Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis — A Comprehensive Review and Guide to Therapy. I. Systemic Disease

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ABSTRACT **The intent of this review is to comprehensively appraise the state of the art with regard to Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with particular attention to the ocular surface complications and their management. SJS and TEN represent two ends of a spectrum of immune-mediated, dermatobullous disease, characterized in the acute phase by a febrile illness followed by skin and mucous membrane necrosis and detachment. The widespread keratinocyte death seen in SJS/TEN is rapid and irreversible, and even with early and aggressive intervention, morbidity is severe and mortality not uncommon. We have divided this review into two parts. Part I summarizes the epidemiology and immunopathogenesis of SJS/TEN and discusses systemic therapy and its possible benefits. We hope this review will help the ophthalmologist better understand the mechanisms of disease in SJS/TEN and enhance their care of patients with this complex and often debilitating disease. Part II (April 2016 issue) will focus on ophthalmic manifestations.**

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OUTLINE

KEY WORDS apoptosis, drug-induced disease, immune-mediated disease, keratinocyte death Stevens-Johnson Syndrome, toxic epidermal necrolysis

I. INTRODUCTION

The spectrum of disease defined by Stevens-Johnson Syndrome (**SJS**), the more severe toxic epidermal necrolysis (**TEN**), and their intermediate (SJS/TEN overlap) characterize a severe immunologic dermatobullous condition with high mortality and significant long-term morbidity. SJS/TEN is characterized by widespread keratinocyte death and epidermal necrosis resulting in splitting of subepidermal layers with attendant tissue loss at skin and mucosal surfaces.[1] The diagnosis of SJS/TEN is made upon recognition of defining clinical signs and skin biopsy demonstrating full-thickness necrosis of the epidermis and keratinocyte apoptosis, with minimal involvement of the underlying dermis.[2-5]

The purpose of Part I of this review is to summarize the most up-to-date information on SJS/TEN, with particular attention to pathogenesis and systemic therapy. SJS/TEN is a rare disease, and there is a paucity of centralized information on best care practices. This comprehensive review critically evaluates contemporary concepts of pathophysiology and the therapies currently in use for patients with the disorder. However, the authors wish to emphasize that the pathophysiology of SJS/TEN is still a matter of debate, and the best systemic therapy for SJS/TEN beyond general supportive burn care remains highly controversial among burn center physicians, often even within the same burn center. The ophthalmic manifestations of SJS/TEN and their management will be covered in Part II.

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. EPIDEMIOLOGY

A. Incidence

The estimated annual incidence (cases/million population/year) of SJS/TEN ranges from 0.4 to 7 cases per million population,[6-8] making it a rare disease.[9] There are suggestions that the incidence in certain areas of the world may be higher. In a retrospective study of 404 hospitalized patients in South India with acute cutaneous drug reactions over a 9-year period, 19.5% were diagnosed with SJS/TEN, somewhat higher than reported in other countries.[10] SJS/TEN carries a significant risk of mortality, ranging from 1-5% in SJS and 25-40% in TEN.[7,11-15] Unfortunately, despite continued efforts, mortality rates remain significant.[4] SJS predominantly affects children and adolescents, whereas TEN occurs in all ages, from premature infants to the elderly.[4] The incidence of cutaneous drug reactions including TEN is 2.7 times higher in the elderly than in younger patients, and mortality from TEN is twice as high in the elderly (51% vs 25%). However, SJS/TEN is more likely recurrent in children. In one series, 18% of 55 children developed recurrent SJS up to 7 years after the index episode, with three children experiencing more than one recurrence.[16]

B. Risk Factors

1. Non-Pharmaceutical Triggers

While SJS/TEN most often represents an idiosyncratic reaction to systemic medications, there are uncommon exceptions and the disorder can be idiopathic.[17,18] SJS/TEN has been associated with vaccination[19-21] and exposure to industrial chemicals and fumes.[19,22,23] TEN has also occurred in patients consuming natural remedies and traditional Chinese herbal medications.[24-27] Infection with *Mycoplasma pneumoniae* is a controversial cause of SJS, because *Mycoplasma* has also been associated with erythema multiforme and, in addition, can cause a primary mucositis.[28-35] Herpes virus infections have been associated with SJS,[36,37] and reactivation of herpes simplex virus has been associated with SJS recurrences, particularly in children.[16,38] Two cases of TEN have been reported in which the skin manifestations occurred specifically

in sun-exposed areas[39,40] or after radiation therapy.[41,42] Photo-induced TEN has also been reported from clobazam.[39] Patients with brain tumors treated with radiation appear to be more susceptible to SJS/TEN when given phenytoin.[43-45] TEN and other drug reactions are also more common in HIV/AIDS.[4]

2. Offending Medications

More than 200 offending medications have been implicated as triggers of SJS/TEN, with new drugs implicated almost as soon as they are on the market.[4] Common causes include sulfonamide antibiotics (trimethoprim/sulfamethoxazole), aromatic anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazapine), beta-lactam antibiotics, nevirapine, abacavir, non-steroidal anti-inflammatory medications, allopurinol, lamotrigine, tetracyclines, quinolones, and others.[1,4,46-49] There are reports of TEN from intranasal mupirocin[50] and from antiglaucoma, antibiotic, and over-the-counter (OTC) eye drops.[51-55] One report described TEN after use of OTC oral pseudoephedrine.[56] Other reports detail SJS/TEN after ingestion of medicines for the common cold.[57,58]

Genetic and environmental variables lead to differences in susceptibility in various populations. In a case-control study in an Asian population, carbamazepine, phenytoin, and allopurinol were the most common offending agents.[59] In general, SJS/TEN develops within the first 8 weeks after starting a new medication.[60] Greater than 90% of SJS/TEN cases in first-time users of antiseizure medications occurred in the first 63 days of therapy, with the risk of a serious cutaneous reaction estimated to be in the range of 1 to 10 per 10,000 new users of this class of medication.[61]

3. Medication Cross-Reactivity

The potential for cross-reactivity between medications to induce recurrent SJS/TEN is a frequent concern of both patients and caregivers. There is no evidence that SJS/TEN in response to one class of medication raises the risk for SJS/TEN with a biochemically different class of medications.[4,62] However, there is cross-reactivity between different beta-lactam antibiotics, such as penicillins and cephalosporins,[63] so caution is advised. The antiepileptic agents, carbamazepine, phenytoin, and phenobarbital are all aromatic compounds and show cross-reactivity in SJS/TEN. Also, antiepileptic-associated SJS/TEN is ten times more likely to occur in patients who have been previously treated with another anti-epileptic medication.[4] However, a reaction to a sulfonamide antibiotic does not imply sensitivity to sulfonamide non-antibiotic drugs (such as thiazide diuretics or COX-2 inhibitors).[64,65]

III. CLINICAL PRESENTATION

The pattern of clinical signs and symptoms at onset of SJS/TEN varies somewhat among affected patients, but in general, a prodrome of fever, malaise, cough, rhinorrhea, and anorexia is followed by inflammation and ulcerations of the ocular, oral, and genital mucosa. Approximately one day after the onset of mucositis,[66,67] a painful generalized erythematous vesiculobullous rash develops (Figure 1). There is a characteristic but not pathognomonic epidermal separation and sloughing with application of shear forces on the skin (positive Nikolsky sign).[68] Epidermal necrolysis with a sparse dermal monocytic infiltrate is the defining sign on histopathologic studies of the skin biopsy specimens

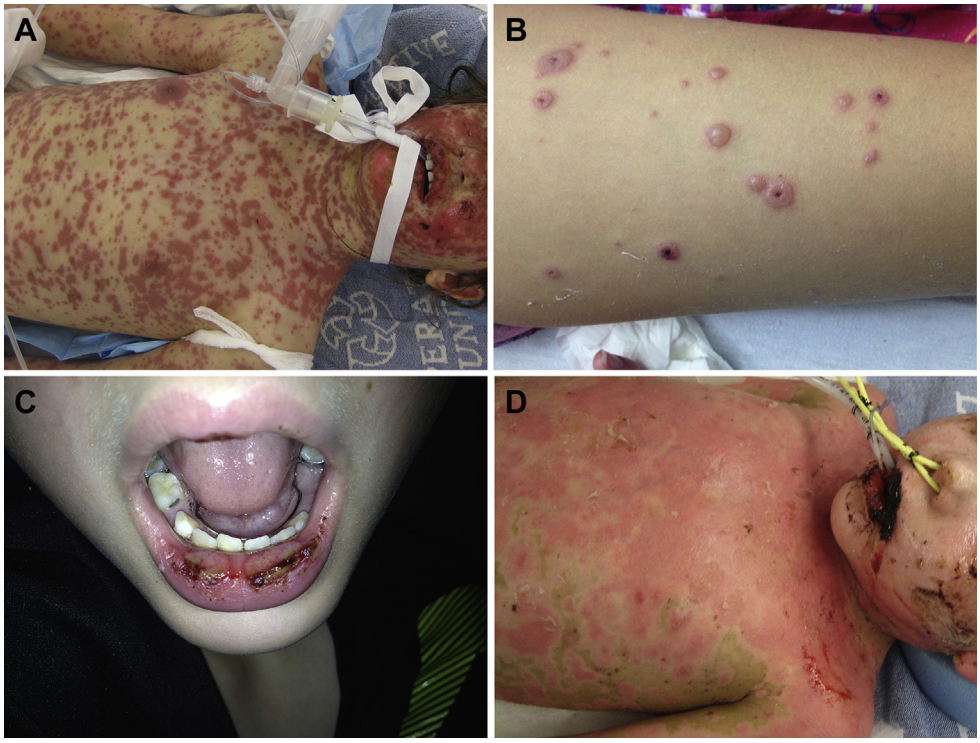

Figure 1. Acute presentations of SJS/TEN. A. Maculopapular rash on trunk. B. Raised bullae and target lesions on extremity. C. Early oral mucositis. D. Skin sloughing on trunk.

from involved areas.[4] Widespread necrolysis involving the skin surface occurs in most patients, with gradual onset over a period of 2-15 days. Fingernail involvement leads to nail loss and deformation.[69] However, even with severe skin involvement, the hairy portion of the scalp is typically spared.[70] Repeated sloughing may occur in areas of re-epithelialization.[66]

TEN is often associated with instability of major body systems.[71] Affected patients may develop severe inflammation of internal mucosal surfaces, including the gastrointestinal and respiratory tracts.[72] Major metabolic abnormalities, sepsis, multi-organ failure, pulmonary embolism, and gastrointestinal hemorrhage can occur.[66,67,73] Anemia and lymphopenia are common. Neutropenia is a particularly poor prognostic sign.[74-76] Serious pulmonary disease may be present even without obvious radiographic abnormalities, leading to dyspnea, tachypnea, and hypoxemia.[77] Survivors may be left with chronic and debilitating sequelae permanently affecting their quality of life (Figure 2).

The ocular complications described later in this review are generally acknowledged as the most debilitating residual effects of SJS/TEN. However, skin scarring and pigmentation; vaginal, urethral, and anal strictures; vulvar adenosis; penile phimosis; dental abnormalities; esophageal strictures; and dry mouth due to decreased salivary flow,[4,66,67,78,79] also commonly reduce function and the quality of life following SJS/TEN. However, it is important to recognize that the acute and chronic manifestations of SJS/TEN vary among patients, and a modest subset survive their disease without apparent sequelae.

SJS/TEN can take a significant psychological toll on survivors[80] and their immediate family members. A study of unsolicited internet posts by SJS/TEN survivors revealed that they had many unanswered questions long after the event, and they desired to connect to other survivors to share their experiences.[81] Survivors had concerns about effects on fertility, fear of recurrences, and genetic inheritance of the disease. One study showed that survivors often choose to avoid medications altogether, and may fear becoming sick and ever needing medications.[82] It is particularly poignant that patients who develop SJS/TEN due to a psychiatric therapeutic may subsequently avoid essential treatment for their mental illness. Similarly, those with chronic medical complications of SJS/TEN[71] may avoid potentially beneficial medications out of anxiety about recurrence.

