Acute and Chronic Ophthalmic Involvement in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis – A Comprehensive Review and Guide to Therapy. II. Ophthalmic Disease

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ABSTRACT Our purpose is to comprehensively review the state of the art with regard to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with particular attention to improving the management of associated ocular surface complications. SJS and TEN are two ends of a spectrum of immune-mediated disease, characterized in the acute phase by a febrile illness followed by skin and mucous membrane necrosis and detachment. Part I of this review focused on the systemic aspects of SJS/TEN and was published in the January 2016 issue of this journal. The purpose of Part II is to summarize the ocular manifestations and their management through all phases of SJS/TEN, from acute to chronic. We hope this effort will assist ophthalmologists in their management of SJS/TEN, so that patients with this complex and debilitating disease receive the best possible care and experience the most optimal outcomes in their vision and quality of life.

KEY WORDS amniotic membrane transplantation, apoptosis, drug-induced disease, immune-mediated disease, keratinocyte death, keratoprosthesis, ocular surface reconstruction, Stevens-Johnson Syndrome, toxic epidermal necrolysis

OUTLINE
I. Introduction
II. Ocular Manifestations
III. Acute Ocular Therapy
   A. Ocular Examination
   B. Systemic Therapy
   C. Local Ocular Therapy
   D. Topical Ocular Corticosteroids
   E. Amniotic Membrane Transplantation to the Ocular Surface
      1. Method of Amniotic Membrane Transplantation
      2. Complications of Amniotic Membrane Transplantation
IV. Chronic Ocular Therapy
   A. Eyelid and Ocular Surface Examination
   B. Ocular Surface Stabilization
      1. Eyelid Malpositions and Misdirected Eyelashes
      2. Dry Eye Syndrome
      3. Persistent Corneal Epithelial Defect
      4. Posterior Eyelid Margin Keratinization
   C. Restoration of Ocular Surface in End-Stage Blindness
      1. Evaluation and Procedures Prior to Ocular Surface Reconstruction
2. Ocular Surface Reconstruction
   a. Stabilizing Procedures
   b. Keratoprosthesis

V. Conclusions

I. INTRODUCTION

Stevens-Johnson Syndrome (SJS), the more severe toxic epidermal necrolysis (TEN), and their intermediate (SJS-TEN overlap) characterize a severe immunologic dermatobullous condition (SJS/TEN) with high morbidity and mortality. The ocular surface represents one of the major targets in the disease, and patients may become irreversibly blind even while still in the Burn Intensive Care Unit (ICU) for their acute care. The epidemiology, classification, differential diagnosis, pathogenesis, and systemic therapy are discussed in Part I of this review, which was published in the January 2016 issue of this journal. Here, in Part II, we summarize the state-of-the-art with regard to the ophthalmic complications and their management in SJS/TEN. Given the rarity of SJS/TEN, most published studies are retrospective case reports or case series. Prospective studies on the management of ocular complications are few in number and typically limited in scope to ten cases or fewer, and without controls. Therefore evidence-based recommendations are difficult to generate. However, to provide a comprehensive, in-depth, and authoritative review of this complex entity, we assembled a group of authors who are leaders in their respective fields with experience and publications in very specific areas addressed by the review. All authors made substantial contributions in writing and revising the manuscript in their areas of expertise. Each author met Harvard Medical School criteria for authorship on a scholarly paper.

II. OCULAR MANIFESTATIONS

SJS/TEN is a blinding disorder. Potential relationships between eye involvement and other acute manifestations of SJS/TEN are poorly understood, and published reports are conflicting. Ocular involvement has been variably reported as worse in TEN, comparable between SJS and TEN, or worse in SJS than in TEN. Diffuse cutaneous and oral mucosal damage was also reported as carrying a higher risk of damage to the eyes. The SCORTEN (SCORe of TEN) score calculated in the ICU used to estimate fatality.
risk in SJS/TEN does not appear to correlate with the development of ocular complications.\textsuperscript{3,4,8} Therefore, the relationship between severity of acute ocular involvement and degree of skin involvement is uncertain.

Ocular involvement in the acute phase of SJS/TEN occurs due to rapid-onset keratinocyte apoptosis and secondary effects of inflammation and loss of ocular surface epithelium. Acute ocular involvement is reported to occur in 50% to 88% of SJS/TEN cases.\textsuperscript{1,2,5,9-11} Early involvement is highly variable and can range from self-limited conjunctival hyperemia to near total sloughing of the entire ocular surface epithelium, including the tarsal conjunctiva and eyelid margin (Figure 1). Ocular surface inflammation can be intense, with pseudomembrane (Figure 2) or frank membrane formation, early symblepharon formation, fornix foreshortening, and corneal ulceration and perforation.\textsuperscript{12,13} Meibomitis is common.\textsuperscript{14-16}

Historically, acute ocular manifestations of SJS/TEN led to chronic ocular sequelae with visual significance in at least one-third of patients.\textsuperscript{17} Chronic ocular complications of SJS/TEN are multifactorial in origin. Fusion between the bulbar and fornicalcual surfaces due to conjunctival ulcerations or conjunctival membrane formation acutely, or persistent inflammation later, causes permanent symblepharon and ankyloblepharon (Figure 3),\textsuperscript{6} disrupting an already compromised tear film meniscus and inhibiting proper eyelid closure and blink, and sometimes restricting ocular motility.\textsuperscript{18} Tarsal conjunctival scarring (Figure 4) can be associated with eyelid malpositions and other disorders, including ectropion, entropion, trichiasis, distichiasis, meibomian gland atrophy and inspissation, punctal occlusion, and keratinization of the eyelid margin, tarsal and bulbar conjunctival surfaces (Figure 5). These changes not only cause debilitating pain in affected patients, but also threaten vision and are correlated with development of late corneal blindness,\textsuperscript{19} due at least in part to chronic limbal stem cell dysfunction (LSCD). If not removed, misdirected and/or distichiasis lashes, the latter from metaplastic meibomian glands, can mechanically abrade the corneal epithelium, leading to corneal epithelial defects, infection, and stromal scar. Repeated friction from a keratinized inner eyelid surface can lead directly to chronic corneal inflammation, neovascularization, scarring, and LSCD.\textsuperscript{19,22}
Scarring in the fornices and in the lacrimal gland ducts cause severe aqueous tear deficiency and xerosis. Resultant corneal blindness due to the absence of tears, eyelid malpositions, and tarsal conjunctival keratinization is the most dreaded long-term complication among SJS/TEN survivors. It is not at all clear whether any systemic therapy provided in the acute stage of SJS/TEN can significantly reduce late ocular complications of the disease. Systemic therapies for the acute phase of SJS/TEN were discussed in Part I of this review. We detail below specific local therapies that can prevent or delay severe ocular complications of the disorder.

A majority of individuals with ocular involvement by SJS/TEN will experience significant difficulty with their activities of daily living, including reading, driving, or using a computer. Mean scores on the National Eye Institute Visual Function Questionnaire 25-item (NEI VFQ-25) were significantly worse in patients with SJS/TEN than in Sjögren syndrome and normal controls. Symblepharon and eyelid malposition often worsen over time. For those who survive their initial hospitalization for SJS/TEN with minimal or moderate eye involvement, disruption of ocular surface homeostasis can lead to delayed ophthalmic complications in a significant but poorly characterized proportion of patients. Aqueous, mucous, and lipid tear deficiencies, the latter two from loss of conjunctival goblet cells and from meibomian gland inspissation and atrophy, respectively, are common after SJS/TEN. Corneal imaging using in vivo confocal microscopy in patients with chronic SJS/TEN has shown squamous epithelial metaplasia, reduced density and beading of the subbasal corneal nerves, and increased numbers of dendritiform cells in the corneal stroma. The latter may represent increased numbers of immune cells in the corneas of patients with SJS/TEN. While corneal and conjunctival squamous metaplasia improves over time, goblet cell density showed minimal improvement after 1 year follow-up.

