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EYELID COMPLICATIONS OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: DIAGNOSIS, PREVENTION, AND TREATMENT OF OCULAR SEQUELAE

COMPLICAÇÕES PALPEBRAIS DA SÍNDROME DE STEVENS-JOHNSON E NECRÓLISE EPIDÉRMICA TÓXICA: DIAGNÓSTICO, PREVENÇÃO E TRATAMENTO DAS SEQUELAS OCULARES

COMPLICACIONES PALPEBRALES DEL SÍNDROME DE STEVENS-JOHNSON Y LA NECRÓLISIS EPIDÉRMICA TÓXICA: DIAGNÓSTICO, PREVENCIÓN Y TRATAMIENTO DE LAS SECUELAS OCULARES

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ABSTRACT

Introduction: Stevens-Johnson syndrome and toxic epidermal necrolysis are severe immune-mediated mucocutaneous reactions that may produce acute ocular inflammation and chronic cicatricial eyelid disease. Eyelid margin keratinization, trichiasis, distichiasis, entropion, symblepharon, lagophthalmos, meibomian gland dysfunction, and exposure-related corneal disease represent clinically relevant pathways toward visual morbidity. Objective: The main objective of this systematic review was to analyze the diagnosis, prevention, and treatment of eyelid complications and ocular sequelae in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Secondary objectives were to evaluate acute-phase predictors of chronic eyelid disease, compare medical and surgical interventions, assess the role of amniotic membrane transplantation, examine long-term ocular surface outcomes, and identify evidence gaps relevant to multidisciplinary care. Methods: A systematic search was planned in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Studies published within the last five years were prioritized, with expansion to ten years if fewer than ten eligible studies were identified. Human studies were prioritized, and animal or in vitro data were considered separately only when directly relevant to mechanisms of ocular surface injury. Evidence was synthesized narratively because substantial heterogeneity was expected in populations, definitions, interventions, follow-up, and outcome measures. Results and Discussion: Twenty studies were selected for the final review. The available literature indicates that early ophthalmologic assessment, grading of acute ocular involvement, lubrication, topical anti-inflammatory therapy, removal of pseudomembranes, fornix surveillance, and timely amniotic membrane transplantation may reduce the risk of chronic cicatricial complications. Chronic eyelid disease often requires individualized reconstruction, including epilation, mucous membrane grafting, correction of lid malposition,

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management of lid margin keratinization, and long-term ocular surface rehabilitation. Conclusion: Eyelid complications in Stevens-Johnson syndrome and toxic epidermal necrolysis are not secondary cosmetic findings, but central determinants of ocular surface failure and visual prognosis. Evidence supports early multidisciplinary intervention and prolonged follow-up, although high-quality comparative studies remain limited. Treatment should be individualized according to disease phase, eyelid architecture, ocular surface inflammation, corneal involvement, and patient-specific functional needs.

Keywords: Stevens-Johnson Syndrome. Toxic Epidermal Necrolysis. Eyelid Diseases. Ocular Surface.

RESUMO

Introdução: A síndrome de Stevens-Johnson e a necrólise epidérmica tóxica são reações mucocutâneas graves de origem imunomediada que podem produzir inflamação ocular aguda e doença palpebral cicatricial crônica. A queratinização da margem palpebral, triquíase, distiquíase, entrópio, simbléfaro, lagoftalmo, disfunção das glândulas de Meibomius e a doença corneana relacionada à exposição representam vias clinicamente relevantes para a morbidade visual. Objetivo: O objetivo principal desta revisão sistemática foi analisar o diagnóstico, a prevenção e o tratamento das complicações palpebrais e sequelas oculares em pacientes com síndrome de Stevens-Johnson e necrólise epidérmica tóxica. Os objetivos secundários foram avaliar preditores da fase aguda para doença palpebral crônica, comparar intervenções médicas e cirúrgicas, avaliar o papel do transplante de membrana amniótica, examinar desfechos de longo prazo da superfície ocular e identificar lacunas de evidência relevantes para o cuidado multidisciplinar. Métodos: Foi planejada uma busca sistemática no PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Estudos publicados nos últimos cinco anos foram priorizados, com expansão para dez anos se menos de dez estudos elegíveis fossem identificados. Estudos em humanos foram priorizados, e dados de animais ou in vitro foram considerados separadamente apenas quando diretamente relevantes aos mecanismos de lesão da superfície ocular. As evidências foram sintetizadas de forma narrativa porque era esperada heterogeneidade substancial em populações, definições, intervenções, acompanhamento e medidas de desfecho. Resultados e Discussão: Vinte estudos foram selecionados para a revisão final. A literatura disponível indica que avaliação oftalmológica precoce, graduação do envolvimento ocular agudo, lubrificação, terapia anti-inflamatória tópica, remoção de pseudomembranas, vigilância dos fórnices e transplante oportuno de membrana amniótica podem reduzir o risco de complicações cicatriciais crônicas. A doença palpebral crônica frequentemente requer reconstrução individualizada, incluindo epilação, enxerto de membrana mucosa, correção de mau posicionamento palpebral, manejo da queratinização da margem palpebral e reabilitação de longo prazo da superfície ocular. Conclusão: As complicações palpebrais na síndrome de Stevens-Johnson e na necrólise epidérmica tóxica não são achados cosméticos secundários, mas determinantes centrais da falência da superfície ocular e do prognóstico visual. As evidências apoiam a intervenção multidisciplinar precoce e o acompanhamento prolongado, embora estudos comparativos de alta qualidade permaneçam limitados. O tratamento deve ser individualizado de acordo com a fase da doença, arquitetura palpebral, inflamação da superfície ocular, envolvimento corneano e necessidades funcionais específicas do paciente.

Palavras-chave: Síndrome de Stevens-Johnson. Necrólise Epidérmica Tóxica. Doenças Palpebrais. Superfície Ocular.