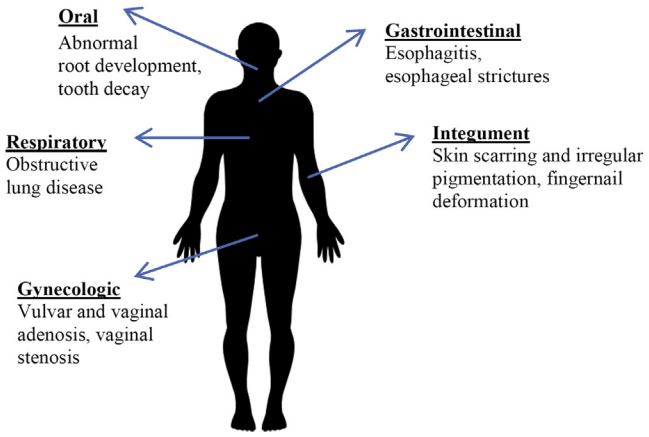

Figure 2. Schematic of body systems frequently affected in chronic SJS/TEN. In general, every body system affected in acute SJS/TEN shows chronic manifestations to variable degrees, later on. Other body systems can also be affected.[71]

IV. CLASSIFICATION

Various classification schemes for SJS/TEN have been proposed, each with its own limitations. Mucosal involvement and the percentage of affected body surface area (**BSA**) are most useful in categorizing the disorder. In 1993, Bastuji-Garin et al[83] divided the SJS/TEN spectrum into three major categories: SJS, defined by epidermal detachment of <10% of the BSA in association with widespread erythematous or purpuric macules or flat atypical targets; SJS/TEN overlap, defined by epidermal detachment of 10% to 30% of BSA plus widespread purpuric macules or flat atypical targets; and TEN defined by epidermal detachment of >30% of the BSA coupled with widespread purpuric macules or flat atypical targets. Bastuji-Garin and coworkers also subclassified TEN as being with or without spots (purpuric macules).[83]

Another acute dermatobullous disorder often confused with SJS/TEN is bullous erythema multiforme. The clinical presentations and histopathology of erythema multiforme and SJS/TEN are distinctly different (Table 1).[84-86] Erythema multiforme is characterized by epidermal detachment of <10% BSA, coupled with localized typical target lesions or raised atypical targets. Erythema multiforme is typically caused by infection, most commonly herpes simplex virus. It most commonly presents with a minimal degree of mucosal involvement, with the skin biopsy characterized histologically by a lichenoid infiltrate, basal epidermal

Table 1. Classification for EM/SJS/TEN

Classification	Bullous EM	SJS	SJS/TEN Overlap	TEN
Detachment	<10%	<10%	10-30%	>30%
Typical target lesions	Yes	No	No	No
Atypical target lesions	Yes, raised	Yes, flat	Yes, flat	Yes, flat

Adapted from.[83]

necrosis, and moderate dermal inflammation. In contrast, SJS/TEN is typically associated with drugs, presents with prominent mucositis, and is identified histologically by full thickness epidermal necrosis with minimal underlying dermal inflammation. The current classification of SJS/TEN used by most clinicians derives from that proposed by Bastuji-Garin et al.[83,87]

V. MORTALITY FROM TOXIC EPIDERMAL NECROLYSIS

Various investigators have attempted to use clinical and pathological findings to predict the risk of mortality from TEN. SCORTEN (SCORe of TEN) is a mathematical model that has proven to be generally accurate in predicting the risk of death from TEN.[88,89] It is intended to be completed within 24 hours of admission and again on day 3 of hospitalization.[89] The SCORTEN uses 7 independent risk factors to predict the risk of mortality from TEN[88]:

1. Age above 40 years
2. Presence of malignancy
3. Heart rate >120 beats per minute
4. Initial epidermal detachment >10%
5. Serum urea >10 mmol/L
6. Serum glucose >14 mmol/L
7. Serum bicarbonate <20 mmol/L

Using the SCORTEN system, each criterion is worth one point, with each additional point associated with a significant increase in mortality (with an increase in the odds ratio by a factor of 3.45).[84] For example, SCORTEN of 0-1 portends a 3.2% mortality, while SCORTEN of 5 or greater predicts a mortality of 90% (Table 2). Other clinical parameters previously reported to be predictive of mortality include thrombocytopenia, leukopenia, delay in hospital admission, and treatment with antibiotics or corticosteroids prior to admission.[74-76,90]

Quinn and colleagues noted that some skin biopsy specimens from TEN patients exhibit more than minimal dermal inflammation, and showed a correlation between dermal mononuclear cell counts with disease severity and mortality.[91] In their study of 37 cases, quantification of dermal mononuclear cells was almost as accurate in predicting outcomes as SCORTEN (68% using mean cell count, vs 71% with SCORTEN).

Table 2. SCORe of TEN (SCORTEN) level and predicted mortality

SCORTEN	Mortality
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%
≥5	90.0%

Adapted from.[88]

VI. DIFFERENTIAL DIAGNOSIS

As mentioned above, erythema multiforme is considered to be an entirely different disease entity than SJS/TEN. The former is marked by a more abbreviated course, occurs in a younger age group, and is most often associated with infection.[86] Erythema multiforme frequently recurs, and skin lesions may be positive for herpes simplex virus and interferon gamma[84] and show significantly lower levels of proinflammatory cytokines than in SJS/TEN.[92] In one study, the proportion of patients with involvement of multiple mucosal sites was significantly greater in SJS/TEN.[93] SJS/TEN is most commonly caused by medications. SJS/TEN is characterized clinically by skin lesions located predominantly on the trunk, which appear as widespread, flat, atypical targets or purpuric macules, and involvement of at least two mucosal sites.[4]

Other important entities in the differential diagnosis in patients with SJS/TEN include staphylococcal scalded skin syndrome, linear IgA bullous dermatosis, paraneoplastic pemphigus, acute graft-versus-host disease, drug-induced pemphigoid and pemphigus, and acute generalized exanthematous pustulosis. These entities are distinguished by specific clinical findings on the skin and mucous membranes and on histopathology (Table 3).[4]

VII. PATHOGENESIS OF SJS/TEN

The pathogenesis of SJS/TEN is both complicated and controversial. However, available evidence points to a synthesis of genetic and innate immune mechanisms leading to keratinocyte cell death by apoptosis and secondary epidermal necrosis (Figure 3).[94] A 2008 review by Nickoloff examines various theories for the mechanisms underlying SJS/TEN, including altered drug metabolism, immune-mediated mechanisms, and activation of death receptors on keratinocytes.[95]

A. Genetic Susceptibility to SJS/TEN

There are several points to keep in mind regarding genetic susceptibility to SJS/TEN. First, the genetic risk factors are drug-specific. Second, genetic risk factors vary among populations and/or ethnic groups. Third, genetic testing for human leukocyte antigen (**HLA**)-B*1502 is available and recommended by the U. S. Food and Drug Administration for one drug, carbamazepine, in at-risk (Asian) populations, and more such recommendations are likely to follow. In patients of Han Chinese descent, HLA-B*1502 was strongly associated with carbamazepine-induced SJS/TEN,[96] and pretesting reduced the rate of SJS/TEN from carbamazepine in Hong Kong patients requiring antiepileptic medications.[97] Other HLA loci also appear to confer an increased risk of SJS/TEN.[98-111] HLA-B12 in one study of 44 TEN survivors was found to be more commonly detected,[112] and HLA-DQB1*0601 was associated with an increased risk of SJS/TEN.[113] The HLA-B*5801 allele was

Table 3. Differential diagnosis of SJS/TEN

Disease	Mucositis	Morphology	Onset
Drug-induced pemphigoid	Rare	Tense bullae, sometimes hemorrhagic	Acute
Staphylococcal scalded skin syndrome	Absent	Erythema, skin tenderness, perioral crusting	Acute
Drug-induced pemphigus	Usually absent	Erosions, crusts, patchy erythema	Gradual
Drug-triggered pemphigus	Present	Mucosal erosions, flaccid bullae	Gradual
Paraneoplastic pemphigus	Present (usually severe)	Polymorphous skin lesions, flaccid bullae	Gradual
Acute graft versus host disease	Present	Morbilliform rash, bullae, and erosions	Acute
Acute generalized exanthematous pustulosis	Rare	Superficial pustules (resembles pustular psoriasis)	Acute
Drug-induced linear IgA bullous dermatosis	Rare	Tense, subepidermal bullae (resembles pemphigoid)	Acute

Adapted from.[4]

found to be present in 100% of 51 patients experiencing severe cutaneous reactions to allopurinol versus 15% of 135 tolerant patients).[114]

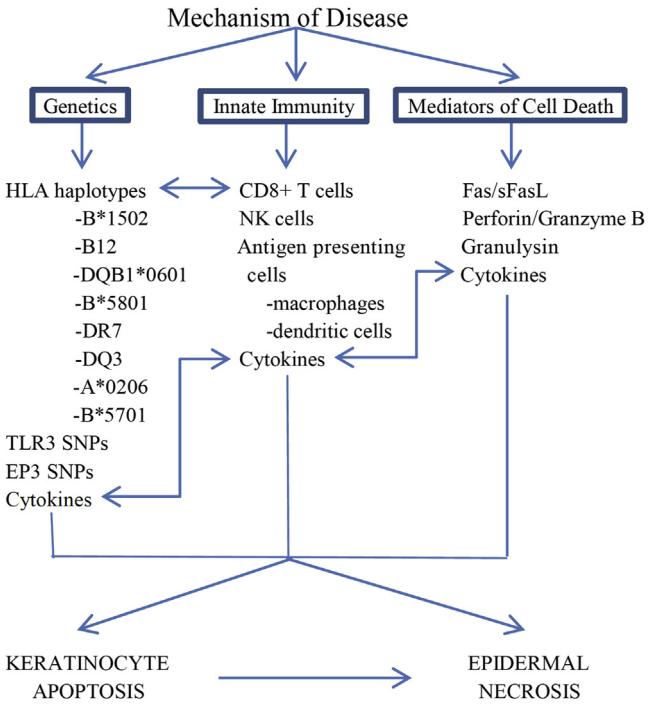

Figure 3. Pathogenic mechanisms involved in SJS/TEN. The schematic presents a simplified depiction of the interplay between genetics, specific components of innate and acquired immunity, and effectors of keratinocyte cell death. See text for detailed discussion. TLR3=Toll-like receptor 3. SNPs=single nucleotide polymorphisms. EP3= prostaglandin E receptor 3. (Adapted from Harp JL, Kinnebrew MA, Shinkai K.[94])

HLA-B*5701 confers an increased risk of hypersensitivity reactions to abacavir,[4] and the presence of all three variants HLA-B*5701, HLA-DR7, and HLA-DQ3 was 100% predictive of developing a hypersensitivity reaction. Genetic associations have also been demonstrated for compound medications, such as over-the-counter cold medications.[57,58] One particularly interesting association was found between SJS/TEN and potentially dominant negative single nucleotide polymorphisms in the IKZF1 gene, which codes for the transcription factor Ikaros.[115] Studies in Japanese patients also showed increased risk of eye involvement associated with HLA-A*0206 and HLA-B*44:03.[57,116-118] Single nucleotide polymorphism analyses using candidate genes associated with innate immunity,[118-121] allergy,[122,123] and apoptosis[124] revealed that polymorphisms in the TLR3 and EP3 genes may also be strongly associated with SJS in the Japanese population. A putative imbalance between TLR3 and EP3 was postulated to play a role in the ocular surface disease severity in SJS/TEN. Another recent study showed a genetic polymorphism in the IFN-gamma gene in Mexican patients with SJS.[125] Taken together, these reports suggest a complex role for immunogenetics in SJS/TEN.