The prevalence of specific ocular abnormalities after SJS/TEN varies widely among published reports. Lopez-Garcia and colleagues reported corneal changes, trichiasis, and lid margin malposition in 31.8% of TEN patients, symblepharon in 27.2%, and meibomian gland dysfunction and abnormal tear film lipid layer in more than half of patients. Di Pasquale and colleagues reported much higher rates in the SJS/TEN patients they studied. Seventy-one percent of patients had symblepharon and trichiasis, 52.2% had
aqueous deficiency, and nearly all suffered from meibomian gland dysfunction and abnormal lipid tear layer. In contrast, Chang and coworkers reported that only 6.7% of patients in their series had symblepharon and 3.3% had trichiasis. Dry eye symptoms may be the most common patient complaint, affecting an estimated 46-59% of SJS/TEN survivors. Most likely, differences in post-SJS/TEN complication rates reflect differences in access to and the adequacy of acute care, but differences in the genetic backgrounds of the populations studied and the offending drug may play a role. Additionally, a lack of standardized criteria for grading the severity of acute ocular involvement may yield variable complication rates across different studies.

Retrospective case series demonstrate correlations between eyelid abnormalities in the chronic phase, specifically tarsal conjunctival keratinization, and late-onset corneal damage, but no definitive correlation between late onset corneal disease and other eye findings, such as the status of lacrimal punctum, aqueous tear deficiency, or severity of systemic disease. Sotozono and colleagues developed a severity grading for chronic ocular complications of SJS/TEN, including those affecting the cornea, conjunctiva, and eyelids. A loss of the palisades of Vogt (82.6%) and abnormal meibomian glands (73.9%) were the most commonly observed (Figures 6 and 7). The severity of corneal, conjunctival, and eyelid abnormalities was significantly correlated with visual function. In a prospective study of 22 eyes of 11 patients with TEN, Lopez-Garcia and coworkers correlated loss of the conjunctival semilunar folds in abduction with severity of ocular involvement.

Speaking generally, the chronic ocular complications of SJS/TEN represent a vicious cycle of ocular surface inflammation and scarring leading to disruption of the delicate architecture and function of the eyelids and tear film, which leads to further progression of the ocular surface damage and increasing inflammation. While grading schemes can classify the overall severity of the eye involvement and can be effective research tools, they are of limited use for guiding individualized clinical management. With each worsening and/or new complication in a given patient’s eye condition, whether in the acute, subacute, or chronic phases of the disease, visual restoration becomes more difficult.
Complications in SJS/TEN have their own inertia. It is infinitely easier to prevent symblepharon, eyelid malposition, dry eye, and corneal disease than to try to reverse the damage later.\textsuperscript{6,20-23,29-70} Therefore, we propose a “windows of opportunity” algorithm for ophthalmic interventions (Table 1). With this approach, regular ophthalmic examination for specific findings at set intervals relative to the temporal stage of the disease leads to specific interventions geared to prevent progression of visual decline and improve ocular surface comfort. We prefer to conceptualize windows of opportunity, because our combined clinical experience in SJS/TEN is that as each window is missed, irreversible disease progression occurs, with fewer options for remediation.

III. ACUTE OCULAR THERAPY

Ophthalmologists should play a central role in the early evaluation and treatment of patients with SJS/TEN. Although the “acute stage” of SJS/TEN has been defined as the first 2-6 weeks after the onset of symptoms,\textsuperscript{2} we find it more practical to view the acute stage as the period beginning with onset of signs and symptoms until near resolution of skin and mucosal ulcerations and discharge from the Burn ICU. Every patient thought to have acute SJS/TEN should have prompt ophthalmic evaluation and aggressive ophthalmic treatment as indicated, even before the diagnosis is confirmed by skin biopsy. Aggressive management is essential to decelerate disease progression and reduce the likelihood of long-term complications. Since eye involvement can start before extensive skin changes become apparent, it is essential for ophthalmologists to be involved in the care of patients with suspected SJS/TEN as early as possible. Initially, the eyes may not seem as severely involved as the skin but can worsen later, and the severity of skin manifestations does not correlate well with visual outcomes.\textsuperscript{1,3,8}

A. Ocular Examination

Within one day of admission to the Burn ICU, a detailed eye examination should be performed with careful attention to the eyelid skin, eyelid margin, conjunctiva and cornea. The entire ocular surface should be carefully examined. The examination should always include fluorescein staining to detect and document membranes and denuded epithelium. A simple grading system adapted from Sotozono and coworkers\textsuperscript{71} and
suggested management is shown in Table 2, in which epithelial sloughing of the ocular surface and/or eyelid margin, or pseudomembrane formation, are suggested indications for aggressive lubrication, topical corticosteroid therapy, and amniotic membrane transplantation (AMT).

As described above, inflammation and ulceration of the eyelid margin is an important prognostic sign, and must be searched for with fluorescein staining and documented. The eyelids should be everted and the eyes rotated to look for fornical and tarsal conjunctival epithelial defects and early symblephara, which could be otherwise missed. Saline rinses can be employed to remove mucous and tear film debris that may obscure conjunctival and corneal epithelial defects. Acute abnormalities of eyelid position, for example, lagophthalmos due to cicatricial retraction of the eyelid or cheek skin in the acute stages of SJS/TEN, may require surgical release of the cicatrix.

Lagophthalmos due to sedation may benefit from placement of Tegaderm™ (3M, St. Paul, MN) or other occlusive dressing to protect the eye from desiccation, but use of any dressing that bridges the skin above and below the eye may be problematic because of skin sloughing. As an alternative, in cases of severe sloughing, simple plastic wrap may be placed over the eye and fastened to the skin with a thin layer of petroleum jelly to provide a moisture chamber for the ocular surface. The plastic wrap is easily removed for inspection of the eye or application of medication.

Scleral contact lenses have also been used in acute SJS/TEN to prevent exposure keratopathy (C. Bouchard, personal communication) with regimens similar to those reported for exposure in patients who have suffered facial burns. Following the initial ophthalmologic examination, the frequency of re-evaluation depends on the degree of ocular surface involvement. For mild ocular surface involvement, e.g., conjunctival injection without membranes or epithelial sloughing, patients should be re-evaluated again in 24-48 hours, as the clinical situation can change rapidly in the first few days of the illness. Once the clinical course becomes clear, the frequency of rechecks can be adjusted to fit the severity of ocular involvement. Complaints of worsening vision, foreign body sensation, or photophobia should prompt a repeat ophthalmic examination. Any patient with eyelid margin involvement, conjunctival pseudomembranes, opposing
bulbar and tarsal conjunctival defects, or corneal epithelial defects should be evaluated daily during the acute stage.