RESUMEN

Introducción: El síndrome de Stevens-Johnson y la necrólisis epidérmica tóxica son reacciones mucocutáneas graves de origen inmunomediado que pueden producir

inflamación ocular aguda y enfermedad palpebral cicatricial crónica. La queratinización del margen palpebral, triquiasis, distiquiasis, entropión, simbléfaron, lagoftalmos, disfunción de las glándulas de Meibomio y la enfermedad corneal relacionada con la exposición representan vías clínicamente relevantes hacia la morbilidad visual. Objetivo: El objetivo principal de esta revisión sistemática fue analizar el diagnóstico, la prevención y el tratamiento de las complicaciones palpebrales y secuelas oculares en pacientes con síndrome de Stevens-Johnson y necrólisis epidérmica tóxica. Los objetivos secundarios fueron evaluar predictores de la fase aguda para la enfermedad palpebral crónica, comparar intervenciones médicas y quirúrgicas, evaluar el papel del trasplante de membrana amniótica, examinar los resultados a largo plazo de la superficie ocular e identificar las brechas de evidencia relevantes para la atención multidisciplinaria. Métodos: Se planificó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Se priorizaron los estudios publicados en los últimos cinco años, con expansión a diez años si se identificaban menos de diez estudios elegibles. Se priorizaron los estudios en humanos, y los datos de animales o in vitro se consideraron por separado solo cuando eran directamente relevantes para los mecanismos de lesión de la superficie ocular. La evidencia se sintetizó de forma narrativa porque se esperaba una heterogeneidad sustancial en poblaciones, definiciones, intervenciones, seguimiento y medidas de resultado. Resultados y Discusión: Se seleccionaron veinte estudios para la revisión final. La literatura disponible indica que la evaluación oftalmológica temprana, la clasificación del compromiso ocular agudo, la lubricación, la terapia antiinflamatoria tópica, la remoción de pseudomembranas, la vigilancia de los fórnices y el trasplante oportuno de membrana amniótica pueden reducir el riesgo de complicaciones cicatriciales crónicas. La enfermedad palpebral crónica a menudo requiere reconstrucción individualizada, incluyendo epilación, injerto de membrana mucosa, corrección de malposición palpebral, manejo de la queratinización del margen palpebral y rehabilitación a largo plazo de la superficie ocular. Conclusión: Las complicaciones palpebrales en el síndrome de Stevens-Johnson y la necrólisis epidérmica tóxica no son hallazgos cosméticos secundarios, sino determinantes centrales de la falla de la superficie ocular y del pronóstico visual. La evidencia respalda la intervención multidisciplinaria temprana y el seguimiento prolongado, aunque los estudios comparativos de alta calidad siguen siendo limitados. El tratamiento debe individualizarse de acuerdo con la fase de la enfermedad, la arquitectura palpebral, la inflamación de la superficie ocular, el compromiso corneal y las necesidades funcionales específicas del paciente.

Palabras clave: Síndrome de Stevens-Johnson. Necrólisis Epidérmica Tóxica. Enfermedades de los Párpados. Superficie Ocular.

1 INTRODUCTION

Stevens-Johnson syndrome and toxic epidermal necrolysis constitute a spectrum of severe immune-mediated mucocutaneous reactions characterized by epidermal necrosis, mucosal detachment, systemic inflammation, and potentially life-threatening multiorgan involvement.[1] Ocular involvement is frequent during the acute phase and may range from conjunctival hyperemia and epithelial defects to pseudomembrane formation, lid margin ulceration, corneal epithelial loss, and rapidly progressive ocular surface inflammation.[1] From an ophthalmologic standpoint, the disease is particularly relevant because early inflammatory injury may later become a chronic cicatricial process involving the eyelids, conjunctiva, limbus, tear film, and cornea.[1]

Although dermatologic severity is commonly classified according to the percentage of body surface area detachment, ocular prognosis depends on a different set of variables, including the intensity of conjunctival inflammation, epithelial loss, lid margin involvement, fornix shortening, and the timeliness of ocular surface-directed treatment.[2] The eyelids occupy a central position in this process because they are both affected tissues and mechanical amplifiers of chronic ocular damage.[2] Once the posterior lid margin becomes keratinized or distorted, each blink may perpetuate epithelial trauma, corneal inflammation, punctate keratopathy, persistent epithelial defects, neovascularization, and stromal scarring.[2]

The acute ocular phase of Stevens-Johnson syndrome and toxic epidermal necrolysis is therefore not merely a transient inflammatory episode, but a decisive window in which preventable structural damage may be established.[3] Pseudomembranes, epithelial sloughing, conjunctival adhesions, and early lid margin inflammation can evolve into symblepharon, ankyloblepharon, entropion, trichiasis, distichiasis, and severe tear film instability.[3] The distinction between acute inflammatory signs and early cicatricial remodeling is clinically difficult, which explains why repeated ophthalmologic examination is required even when initial ocular manifestations appear mild.[3]

Chronic ocular sequelae may emerge months after systemic recovery and may occur even in patients whose acute dermatologic disease has stabilized.[4] In this chronic phase, eyelid complications are frequently interdependent with conjunctival scarring, lacrimal dysfunction, limbal stem cell deficiency, meibomian gland damage, and neurotrophic or exposure-related corneal disease.[4] This interconnected anatomy makes isolated treatment of the cornea insufficient when persistent eyelid trauma continues to drive epithelial breakdown.[4]

Lid margin keratinization is among the most vision-threatening eyelid sequelae because it converts the normally mucosal posterior lid border into a rigid, abrasive surface.[5]

The resulting blink-related microtrauma may produce chronic pain, photophobia, foreign body sensation, recurrent epithelial defects, infectious keratitis, corneal thinning, and irreversible visual loss.[5] In advanced cases, eyelid reconstruction and ocular surface reconstruction must be coordinated because corneal procedures alone tend to fail when the eyelid margin remains keratinized or malpositioned.[5]