Family members of SJS/TEN patients may be susceptible to the same drugs and should be counseled to avoid culprit medications when possible. However, HLA testing is not routinely performed prior to starting most new medications. Patch testing in SJS/TEN to test for susceptibility to a specific drug has been attempted, but the results have been disappointing.[126] Provocation tests are dangerous and should not be performed.[127] An in vitro lymphocyte toxicity assay to measure activity of detoxification enzymes exists but only as a research tool.[128]

B. Immunology of Acute SJS/TEN

The molecular pathogenesis of SJS/TEN is still under investigation, and there are many contradictory studies and observations. In general, acute SJS/TEN is considered a T-cell mediated, type IV hypersensitivity disorder, and could be considered an "immunologic burn." Affected patients show an exuberant response on re-exposure to the offending agent, and unlike many other types of hypersensitivity reactions, cytotoxic antibodies, immune complexes, and complement activation, all components of type II or III hypersensitivity reactions, are rarely found. On occasion, C3 and IgG may be detected at the dermal-epidermal junction and around the blood vessels but are thought to be related to nonspecific exudation.[129]

There is compelling evidence to support a role for cytotoxic T cells as major effectors in the pathogenesis of SJS/TEN, especially in the acute stages. The blister fluid of TEN patients contains predominantly T lymphocytes. However, unlike most allergic skin reactions where CD4+ lymphocytes are the predominant cell type,[130] in the early stages of TEN, CD8+ lymphocytes concentrate in blister fluid and epidermis, while CD4+ lymphocytes are localized to the dermal layers.[131] As the disease progresses, however, there is a relative decrease in lymphocytes and increase in activated monocytes. Furthermore, soluble IL-2 receptor (sIL-2R), a marker for activated T cells, is present in high levels in blister fluid and serum of TEN patients, and levels correlate with disease activity.[132] One study demonstrated an increase in the number of activated T lymphocytes expressing cutaneous lymphocyte antigen (CLA), a skin-homing receptor, in the peripheral blood of TEN patients. Levels correlated with disease activity and normalized after resolution of SJS/TEN.[133]

Chung and colleagues found that blister fluid of SJS/TEN patients contained both cytotoxic T lymphocytes, and natural killer cells.[134] In addition, characterization of CD8+ T cells in the epidermis and blister fluid of TEN patients has shown that a majority of these cells also express surface markers normally found on natural killer cells. CD8+ T cells in the epidermis expressed the killer inhibitory receptor (KIR) and killer activating receptor (KAR),[135] and a high percentage of CD8+ T cells from blister fluid showed CD56 neural cell adhesion molecule (NCAM), another marker found on natural killer and highly cytotoxic CD8+ T cells.[136]

Although the aforementioned findings support a major role for T cells in acute SJS/TEN, there are also studies that point to the involvement of other types of immune cells. For example, although the blister fluid of TEN lesions shows a predominance of lymphocytes, immunohistochemistry of skin biopsies shows a predominance of cells of the monocyte-macrophage lineage and high levels of TNF-alpha.[129] Paquet and colleagues studied 23 patients with TEN and found that MAC 387^{+} macrophages were the most numerous cells in the epidermis, while factor $XIIIa^{+}$ dendritic cells were the most common cells in the dermis.[137] MAC 387 is a monoclonal antibody clone that binds to cytoplasmic antigen expressed by monocytes and macrophages in inflammatory skin diseases.[138] Factor XIIIa+ dendritic cells (dermal dendrocytes) play a major role in phagocytosis and antigen presentation. There is an increase in these dermal dendrocytes in other immunologic skin disorders such as atopic dermatitis and psoriasis, and they may also be involved with tissue repair.[139,140]

C. Mechanisms of Cell Death in SJS/TEN

Cellular demise occurs via two major pathways: necrosis and apoptosis. Necrosis is associated with intense inflammation, while in apoptosis, T lymphocytes induce programmed cell death by activating intracellular caspases within the target cells leading to cell death with minimal inflammation. There is general consensus that keratinocyte cell death in SJS/TEN occurs via apoptosis.[141] Light and electron microscopy of SJS/TEN-involved epidermis shows characteristic physical changes and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining of keratinocytes associated with apoptosis.[141,142]

Apoptotic death receptors are transmembrane proteins of the tumor necrosis factor (**TNF**) superfamily.[143] Several different types of death receptors have been isolated, but the first and most extensively studied is Fas (CD-95), and its ligand, FasL.[144] Dysregulation of the Fas pathway has been implicated in the pathogenesis of a variety of tissue-destructive processes, including graft-versus-host disease, multiple sclerosis, stroke, and TEN.[144] The molecular mechanism by which Fas activates apoptosis has been extensively studied, and a detailed review is beyond the scope of this paper. Briefly, intracellular FasL in affected cells is transported via intermediate filaments to the cell surface, where it may be released as soluble FasL (**sFasL**). Binding of FasL to Fas on the surface of epidermal cells induces a conformational change in Fas and recruitment of Fas-associated death domain protein, an intracellular adaptor protein that attaches to both the Fas death domain and to procaspase 8, which is then proteolytically processed to form caspase 8. Activation of the caspase cascade leads to disassembly of cellular components and cell death.[145,146]

Work by Viard and colleagues showed mediation of keratinocyte death in TEN through activation of Fas.[147] They demonstrated elevated expression of FasL on the cell surface of keratinocytes and high levels of soluble sFasL in TEN serum, in sharp distinction to patients with other maculopapular drug reactions or normal controls.[147] In addition, frozen skin sections of TEN patients induced apoptosis in a Fas-sensitive cell line, while apoptosis was blocked by anti-FasL-monocolonal antibody (Fas-Fc). These findings suggest that Fas may play a key role in inducing apoptosis in keratinocytes in TEN.

Conflicting data exist regarding the source of FasL. Chang and colleagues measured serum sFasL levels over time in a patient with TEN, and found that sFasL levels peaked 24-48 hours after the onset of significant skin damage,[148] suggesting that sFasL may merely be a byproduct of FasL expressed on epidermal cells and not a direct inducer of apoptosis. Metalloproteinases downregulate FasL expression by cleaving the TNF-homologous portion

of membrane-bound FasL, releasing sFasL, and increased MP activity results in increased sFasL concentrations in the serum.[149,150] Therefore, elevated sFasL serum concentration in TEN patients may be due to action of metalloproteinases at the surface of epidermal cells.[145]

Gelatinase A (MMP2) and B (MMP9) have also been implicated in SJS/TEN.[151] Abe and coworkers studied 22 patients with SJS/TEN and found consistently elevated levels of sFasL in serum from these patients.[152] Adding the patients' serum to epidermal cell culture led to induction of apoptosis, while addition of anti-FasL monoclonal antibody blocked apoptosis. Stimulation of peripheral blood mononuclear cells (**PBMC**s) from TEN patients with the causative agent led to production of high levels of sFasL. In addition, direct immunofluorescence testing of skin specimens of 3 out of 22 patients could not detect FasL on the keratinocyte surface. The authors concluded that sFasL may be released by PBMCs instead of keratinocytes and that sFasL binds Fas on the cell surface to induce apoptosis, and it may serve as a serologic marker for TEN.

Other death receptors, such as TNF-R1 and TNF-related apoptosis-inducing ligand (**TRAIL**) may also be involved in TEN pathogenesis.[153] There are elevated levels of TNF-alpha in blister fluid, skin, mononuclear cells, and blood of affected patients. TNF-alpha activates TNF-R1, which leads to activation of Fas-associated death domain protein and downstream caspase pathways. However, TNF-R1 also activates anti-apoptotic pathways by activating NF-kB.[153] Therefore, TNF-alpha may either induce or block apoptosis, and as such, the use of anti-TNF medications in TEN patients is controversial.[153]

Despite findings that point to Fas-FasL pathway as a key mediator of apoptosis in SJS/TEN, there are experimental studies that challenge this hypothesis. The lytic granules of cytotoxic T lymphocytes contain perforin and granzyme. Once T lymphocytes recognize a target cell, perforin creates 16 nm channels in the cell membrane of the affected cell, allowing granzyme B to enter the cell and activate the intracellular caspase cascade, leading to apoptotic cell death.[154] After exposure to the causative agent, mononuclear cells from the blister fluid of TEN patients became cytotoxic, but peripheral blood mononuclear cells did not. Anti-Fas monoclonal antibodies failed to inhibit this cytotoxicity, while distinct inhibitors of the perforin/granzyme pathway did.[136,155] These findings implicate perforin/granzyme as mediators of the pathogenesis of TEN.

Nassif and coworkers evaluated cytokines in blister fluid of TEN patients and reported elevated IFN gamma, TNF-alpha, sFasL, IL-18, and IL-10.[156] They showed that FasL and TNF-alpha found in blister fluid were expressed by keratinocytes rather than by mononuclear cells in the fluid. Cell-free supernatants of blister fluid did not induce apoptosis in cultured keratinocytes, leading to the conclusion that apoptosis in TEN was not mediated through the sFas-FasL pathway. The authors proposed that activated CD8+ T cells secrete IFN-gamma, which in turn stimulates keratinocytes to produce TNF-alpha, FasL, and IL-10. TNF-alpha induces upregulation of MHC 1 molecules, which makes keratinocytes more sensitive to cytotoxic T lymphocytes and perforin/granzyme-mediated apoptosis. Nassif and colleagues hypothesized that FasL and IL10 production may actually be protective and serve to downregulate inflammation by inducing apoptosis in cytotoxic T lymphocytes, rather than inducing demise of the keratinocytes.

Posadas and colleagues looked at cytokine expression in peripheral blood and from mononuclear cells in patients' blister fluid in a study of four severity levels of delayed dermatologic drug reactions: benign maculopapular rashes, desquamative exanthema, SJS, and TEN.[157] They found that perforin/granzyme B concentration directly correlated with disease severity. Levels of perforin/granzyme B produced by peripheral blood mononuclear cells of patients with maculopapular drug reactions were much lower than from patients with SJS/TEN. Interestingly, analysis of cytokine expression by peripheral blood and mononuclear cells from blister fluid of SJS/TEN patients also showed elevated FasL. These data suggest that both pathways may play a role in SJS/TEN. A study of biopsy specimens in TEN also showed abnormal expression of calprotectin,[158,159] an antimicrobial protein not found in normal skin. Other studies have shown increased nitric oxide.[160]

Chung and colleagues used gene expression profiling followed by quantitative PCR and immunohistochemistry and reported that a secretory form of granulysin was expressed at levels two to four times that of perforin/granzyme B or s-FasL.[134] Removing granulysin reduced the cytotoxicity of blister fluid. Injection of granulysin into mouse skin resulted in changes that mimicked SJS/TEN. Their findings suggest that secretory granulysin may be an important mediator of SJS/TEN.

To summarize, keratinocyte cell death in SJS/TEN appears to occur by apoptosis. Several mechanisms are likely involved to varying degrees. While T lymphocytes play a major role, other components of the immune system closely participate in the process.

VIII. ACUTE SYSTEMIC THERAPY

A. Supportive Care

The mainstay of treatment for SJS/TEN is early and aggressive supportive care in a Burn Intensive Care Unit (ICU). Prognosis improves the earlier the offending agent is discontinued.[161] While it is critical that the offending agent be identified and immediately stopped, medications with a long half-life are problematic.[161] A direct correlation was also shown between survival and the speed with which the patient is admitted to a Burn ICU,[162-164] where urgent care can be initiated by personnel trained in the management of the respiratory tract, kidneys, fluid and electrolyte balance, infections, nutrition, skin and ocular surface, and pain control.[165-167] In the Burn ICU, necrotic skin is debrided, and the exposed areas covered with artificial membranes or biologic dressings which enhance healing, and reduce discomfort, scarring, and infection.[168] Given high rates of infection in SJS/TEN, frequent skin, blood, urine, and line cultures are performed.

Routine antibiotic prophylaxis is typically avoided due to emergence of resistance leading to increased mortality from sepsis.[169] When patients do become septic, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are common inciting agents.[170] Early supportive care in a Burn ICU can be effective in reducing mortality. Sheridan and colleagues reported no deaths in 10 children with TEN treated with supportive care alone.[171] In another study, 21 children with SJS/TEN were treated with conservative measures alone, and none died.[172] In another, 15 children with SJS/TEN treated in a Burn ICU with supportive care alone had a reported mortality of 7%.[173]

B. Therapeutic Agents

Proposed systemic interventions in acute SJS/TEN are described in the sections that follow and in Table 4.