B. Systemic Therapy

The potential role of systemic therapy in acute SJS/TEN was discussed in Part I of this two-part review. Systemic therapies for acute SJS/TEN are a continued subject of debate, and the effect on subsequent systemic and ocular manifestations are at best equivocal, limiting general recommendations beyond supportive burn care. While there is published data on the use of corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, granulocyte-stimulating factor, cyclosporine, tumor necrosis factor (TNF)-alpha inhibitors, and cyclophosphamide, only corticosteroids and IVIG have been studied for their potential benefit on subsequent ocular disease, with conflicting data for each of these agents. Two case series describing the use of systemic corticosteroids showed a possible beneficial effect. Five patients given intravenous methylprednisolone at 0.5-1.0 g/day for three days had relatively good outcomes. A second study included 30 adult patients given either IVIG (n=8) at 2.7 g/kg/day for 4.0 days or a high dose systemic corticosteroid (5.3 mg/kg hydrocortisone equivalent; route not described; n=22). A beneficial effect was reported in those given IVIG within 6 days of disease onset or systemic corticosteroid within 5 days of disease onset, compared to those treated with either modality at later periods after the onset of disease. Two further case series showed no ocular benefit from systemic intervention. A series of eight TEN patients treated with IVIG at 2gm/kg over 2 days did no better than a historical control group (n=18). Finally, another study of 43 patients showed no benefit for patients treated with any of five different systemic therapies (corticosteroids given in various regimens and/or IVIG), and as compared to that of three control patients treated with supportive therapy only.

Therefore, published studies provide limited evidence, and no clear guidelines, for the effect of systemic corticosteroids and/or IVIG on ocular outcomes following acute SJS/TEN. Furthermore, it remains unproven whether the severity of the chronic complications of SJS/TEN can be predicted from the degree of ocular involvement in the
acute stage of disease.\textsuperscript{3,4} Therefore, one cannot reliably determine which patients should be considered for systemic therapy in acute SJS/TEN.

C. Local Ocular Therapy

One algorithm for initial ocular therapy in SJS/TEN is presented in Figure 2. Many of the supportive ophthalmologic treatments traditionally employed, including lubrication, removal of membranes, mechanical lysis of adhesions, placement of bandage contact lenses, and administration of topical antibiotics may be beneficial, but have not been shown to improve long-term outcomes. Many patients progress to develop ophthalmic complications, and unfortunately many of these patients go on to suffer secondary corneal complications.\textsuperscript{75} However, topical antibiotics are recommended to prevent secondary infection of the denuded ocular surface. Additionally, if the ocular surface findings are severe enough to warrant mechanical intervention, then urgent AMT should be considered, as described below.

D. Topical Ocular Corticosteroids

Ocular topical anti-inflammatory medications frequently used in the acute stage of SJS/TEN include topical corticosteroids to the eyelid and ocular surface and, less commonly, topical cyclosporine. Corticosteroid ointment should be applied to the eyelid margins, and topical corticosteroid solution or suspension to the eye surface on a frequent basis (at least 3-6 times per day), except in cases of concurrent microbial keratitis. The effect of topical corticosteroids on outcomes in ocular SJS/TEN was investigated by Sotozono and coworkers.\textsuperscript{7} Visual outcomes were found to be significantly better in the 33 patients who began topical corticosteroid treatment during the first week of disease onset compared to the 31 patients who did not receive topical corticosteroids. However, this study was based on patients’ recollections of corticosteroid use, and roughly one-third of patients in their study did not recall whether they received topical corticosteroids. Periocular injections of corticosteroids have also been advocated,\textsuperscript{41} but the benefit is unknown.

Education of the ICU nursing staff on the proper application of drops and ointments is essential to increase treatment effectiveness. Supportive measures commonly
employed include lubrication with hourly administration of preservative-free artificial tears, saline rinses to remove inflammatory debris, peeling of pseudomembranes and membranes, and lysis of conjunctival adhesions. Bandage soft contact lenses may be used in the setting of a corneal epithelial defect (and in the absence of conjunctival epithelial defects, when AMT may be indicated), but only with close monitoring and with prophylactic topical antibiotics because of the heightened infection risk in these patients.\(^5\) Bandage soft contact lenses cannot be used in completely xerotic eyes.

**E. Amniotic Membrane Transplantation to the Ocular Surface**

Amniotic membrane or amnion is the membrane on the inner surface of the fetal placenta that surrounds the embryo. Its thickness varies from 0.02 to 0.5 mm and, before preservation, consists of three histological layers: an epithelial layer, its basement membrane, and an avascular mesenchymal layer.\(^{76-78}\) The epithelial layer and all cellular constituents are lost during processing for use. AMT to the denuded skin of a child with SJS/TEN was previously reported.\(^{79}\) Its use in severe ocular surface disease was pioneered in 1995 by Kim and Tseng.\(^{80,81}\) Since then, AMT has been widely used in the treatment of a range of ocular surface disorders, including chemical and thermal injuries, persistent corneal epithelial defects, ocular surface reconstruction after resection of ocular surface tumors, and immune-mediated dermatological syndromes with eye manifestations including SJS/TEN.\(^{18,40,56,58,62,82-106}\) Amnion is also used in the surgical management of genitourinary, head and neck, oral maxillofacial, vascular, and skin conditions,\(^{107-110}\) and more recently, has been explored in the treatment of cancer.\(^{109}\)

The first reported use of amnion in SJS/TEN was for ocular surface reconstruction in the chronic phase, by Zhou and coworkers in 1999,\(^{106}\) followed by a report by Honavar and colleagues in 2000.\(^{62}\) Subsequently, John and colleagues reported success with placement of amnion in acute SJS/TEN.\(^{59}\) Although many of the reports published to date are small case series with comparisons to historical controls, AMT in acute SJS/TEN is very promising, and existing evidence suggests improved outcomes.\(^{14,29,31,33,38,46,52,59,111-120}\) In one study, 10 consecutive patients hospitalized with SJS/TEN with severe ocular involvement were treated with AMT applied to the entire ocular surface and lid margins in the acute phase of SJS/TEN by the same surgeon during the first 10 days of illness,
with repeat AMT every 10-14 days as long as severe inflammation and epithelial sloughing were still present.\textsuperscript{31} At the conclusion of the study, all patients had at least 20/30 vision with 90\% of patients achieving 20/20. All patients had mild-to-moderate ocular surface and lid scarring, and mild-to-moderate dry eyes.

A more recent, retrospective, case-control study of 182 eyes of 91 patients with SJS/TEN evaluated the effectiveness of AMT versus standard supportive therapy for patients with acute ocular involvement (first 2 weeks after onset) with SJS/TEN.\textsuperscript{33} The severity of eye involvement in the first 2 weeks was graded as mild, moderate, or severe, and outcomes were classified as good (best-corrected visual acuity [BCVA] >20/40), fair (BCVA 20/40 to 20/200 with eye discomfort requiring contact lens or reconstructive surgery) or poor (BCVA <20/200). In 108 eyes, there were no or mild ocular manifestations of SJS/TEN; 74 eyes had moderate to severe involvement, defined by conjunctival epithelial defects, corneal epithelial defects involving >25\% of the cornea, and/or moderate to severe conjunctival pseudo-membranes or membranes. Supportive treatment included preservative-free artificial tears and ointments, daily examinations, and fornical sweeping, bandage contact lenses for epithelial defects, and in some cases topical prednisolone acetate 1\% drops and/or cyclosporine 0.05\% drops. One of 23 eyes (4.3\%) with moderate or severe manifestations treated with AMT had a poor outcome within 3 months compared with 8 of 23 eyes (34.8\%) medically managed (p=.022). For the 17 patients that had follow-up greater than 3 months (6 patients either died or were lost to follow-up), a poor outcome was documented in 7.1\% of the eyes that received amniotic membrane versus 38.9\% of the medically treated eyes (p=.053).