Trichiasis, distichiasis, entropion, and cicatricial lagophthalmos represent additional mechanical consequences of eyelid scarring in Stevens-Johnson syndrome and toxic epidermal necrolysis.[6] These abnormalities may coexist with severe aqueous-deficient dry eye and mucin deficiency, creating a hostile ocular surface in which even minor eyelash-cornea contact becomes clinically significant.[6] Management often requires staged care, beginning with control of inflammation and surface protection before definitive correction of eyelid architecture is attempted.[6]

Amniotic membrane transplantation has become one of the most discussed preventive strategies in acute ocular Stevens-Johnson syndrome and toxic epidermal necrolysis.[7] Its rationale is based on anti-inflammatory, anti-fibrotic, epithelial-supportive, and barrier-restoring properties that may reduce conjunctival scarring and later eyelid-related ocular surface injury.[7] However, the effectiveness of this intervention depends on timing, extent of membrane coverage, technical feasibility, disease severity, and coordination between dermatology, burn care, ophthalmology, anesthesia, and intensive care teams.[7]

Despite growing clinical experience, the literature remains heterogeneous in definitions of ocular severity, timing of intervention, surgical techniques, follow-up duration, and outcome measures.[8] Some studies emphasize acute ocular grading and early amniotic membrane transplantation, whereas others focus on chronic reconstruction, mucous membrane grafting, scleral lenses, limbal stem cell deficiency, or quality-of-life outcomes.[8] This heterogeneity limits direct comparison between studies and reinforces the need for systematic synthesis centered specifically on eyelid complications rather than ocular involvement as a broad category.[8]

The diagnosis of eyelid complications requires careful slit-lamp evaluation of the anterior and posterior lid margin, eyelash position, meibomian gland orifices, blink dynamics, lid closure, fornix depth, symblepharon formation, tear film quality, and corneal epithelial integrity.[9] Ancillary assessment may include ocular surface staining, photographic documentation, severity grading, microbiologic evaluation when infection is suspected, and longitudinal comparison during follow-up.[9] In clinical practice, the most important diagnostic principle is to identify eyelid-driven ocular surface trauma before irreversible corneal opacification, vascularization, or perforation occurs.[9]

A systematic review focused on eyelid complications is justified because these sequelae are common, disabling, anatomically complex, and frequently underrepresented in general dermatologic discussions of Stevens-Johnson syndrome and toxic epidermal necrolysis.[10] For ophthalmologists, the eyelid is not a peripheral structure in this disease, but a determinant of whether the ocular surface heals, scars, or progressively deteriorates.[10] For dermatologists, intensivists, and emergency physicians, early recognition of ocular and eyelid involvement should trigger urgent ophthalmologic management rather than delayed outpatient referral.[10]

Recent literature also suggests that severe ocular complications are influenced by geographic, genetic, pharmacologic, infectious, and immunologic factors, which may explain differences in clinical patterns across cohorts.[11] These differences are relevant because drug exposures, HLA associations, access to early ophthalmologic care, and availability of amniotic membrane transplantation may affect both acute severity and chronic sequelae.[11] Therefore, prevention and treatment strategies should not be interpreted as universally interchangeable without considering healthcare setting, disease phenotype, and timing of intervention.[11]

The present review addresses eyelid disease as a practical clinical problem that spans diagnosis, prevention, acute care, chronic reconstruction, and long-term rehabilitation.[12] By integrating studies on acute ocular manifestations, chronic sequelae, amniotic membrane transplantation, surgical correction, and ocular surface outcomes, this review aims to clarify which interventions are supported by current evidence and where uncertainty persists.[12] This approach is intended to support evidence-based, multidisciplinary, and individualized management of patients at risk of permanent visual disability after Stevens-Johnson syndrome or toxic epidermal necrolysis.[12]

2 OBJECTIVES

The main objective of this systematic review was to evaluate the diagnosis, prevention, and treatment of eyelid complications associated with Stevens-Johnson syndrome and toxic epidermal necrolysis, with emphasis on their role in chronic ocular surface disease and visual prognosis. The first secondary objective was to describe the spectrum of eyelid abnormalities reported in the acute and chronic phases, including lid margin ulceration, lid margin keratinization, trichiasis, distichiasis, entropion, lagophthalmos, symblepharon, ankyloblepharon, and meibomian gland dysfunction. The second secondary objective was to identify acute-phase clinical findings associated with subsequent chronic eyelid and ocular surface sequelae. The third secondary objective was to compare preventive strategies,

particularly early ophthalmologic evaluation, topical anti-inflammatory therapy, lubrication, pseudomembrane removal, fornix management, and amniotic membrane transplantation. The fourth secondary objective was to analyze chronic treatment strategies, including epilation, electrolysis, mucous membrane grafting, eyelid malposition repair, scleral lens rehabilitation, and combined ocular surface reconstruction. The fifth secondary objective was to assess the certainty of available evidence and identify methodological gaps that should guide future prospective studies and multidisciplinary care protocols.

3 METHODOLOGY

This systematic review was designed according to PRISMA principles to synthesize recent evidence on eyelid complications and ocular sequelae in Stevens-Johnson syndrome and toxic epidermal necrolysis. The search strategy included PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Search terms combined controlled vocabulary and free-text expressions related to “Stevens-Johnson syndrome,” “toxic epidermal necrolysis,” “ocular sequelae,” “eyelid,” “lid margin keratinization,” “trichiasis,” “entropion,” “symblepharon,” “amniotic membrane transplantation,” and “ocular surface reconstruction.” No language restriction was applied.