1. Systemic Corticosteroids

Because SJS/TEN is thought to represent an immune response to an exogenous agent, systemic administration of corticosteroids has been used with the hope of improving clinical outcomes. However, the use of systemic corticosteroids in the treatment of SJS/TEN is highly controversial. Patients taking systemic corticosteroids for other conditions still develop SJS/TEN,[12,174-176] and corticosteroids do not appear to influence TEN progression once the reaction is initiated.[175,177] In the pediatric literature, two[178,179] out of four[178-181] observational studies found that systemic corticosteroids significantly increased the rate of complications (sepsis, urinary tract infection, gastrointestinal hemorrhage) in children with SJS compared to children who only received supportive measures. Among the outcomes studied (duration of fever and of acute eruption, length of hospital stay, number of complications), the only parameter to show improvement from corticosteroid administration was duration of fever.[178,180]

The evidence for the use of systemic corticosteroids for SJS/TEN in adults is also inconsistent. A few small retrospective case series have shown a mortality benefit from corticosteroids,[182-185] but most reports have suggested either a lack of efficacy[90,186,187] or increased mortality.[188,189] In one large retrospective study, the use of systemic corticosteroids

Table 4. Proposed systemic interventions in acute SJS/TEN

Therapy*	Proposed Mechanism of Action	Effect on Ocular Disease	Evidence-based Recommendations
Systemic Corticosteroids/ High-dose Pulsed Steroids (HDPS)	Dampens immune response to exogenous agent	Equivocal	Equivocal; inconsistent results with most reports suggesting lack of efficacy or increased mortality; however, HDPS in the earliest stages of disease may limit progression and mortality.
Human Intravenous Immune Globulin (IVIG)	Autoantibodies against Fas in IVIG prevent Fas-FasL mediated apoptosis	Equivocal	Equivocal; numerous studies reflecting a spectrum of benefit from improved mortality to no benefit to increased mortality. Most significant complication is acute renal failure.
Plasmapheresis	Removes non-dialyzable pathogenic elements found in the plasma	Unknown	Overall results have been favorable; limited data. Generally safe with minimal complications.
Granulocyte Colony Stimulating Factor (GCSF)	Boosts neutrophil counts to decrease risk of infection	Unknown	May play a role in the neutropenic SJS/TEN patient
Cyclosporine	Inhibition of apoptosis by down regulation of NF-kB	Unknown	Current reports suggest minimal benefit to reduction in mortality. Complications include leukoencephalopathy, neutropenia, pneumonia, and nephropathy
TNF-alpha Inhibitors	Inhibition of TNF-alpha prevents apoptosis	Unknown	Not recommended; associated with increased mortality
Cyclophosphamide	Inhibition of cell-mediated cytotoxicity	Unknown	Not recommended; associated with increased mortality

* In order of appearance in text.

in 119 patients did not definitively alter mortality compared with supportive care alone in 87 patients, though a trend toward a possible benefit was observed.[186] In a large study of SJS/TEN patients in France and Germany enrolled in the International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR), including 460 patients in the cohort, the use of systemic corticosteroids or any other immune modulating drug was not associated with a significant change in survival.[187]

Despite a widely held recommendation against use of systemic corticosteroids, there is also support for high-dose pulsed corticosteroids in the earliest stages of TEN when secondary sepsis is less likely.[190] In one study, twelve patients with SJS/TEN were treated with a 3-day course of pulsed intravenous dexamethasone (1.5mg/kg/day); the predicted mortality based on SCORTEN in this cohort was four deaths, but only one patient died.[184] High-dose dexamethasone appeared to stop disease progression in three days on average, and healing occurred within three weeks. The possible effects of high-dose pulsed corticosteroids on ophthalmic complications of SJS/TEN are described below.

2. Human Intravenous Immune Globulin

Human intravenous immune globulin (**IVIG**) is produced by pooling plasma from several thousand donors. IVIG contains a mixture of immunoglobulins, mostly immunoglobulin G (**IgG**) with trace amounts of IgM and IgA,[191] against a variety of "self" molecules. The use of IVIG has been approved by the U. S. Food and Drug Administration for patients undergoing hematopoietic stem cell transplantation and for the treatment of a variety of inflammatory and autoimmune diseases, such as common variable immunodeficiency, immune-mediated thrombocytopenia, Kawasaki disease, chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, and pediatric HIV type I infection.[192,193] IVIG includes autoantibodies against Fas, and in a pilot study, ten patients with biopsy-proven TEN were treated with IVIG with no deaths and no systemic side effects.[147] Exogenous IVIG reaches the epidermis, in particular the blister fluid and epidermal layers of clinically involved and uninvolved skin of TEN patients.[194]

Autoantibodies against Fas in IVIG are thought to reduce TEN complications by interfering with Fas-FasL interactions. Removing anti-Fas IgG from IVIG blocks the ability to prevent Fas-FasL mediated apoptosis in vitro.[147,195] IVIG-treated patients demonstrate reduced Fas and FasL in post-treatment skin biopsies.[196]

There have been numerous SJS/TEN case reports and case series showing benefit from IVIG.[197-213] In a small retrospective study of 8 pediatric TEN patients treated with IVIG, all patients survived.[201] In a prospective study of 12 TEN patients from Kuwait, 100% of patients treated with IVIG survived.[207] In a retrospective study of 12 SJS patients receiving adjunctive treatment with IVIG in doses of 0.6 g/kg/day, all patients survived and the investigators reported objective response within 2 days of starting therapy.[206] Another retrospective review of 15 patients along the SJS/TEN spectrum treated with IVIG within 24 hours of diagnosis reported 80% survival.[210] In another small study, 16 TEN patients with predicted SCORTEN mortality of 5.8 deaths were treated with IVIG (most receiving 1g/kg/day for 4 days); only one patient died.[213] In a larger retrospective study involving 14 American and European academic centers, 48 consecutive TEN patients were treated with adjunctive IVIG (1 gm/kg/day for 3 days).[205] The survival rate was 88%. The most significant IVIG-related complication was acute renal failure. In another study of 9 TEN patients treated with combination of IVIG and pulsed methylprednisolone in another study, 8 survived.[211]

IVIG was also used as an adjunct to systemic corticosteroids. In a study by Yang and coworkers, 45 patients who had received corticosteroids only for SJS/TEN were compared to 20 patients who received a combination of corticosteroids and IVIG.[214] Combination therapy reduced the time to arrest of progression and the total hospitalization time, and though not statistically significant, showed a tendency to decrease mortality rate compared to the use of corticosteroids as sole treatment.

Metry and colleagues shared their experience with 7 pediatric patients who were treated with IVIG and also reviewed 28 reports in the literature.[209] They concluded that IVIG was helpful in children with SJS/TEN. There were no mortalities and consistent recovery was observed in every child who was treated with IVIG. In one case, IVIG successfully prevented recurrent SJS in a patient with multiple episodes after exposure to intravenous contrast.[208]

On the other hand, there are multiple reports that show minimal to no benefit and increased mortality with IVIG.[186,215-219] IVIG was found to be of minimal value in 7 children with SJS when compared to 5 children with SJS treated with corticosteroids or supportive care alone.[217] In a comparison of 10 treated patients with 18 historical controls, IVIG did not reduce the severity of the ocular complications of TEN.[219] Another retrospective study compared 24 patients who received IVIG to 21 patients who did not.[216] All patients were treated by the same team using a standard protocol. The dose of IVIG used was 0.4 g/kg/day, below that used in other studies. The investigators found no advantage to IVIG at any SCORTEN level, and there was higher mortality in the group that received IVIG versus the control group. (41.7% vs 28.6%). One retrospective study compared 16 TEN patients treated with IVIG to 16 patients who did not receive IVIG, and found no statistically significant differences in mortality, length of hospitalization, length of mechanical ventilation, sepsis, or the severity of systemic inflammatory response syndrome and multiple organ dysfunction syndrome.[218]

A prospective trial of 34 patients with SJS/TEN who were treated with IVIG (2g/kg/day for 2 days with modified renal dosing as needed) evaluated the effect on total body surface area involvement pre- and post-IVIG treatment as well as mortality.[215] There was no significant improvement in treated patients, and the mortality rate was both higher than the predicted by SCORTEN (11 actual deaths vs 8.2 predicted deaths), and higher than the hospital's historical death rate of approximately 20% in TEN patients. Most

deaths occurred in elderly patients with impaired baseline renal function. In this study, the investigators used a higher dose and shorter duration of IVIG compared with some other studies showing positive effects.

A retrospective case-control analysis of patients that were included in the prospective EuroSCAR observational study, the largest cohort of SJS/TEN patients collected to date, found that compared to supportive care (87 patients) or systemic corticosteroids (119 patients) the odds ratio for death was nonsignificantly increased with IVIG therapy (35 patients).[186] The study design may have been limited by diverse treatment facilities in different countries, and non-standardized protocols for supportive care, treatment doses, and treatment duration.

With regard to whether IVIG reduces ocular complications in SJS/TEN, two small case series provided contradictory results. In a study by Yip and coworkers, IVIG did not mitigate the severity of the acute manifestations of ocular SJS/TEN in 8 patients compared to 18 historical controls managed conservatively.[219] Yet in another study, early intervention with IVIG, when compared to supportive care only, appeared to significantly improve ocular involvement and best corrected visual acuity in adults but not in children.[220] Overall, it is difficult to reconcile these contradictory results, and the initial enthusiasm for IVIG in the treatment of SJS/TEN has dampened.

3. Plasmapheresis

Plasmapheresis removes non-dialyzable pathogenic elements found in the plasma.[221] Whole blood is drawn from the patient and is separated into its cellular components and plasma, with the patient's plasma typically discarded. Blood is then reconstituted by adding albumin to artificial plasma, and/or with banked plasma, to the cellular constituents and reinfused back into the patient. The procedure is generally safe. Overall, the results in TEN have been favorable with reported survivals of 77 to 100% after one to eight exchanges.[222-224] However, one report of a series of eight patients treated with plasmapheresis in Sweden showed no difference in survival compared to groups treated with supportive care alone.[225]

4. Granulocyte Colony Stimulating Factor

Neutropenia portends a poor prognosis in SJS/TEN due to heightened risk of infection. Several case reports have described patients in whom granulocyte colony-stimulating factor was used to boost neutrophil counts.[74,198,226-229] This agent may play a role in management of the neutropenic TEN patient.

5. Cyclosporine

In addition to its immunosuppressive effects, cyclosporine may inhibit apoptosis by inhibiting down regulation of NF-kB.[153,230] It has been used in doses of 3mg/kg/day in individual cases of SJS/TEN with good results reported.[230-233] There were no mortalities in a case series of 11 patients treated with cyclosporine.[233] An open, phase 2 clinical trial of 29 treated patients (3mg/kg/day for 10 days, followed by taper over 1 month) showed a modest and nonstatistically significant reduction in SCORTEN predicted mortality.[234] Side-effects included leukoencephalopathy, neutropenia, pneumonia, and nephropathy.