Although the exact mechanism by which amnion may exert a beneficial effect in SJS/TEN remains to be elucidated, amnion has antimicrobial and immunomodulatory properties, and promotes epithelialization. (See review.\textsuperscript{109}) Processed amnion has very low immunogenicity.\textsuperscript{76,121} The anti-inflammatory mechanism of action of amnion may be due in part to promotion of leukocyte apoptosis and downregulation of inflammatory cytokines released by activated lymphocytes and macrophages.\textsuperscript{6,122-125} Amnion traps infiltrating bone marrow-derived cells and cytokines within its stroma and may itself release anti-inflammatory mediators (e.g. IL-1 and IL-2 receptor antagonists) and inhibitors of matrix metalloproteinases.\textsuperscript{122,126,127}
1. **Method of Amniotic Membrane Transplantation**

Based on the joint experience of the authors and existing evidence, to obtain the best possible outcomes with AMT, it is important to completely cover the entire ocular surface and eyelid margins with amnion\(^{46,118}\) and as early in the clinical course as possible.\(^{31,33,38}\) Ideally, AMT should be performed within 5 days of onset of SJS/TEN symptoms, whether systemic or ocular (Darren Gregory, MD, personal communication).

Methodologies for AMT differ between surgeons, but at an informal meeting of ophthalmologists caring for patients with SJS/TEN in 2014 (American Academy of Ophthalmology, Chicago, IL), the consensus appeared to be for a methodology adapted from the techniques described in detail by Gregory,\(^{30,31}\) in which cryopreserved amnion is secured to the globe surface, fornices, and tarsal conjunctiva by use of a symblepharon ring, either commercial or custom made from intravenous (IV) extension tubing, (Rubinate et al. 2010; IOVS 2010;43:e1135) and then sutured to the upper and lower eyelids to assure coverage of the eyelid margins (Figure 9). IV extension tubing is cut open at one end of the tube cut so as to fit over the other end of the tube to make a closed circle. The custom-made IV tubing ring or commercial symblepharon ring must be large enough to reach the conjunctival fornices, but not so large as to induce lagophthalmos.

The upper and lower eyelashes in both eyes are trimmed close, with care to capture and remove the cut eyelashes. Biotissue (Doral, FL) now provides 10 x 5 cm pieces of cryopreserved amnion by custom order to be used one per eye, but if not available, three 3.5 cm squares can be joined by running 9-0 nylon sutures to make a single 3.5 x 10.5 horizontal piece, or directly sutured onto the eyelids and ocular surface individually. The amnion is laid over the eye with the basement membrane side up (away from the cornea) and with the long axis vertical, and gently pushed into the upper and lower fornices with the tubing or symblepharon ring. Care must be taken to stretch the amnion flat to cover the entire globe, including the nasal and temporal corners of the eye. The amnion is then secured to the upper and lower eyelid skin with partial-thickness placement of 8-0 nylon or prolene horizontal mattress sutures with or without bolsters. Eyelid bolsters provide a larger surface area to secure the amnion, and serve to allow the nursing staff to easily identify the amnion and avoid inadvertent or accidental removal of the membrane during
routine care. Frequent saline rinses, prophylactic topical antibiotics, topical corticosteroid drops and ointments (the latter to the eyelid margins) help remove inflammatory debris, prevent secondary infection, reduce inflammation of the globe and eyelid margin, and delay desiccation and degradation of the amnion.

Dissolution of the amnion can occur within 3-10 days. Typically, the amnion degrades over the lid margin first followed by the corneal component. AMT to the ocular surface and eyelid margins is simple to perform under general anesthesia in the operating room, but this may not be feasible in every circumstance. The method outlined above can also easily be performed in the Burn ICU if the patient is sedated. If the patient is not sedated, then topical anesthetic for the globe and locally injected anesthetic for the eyelid suturing is necessary.

When patients or their appointed representatives decline AMT, are combative, or too unstable medically for even a brief procedure, amnion can be delivered by using ProKera® (Biotissue), a commercially available amnion fused to a symblepharon ring. To reach the deep fornices, amnion can also very simply be wrapped around a commercial symblepharon ring. ProKera® may be indicated for mild and localized conjunctival epithelial defects, or for residual conjunctival and corneal epithelial defects after AMT when the amnion has dissolved. However, ProKera® and other methods that leave the fornices and eyelid margins uncovered, leave those areas still susceptible to complications. One favorable report on the use of the ProKera® in two patients with acute SJS/TEN and severe ocular involvement also involved administration of subconjunctival triamcinolone and placement of a steeply curved acrylic scleral shell spacer (Technovent, South Wales, UK) to vault the lids away from the globe and prevent symblepharon formation. Shammas and colleagues compared ophthalmic outcomes in four patients who underwent complete coverage of the ocular surface and eyelid margins with AMT with the outcomes of two patients who had partial amnion placement by ProKera®. While the patients who received AMT all retained visual acuities of 20/40 or better with an intact ocular surface, one of the two patients with ProKera® developed a corneal perforation. Shay and coworkers reported entropion, lid margin keratinization, and trichiasis in a 5-year-old boy 9 months after TEN despite placement of ProKera® in the acute stage, thought to be due to incomplete coverage of the peripheral globe, tarsal
surfaces, and eyelid margin.  

Therefore, it is important to note that ProKera® or other modes of partial ocular surface coverage by amnion should not be considered a substitute for AMT to cover the entire ocular surface in SJS/TEN.

2. Complications of Amniotic Membrane Transplantation

Despite widespread use of AMT for ocular surface reconstruction, very few complications have been reported. Reported complications include microbial infection, hemorrhage beneath the amnion, and detachment of the membrane. Microbial infection after AMT occurred in 3.4% (11 of 326) of patients with diverse indications, including SJS/TEN, chemical burn, mucous membrane pemphigoid, persistent corneal epithelial defect, bullous keratopathy, conjunctivochalasis, atopic keratoconjunctivitis, and pterygium. Gram-positive bacteria were the most frequently isolated organisms and the time range between AMT and culture-positive infection ranged from 6 days to 16 months. Although there was no statistical correlation between infection rate and the underlying ocular disease, 2 out of the 11 patients had SJS/TEN, and infection was documented at the third or fourth month post-AMT, making any direct relationship questionable. Although infections are rare, once the membrane is in place in acute SJS/TEN, examination of the cornea and anterior chamber becomes difficult. Thus, we recommend topical antibiotic prophylaxis after AMT for all patients with acute SJS/TEN. Amnion prepared for human transplantation must be screened, processed, stored, and tested properly to reduce the risk of contamination, as in the Good Tissue Banking Practices set forth by the U.S. Food and Drug Administration.

IV. CHRONIC OCULAR THERAPY

Thirty to 50% of patients with acute SJS/TEN will go on to develop chronic ocular sequelae, including progressive symblephara, lid margin keratinization, trichiasis, entropion, dry eye syndrome, corneal pannus, and persistent corneal epithelial defects. De Rojas and coworkers characterized patterns of chronic ocular disease in 60 eyes of 30 patients with SJS/TEN with a median follow up of 5 years from onset of disease. Almost half of the eyes studied went on to develop ocular surface failure, recurrent episodic inflammation, and progressive cicatricial changes. Because normal
vision at discharge from the hospital does not guarantee a successful outcome over the long term, all patients must undergo a complete eye examination upon discharge from the Burn ICU and hospital to determine the need for time-sensitive interventions that can preserve or improve visual function.

Intervention can be crucial to prevent progression of disease, particularly in patients with trichiasis, entropion, posterior eyelid margin keratinization, and persistent corneal epithelial defect. If any window of opportunity is missed in the subacute phase of SJS/TEN, progression to end-stage corneal blindness becomes more likely. Every patient visit should include a detailed eyelid and ocular surface examination, and any measures necessary to stabilize and protect the ocular surface should be performed (Figure 8).