Eligible studies included randomized trials, nonrandomized comparative studies, cohort studies, case-control studies, cross-sectional studies, case series, diagnostic studies, surgical outcome studies, and systematic reviews when they directly addressed ocular or eyelid outcomes in Stevens-Johnson syndrome or toxic epidermal necrolysis. The primary time window was the last five years, but expansion to ten years was allowed if fewer than ten eligible studies were identified. Human studies were prioritized. Animal, in vitro, or translational studies were not pooled with clinical studies and were considered only when they provided relevant mechanistic information on ocular surface inflammation, epithelial injury, or cicatricial remodeling.

Studies were excluded if they did not address Stevens-Johnson syndrome or toxic epidermal necrolysis, did not report ocular or eyelid outcomes, focused exclusively on non-ophthalmic systemic treatment without ocular endpoints, consisted only of narrative commentary without extractable data, or included duplicate populations without additional relevant information. Small samples were accepted because the condition is rare, but this limitation was recorded during evidence appraisal. When multiple publications reported overlapping cohorts, the most complete or most recent dataset was prioritized unless separate outcomes justified inclusion of both records.

Study selection was planned in two independent phases. Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements were resolved by consensus or by a third reviewer. Extracted data included author, year, country, study design, population, age group, diagnostic criteria, disease phase, ocular severity, eyelid findings, intervention, comparator when available, timing of intervention, follow-up duration, outcomes, complications, and main conclusions. Duplicate records were removed before screening, and the final process was summarized using a PRISMA flow structure.

Risk of bias was assessed according to study design. RoB 2 was planned for randomized trials, ROBINS-I for nonrandomized intervention studies, and QUADAS-2 for diagnostic accuracy studies. Observational studies and case series were appraised with attention to selection bias, incomplete follow-up, outcome definition, confounding, and reporting quality. The certainty of evidence was summarized with GRADE, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. A narrative synthesis was selected because clinically meaningful heterogeneity was expected in ocular severity grading, eyelid outcome definitions, timing of intervention, surgical techniques, and follow-up.

4 RESULTS

No randomized clinical trial specifically designed to compare eyelid-directed interventions in Stevens-Johnson syndrome and toxic epidermal necrolysis was identified in the working evidence set. The included literature was composed mainly of retrospective cohorts, observational clinical series, technique-focused studies, systematic reviews, and narrative reviews with direct relevance to acute ocular involvement, chronic ocular sequelae, eyelid margin disease, amniotic membrane transplantation, or long-term ocular surface reconstruction. Because eyelid complications are often reported within broader ocular outcome categories, studies were included when they addressed eyelid margin keratinization, trichiasis, entropion, symblepharon, fornix shortening, meibomian gland dysfunction, ocular surface cicatrization, or interventions intended to prevent chronic eyelid-driven corneal damage.

Tabela 1

Included studies ordered from oldest to newest

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions

Shanbhag *et al.*, 2020	This retrospective cohort evaluated patients with acute Stevens-Johnson syndrome or toxic epidermal necrolysis who received amniotic membrane treatment for acute ocular involvement, with comparison based on long-term ocular outcomes after early ocular surface intervention.	The study assessed visual acuity, chronic ocular surface complications, dry eye disease, meibomian gland dysfunction, corneal outcomes, and the need for additional ocular treatment during follow-up.	Early amniotic membrane treatment appeared to reduce severe visual loss and mitigate chronic ocular complications, although eyelid-related disease and dry eye remained frequent during long-term follow-up.
Hall *et al.*, 2021	This retrospective study evaluated patients with acute Stevens-Johnson syndrome or toxic epidermal necrolysis treated with systemic cyclosporine, with attention to ocular disease severity and later ocular outcomes.	The outcomes included acute ocular involvement, chronic ocular complications, systemic treatment exposure, and the relationship between immunomodulatory therapy and ocular prognosis.	Systemic cyclosporine may influence the inflammatory trajectory of acute disease, but ocular-specific prevention still required direct ophthalmologic management and did not eliminate the need for close follow-up.
Yang *et al.*, 2021	This clinical series reported the Toronto experience with amniotic membrane transplantation in patients with Stevens-Johnson syndrome or toxic epidermal necrolysis and acute ocular involvement.	The study assessed feasibility, timing of amniotic membrane transplantation, ocular surface healing, chronic ocular complications, and visual outcomes.	Amniotic membrane transplantation was considered a valuable acute-phase strategy for protecting the ocular surface, especially when performed early and with adequate coverage of the ocular surface and eyelid margins.
Pradeep *et al.*, 2021	This observational study described acute ocular manifestations in patients with Stevens-Johnson syndrome or toxic epidermal necrolysis during the active phase of disease.	The outcomes included conjunctival involvement, corneal epithelial defects, eyelid abnormalities, pseudomembrane formation, ocular severity, and early complications.	Acute ocular involvement was common and clinically heterogeneous, supporting systematic ophthalmologic examination during hospitalization rather than delayed evaluation after dermatologic stabilization.
Shanbhag *et al.*, 2021	This multicenter Indian study evaluated clinical aspects of Stevens-Johnson syndrome and toxic epidermal necrolysis	The study assessed acute and chronic ocular sequelae, visual impairment, ocular surface disease, lid-related	Severe ocular complications were associated with high rates of chronic morbidity, and delayed ophthalmologic care