6. TNF-alpha Inhibitors

As discussed above, TNF-alpha is likely to play a role in SJS/TEN.[153] TNF-alpha inhibitors including infliximab, pentoxiphylline, and thalidomide have been used in individual cases.[13,235] In one report, a 56-year-old woman with TEN who was treated with a single infliximab infusion showed significant improvement.[235] However, a prospective trial in TEN patients comparing thalidomide to placebo was stopped due to higher than predicted mortality rates in patients receiving thalidomide.[236]

7. Cyclophosphamide

Cyclophosphamide was previously reported to benefit patients with acute TEN,[237,238] but was later associated with increased mortality and is not recommended in the treatment of acute SJS/TEN.[4,75]

C. Effect of Systemic Treatments of Acute SJS/TEN on Ocular Disease

The effects of adjuvant systemic treatments on the ocular manifestations of SJS/TEN are unclear and controversial, limiting general recommendations for systemic management beyond supportive burn care. For example, one study comparing 10 IVIG-treated TEN patients to 18 historical controls concluded that treatment did not mitigate the severity of vision-threatening complications.[219] Reported ocular outcomes after administration of systemic corticosteroids in acute SJS/TEN vary from no effect to possible reduction of ocular complications. In a relatively large study in children, there was no significant difference in the number of patients with ocular involvement or in the severity of ocular manifestations between those treated with systemic corticosteroids (51 patients) and those who were not (38 patients).[239] In a recent report on the effect of various systemic treatment modalities on ocular SJS/TEN, systemic corticosteroids did not ameliorate the ocular disease of the pediatric group (mean hydrocortisone equivalent dosage, 2.9 mg/kg/day for 3.5 days). Corticosteroids provided a nonstatistically significant improvement in visual acuity during the course of SJS/TEN in the 22 adults who received them within 5 days of disease onset (mean hydrocortisone equivalent dosage, 5.3 mg/kg/day for 3.5 days).[220]

However, in a study of five adult patients with SJS/TEN who received pulsed methylprednisolone (500 mg or 1 gram) for 3-4 days, with ocular topical 0.1% betamethasone instilled 5 times per day for 2 weeks starting within 4 days of disease onset, all experienced good visual outcomes.[240] At the initial examination, all patients in the study had membranous conjunctivitis with corneal and/or conjunctival defects. There were no significant adverse effects of systemic and topical corticosteroids during the course of their study. At 1 year, all eyes had normal architectural features of the palisades of Vogt

without evidence of limbal stem cell dysfunction, with best-corrected visual acuity of 20/20. Five eyes demonstrated corneal superficial punctate keratopathy, and all eyes showed mild irregularity of the mucocutaneous junction. Followup examinations were not reported beyond 1 year. However, in a recent retrospective, non-case-controlled study by Kim et al, the authors reported no apparent benefit from various immunomodulatory treatments in chronic ocular outcomes of SJS/TEN.[241]

IX. SUMMARY AND CONCLUSIONS

SJS/TEN is a severe, T cell-mediated, dermatobullous drug reaction with significant and sometimes devastating long-term morbidity in survivors, including ocular sequelae that can result in total blindness. Once triggered, keratinocyte cell death in SJS/TEN occurs rapidly with irreversible consequences. Early and aggressive intervention in a Burn ICU is essential to survival. The rarity of SJS/TEN and the diversity of inciting agents make the disorder challenging to study. A broad range of systemic interventions have been proposed and attempted, most with conflicting results, and some with profoundly negative consequences for patients. Unfortunately, because SJS/TEN is rare, prospective controlled clinical trials of individual therapies are not feasible. High-dose intravenous corticosteroids, IVIG, and plasmapheresis may yet be shown beneficial, and large, registry-based, retrospective studies may in the future illuminate best practices in the care of SJS/TEN.

We are unable to make recommendations regarding specific systemic therapies for the acute stage of the disorder, as existing reports are contradictory. Nevertheless, significant advances have been made in recent years in the treatment of ocular manifestations of SJS/TEN in both acute and chronic stages of the disorder. These will be covered in Part II of this review, which will be published in the April 2016 issue of this journal. Ophthalmologists play an essential role in evaluation and treatment of patients with SJS/TEN in the acute and chronic stages to minimize long-term vision loss and ocular morbidity.

REFERENCES

1. Letko E, Papaliodis DN, Papaliodis GN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. *Ann Allergy Asthma Immunol* 2005;94:419-36. quiz 36-8, 56
2. Borchers AT, Lee JL, Naguwa SM, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev* 2008;7:598-605
3. Endorf FW, Cancio LC, Gibran NS. Toxic epidermal necrolysis clinical guidelines. *J Burn Care Res* 2008;29:706-12
4. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *Journal of the American Academy of Dermatology* 2007;56:181-200
5. Becker DS. Toxic epidermal necrolysis. *Lancet* 1998;351:1417-20
6. Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. *Arch Dermatol* 1990;126:1103-4
7. Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. *Arch Dermatol* 1991;127:839-42
8. Strom BL, Carson JL, Halpern AC, et al. A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. *Arch Dermatol* 1991;127:831-8
9. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab* 2009;96:20-6
10. Sushma M, Noel MV, Ritika MC, et al. Cutaneous adverse drug reactions: a 9-year study from a South Indian Hospital. *Pharmacoepidemiol Drug Saf* 2005;14:567-70
11. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331:1272-85
12. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Arch Dermatol* 1990;126:37-42
13. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. *Dermatology Online J* 2002;8:5
14. Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthonpalin P. Stevens-Johnson syndrome and toxic epidermal necrolysis in Thailand. *Int J Dermatol* 1993;32:428-31
15. Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. *Indian J Dermatol Venereol Leprol* 2013;79:389-98
16. Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Pediatrics* 2011;128:723-8
17. Yetiv JZ, Bianchine JR, Owen Jr JA. Etiologic factors of the Stevens-Johnson syndrome. *South Med J* 1980;73:599-602
18. Franca MD, Lima JP, Freitas D, et al. Study of the ocular findings in Stevens-Johnson syndrome patients from a tertiary ophthalmologic center. *Arq Bras Oftalmol* 2009;72:370-4. Portuguese
19. Ball R, Ball LK, Wise RP, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J* 2001;20:219-23
20. Hwang YH, Kang MS, Lim KO, Lee SM. Toxic epidermal necrolysis with ocular involvement following vaccination for hemorrhagic fever with renal syndrome. *Yonsei Med J* 2012;53:228-30
21. Dobrosavljevic D, Milinkovic MV, Nikolic MM. Toxic epidermal necrolysis following morbilli-parotitis-rubella vaccination. *J Eur Acad Dermatol Venereol* 1999;13:59-61
22. Radimer GF, Davis JH, Ackerman AB. Fumigant-induced toxic epidermal necrolysis. *Arch Dermatol* 1974;110:103-4
23. House RA, Jakubovic H, Wong L, Holness DL. Work-related toxic epidermal necrolysis? *J Occup Med* 1992;34:135-9
24. Hemmige V, Jenkins E, Lee JU, Arora VM. Toxic epidermal necrolysis (TEN) associated with herbal medication use in a patient with systemic lupus erythematosus. *J Hosp Med* 2010;5:491-3
25. Fogh K. Toxic epidermal necrolysis following intake of vitamins and natural medication. *Ugeskr Laeger* 1995;157:3631-3. Danish
26. Mochitomi Y, Inoue A, Kawabata H, et al. Stevens-Johnson syndrome caused by a health drink (Eberu) containing ophiopogonis tuber. *J Dermatol* 1998;25:662-5
27. Lim YL, Thirumoorthy T. Serious cutaneous adverse reactions to traditional Chinese medicines. *Singapore Med J* 2005;46:714-7
28. Figueira-Coelho J, Lourenco S, Pires AC, et al. Mycoplasma pneumoniae-associated mucositis with minimal skin manifestations. *Am J Clin Dermatol* 2008;9:399-403
29. Fournier S, Bastuji-Garin S, Mentec H, et al. Toxic epidermal necrolysis associated with Mycoplasma pneumoniae infection. *Eur J Clin Microbiol Infect Dis* 1995;14:558-9
30. Kunimi Y, Hirata Y, Aihara M, et al. Statistical analysis of Stevens-Johnson syndrome caused by Mycoplasma pneumonia infection in Japan. *Allergol Int* 2011;60:525-32
31. Meyer Sauteur PM, Goetschel P, Lautenschlager S. Mycoplasma pneumoniae and mucositis—part of the Stevens-Johnson syndrome spectrum. *J Dtsch Dermatol Ges* 2012;10:740-6

32. Prindaville B, Newell BD, Nopper AJ, Horii KA. Mycoplasma pneumoniae-Associated Mucocutaneous Disease in Children: Dilemmas in Classification. *Pediatr Dermatol* 2014;31:670-5
33. Stevens D, Swift PG, Johnston PG, et al. Mycoplasma pneumoniae infections in children. *Arch Dis Child* 1978;53:38-42
34. Vujic I, Shroff A, Grzelka M, et al. Mycoplasma pneumoniae-associated mucositis - case report and systematic review of literature. *J Eur Acad Dermatol Venereol* 2014
35. Schalock PC, Dinulos JG. Mycoplasma pneumoniae-induced Stevens-Johnson syndrome without skin lesions: fact or fiction? *J Am Acad Dermatol* 2005;52:312-5
36. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf* 2002;25:965-72
37. Choy AC, Yarnold PR, Brown JE, et al. Virus induced erythema multiforme and Stevens-Johnson syndrome. *Allergy Proc* 1995;16:157-61
38. Cheriyan S, Patterson R. Recurrent Stevens-Johnson syndrome secondary to herpes simplex: a follow up on a successful management program. *Allergy Asthma Proc* 1996;17:71-3
39. Redondo P, Vicente J, Espana A, et al. Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996;135:999-1002
40. Mansur AT, Aydingoz IA. A case of toxic epidermal necrolysis with lesions mostly on sun-exposed skin. *Photodermatol Photoimmunol Photomed* 2005;21:100-2
41. Vern-Gross TZ, Kowal-Vern A. Erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis syndrome in patients undergoing radiation therapy: a literature review. *Am J Clin Oncol* 2014;37:506
42. Sommers KR, Kong KM, Bui DT, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis in a patient receiving concurrent radiation and gemcitabine. *Anti-cancer Drugs* 2003;14:659-62
43. Micali G, Linthicum K, Han N, West DP. Increased risk of erythema multiforme major with combination anticonvulsant and radiation therapies. *Pharmacotherapy* 1999;19:223-7
44. Gomez-Criado MS, Ayani I, Leon-Colombo T, et al. Stevens-Johnson syndrome, toxic epidermal necrolysis and phenytoin. Factors linked to a higher risk. *Rev Neurol* 2004;38:1056-60. Spanish
45. Aguiar D, Pazo R, Duran I, et al. Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: a risk to consider. *J Neurooncol* 2004;66:345-50
46. Pushker N, Tandon R, Vajpayee RB. Stevens-Johnson syndrome in India - risk factors, ocular manifestations and management. *Ophthalmologica* 2000;214:285-8
47. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333:1600-7
48. Caumes E, Bossi P, Katlama C, Bricaire F. Antiretroviral-induced toxiderma in HIV-infected patients. *Presse Med* 2003;32:1325-33. French
49. Leone R, Venegoni M, Motola D, et al. Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three italian regions. *Drug Saf* 2003;26:109-20
50. Praz SM, de Torrente A, Zender H, et al. Toxic epidermal necrolysis after topical intranasal application of mupirocin. *Infect Control Hosp Epidemiol* 2003;24:459-60
51. Florez A, Roson E, Conde A, et al. Toxic epidermal necrolysis secondary to timolol, dorzolamide, and latanoprost eyedrops. *J Am Acad Dermatol* 2005;53:909-11
52. Fine HF, Kim E, Eichenbaum KD, et al. Toxic epidermal necrolysis induced by sulfonamide eyedrops. *Cornea* 2008;27:1068-9
53. Byrom L, Zappala T, Muir J. Toxic epidermal necrolysis caused by over the counter eyedrops. *Australas J Dermatol* 2013;54:144-6
54. Schmutz JL, Barbaud A, Trechot P. Toxic epidermal necrolysis following eyedrop treatment for glaucoma. *Ann Dermatol Venereol* 2007;134:417. Spanish
55. Asensio-Sanchez VM. Toxic epidermal necrolysis following dorzolamide eyedrops. *An Med Interna* 2008;25:47-8. Spanish
56. Nagge JJ, Knowles SR, Juurlink DN, Shear NH. Pseudoephedrine-induced toxic epidermal necrolysis. *Arch Dermatol* 2005;141:907-8
57. Ueta M, Kaniwa N, Sotozono C, et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. *Sci Rep* 2014;4:4862
58. Ueta M, Kannabiran C, Wakamatsu TH, et al. Trans-ethnic study confirmed independent associations of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe ocular surface complications. *Sci Rep* 2014;4:5981
59. Lin MS, Dai YS, Pwu RF, et al. Risk estimates for drugs suspected of being associated with Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control study. *Intern Med J* 2005;35:188-90
60. Wolkenstein PE, Roujeau JC, Revuz J. Drug-induced toxic epidermal necrolysis. *Clin Dermatol* 1998;16:399-408
61. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;64:1134-8
62. Kumar R, Dohlman CH, Chodosh J. Oral acetazolamide after Boston keratoprosthesis in Stevens-Johnson syndrome. *BMC Res Notes* 2012;5:205
63. Paquet P, Jacob E, Damas P, Pierard GE. Recurrent fatal drug-induced toxic epidermal necrolysis (Lyell's syndrome) after putative beta-lactam cross-reactivity: Case report and scrutiny of antibiotic imputability. *Crit Care Med* 2002;30:2580-3
64. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am* 2004;24:477-90. vii
65. Lee AG, Anderson R, Kardon RH, Wall M. Presumed "sulfa allergy" in patients with intracranial hypertension treated with acetazolamide or furosemide: cross-reactivity, myth or reality? *Am J Ophthalmol* 2004;138:114-8
66. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol* 1987;123:1160-5
67. Revuz J, Roujeau JC, Guillaume JC, et al. Treatment of toxic epidermal necrolysis. Creteil's experience. *Arch Dermatol* 1987;123:1156-8
68. Goodman H. Nikolsky sign; page from notable contributors to the knowledge of dermatology. *AMA Arch Derm Syphilol* 1953;68:334-5
69. Fu Y, Gregory DG, Sippel KC, et al. The ophthalmologist's role in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ocul Surf* 2010;8:193-203
70. Roujeau JC. Drug-induced toxic epidermal necrolysis. II. Current aspects. *Clin Dermatol* 1993;11:493-500
71. Saeed H, Mantagos IS, Chodosh J. Complications of Stevens-Johnson syndrome beyond the eye and skin. *Burns* 2015
72. Sugimoto Y, Mizutani H, Sato T, et al. Toxic epidermal necrolysis with severe gastrointestinal mucosal cell death: a patient who excreted long tubes of dead intestinal epithelium. *J Dermatol* 1998;25:533-8
73. Wolkenstein P, Revuz J. Toxic epidermal necrolysis. *Dermatol Clin* 2000;18:485-95. ix
74. Ang CC, Tay YK. Hematological abnormalities and the use of granulocyte-colony-stimulating factor in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Int J Dermatol* 2011;50:1570-8
75. Rajaratnam R, Mann C, Balasubramaniam P, et al. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. *Clin Exp Dermatol* 2010;35:853-62