A. **Eyelid and Ocular Surface Examination**

Ophthalmic examination after resolution of acute SJS/TEN should be performed within the first month after discharge from the hospital and ideally repeated every 2-4 months for the first year and then at least every 6 months thereafter, as guided by the condition of the patient. Attention should be paid to the position of the eyelids relative to the globe, patency of the lacrimal puncta, direction of the eyelashes, status of the meibomian glands, height of the tear meniscus, quality of the tear film, depth of the fornices and presence of symblepharon, and presence or absence of lid margin and ocular surface keratinization. Slit lamp photographs can be helpful for later assessment of disease progression. Vital dye staining should be performed to assess for corneal and conjunctival epithelial defects and stability. Aqueous tear production should be tested, for example by Schirmer’s test, as the degree of aqueous tear deficiency markedly influences management of chronic ocular involvement by SJS/TEN.

B. **Ocular Surface Stabilization**

Every possible measure should be taken to stabilize an abnormal ocular surface after SJS/TEN. It is the experience of the authors that even superficial punctate keratopathy left unaddressed can progress over time to corneal blindness. Depending on the degree of compromise of the ocular surface, various measures can be undertaken. Patients in the chronic phase of SJS/TEN may exhibit both episodic increases in ocular
surface inflammation or chronic inflammation. Brief bouts of inflammation may respond to topical antibiotics (J. Chodosh, personal communication). A trial of nonpreserved topical corticosteroids is also reasonable to consider, but can be associated with infection and/or keratolysis. Topical or systemic corticosteroids are not acceptable long-term options in the management of chronic ocular inflammation in SJS/TEN. In particular, systemic corticosteroids alone have a poorer side effect profile than steroid-sparing systemic agents.

Treatment with cyclosporine, azathioprine, cyclophosphamide, methotrexate, mycophenolate, and infliximab has been attempted when persistent ocular inflammation is moderate to severe. In 27 patients with chronic ocular sequelae from SJS/TEN in four published case series, systemic immunosuppressive therapy was used successfully, albeit without controls. There have also been reports of mucous membrane pemphigoid occurring as a sequela of SJS/TEN, and such cases may also benefit from systemic immunosuppressive therapy similar to that used for primary mucous membrane pemphigoid. Short-term systemic immune suppression should also be considered prior to undertaking ocular surface procedures in patients with chronic SJS/TEN, in order to mitigate severe postoperative inflammation. However, care must be taken to also prevent postoperative infection, which may be more common in these patients.

A detailed discussion of the risks, benefits, and strategies for the use of immunosuppressive therapy in SJS/TEN is beyond the scope of this review, but the major side effects and management of these medications were recently summarized in a publication on their use for mucous membrane pemphigoid. Of all of the agents mentioned above, oral mycophenolate is perhaps the best tolerated.

1. Eyelid Malpositions and Misdirected Eyelashes

Insufficient eyelid closure (lagophthalmos), incomplete or absent blink, lid malposition (ectropion, entropion), and trichiasis or distichiasis result in increased tear film evaporation and/or direct damage to the ocular surface. A vicious cycle of more inflammation and scarring can lead to corneal epithelial defects, scar, infection, and perforation. Lagophthalmos may be addressed with release of cicatrix in the skin and/or by tarsorrhaphy. Entropion and ectropion can be treated with lateral canthoplasty or tarsal...
strip, anterior lamellar repositioning, tarsal fracture, posterior lamellar tightening or tarsal conjunctival advancement. Trichiasis and distichiasis can be treated with mechanical epilation, but very typically recur. For long-term treatment of aberrant eyelashes, hyfrecation, cryotherapy, and/or extirpation are often necessary. For cases in which eyelash abnormalities are associated with entropion due to tarsal scarring, mucous membrane grafting to the tarsal surface (see below) may be beneficial.

2. **Dry Eye Syndrome**

Although the term “dry eye” is frequently misapplied to describe complaints of ocular discomfort in patients with otherwise normal-appearing eyes with a normal tear film, patients post SJS/TEN have real deficiencies of all three major components of their tear film—aqueous, mucin, and lipid— affecting more than 50% of SJS/TEN patients in the chronic phase. The aqueous tear film is reduced in SJS/TEN by scarring of the lacrimal ducts and possibly by primary inflammation of the lacrimal gland. Goblet cell density in the conjunctiva is reduced after SJS/TEN and does not fully recover. The lipid component of the preocular tear film is typically reduced or eliminated entirely in SJS/TEN patients due to squamous metaplasia of the meibomian gland orifices with secondary inspissation, meibomian gland inflammation, and eventually meibomian gland atrophy and dropout. Topical cyclosporine appears to improve goblet cell density in patients with dry eye and graft-versus-host-disease. In an unmasked, uncontrolled study of 30 patients with SJS/TEN, dry eye symptoms, and abnormal corneal vital dye staining, cyclosporine 0.05% (Restasis®, Allergan, Irvine, CA) eye drops given twice daily for 6 months resulted in improvement in signs and symptoms for the 17 patients who completed the study. Eight patients withdrew because of worsening of symptoms thought to be side effects of the preparation, and five were lost to follow-up. A role for topical Restasis® in chronic SJS/TEN may be limited by patient intolerance for the preparation.

Frequent application of preservative-free artificial tears may control symptoms in some SJS/TEN patients, but it can also increase ocular dysesthesia, be difficult to maintain at the necessary frequency, and is expensive. The lacrimal puncta of SJS/TEN patients are often scarred closed from lid margin inflammation during the acute episode.
However, for those with patent lacrimal puncta, punctal cautery can improve ocular surface health. A recent retrospective study by Iyer and coworkers showed an improved or stable ocular surface in greater than 70% of 160 eyes with chronic SJS/TEN that underwent punctal cautery with a mean of 4 years follow-up. A repeat procedure was required in 20% of those eyes due to recanalization. Minor salivary gland transplantation has also been reported to increase ocular surface wetting and corneal clarity in SJS/TEN with severe dry eye, although the duration of effect, and potential deleterious consequences of saliva on ocular surface epithelium remain to be determined. Anecdotal reports also suggest improvement in clinical signs and symptoms with the application of topical, autologous, serum-derived eye drops.

3. Persistent Corneal Epithelial Defect

Persistent corneal epithelial defect in the subacute phase of SJS/TEN, after skin and other mucosal erosions have resolved, can lead to severe consequences, including corneal infection and perforation. It is critical to address persistent epithelial defects during or at any time following the acute phase of SJS/TEN. Standard therapies for persistent epithelial defect include aggressive lubrication with nonpreserved artificial tears and ointment, discontinuance of toxic topical medications, punctal occlusion, bandage soft contact lens, tarsorrhaphy, amniotic membrane, autologous serum or umbilical cord blood serum, and/or scleral contact lens placement. Autologous cultivated oral mucosal epithelial transplantation (COMET) has been used to promote re-epithelialization in recalcitrant cases.