	with severe ocular complications in a population with substantial chronic ocular morbidity.	complications, and regional clinical patterns.	contributed to advanced cicatricial ocular surface disease.
Ma *et al.*, 2021	This Taiwanese study analyzed clinical aspects of Stevens-Johnson syndrome and toxic epidermal necrolysis with severe ocular complications, including drug triggers, genetic background, and ocular phenotype.	The outcomes included severe ocular complications, acute disease characteristics, chronic ocular manifestations, causative medications, and population-specific clinical associations.	Severe ocular disease showed distinct regional and pharmacogenetic associations, reinforcing the need for early recognition and population-sensitive prevention strategies.
Sotozono *et al.*, 2021	This Japanese consensus-oriented article addressed diagnosis and management of Stevens-Johnson syndrome and toxic epidermal necrolysis with severe ocular complications.	The outcomes included diagnostic criteria, severe ocular complication phenotypes, clinical classification, and management principles for acute and chronic ocular disease.	Severe ocular complications required disease-specific recognition and structured management, with emphasis on early ophthalmologic intervention and long-term monitoring of cicatricial sequelae.
Ueta *et al.*, 2021	This mechanistic and clinical review examined the pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis with severe ocular complications.	The outcomes included immunologic mechanisms, genetic susceptibility, ocular surface inflammation, cold medicine-related phenotypes, and pathways leading to severe ocular involvement.	The pathogenesis of severe ocular complications involved complex interactions among genetic predisposition, immune activation, drug exposure, mucosal inflammation, and ocular surface-specific vulnerability.
Ma *et al.*, 2022	This genetic association study evaluated human leukocyte antigen associations in Han Chinese patients with Stevens-Johnson syndrome or toxic epidermal necrolysis and severe ocular complications.	The outcomes included HLA associations, severe ocular complication status, drug-related phenotypes, and population-specific risk markers.	Genetic susceptibility appeared to contribute to the risk of severe ocular complications, suggesting that pharmacogenomic data may eventually improve prevention in selected populations.
Mortensen *et al.*, 2023	This clinical study analyzed outcomes of amniotic membrane transplantation in patients with ocular Stevens-Johnson	The outcomes included visual acuity, corneal status, ocular surface stabilization, chronic sequelae, and complications after	Amniotic membrane transplantation was associated with clinically meaningful ocular surface stabilization, but the

	syndrome or toxic epidermal necrolysis.	amniotic membrane transplantation.	persistence of chronic complications indicated that the procedure should be integrated into a broader long-term care strategy.
Tóth *et al.*, 2023	This narrative review synthesized ophthalmic aspects of Stevens-Johnson syndrome and toxic epidermal necrolysis, including acute findings, chronic complications, and treatment options.	The outcomes included acute ocular inflammation, chronic ocular sequelae, eyelid abnormalities, corneal involvement, and medical or surgical treatment approaches.	Ophthalmic disease in Stevens-Johnson syndrome and toxic epidermal necrolysis required phase-specific management, and eyelid disease was emphasized as a major driver of chronic ocular surface deterioration.
Cekic *et al.*, 2023	This comprehensive assessment evaluated long-term sequelae in survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis across multiple organ systems, including ocular morbidity.	The outcomes included chronic ocular symptoms, functional sequelae, systemic long-term morbidity, quality of life, and persistent complications after the acute episode.	Long-term sequelae were frequent and clinically relevant, supporting prolonged multidisciplinary surveillance after hospital discharge rather than short-term dermatologic follow-up alone.
Rashad *et al.*, 2024	This study evaluated long-term outcomes of glued sutureless amniotic membrane transplantation in acute Stevens-Johnson syndrome and toxic epidermal necrolysis.	The outcomes included ocular surface stabilization, visual outcomes, chronic ocular complications, feasibility of glued technique, and comparison with sutured approaches.	Glued sutureless amniotic membrane transplantation appeared feasible and effective for stabilizing the ocular surface, with potential practical advantages in acutely ill patients who may not tolerate complex operative procedures.
Kojima *et al.*, 2024	This study investigated improvement in ocular prognosis in Stevens-Johnson syndrome and toxic epidermal necrolysis, focusing on incidence and prognostic factors of ocular sequelae.	The outcomes included ocular sequelae, prognostic factors, acute-phase management, temporal trends, and long-term ocular morbidity.	Ocular prognosis appeared to improve when acute ocular disease was recognized and treated earlier, although severe acute involvement remained a major risk factor for chronic sequelae.
Tóth *et al.*, 2024	This retrospective tertiary-center study analyzed clinical characteristics and treatment of ophthalmic sequelae	The outcomes included causative factors, acute and chronic ocular findings, lid abnormalities, corneal	Chronic ophthalmic sequelae remained clinically significant even in a developed healthcare setting, and individualized

	in Stevens-Johnson syndrome and toxic epidermal necrolysis in Hungary.	complications, therapeutic interventions, and visual outcomes.	treatment was required because ocular surface disease, eyelid pathology, and corneal complications frequently coexisted.
Pisitpayat *et al.*, 2024	This review examined ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis, including pathophysiology, biomarkers, acute care, and chronic complications.	The outcomes included mechanisms of ocular injury, biomarkers, ocular severity, chronic ocular sequelae, amniotic membrane transplantation, and long-term management.	The review supported early ophthalmologic consultation and highlighted the need for biomarker-informed risk stratification, although clinical decision-making still depended primarily on examination findings and disease severity.
Shah *et al.*, 2024	This update reviewed diagnosis and management of Stevens-Johnson syndrome and toxic epidermal necrolysis from a systemic and multidisciplinary perspective, including ocular care considerations.	The outcomes included diagnostic approach, acute systemic management, supportive care, immunomodulatory treatment, complications, and multidisciplinary management principles.	Multidisciplinary management was essential, and ocular evaluation was identified as a key component of acute care because chronic ocular sequelae may persist after systemic recovery.
Singh *et al.*, 2025	This technique-focused review discussed amniotic membrane grafting for acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis.	The outcomes included preoperative preparation, operative technique, postoperative care, ocular surface healing, and prevention of chronic cicatricial complications.	Successful amniotic membrane grafting required timely intervention, adequate anatomical coverage, and close postoperative care, particularly when eyelid margins and fornices were involved.
Narang *et al.*, 2025	This review addressed chronic ocular sequelae of Stevens-Johnson syndrome, including dry eye disease, lid margin keratinization, conjunctival scarring, and limbal stem cell deficiency.	The outcomes included chronic ocular surface disease, eyelid margin pathology, corneal complications, ocular surface reconstruction, and visual rehabilitation.	Chronic sequelae were driven by persistent inflammation, cicatrization, and mechanical eyelid-related trauma, making eyelid assessment central to long-term preservation of the ocular surface.
Paris *et al.*, 2026	This systematic review evaluated	The outcomes included surgical	Technique heterogeneity limited

	amniotic membrane transplantation techniques in acute ocular Stevens-Johnson syndrome and toxic epidermal necrolysis.	technique, timing, membrane fixation strategy, extent of coverage, complications, and chronic ocular outcomes.	direct comparison between approaches, but the available evidence favored early and extensive amniotic membrane coverage when acute ocular involvement was clinically significant.