76. Westly ED, Wechsler HL. Toxic epidermal necrolysis. Granulocytic leukopenia as a prognostic indicator. *Arch Dermatol* 1984;120:721-6
77. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* 1997;23:1237-44
78. Gaultier F, Rochefort J, Landru MM, et al. Severe and unrecognized dental abnormalities after drug-induced epidermal necrolysis. *Arch Dermatol* 2009;145:1332-3
79. Herman TE, Kushner DC, Cleveland RH. Esophageal stricture secondary to drug-induced toxic epidermal necrolysis. *Pediatr Radiol* 1984;14:439-40
80. Nogueira RFM, Lobato MG, Belfort R, Souza CB, Gomes JAP. Quality of life of patients with Stevens-Johnson syndrome. *Arq Bras Oftalmol* 2003;66:67-70. Portuguese
81. Butt TF, Cox AR, Oyebode JR, Ferner RE. Internet accounts of serious adverse drug reactions: a study of experiences of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Drug Saf* 2012;35:1159-70
82. Butt TF, Cox AR, Lewis H, Ferner RE. Patient experiences of serious adverse drug reactions and their attitudes to medicines: a qualitative study of survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. *Drug Saf* 2011;34:319-28
83. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129:92-6
84. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* 1995;131:539-43
85. Cote B, Wechsler J, Bastuji-Garin S, et al. Clinicopathologic correlation in erythema multiforme and Stevens-Johnson syndrome. *Arch Dermatol* 1995;131:1268-72
86. Tomasini C, Derlino F, Quaglino P, et al. From erythema multiforme to toxic epidermal necrolysis. Same spectrum or different diseases? *G Ital Dermatol Venereol* 2014;149:243-61
87. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol* 2011;7:803-13. quiz 14-15
88. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000;115:149-53
89. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, et al. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *The J Investigative Dermatol* 2006;126:272-6
90. Engelhardt SL, Schurr MJ, Helgerson RB. Toxic epidermal necrolysis: an analysis of referral patterns and steroid usage. *J Burn Care Rehab* 1997;18:520-4
91. Quinn AM, Brown K, Bonish BK, et al. Uncovering histologic criteria with prognostic significance in toxic epidermal necrolysis. *Arch Dermatol* 2005;141:683-7
92. Caproni M, Torchia D, Schincaglia E, et al. Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 2006;155:722-8
93. Watanabe R, Watanabe H, Sotozono C, et al. Critical factors differentiating erythema multiforme majus from Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). *Eur J Dermatol* 2011;21:889-94
94. Harp JL, Kinnebrew MA, Shinkai K. Severe cutaneous adverse reactions: impact of immunology, genetics, and pharmacology. *Semin Cutan Med Surg* 2014;33:17-27
95. Nickoloff BJ. Saving the skin from durg-induced detachment. *Nature Med* 2008;14:1311-3
96. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004;428:486
97. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology* 2014;83:2077-84
98. Maekawa K, Nishikawa J, Kaniwa N, et al. Development of a rapid and inexpensive assay for detecting a surrogate genetic polymorphism of HLA-B*58:01: a partially predictive but useful biomarker for allopurinol-related Stevens-Johnson syndrome/toxic epidermal necrolysis in Japanese. *Drug Metab Pharmacokinet* 2012;27:447-50
99. Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, et al. HLA-B*1502 strongly predicts carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Thai patients with neuropathic pain. *Pain Pract* 2012;12:202-8
100. Zhang Y, Wang J, Zhao LM, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. *EurJ Clin Pharmacol* 2011;67:885-7
101. Somkrua R, Eickman EE, Saokaew S, et al. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011;12:118
102. Cristallo AF, Schroeder J, Citterio A, et al. A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Int J Immunogenet* 2011;38:303-9
103. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *Int J Dermatol* 2011;50:221-4
104. Odueyungbo MA, Sheehan MP, Haggstrom AN. HLA-B*1502 allele associated with carbamazepine-induced epidermal necrolysis. *Arch Dermatol* 2010;146:1437-8
105. Kim SH, Kim M, Lee KW, et al. HLA-B*5901 is strongly associated with methazolamide-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Pharmacogenomics* 2010;11:879-84
106. Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 2010;51:2461-5
107. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics* 2009;19:704-9
108. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;18:99-107
109. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2008;9:1617-22
110. Ferrell Jr PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* 2008;9:1543-6
111. Dainichi T, Uchi H, Moroi Y, Furue M. Stevens-Johnson syndrome, drug-induced hypersensitivity syndrome and toxic epidermal necrolysis caused by allopurinol in patients with a common HLA allele: what causes the diversity? *Dermatology* 2007;215:86-8
112. Roujeau JC, Huynh TN, Bracq C, et al. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol* 1987;123:1171-3
113. Power WJ, Saidman SL, Zhang DS, et al. HLA typing in patients with ocular manifestations of Stevens-Johnson syndrome. *Ophthalmology* 1996;103:1406-9

114. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A* 2005;102:4134-9
115. Ueta M, Sawai H, Sotozono C, et al. IKZF1, a new susceptibility gene for cold medicine-related Stevens-Johnson syndrome/toxic epidermal necrolysis with severe mucosal involvement. *J Allergy Clin Immunol* 2015;135:1538-1545.e17
116. Nakaji S, Ueta M, Sotozono C, et al. HLA-class I gene polymorphisms in Japanese Stevens-Johnson syndrome patients with ocular surface complications. *Nihon Ganka Gakkai Zasshi* 2012;116:581-7. Japanese
117. Ueta M, Tokunaga K, Sotozono C, et al. HLA class I and II gene polymorphisms in Stevens-Johnson syndrome with ocular complications in Japanese. *Mol Vis* 2008;14:550-5
118. Ueta M, Tokunaga K, Sotozono C, et al. HLA-A*0206 with TLR3 polymorphisms exerts more than additive effects in Stevens-Johnson syndrome with severe ocular surface complications. *PLoS One* 2012;7: e43650
119. Ueta M, Tamiya G, Tokunaga K, et al. Epistatic interaction between Toll-like receptor 3 (TLR3) and prostaglandin E receptor 3 (PTGER3) genes. *J Allergy Clin Immunol* 2012;129:1413-1416 e11
120. Ueta M, Sotozono C, Inatomi T, et al. Toll-like receptor 3 gene polymorphisms in Japanese patients with Stevens-Johnson syndrome. *Br J Ophthalmol* 2007;91:962-5
121. Ueta M, Kinoshita S. Ocular surface inflammation is regulated by innate immunity. *Prog Retin Eye Res* 2012;31:551-75
122. Ueta M, Sotozono C, Inatomi T, et al. Association of combined IL-13/IL-4R signaling pathway gene polymorphism with Stevens-Johnson syndrome accompanied by ocular surface complications. *Invest Ophthalmol Vis Sci* 2008;49:1809-13
123. Ueta M, Sotozono C, Inatomi T, et al. Association of IL4R polymorphisms with Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2007;120:1457-9
124. Ueta M, Sotozono C, Inatomi T, et al. Association of Fas Ligand gene polymorphism with Stevens-Johnson syndrome. *Br J Ophthalmol* 2008;92:989-91
125. Charli-Joseph Y, Lima G, Ramos-Bello D, et al. Genetic association of IFN-gamma +874T/A polymorphism in Mexican patients with drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Arch Dermatol Res* 2013;305:353-7
126. Revuz J. New advances in severe adverse drug reactions. *Dermatol Clin* 2001;19:697-709. ix
127. Gruchalla RS, Pirmohamed M. Clinical practice. Antibiotic allergy. *N Engl J Med* 2006;354:601-9
128. Neuman MG, Malkiewicz IM, Shear NH. A novel lymphocyte toxicity assay to assess drug hypersensitivity syndromes. *Clin Biochem* 2000;33: 517-24
129. Paquet P, Nikkels A, Arrese JE, et al. Macrophages and tumor necrosis factor alpha in toxic epidermal necrolysis. *Arch Dermatol* 1994;130: 605-8
130. Friedmann PS, Strickland I, Pirmohamed M, Park BK. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. *Arch Dermatol* 1994;130:598-604
131. Correia O, Delgado L, Ramos JP, et al. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. *Arch Dermatol* 1993;129:466-8
132. Correia O, Delgado L, Roujeau JC, et al. Soluble interleukin 2 receptor and interleukin 1alpha in toxic epidermal necrolysis: a comparative analysis of serum and blister fluid samples. *Arch Dermatol* 2002;138: 29-32
133. Leyva L, Torres MJ, Posadas S, et al. Anticonvulsant-induced toxic epidermal necrolysis: monitoring the immunologic response. *J Allergy Clin Immunol* 2000;105:157-65
134. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med* 2008;14:1343-50
135. Le Cleach L, Delaire S, Boumsell L, et al. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol* 2000;119:225-30
136. Nassif A, Bensussan A, Dorothee G, et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *The Journal of investigative dermatology* 2002;118:728-33
137. Paquet P, Paquet F, Al Saleh W, et al. Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis. *Am Journal Dermatopathol* 2000;22:413-7
138. Kirkham N, Peacock SJ, Jones DB. Monoclonal antibody MAC 387 recognizes a myelomonocytic antigen shared by epithelial cells in inflammatory skin diseases. *Br J Dermatol* 1990;122:61-9
139. Monteiro MR, Murphy EE, Galaria NA, et al. Cytological alterations in dermal dendrocytes in vitro: evidence for transformation to a non-dendritic phenotype. *Br J Dermatol* 2000;143:84-90
140. Paquet P, Quatresooz P, Pierard GE. Factor-XIIIa-positive dendrocytes in drug-induced toxic epidermal necrolysis (Lyell's syndrome): paradoxical activation in skin and rarefaction in lymph nodes. *Dermatology* 2003;206:374-8
141. Paul C, Wolkenstein P, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. *Br J Dermatol* 1996;134:710-4
142. Inachi S, Mizutani H, Shimizu M. Epidermal apoptotic cell death in erythema multiforme and Stevens-Johnson syndrome. Contribution of perforin-positive cell infiltration. *Arch Dermatol* 1997;133:845-9
143. Wehrli P, Viard I, Bullani R, et al. Death receptors in cutaneous biology and disease. *The J Invest Dermatol* 2000;115:141-8
144. French LE, Tschopp J. Protein-based therapeutic approaches targeting death receptors. *Cell Death Differ* 2003;10:117-23
145. Viard-Leveugle I, Bullani RR, Meda P, et al. Intracellular localization of keratinocyte Fas ligand explains lack of cytolytic activity under physiological conditions. *J Biol Chem* 2003;278:16183-8
146. Filipowicz E, Adegboyega P, Sanchez RL, Gatalica Z. Expression of CD95 (Fas) in sun-exposed human skin and cutaneous carcinomas. *Cancer* 2002;94:814-9
147. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3
148. Chang HY, Cooper ZA, Swetter SM, Marinkovich MP. Kinetics and specificity of fas ligand induction in toxic epidermal necrolysis. *Arch Dermatol* 2004;140:242-4
149. Tanaka M, Itai T, Adachi M, Nagata S. Downregulation of Fas ligand by shedding. *Nat Med* 1998;4:31-6
150. Knox PG, Milner AE, Green NK, et al. Inhibition of metalloproteinase cleavage enhances the cytotoxicity of Fas ligand. *J Immunol* 2003;170: 677-85
151. Gaultier F, Ejeil AL, Igondjo-Tchen S, et al. Possible involvement of gelatinase A (MMP2) and gelatinase B (MMP9) in toxic epidermal necrolysis or Stevens-Johnson syndrome. *Archives of dermatological research* 2004;296:220-5
152. Abe R, Shimizu T, Shibaki A, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. *Am J Pathol* 2003;162:1515-20
153. Chave TA, Mortimer NJ, Sladden MJ, et al. Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol* 2005;153:241-53
154. Bolitho P, Voskoboinik I, Trapani JA, Smyth MJ. Apoptosis induced by the lymphocyte effector molecule perforin. *Curr Opin Immunol* 2007;19:339-47