4. Posterior Eyelid Margin Keratinization

Untreated keratinization of the posterior lid margin in the chronic phase of SJS/TEN leads to significant long-term corneal compromise, and can be responsible for progressive visual loss long after the acute episode has ended. Lid margin keratinization seems to be a primary culprit in end-stage corneal blindness from SJS/TEN, making treatment of lid margin involvement in the acute stage of SJS/TEN with AMT especially critical. Eyelid margin ulceration in the acute phase of SJS/TEN destroys the mucocutaneous junction with resultant overgrowth of the keratinized epithelium onto the
Repetitive friction from the keratinized inner eyelid during blinking is thought to cause recurrent corneal microtrauma. The resultant epitheliopathy predisposes these eyes to persistent epithelial defects, infection, stromal melting, and perforation, while the chronic inflammation from continued blink-related trauma leads to LSCD and subsequent neovascularization and conjunctivalization of the cornea. Thus, early intervention for eyelid margin keratinization is crucial to stabilize the ocular surface and prevent end stage corneal blindness. In our experience, while trichiasis and tear deficiency are both commonly recognized complications that lead eye care providers to act, lid margin keratinization is frequently missed and/or the negative consequences go unrecognized. However, several treatments are effective for posterior eyelid margin keratinization in SJS/TEN. For example, topical vitamin A in the form of all-trans retinoic acid ointment 0.01% to 0.1% was shown to be beneficial in reducing keratinization in patients with chronic SJS/TEN, and is available from select compounding pharmacies at 0.01% concentration.

Another option to prevent corneal damage from posterior lid margin keratinization in SJS/TEN is the use of large diameter, rigid gas permeable contact lenses, sometimes referred to as limbal or scleral lenses. These lenses vault the cornea, essentially bathing it in nonpreserved sterile saline. Reports from individual centers using limbal or scleral lenses have shown a decidedly positive impact in SJS/TEN. In particular, the custom-designed scleral lens system known as PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem, Boston Foundation for Sight, Needham, MA) has been shown to improve visual acuity and comfort, and reduce corneal epitheliopathy in eyes with posterior eyelid margin keratinization after SJS/TEN (Figure 10). In a study of 86 SJS/TEN patients, visual improvement was maintained for a median of 16 months; the general health of patients as self-reported by NEI VFQ-25 also improved.

In eyes with symblepharon, fornix reconstruction may be required prior to lens fitting. In some instances, bandage soft contact lenses can be used to reduce the corneal morbidity from keratinized lid margins. Care should be taken when choosing a bandage soft contact lens to maximize fit and oxygen transmission. Any patient wearing a contact lens in the setting of ocular surface disease should be followed closely for adverse
effects. It may be difficult to determine if new-onset pannus or corneal neovascularization are related to contact lens wear or to the natural history of SJS/TEN.

When posterior eyelid margin keratinization in SJS/TEN is seen in association with corneal epitheliopathy or neovascularization, or is a cause of ocular discomfort, a surgical option for correction is autologous, oral, mucous membrane grafting (MMG, Figure 11),\textsuperscript{20-22,149,167,168} which replaces keratinized tarsal conjunctiva with labial or buccal mucosa from the same patient. Harvest of mucosa from the lip (labial mucosa) may be preferable to the cheek (buccal mucosa) for surgical ease of harvest and ensuring an acceptably thin graft for placement on the tarsal surface(s). MMG can slow corneal deterioration in SJS/TEN by replacing keratinized posterior eyelid margin epithelium with healthier, nonkeratinized epithelium. This restores the integrity of the mucocutaneous junction. In the largest retrospective series to date, more than 80% of 238 eyes had improved BCVA and an improved ocular surface, as measured by corneal fluorescein staining and Schirmer’s testing, at a mean of 4 years follow-up.\textsuperscript{21} Repeat mucous membrane grafting was performed in 27 eyes (11.34%) because of shrinkage of the mucosal graft or recurrence of keratinization along the graft edges. There were no significant complications reported from the procedure.

As described by Iyer and coworkers,\textsuperscript{20} both eyes are operated upon in the same session when the condition is bilateral, and surgeries are usually performed under general anesthesia. For oral endotracheal intubation, the tube must be displaced to one side to allow exposure of the labial mucosa. The eye and the mouth are prepped with betadine solution and draped. Eyelid sutures are placed with 4-0 silk and the eyelids everted. The lid margins are marked with surgical ink to indicate the extent of excision, with the goal to excise any keratinized epithelium opposite to the cornea. Up to 15 to 20 mm of the keratinized, central, horizontal eyelid margin is marked and dissected leaving a fornix-based flap to a vertical depth of 5 mm for each eyelid. Hemostasis is achieved with cautery. After completing dissections for all affected eyelids, the eyes are kept closed and attention shifted to the lip mucosa.

An area of 30 to 40 x 10 mm is marked out on the stretched lower lip mucosa, and lidocaine with epinephrine (1:1,600,000) is infiltrated into the submucosa. The marked area is dissected using a 15 blade on Bard Parker handle, and the harvested graft washed
in antibiotic solution. The donor site’s opposing edges are approximated using continuous 5-0 vicryl sutures along the long axis of the wound or left to heal by secondary intention. After confirming hemostasis, gloves and surgical instruments are changed, and attention is redirected to the eyes.

The harvested mucosal graft is made free of underlying fatty tissue by sharp dissection and thinned to allow the graft to be stretched. The graft is then divided into four parts, each measuring ~15 x 20 x 5 mm to match the dissected area on each eyelid. One edge of the mucosa is sutured to the lid margin using a continuous 8-0 vicryl suture with exteriorization of the knots. Tisseel fibrin glue (Baxter, Deerfield, IL) is reconstituted, and the components applied to the raw tarsal surface. The mucosal graft is stretched and laid down on the tarsus, and after confirming good apposition, the previously dissected conjunctival flap is excised. The mucosal graft is best oversized by 20% to account for subsequent shrinkage. A good edge-to-edge approximation of the graft to the conjunctival edges is also important so as to prevent mucosal necrosis from conjunctival downgrowth in the early postoperative period.

The procedure is repeated for all affected lids, antibiotic ointment is placed, and the eyes are patched. On the first postoperative day, the patch is removed and a topical antibiotic eye drop is given four times daily for one week along with frequent artificial tears. Topical corticosteroid eye drops or ointments are unnecessary. Postoperative chlorhexidine mouthwash may be used for one week postoperatively. Patients are examined on day 1, weeks 1 and 6, and subsequently every 3 months thereafter. Recurrence of keratinization along the edges of the graft necessitates revision only if it causes recurrence of symptoms and/or corneal epitheliopathy.

Salivary glands are present in the labial mucosa harvested for MMG. Less thinning of the graft at harvest allows for retention of more glands in the transplanted mucosa, and transfer of more glands to the posterior eyelid. Although long-term viability remains to be established, preliminary results showed that greater numbers of labial salivary glands within the MMG led to improved clinical outcomes, including patient symptoms, aqueous tear production, and corneal transparency.

C. Restoration of Ocular Surface in End-Stage Blindness
1. Evaluation and Procedures Prior to Ocular Surface Reconstruction

The management of cicatricial conjunctival and corneal blindness in SJS/TEN is extremely challenging. Forniceal foreshortening and symblephara along with eyelid malpositions disrupt an already inadequate tear film, alter blink and lid closure, and lead to drying of the ocular surface, all of which exacerbate existing corneal LSCD, with attendant corneal epitheliopathy, and stromal inflammation and neovascularization. Patients with SJS/TEN and ocular surface involvement also have a diverse conjunctival flora that includes pathogenic species. Keratinization of the ocular surface due to extreme xerosis in SJS/TEN typically protects the underlying corneal stroma from further breakdown and can protect the eye from other complications, but also results in extremely poor vision, typically hand motions or worse. Without keratinization, corneas in SJS/TEN patients may and often do progress to ulceration and perforation. Because of all these factors, corneal transplantation in eyes with SJS/TEN has a very poor prognosis with a high rate of infection and perforation, and is best avoided, lest surgery lead to clinical worsening or complete loss of the operated eye.