5 RESULTS AND DISCUSSION

Shanbhag *et al.* emphasized that acute ocular disease in Stevens-Johnson syndrome and toxic epidermal necrolysis should be interpreted as a time-sensitive inflammatory emergency rather than as a secondary mucosal manifestation of dermatologic disease.[13] Their findings supported early amniotic membrane therapy as a strategy capable of reducing severe visual loss and mitigating later ocular surface morbidity, although chronic dryness, meibomian gland dysfunction, and lid-related sequelae remained clinically relevant during follow-up.[13] For eyelid complications specifically, this study reinforced the concept that prevention is more effective than late reconstruction, because lid margin inflammation and conjunctival scarring can become self-perpetuating sources of corneal trauma.[13]

Hall *et al.* broadened the discussion by evaluating systemic cyclosporine in acute Stevens-Johnson syndrome and toxic epidermal necrolysis, highlighting the possibility that systemic immunomodulation may alter the inflammatory course of the disease.[14] However, their work also showed that systemic control cannot replace ophthalmic surveillance, because ocular complications depend on local epithelial injury, pseudomembrane formation, lid margin involvement, and mechanical factors that require targeted eye care.[14] In this sense, systemic therapy should be viewed as complementary rather than substitutive, particularly when the clinical objective is to prevent chronic eyelid malposition, lid margin keratinization, and ocular surface cicatrization.[14]

The Toronto experience reported by Yang *et al.* added important technical and practical information regarding amniotic membrane transplantation in acutely ill patients with ocular Stevens-Johnson syndrome and toxic epidermal necrolysis.[15] Their study suggested that the benefit of amniotic membrane transplantation depends not only on the biological properties of the membrane, but also on timing, anatomical coverage, and the ability to protect the eyelid margins and fornices.[15] This observation is particularly relevant because incomplete coverage may leave the tarsal conjunctiva, posterior lid margin, or fornix exposed to ongoing inflammation, thereby allowing the later development of symblepharon, entropion, and lid margin keratinization.[15]

Pradeep *et al.* described acute ocular manifestations and demonstrated that early disease may involve multiple structures simultaneously, including conjunctiva, cornea, eyelid margin, and fornices.[16] Their findings are clinically important because acute eyelid edema or erythema may conceal posterior lid margin ulceration, pseudomembranes, and early adhesive changes that are only detected through careful ophthalmologic examination.[16] From a preventive standpoint, this reinforces that every hospitalized patient with Stevens-Johnson syndrome or toxic epidermal necrolysis should undergo repeated ocular assessment, even when the initial ocular symptoms appear disproportionally mild compared with systemic disease severity.[16]

The Indian multicenter study by Shanbhag *et al.* provided a broader regional perspective on severe ocular complications and highlighted the burden of chronic ocular morbidity in patients referred after the acute stage.[17] The study was particularly relevant to eyelid disease because chronic ocular surface failure was frequently associated with cicatricial changes, lid-related trauma, tear film abnormalities, and corneal damage.[17] The main clinical message is that delayed ophthalmologic care may convert potentially modifiable acute inflammation into complex chronic disease requiring staged reconstruction and prolonged rehabilitation.[17]

Ma *et al.* reported clinical aspects of severe ocular complications in Taiwan and emphasized the interaction between drug triggers, population-specific susceptibility, and ocular phenotype.[18] Their findings suggest that prevention cannot be restricted to acute supportive care, since pharmacogenomic and regional prescribing patterns may influence which patients develop severe ocular complications.[18] Although genetic screening is not yet a universal solution for preventing eyelid sequelae, population-sensitive risk recognition may eventually help identify individuals requiring particularly urgent ophthalmologic monitoring after high-risk drug exposure.[18]

Sotozono *et al.* contributed to the field by emphasizing disease-specific diagnostic and management frameworks for Stevens-Johnson syndrome and toxic epidermal necrolysis with severe ocular complications.[19] This approach is valuable because chronic eyelid sequelae are often underdiagnosed when clinicians focus only on corneal opacity, visual acuity, or conjunctival injection.[19] Structured grading systems can improve communication between ophthalmologists and other specialists, allowing early identification of lid margin disease, fornix shortening, symblepharon, and ocular surface cicatrization before irreversible corneal injury predominates.[19]

Ueta *et al.* strengthened the biological rationale for ocular-specific management by discussing immunologic mechanisms, genetic susceptibility, mucosal inflammation, and

ocular surface vulnerability.[20] Their review helps explain why two patients with similar skin detachment may develop markedly different ocular outcomes, including different degrees of eyelid scarring and corneal damage.[20] Mechanistic heterogeneity also explains why a single therapeutic strategy is unlikely to be sufficient for all patients, especially when chronic sequelae result from the combined effects of inflammation, epithelial loss, tear film failure, and repetitive eyelid-induced trauma.[20]

The genetic association study by Ma *et al.* advanced the discussion by linking severe ocular complications with human leukocyte antigen patterns in a Han Chinese population.[21] Although this type of evidence does not directly define eyelid treatment, it is relevant to prevention because severe ocular complications may arise from identifiable host susceptibility factors.[21] In the future, risk stratification combining drug exposure, genotype, ethnicity, early ocular findings, and systemic severity may allow more individualized decisions regarding monitoring intensity, transfer to specialized centers, and early ocular surface intervention.[21]

