the definition of a purely dermatological disorder and instead represents a critical model of **multiorgan epithelial failure**. Ocular pathophysiology, rather than being a secondary reactive phenomenon, follows a compartmentalized immunopathological dynamic in which disruption of immune privilege and selective granulysin-mediated cytotoxicity orchestrate the breakdown of mucosal surfaces.

The evidence analyzed highlights that the biological autonomy of the ocular surface allows progression of damage that is largely independent of the extent of cutaneous epidermal denudation. This observation suggests that the ocular epithelium possesses an intrinsic susceptibility determined by its high cellular turnover and the density of death receptors expressed on epithelial cells.

The biological event that ultimately defines chronicity is the **functional annihilation of the limbal stem cell niche**. The transition from an acute cytotoxic phase to persistent **limbal stem cell deficiency (LSCD)** represents the definitive failure of epithelial homeostatic and self-renewal mechanisms. This collapse transforms a transparent and dynamic functional unit into a fibrovascular and keratinized tissue.

Ultimately, the chronic manifestations of SJS/TEN are not the consequence of persistent external aggression but rather the result of the **loss of regenerative memory within the corneal epithelium**. Understanding these molecular cascades is essential for appreciating the true dimension of this disease, in which the visual prognosis is determined by the integrity of the regenerative niche and the resilience of the ocular surface against immune-mediated injury.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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