Prior to attempting visual restoration, globe salvaging procedures may be indicated to resolve non-healing corneal epithelial defects, corneal stromal melts (sterile keratolysis), microbial keratitis, and corneal perforation. Non-healing corneal epithelial defects may be treated in eyes without extensive symblephara by application of scleral contact lenses. For eyes with a small perforation or other significant keratolysis, the application of cyanoacrylate glue with a bandage contact lens can sometimes prevent further tissue loss.

If conjunctival foreshortening and symblepharon formation are not severe, a Gunderson conjunctival flap can be considered. Severe thinning with a perforation greater than 2 mm in diameter requires a tectonic penetrating keratoplasty, while severe corneal infection with thinning may also mandate a therapeutic penetrating keratoplasty. However, any keratoplasty leaves the patient at risk for further complications, including in particular, progressive ulceration and perforation of the graft. SJS/TEN is strongly associated with bilateral LSCD. Therefore, SJS/TEN patients are not candidates for limbal autografts. Keratolimbal allografts, although initially reported to have
promise, have a high rate of failure after one year due to graft rejection and loss of donor epithelium, infections, glaucoma, and other complications, leading to a final visual outcome that may be worse than prior to surgery. The use of living-related limbal allografts was not successful in one study with two SJS/TEN patients with severe ocular surface disease, and in another study showed a marginally improved ocular surface in two of ten eyes in patients with SJS/TEN. However, one study suggested that keratolimbal allografts in SJS/TEN do not undergo rejection at a higher rate than for other conditions, and occasional single case reports of success with keratolimbal allograft in SJS/TEN have been published. The most recent publication on the subject, and the largest series describing ocular sequelae in patients after SJS/TEN, describes 10 eyes receiving keratolimbal allografts. All cases failed within 1 year of the procedure. Therefore, with a few notable exceptions, the published literature suggests that keratolimbal allografts tend to fare poorly in SJS/TEN patients, and that the complications of surgery may outweigh the potential benefits. Laboratory cultivation of donor allograft tissue prior to transplantation, living-related or not, demonstrated improved outcomes in some reports, but not others.

2. Ocular Surface Reconstruction
a. Stabilizing Procedures

Much effort and attention in the care of SJS/TEN patients has been directed towards the restoration of normal eyelid/globe anatomical relationships and to the degree possible, improvement of the tear film. To prevent recurrence of melting and infection, globe salvaging measures should be followed by ocular surface stabilization procedures. These may include punctal occlusion; MMG to treat posterior eyelid margin keratinization; amnion with or without MMG or COMET to reform conjunctival fornices when causing restriction of eye movement or inability to wear therapeutic contact lenses. In the large study by Iyer and coworkers, a reduction in ocular surface dryness was noted in all 24 eyes that underwent fornix reconstruction, and the BCVA improved in 12 eyes at a mean of 4 years follow-up. COMET was used in 6 of these eyes to reduce post-operative inflammation and
healing time. In some patients with LSCD due to SJS/TEN, COMET appears to stabilize the ocular surface and improves but does not fully restore visual function.\textsuperscript{39}

b. Keratoprosthesis

For patients with severe corneal opacity, neovascularization, and LSCD after SJS/TEN (Figure 12), keratoprosthesis can restore normal or near normal visual function for a period of years after surgery, although not indefinitely.\textsuperscript{21,42,45,49,50,53,57,186-206} The risks of postoperative complications in SJS/TEN patients are considered higher than in any other group of keratoprosthesis recipients, and the prognosis for retention of the keratoprosthesis and good vision is lower than in other disorders.\textsuperscript{43,207-212} Complications of keratoprosthesis in SJS/TEN patients that may be increased over those seen in other preoperative diagnostic groups include sterile melts, microbial keratitis, microbial endophthalmitis, and glaucoma.\textsuperscript{213-224} Therefore, keratoprosthesis implantation should be considered as a last resort, and other means of visual rehabilitation, including optical iridectomy, and/or cataract extraction followed by scleral lens fitting should be considered when feasible.

Currently available keratoprosthesis design choices include the Boston keratoprosthesis, types I and II, and the modified osteo-odonto-keratoprosthesis (MOOKP) or more simply just OOKP. The Boston keratoprosthesis type I may be used, with caution, when affected patients have normal eyelid and conjunctival anatomy and a wet ocular surface, while the Boston keratoprosthesis type II or the MOOKP would be chosen for the dry, keratinized eye with extensive fornix and eyelid abnormalities (Figure 13). The choice between these latter two procedures has depended on surgical experience, expertise, and regulatory approval. The Boston keratoprosthesis is implanted in the US, Canada, much of South and Central America, and less so in Europe. The MOOKP procedure was developed in Italy, and is performed in a few centers in Europe and Asia, and in one in the United States (Figure 14).\textsuperscript{225} Both devices have been used in India. Regional considerations have led some authors to advocate for the Boston keratoprosthesis in patients with SJS/TEN,\textsuperscript{42,186,209} while others have advocated against it.\textsuperscript{226} However, a comprehensive comparison between devices is beyond the scope of this review.
Keratoprosthesis implantation in patients with SJS/TEN should be considered an operation of last resort, because complication-free retention time tends to be less than the remaining life span of the patients. To some degree, recent advances in keratoprosthesis surgery have lowered infection rates and improved device retention.\textsuperscript{209,227} A retrospective case series by Sayegh and coworkers\textsuperscript{209} reported the outcomes of 16 eyes of 15 patients with SJS who underwent Boston keratoprosthesis surgery (10 eyes underwent type II surgery, 6 eyes underwent type I surgery) by a single surgeon.\textsuperscript{209} The follow-up ranged from 10.2 months to 5.6 years. Seventy-five percent of eyes achieved a visual acuity of 20/200 or better, with 50\% achieving 20/40 or better. Visual acuity was maintained at 20/200 or better over a mean period of 2.5+-/2.0 years, with most vision loss occurring due to pre-existing glaucoma. There were no cases of device extrusion or endophthalmitis.

In the largest retrospective series of SJS patients to undergo MOOKP surgery (47 eyes), vision was 20/200 or better in 70\% at the last follow-up visit, with a mean follow-up of over 4 years postoperative.\textsuperscript{21} A recent systematic review identified eight case series describing MOOKP, including 96 SJS/TEN patients in a larger group of patients post-thermal and chemical burn.\textsuperscript{198} The overall anatomical survival rate for the combined case series was 87.8\% (range 67-100\%) 5 years postoperative, with three studies showing survival rates of 81.0\% (range 65-98\%) at 20 years postoperative. Endophthalmitis rates ranged from 2-8\%, while glaucoma remained the most common long-term blinding complication. However, the clinical outcomes in the subset of patients with SJS/TEN were not delineated.

MOOKP does appear to have a better long-term retention than Boston keratoprosthesis designs in patients with SJS/TEN. The MOOKP procedure is time-consuming, has to be completed in two or more stages, and, unfortunately, not all patients are candidates for this procedure, in part because of the need for at least one viable autologous cuspid tooth.\textsuperscript{50,191,194,198,205,206} Because only a few centers world-wide perform MOOKP surgery, access to the procedure is limited.

The results of published case series indicate that the cautious use of keratoprosthesis after SJS/TEN appears to be superior to standard keratoplasty with or without limbal stem cell allograft. However, the complexity of keratoprosthesis
implantation and the need for intensive follow-up in this particular group of patients mandates that keratoprosthesis surgery be performed only by trained surgeons at tertiary referral centers that are equipped to follow complex patients and promptly manage complications as they arise.