Mortensen *et al.* evaluated outcomes after amniotic membrane transplantation and reinforced that this intervention can stabilize the ocular surface during a biologically vulnerable period.[22] Nevertheless, the persistence of chronic sequelae in some patients shows that amniotic membrane transplantation should not be interpreted as definitive protection against all eyelid-related complications.[22] For patients who later develop lid margin keratinization, trichiasis, entropion, or severe dry eye, additional long-term treatment remains necessary to interrupt mechanical trauma and preserve epithelial integrity.[22]

Tóth *et al.* synthesized ophthalmic aspects of Stevens-Johnson syndrome and toxic epidermal necrolysis and clarified that acute and chronic disease require different therapeutic priorities.[23] In the acute phase, the objective is to control inflammation, prevent adhesions, protect the ocular surface, and reduce cicatricial remodeling, whereas in the chronic phase the priority shifts toward mechanical correction, surface stabilization, and visual rehabilitation.[23] This distinction is essential for eyelid disease because procedures that are appropriate for stable chronic cicatricial entropion may be ineffective or harmful if performed before inflammation and epithelial instability are adequately controlled.[23]

Cekic *et al.* examined long-term sequelae across organ systems and demonstrated that survivorship after Stevens-Johnson syndrome and toxic epidermal necrolysis may be accompanied by persistent functional impairment.[24] Ocular morbidity is especially important in this context because chronic eyelid abnormalities, photophobia, pain, and recurrent epithelial breakdown can compromise daily function even when systemic recovery appears complete.[24] Their findings support the need for structured follow-up pathways that include

ophthalmology, dermatology, rehabilitation, pain management, psychology when needed, and patient education regarding warning signs of ocular surface deterioration.[24]

Rashad *et al.* introduced the possibility that glued sutureless amniotic membrane transplantation may reduce procedural complexity while maintaining clinically meaningful ocular surface protection.[25] This is relevant in acute Stevens-Johnson syndrome and toxic epidermal necrolysis because patients may be critically ill, painful, difficult to transfer, or poorly suited for prolonged operative manipulation.[25] If confirmed in larger comparative studies, simplified amniotic membrane techniques may improve access to early intervention and reduce the number of patients progressing to chronic eyelid margin disease and cicatricial ocular surface failure.[25]

Kojima *et al.* evaluated prognostic factors and temporal improvement in ocular outcomes, suggesting that better recognition and earlier treatment may be changing the natural history of ocular Stevens-Johnson syndrome and toxic epidermal necrolysis.[26] Their results are consistent with the broader clinical impression that severe chronic sequelae are less likely when acute ocular inflammation is aggressively monitored and treated.[26] However, severe acute ocular involvement remains a major warning sign, and patients with lid margin ulceration, pseudomembranes, extensive epithelial defects, or fornix involvement should be considered at high risk for chronic eyelid and corneal complications.[26]

The Hungarian tertiary-center study by Tóth *et al.* provided important real-world evidence from a developed healthcare setting and showed that chronic ophthalmic sequelae remain clinically significant despite access to specialized care.[27] This finding is important because it argues against the assumption that modern supportive care alone is sufficient to prevent eyelid-driven ocular surface disease.[27] The coexistence of eyelid pathology, corneal disease, conjunctival scarring, and tear film instability in their cohort supports individualized treatment planning rather than isolated correction of a single visible abnormality.[27]

Pisitpayat *et al.* reviewed ocular involvement with attention to mechanisms, biomarkers, acute treatment, and chronic sequelae, placing eyelid disease within a broader inflammatory and cicatricial framework.[28] Their analysis supports the view that biomarkers may eventually refine risk prediction, but that bedside ocular findings remain the most actionable determinants of management.[28] Until validated biomarker-guided algorithms are available, clinicians should treat posterior lid margin involvement, pseudomembranes, epithelial defects, and fornix inflammation as practical indicators of high risk.[28]

Shah *et al.* approached Stevens-Johnson syndrome and toxic epidermal necrolysis as systemic emergencies requiring coordinated multidisciplinary care.[29] Their review is relevant to this ophthalmic synthesis because ocular complications may be overlooked when airway,

infection, fluid balance, analgesia, and skin care dominate the acute clinical agenda.[29] The practical implication is that ophthalmologic consultation should be embedded into acute care protocols rather than requested only after visual symptoms become prominent or after discharge planning begins.[29]

Singh *et al.* focused on amniotic membrane grafting technique and emphasized that surgical success depends on preparation, coverage, fixation, postoperative care, and follow-up.[30] This technical emphasis is important because studies that simply categorize patients as having received or not received amniotic membrane transplantation may conceal major differences in quality and extent of treatment.[30] For eyelid complications, adequate coverage of the palpebral conjunctiva, lid margins, and fornices may be particularly relevant because these structures determine later blink mechanics and the risk of cicatricial contact with the cornea.[30]

Narang *et al.* reviewed chronic ocular sequelae and highlighted dry eye disease, lid margin keratinization, conjunctival cicatrization, and limbal stem cell deficiency as interrelated elements of chronic disease.[31] This chronic-phase perspective is essential because many patients present long after the acute dermatologic episode, when the main therapeutic target is no longer acute inflammation but the structural consequences of scarring.[31] In such cases, effective care often requires a staged sequence combining lubrication, anti-inflammatory treatment, scleral lenses, eyelid margin reconstruction, mucous membrane grafting, correction of malposition, and selective corneal or limbal procedures.[31]

Paris *et al.* systematically evaluated amniotic membrane transplantation techniques and identified substantial heterogeneity in timing, fixation method, anatomical coverage, and outcome reporting.[32] Their findings help explain why the literature generally supports early amniotic membrane transplantation while still providing limited certainty regarding the superiority of any single technique.[32] The evidence suggests that early and extensive coverage is preferable when acute ocular involvement is significant, but comparative trials or standardized prospective registries are needed to define the optimal method for preventing eyelid-specific sequelae.[32]

Across the included studies, the most consistent finding is that eyelid complications represent both a marker of disease severity and an active mechanism of progressive ocular surface damage.[33] Lid margin keratinization, trichiasis, distichiasis, entropion, symblepharon, and lagophthalmos do not merely coexist with corneal disease, but may directly perpetuate epithelial trauma and inflammation.[33] Therefore, long-term management should not be limited to corneal clarity or visual acuity, but should include systematic assessment of the posterior

lid margin, eyelash orientation, fornix depth, blink closure, tear film, and meibomian gland function.[33]

The certainty of evidence according to GRADE was low to very low for most eyelid-specific interventions because the literature was dominated by retrospective cohorts, small series, heterogeneous populations, and nonstandardized outcome definitions.[34] Evidence for early amniotic membrane transplantation was more consistent than evidence for any single chronic eyelid reconstruction technique, but certainty remained limited by confounding by indication and variation in timing and coverage.[34] Evidence for chronic surgical strategies was clinically persuasive but methodologically weaker, because many reports involved selected patients treated in tertiary centers with complex combinations of procedures.[34]

Heterogeneity was substantial across studies in diagnostic criteria, ocular severity grading, disease phase, intervention timing, follow-up duration, and reporting of eyelid outcomes.[35] Some studies grouped all ocular sequelae together, whereas others specifically reported lid margin keratinization, entropion, trichiasis, symblepharon, or ocular surface cicatrization.[35] This inconsistency makes quantitative synthesis inappropriate and supports a narrative approach centered on clinically meaningful patterns rather than pooled effect estimates.[35]

In comparison with previous reviews and contemporary practice recommendations, the present synthesis reinforces the importance of immediate ophthalmologic evaluation, early ocular surface protection, and careful long-term monitoring.[36] It also adds emphasis to the eyelid as a therapeutic target, because prevention of corneal blindness depends not only on suppressing inflammation but also on preserving the lid margin, fornix anatomy, tear film environment, and blink-related biomechanics.[36] Future studies should separate eyelid-specific endpoints from broad ocular outcomes so that interventions can be evaluated according to the mechanisms they are intended to modify.[36]

From a clinical perspective, acute care should prioritize frequent lubrication, removal of inflammatory debris when appropriate, topical anti-inflammatory therapy under ophthalmologic supervision, infection vigilance, fornix monitoring, and early amniotic membrane transplantation in patients with significant ocular involvement.[37] Chronic care should be individualized according to whether the dominant mechanism is dryness, eyelid margin keratinization, eyelash-cornea touch, lid malposition, conjunctival cicatrization, limbal stem cell deficiency, or corneal opacity.[37] The best outcomes are likely to occur when eyelid surgery, ocular surface reconstruction, scleral lens rehabilitation, and medical control of inflammation are planned as parts of a coordinated strategy rather than as isolated procedures.[37]

6 CONCLUSION

The evidence analyzed in this systematic review indicates that eyelid complications are central determinants of ocular prognosis in Stevens-Johnson syndrome and toxic epidermal necrolysis. Acute lid margin inflammation, pseudomembrane formation, fornix involvement, and conjunctival epithelial injury may evolve into chronic lid margin keratinization, trichiasis, distichiasis, entropion, symblepharon, lagophthalmos, tear film dysfunction, and corneal epithelial instability. The most consistent therapeutic message across the literature is that early ophthalmologic assessment and aggressive ocular surface protection are essential to reduce the risk of chronic cicatricial disease.

The clinical relevance of these findings is substantial because eyelid disease is both a marker of severe ocular involvement and an active driver of progressive ocular surface damage. In chronic disease, the eyelid may become a mechanically abrasive structure that perpetuates epithelial breakdown, inflammation, pain, photophobia, corneal vascularization, stromal scarring, and visual loss. Therefore, management should not focus exclusively on the cornea, but must include careful evaluation of lid margin architecture, eyelash position, blink mechanics, fornix anatomy, meibomian gland function, ocular surface lubrication, and conjunctival cicatrization.

The main limitation of the available literature is the low certainty of evidence for most eyelid-specific interventions. Most studies are retrospective, nonrandomized, heterogeneous in design, and limited by small samples, variable follow-up, inconsistent ocular severity grading, and incomplete separation between eyelid-specific outcomes and broader ocular surface endpoints. Although early amniotic membrane transplantation is repeatedly supported as a preventive strategy in acute ocular disease, the optimal timing, extent of coverage, fixation method, and comparative efficacy of different techniques remain incompletely defined.

Future research should prioritize prospective multicenter registries and standardized outcome measures that distinguish corneal, conjunctival, tear film, and eyelid-specific sequelae. Studies should report posterior lid margin status, lid margin keratinization, trichiasis, distichiasis, entropion, symblepharon, lagophthalmos, meibomian gland dysfunction, corneal epithelial integrity, visual acuity, ocular pain, photophobia, quality of life, and need for staged reconstruction. Comparative studies are also needed to determine which acute interventions most effectively prevent chronic eyelid-driven ocular surface failure and which chronic surgical approaches provide durable anatomical and functional improvement.

In final terms, eyelid complications of Stevens-Johnson syndrome and toxic epidermal necrolysis require evidence-based, multidisciplinary, individualized, and phase-specific care.

Acute management should involve dermatology, intensive care, burn care, ophthalmology, anesthesia, and nursing teams, while chronic management may require cornea specialists, oculoplastic surgeons, ocular surface rehabilitation, scleral lens fitting, and long-term anti-inflammatory treatment. Preserving vision in these patients depends on recognizing that the eyelid is not a secondary structure, but one of the principal anatomical determinants of ocular surface survival.

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