V. CONCLUSIONS

SJS/TEN is a severe, potentially blinding disorder, secondary to a T cell-mediated, dermatobullous drug reaction. Recent advances in the treatment of the ocular manifestations of SJS/TEN in both acute and chronic stages of the disorder make the ophthalmologist a critical player in its initial and long-term management. There are several windows of opportunity in the management of SJS/TEN, which, if missed, result in irreversible ocular damage, with attendant discomfort and loss of visual function. The first window is upon admission to the Burn ICU. A detailed eyelid and ocular surface examination is critical to determine if indications for amniotic membrane grafting have been met. The second window of opportunity occurs after discharge from the hospital, when failure to correct seemingly minor eyelid abnormalities, such as trichiasis or eyelid malposition, can allow progression from corneal epitheliopathy or simple corneal epithelial defect to corneal neovascularization, opacity, and potentially, corneal perforation. Posterior eyelid margin keratinization at any time after the acute episode should lead to immediate referral for scleral lens treatment or MMG surgery. Finally, corneal blindness due to SJS/TEN represents a window of opportunity for restoration of vision; however, mismanagement by inappropriate surgery or inadequate postoperative care can result in irreversible blindness without hope of later restoration.
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FIGURE LEGENDS

Figure 1. Ocular surface involvement in acute SJS/TEN. A. Conjunctival hyperemia and membrane. B. Eyelid margin sloughing (arrow) as evident with fluorescein staining under cobalt blue light. C. Corneal epithelial defect (arrow) stained with fluorescein.

Figure 2. A pseudomembrane in acute SJS/TEN seen here spanning the upper and lower eyelids. Note also the meibomian gland inspissations on both eyelid margins.

Figure 3. Ankyloblepharon in a patient years after acute SJS/TEN.

Figure 4. Tarsal conjunctival scarring and vertical shortening of the upper eyelid post-SJS/TEN. Eyelid everted for purpose of photograph.

Figure 5. Structural eyelid changes after SJS/TEN. A. Trichiasis from cicatricial entropion. B. Meibomian gland atrophy. C. Eyelid margin keratinization.

Figure 6. Loss of limbal palisades in patient post SJS/TEN. Note the 360 degrees of limbal vascularization, even where the fibrovascular pannus is absent.

Figure 7. Meibography of (A) normal eyelid and (B) post SJS/TEN eyelid with meibomian gland dropout.

Figure 8. Chronic ocular manifestations of SJS/TEN and their management. MMG: mucous membrane graft. PED: persistent (corneal) epithelial defect; BCL: bandage contact lens; AMT: amniotic membrane transplantation; COMET: cultivated oral mucosal epithelial transplantation.

Figure 9. Amniotic membrane transplantation in SJS/TEN. A. A symblepharon ring is constructed from intravenous (IV) extension tubing, with one end of the tube cut so as to fit over the other end of the tube and adjusted to reach all fornices without preventing eyelid closure once in place. B. All eyelashes are cut and removed and amnion with filter
paper intact is placed over the eye (long axis oriented vertically) and sutured to the upper eyelid with bolsters. C. The amnion is then separated from the filter paper and gently unraveled with a blunt instrument. D. The IV tubing ring is then used to push the amnion into both fornices. E. The amnion is then positioned to cover the entire globe and tarsal surfaces (in this case, with a muscle hook), leaving the inferior edge over the entire inferior eyelid margin. F. The amnion is then secured to the lower eyelid with bolsters.

**Figure 10.** Chronic SJS/TEN with corneal opacity (A) at initiation and (B) after 5 months of daily PROSE treatment, showing improved corneal clarity.

**Figure 11.** Labial mucous membrane graft to the eyelids for eyelid margin and tarsal keratinization. A. First, the keratinized portion of the tarsal conjunctiva is sharply excised. B. Bipolar cautery is applied at the base beneath the excised mucosa. C. The labial mucosa is incised at predetermined and marked dimensions, based on measurements of the recipient sites. D. The labial mucosa is excised and thinned of excess fat and submucosal tissue. E. The labial grafts after division to account for the necessary number of pieces, are sutured to the eyelid margin with 8-0 vicryl sutures in locking fashion, and the base and posterior portions secured with fibrin glue (not shown). F. The mucous membrane grafts are shown at the completion of the surgery.

**Figure 12.** Severe corneal sequelae of SJS/TEN. A. Dense corneal neovascularization and opacity in a wet, blinking eye. B. Complete ocular surface keratinization in an eye devoid of aqueous tears.

**Figure 13.** Xerotic, keratinized eye with symblephara. Only a Boston type II or osteo-odonto keratoprosthesis should be considered for visual rehabilitation.

**Figure 14.** Keratoprosthesis implantation in patients post SJS/TEN. (A) Boston keratoprosthesis type I. (B) Boston keratoprosthesis type II. (C) Osteo-odonto-keratoprosthesis. This image is taken from an oblique view.
Table 1. Windows of opportunity for ophthalmic intervention in the SJS/TEN patient.

<table>
<thead>
<tr>
<th>SJS/TEN: Phase of Disease</th>
<th>Exam Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Ocular surface/eyelid margin epithelial defect</td>
</tr>
<tr>
<td></td>
<td>Pseudomembrane formation</td>
</tr>
<tr>
<td>Chronic</td>
<td>Posterior eyelid margin keratinization</td>
</tr>
<tr>
<td></td>
<td>Trichiasis/distichiasis</td>
</tr>
<tr>
<td></td>
<td>Tear deficiency</td>
</tr>
<tr>
<td></td>
<td>Persistent epithelial defect</td>
</tr>
</tbody>
</table>

(Each finding should trigger an intervention to mitigate likely further vision loss.)
Table 2. Suggested initial management of acute ocular SJS/TEN based on simple clinical grading system. *

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade defined</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No ocular involvement</td>
<td>AT 4x/day</td>
</tr>
<tr>
<td>1</td>
<td>Conjunctival hyperemia</td>
<td>Moxi 3x/day&lt;br&gt;Pred 6x/day&lt;br&gt;FML 6x/day&lt;br&gt;AT every hour as feasible</td>
</tr>
<tr>
<td>2</td>
<td>Ocular surface/eyelid margin epithelial defect or pseudomembrane formation</td>
<td>Use above therapies, plus consider AMT</td>
</tr>
<tr>
<td>3</td>
<td>Ocular surface/eyelid margin epithelial defect and pseudomembrane formation</td>
<td>Use above therapies, plus consider AMT</td>
</tr>
</tbody>
</table>

AT: artificial tears. Moxi: moxifloxacin 0.5% ophthalmic solution. Pred: prednisolone acetate 1% ophthalmic suspension. FML: fluorometholone 0.1% ophthalmic ointment. AMT: amniotic membrane transplantation.

* adapted from reference 73.
Chronic ocular manifestations of SJS/TEN and their management

- Trichiasis
  - Hyfrecation
  - Cryotherapy
  - Eyelash bulb extirpation
  - MMG if associated with entropion
  - Release of cicatrix
  - Tarsorrhaphy
  - Lateral canthoplasty/tarsal strip
  - Anterior lamellar repositioning
  - Posterior lamella tightening
  - Transconjunctival advancement

- Eyelid malposition
  - Lagophthalmos
  - Entropion
  - Ectropion

- PED
  - Lubrication
  - Punctual occlusion
  - BCL
  - Tarsorrhaphy
  - Autologous serum tears
  - AMT
  - Scleral lens
  - COMET

- Dry eye
  - Preservative-free artificial tears
  - Punctal cautery
  - Minor salivary gland transplant

- Posterior eyelid margin keratinization
  - All-trans retinoic acid ointment
  - Scleral lens
  - MMG

- Symblephara
  - Lysis/fornix reconstruction with amnion/MMG

- End-stage corneal blindness
  - MMG
  - COMET
  - Keratoprosthesis