155. Nassif A, Bensussan A, Boumsell L, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J Allergy Clin Immunol* 2004;114:1209-15
156. Nassif A, Moslehi H, Le Gouvello S, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. *J Invest Dermatol* 2004;123:850-5
157. Posadas SJ, Padial A, Torres MJ, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. *J Allergy Clin Immunol* 2002;109:155-61
158. Paquet P, Pierard GE. Epidermal calprotectin in drug-induced toxic epidermal necrolysis. *J Cutan Pathol* 1999;26:301-5
159. Paquet P, Pierard GE. Keratinocyte injury in drug-induced toxic epidermal necrolysis: Simultaneous but distinct topographic expression of CD95R and calprotectin. *Int J Mol Med* 2002;10:145-7
160. Lerner LH, Qureshi AA, Reddy BV, Lerner EA. Nitric oxide synthase in toxic epidermal necrolysis and Stevens-Johnson syndrome. *J Invest Dermatol* 2000;114:196-9
161. Garcia-Doval I, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000;136:323-7
162. McGee T, Munster A. Toxic epidermal necrolysis syndrome: mortality rate reduced with early referral to regional burn center. *Plast Reconstruct Surg* 1998;102:1018-22
163. Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. *J Burn Care Rehab* 2002;23:87-96
164. Ellis MW, Oster CN, Turiansky GW, Blanchard JR. A case report and a proposed algorithm for the transfer of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis to a burn center. *Military Med* 2002;167:701-4
165. Yarbrough 3rd DR. Experience with toxic epidermal necrolysis treated in a burn center. *J Burn Care Rehab* 1996;17:30-3
166. Khoo AK, Foo CL. Toxic epidermal necrolysis in a burns centre: a 6-year review. *Burns* 1996;22:275-8
167. Yarbrough 3rd DR. Treatment of toxic epidermal necrolysis in a burn center. *J S Carolina Med Assoc* 1997;93:347-50
168. Boorboor P, Vogt PM, Bechara FG, et al. Toxic epidermal necrolysis: use of Biobrane or skin coverage reduces pain, improves mobilisation and decreases infection in elderly patients. *Burns* 2008;34:487-92
169. Schulz JT, Sheridan RL, Ryan CM, et al. A 10-year experience with toxic epidermal necrolysis. *J Burn Care Rehab* 2000;21:199-204
170. de Prost N, Ingen-Housz-Oro S, Duong T, et al. Bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. *Medicine (Baltimore)* 2010;89:28-36
171. Sheridan RL, Weber JM, Schulz JT, et al. Management of severe toxic epidermal necrolysis in children. *J Burn Care Rehab* 1999;20:497-500
172. Prendiville JS, Hebert AA, Greenwald MJ, Esterly NB. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr* 1989;115:881-7
173. Spies M, Sanford AP, Aili Low JF, et al. Treatment of extensive toxic epidermal necrolysis in children. *Pediatrics* 2001;108:1162-8
174. Lee HY, Dunant A, Sekula P, et al. The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. *Br J Dermatol* 2012;167:555-62
175. Guibal F, Bastuji-Garin S, Chosidow O, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol* 1995;131:669-72
176. Rzany B, Schmitt H, Schopf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. *Acta Derm Venereol* 1991;71:171-2
177. Samimi SS, Siegfried E. Stevens-Johnson syndrome developing in a girl with systemic lupus erythematosus on high-dose corticosteroid therapy. *Pediatr Dermatol* 2002;19:52-5
178. Rasmussen JE. Erythema multiforme in children. Response to treatment with systemic corticosteroids. *Br J Dermatol* 1976;95:181-6
179. Ginsburg CM. Stevens-Johnson syndrome in children. *Pediatr Infect Dis* 1982;1:155-8
180. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr* 1997;156:90-3
181. Leaute-Labreze C, Lamireau T, Chawki D, et al. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child* 2000;83:347-52
182. Yamane Y, Aihara M, Tatewaki S, et al. Analysis of treatments and deceased cases of severe adverse drug reactions—analysis of 46 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arerugi = [Allergy]* 2009;58:537-47
183. Criton S, Devi K, Sridevi PK, Asokan PU. Toxic epidermal necrolysis—a retrospective study. *Int J Dermatol* 1997;36:923-5
184. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol* 2007;87:144-8
185. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc* 2000;21:101-5
186. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008;58:33-40
187. Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with stevens-johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol* 2013;133:1197-204
188. Halebian PH, Corder VJ, Madden MR, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg* 1986;204:503-12
189. Kelemen 3rd JJ, Cioffi WG, McManus WF, et al. Burn center care for patients with toxic epidermal necrolysis. *J Am Coll Surg* 1995;180:273-8
190. van der Meer JB, Schuttelaar ML, Toth GG, et al. Successful dexamethasone pulse therapy in a toxic epidermal necrolysis (TEN) patient featuring recurrent TEN to oxazepam. *Clin Exp Dermatol* 2001;26:654-6
191. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005;142:1-11
192. Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med* 1992;326:107-16
193. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. *Arch Dermatol* 1998;134:80-6
194. Paquet P, Kaveri S, Jacob E, et al. Skin immunoglobulin deposition following intravenous immunoglobulin therapy in toxic epidermal necrolysis. *Exp Dermatol* 2006;15:381-6
195. French LE, Tschopp J. Fas-mediated cell death in toxic epidermal necrolysis and graft-versus-host disease: potential for therapeutic inhibition. *Schweiz Med Wochenschr* 2000;130:1656-61
196. Romanelli P, Schlam E, Green JB, et al. Immunohistochemical evaluation of toxic epidermal necrolysis treated with human intravenous immunoglobulin. *G Ital Dermatol Venereol* 2008;143:229-33
197. Sidwell RU, Swift S, Yan CL, et al. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin. *Int J Clin Pract* 2003;57:643-5

198. Kalyoncu M, Cimsit G, Cakir M, Okten A. Toxic epidermal necrolysis treated with intravenous immunoglobulin and granulocyte colony-stimulating factor. *Indian Pediatrics* 2004;41:392-5
199. Simeone F, Rubio ER. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin. *J La State Med Soc* 2003;155:266-9
200. Mayorga C, Torres MJ, Corzo JL, et al. Improvement of toxic epidermal necrolysis after the early administration of a single high dose of intravenous immunoglobulin. *Ann Allergy Asthma Immunol* 2003;91:86-91
201. Tristani-Firouzi P, Petersen MJ, Saffle JR, et al. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children. *J Am Acad Dermatol* 2002;47:548-52
202. Tan AW, Thong BY, Yip LW, et al. High-dose intravenous immunoglobulins in the treatment of toxic epidermal necrolysis: an Asian series. *J Dermatol* 2005;32:1-6
203. Tan A, Tan HH, Lee CC, Ng SK. Treatment of toxic epidermal necrolysis in AIDS with intravenous immunoglobulins. *Clin Exp Dermatol* 2003;28:269-71
204. Phan TG, Wong RC, Crotty K, Adelstein S. Toxic epidermal necrolysis in acquired immunodeficiency syndrome treated with intravenous gammaglobulin. *Australas J Dermatol* 1999;40:153-7
205. Prins C, Kerdel FA, Padilla RS, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003;139:26-32
206. Prins C, Vittorio C, Padilla RS, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology* 2003;207:96-9
207. Al-Mutairi N, Arun J, Osama NE, et al. Prospective, noncomparative open study from Kuwait of the role of intravenous immunoglobulin in the treatment of toxic epidermal necrolysis. *Int J Dermatol* 2004;43:847-51
208. Hebert AA, Bogle MA. Intravenous immunoglobulin prophylaxis for recurrent Stevens-Johnson syndrome. *J Am Acad Dermatol* 2004;50:286-8
209. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;112:1430-6
210. Molgo M, Carreno N, Hoyos-Bachiloglu R, et al. Use of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis and Stevens-Johnson/toxic epidermal necrolysis overlap syndrome. Review of 15 cases. *Rev Med Chile* 2009;137:383-9. Spanish
211. Stella M, Cassano P, Bollero D, et al. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology* 2001;203:45-9
212. Trent JT, Kerdel FA. Intravenous immunoglobulin for the treatment of toxic epidermal necrolysis. *Arch Dermatol* 2003;139:1081
213. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. *Arch Dermatol* 2003;139:39-43
214. Yang Y, Xu J, Li F, Zhu X. Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China. *Int J Dermatol* 2009;48:1122-8
215. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003;139:33-6
216. Brown KM, Silver GM, Halerz M, et al. Toxic epidermal necrolysis: does immunoglobulin make a difference? *J Burn Care Rehab* 2004;25:81-8
217. Morici MV, Galen WK, Shetty AK, et al. Intravenous immunoglobulin therapy for children with Stevens-Johnson syndrome. *J Rheumatol* 2000;27:2494-7
218. Shortt R, Gomez M, Mittman N, Cartotto R. Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis. *J Burn Care Rehab* 2004;25:246-55
219. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye* 2005;19:846-53
220. Kim KH, Park SW, Kim MK, Wee WR. Effect of age and early intervention with a systemic steroid, intravenous immunoglobulin or amniotic membrane transplantation on the ocular outcomes of patients with Stevens-Johnson syndrome. *Korean J Ophthalmol* 2013;27:331-40
221. McLeod BC. Plasma and plasma derivatives in therapeutic plasmapheresis. *Transfusion* 2012;52(Suppl 1):38S-44S
222. Chaidemenos GC, Chrysomallis F, Sombolos K, et al. Plasmapheresis in toxic epidermal necrolysis. *Int J Dermatol* 1997;36:218-21
223. Bamichas G, Natse T, Christidou F, et al. Plasma exchange in patients with toxic epidermal necrolysis. *Ther Apher* 2002;6:225-8
224. Yamada H, Takamori K, Yaguchi H, Ogawa H. A study of the efficacy of plasmapheresis for the treatment of drug induced toxic epidermal necrolysis. *Ther Apher* 1998;2:153-6
225. Furubacke A, Berlin G, Anderson C, Sjoberg F. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis? *Intensive Care Med* 1999;25:1307-10
226. Winfred RI, Nanda S, Horvath G, Elnicki M. Captopril-induced toxic epidermal necrolysis and agranulocytosis successfully treated with granulocyte colony-stimulating factor. *South Med J* 1999;92:918-20
227. Goulden V, Goodfield MJ. Recombinant granulocyte colony-stimulating factor in the management of toxic epidermal necrolysis. *Br J Dermatol* 1996;135:305-6
228. Jarrett P, Rademaker M, Havill J, Pullon H. Toxic epidermal necrolysis treated with cyclosporin and granulocyte colony stimulating factor. *Clin Exp Dermatol* 1997;22:146-7
229. Bae RJ, Orgill DP, DeBiasse MA, Demling R. Management of a patient with advanced AIDS and toxic epidermal necrolysis using human growth hormone and G-CSF. *AIDS Patient Care STDS* 1997;11:125-9
230. Paquet P, Pierard GE. Would cyclosporin A be beneficial to mitigate drug-induced toxic epidermal necrolysis? *Dermatology* 1999;198:198-202
231. Renfro L, Grant-Kels JM, Daman LA. Drug-induced toxic epidermal necrolysis treated with cyclosporin. *Int J Dermatol* 1989;28:441-4
232. Hewitt J, Ormerod AD. Toxic epidermal necrolysis treated with cyclosporin. *Clin Exp Dermatol* 1992;17:264-5
233. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000;48:473-8
234. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2010;163:847-53
235. Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002;146:707-9
236. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998;352:1586-9
237. Frangogiannis NG, Boridy I, Mazhar M, et al. Cyclophosphamide in the treatment of toxic epidermal necrolysis. *South Med J* 1996;89:1001-3

238. Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis. Clinical and pathophysiologic aspects. *J Am Acad Dermatol* 1991;25:778-86

239. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology* 1995;102:1669-76

240. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol* 2009;147:1004-11. 11 e1

241. Kim DH, Yoon KC, Seo KY, et al. The role of systemic immunomodulatory treatment and prognostic factors on chronic ocular complications in Stevens-Johnson syndrome. *Ophthalmology* 2015;122:254-64

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,**

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Dr. Jacobs is an employee at the Boston Foundation for Sight, a nonprofit organization. Dr. Tseng has obtained a patent for the method of preparation and clinical uses of amniotic membrane and has licensed the right to Bio-Tissue, which procures, processes, and distributes preserved amniotic membrane for clinical and research uses. Dr. Chodosh is an employee of the Mass. Eye and Ear Infirmary, a non-profit hospital, which manufactures and distributes the Boston keratoprosthesis.

The other authors have no commercial or proprietary interest in any concept or product discussed in this article.

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OUTLINE

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**

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. 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.[1-5] Ocular involvement has been variably reported as worse in TEN,[3] comparable between SJS and TEN,[4] or worse in SJS than in TEN.[5] Diffuse cutaneous and oral mucosal damage was also reported as carrying a higher risk of damage to the eyes.[6,7] 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.[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.[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.[12,13] Meibomitis is common.[14-16]

Historically, acute ocular manifestations of SJS/TEN led to chronic ocular sequelae with visual significance in at least one-third of patients.[17] Chronic ocular complications of SJS/TEN are multifactorial in origin. Fusion between the bulbar and forniceal surfaces due to conjunctival ulcerations or conjunctival membrane formation acutely, or persistent inflammation later, causes permanent symblepharon and ankyloblepharon (Figure 3),[6] disrupting an already compromised tear film meniscus and inhibiting proper eyelid closure and blink, and sometimes restricting ocular motility.[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

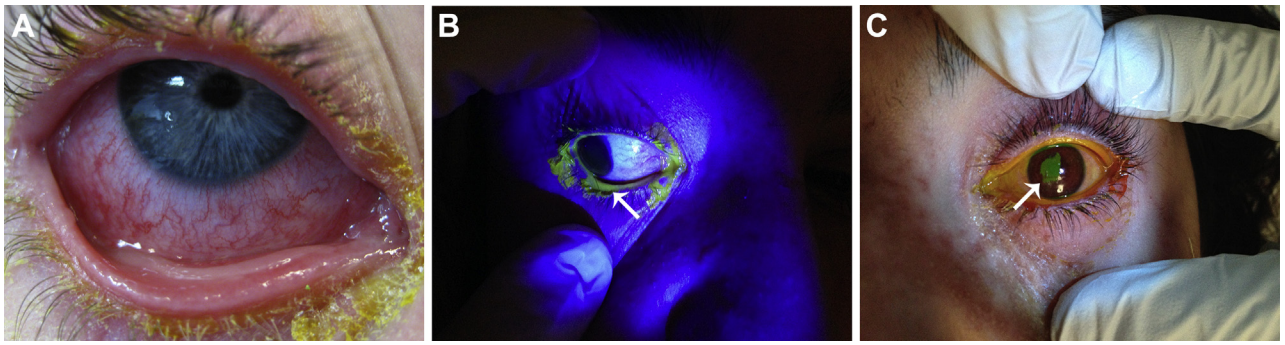

Figure 1. Ocular surface involvement in acute SJS/TEN. A. Conjunctival hyperemia and membrane. B. Eyelid margin sloughing (arrow) as evident with fluorescein staining under cobalt blue light. C. Corneal epithelial defect (arrow) stained with fluorescein.

vision and are correlated with development of late corneal blindness,[19] due at least in part to chronic limbal stem cell dysfunction (**LSCD**). If not removed, misdirected and/or distichiatic 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.[19-22]

Scarring in the fornices and in the lacrimal gland ducts cause severe aqueous tear deficiency and xerosis.[23] 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.[3,4,24] 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.[3] 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.[25] 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.[1,15,16,19,26,27] 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.[28] 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.[1]

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.[1] Di Pascuale and colleagues reported much higher rates in the SJS/TEN patients they studied. Seventy-one percent of

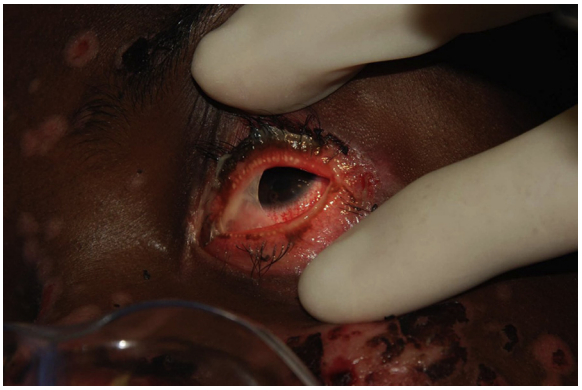

Figure 2. A pseudomembrane in acute SJS/TEN seen here spanning the upper and lower eyelids. Note also the meibomian gland inspissations on both eyelid margins.

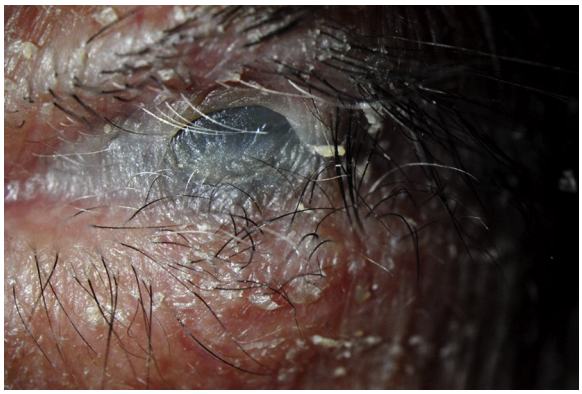

Figure 3. Ankyloblepharon in a patient years after acute SJS/TEN.

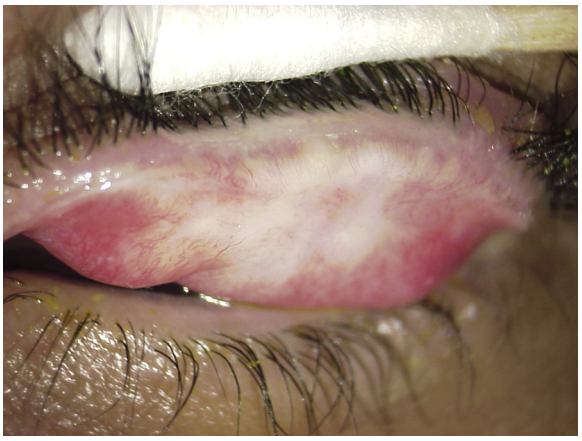

Figure 4. Tarsal conjunctival scarring and vertical shortening of the upper eyelid post- SJS/TEN. Eyelid everted for purpose of photograph.

patients had symblepharon and trichiasis, 52.2% had aqueous deficiency, and nearly all suffered from meibomian gland dysfunction and abnormal lipid tear layer.[19] In contrast, Chang and coworkers reported that only 6.7% of patients in their series had symblepharon and 3.3% had trichiasis.[5] Dry eye symptoms may be the most common patient complaint, affecting an estimated 46-59% of SJS/TEN survivors.[3,4,24] 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.[19] Sotozono and colleagues developed a severity grading for chronic ocular complications of SJS/TEN, including those affecting the cornea, conjunctiva, and eyelids.[16] 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.[16] 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.[1]

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.[6,20-23,29-70] Therefore, we propose a "windows of opportunity" algorithm for ophthalmic interventions (Table 1, Figure 8). 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,[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

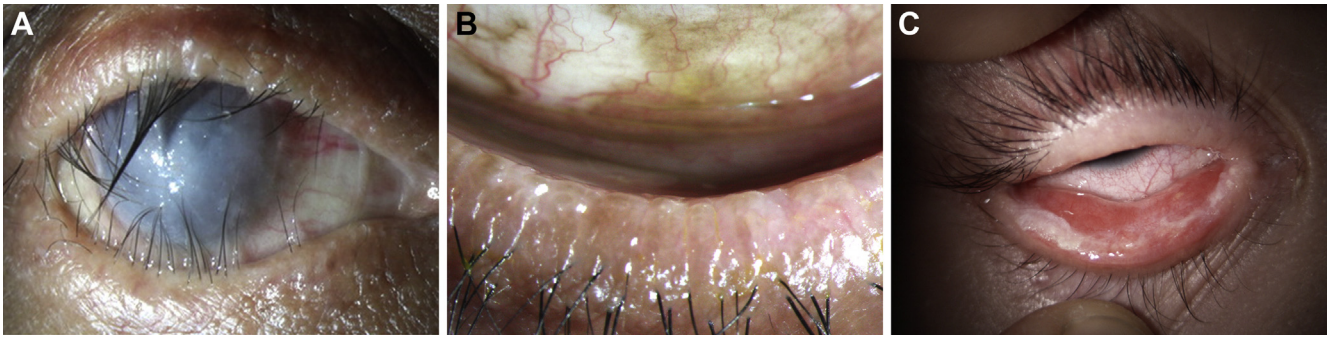

Figure 5. Structural eyelid changes after SJS/TEN. A. Trichiasis from cicatricial entropion. B. Meibomian gland atrophy. C. Eyelid margin keratinization.

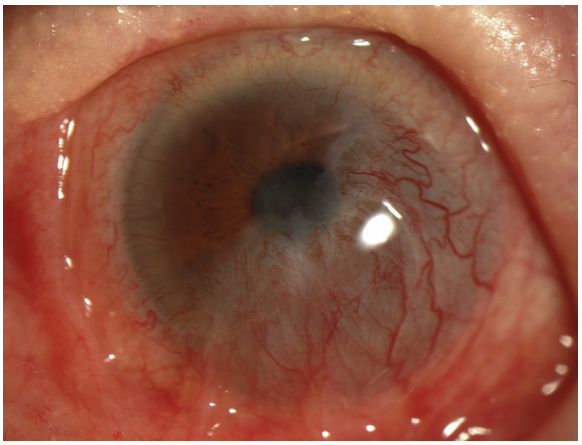

Figure 6. Loss of limbal palisades in patient post SJS/TEN. Note the 360 degrees of limbal vascularization, even where the fibrovascular pannus is absent.

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.[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[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 forniceal and tarsal conjunctival epithelial defects and early symblephara, which could be otherwise missed.[19] 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.[32,72] 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.

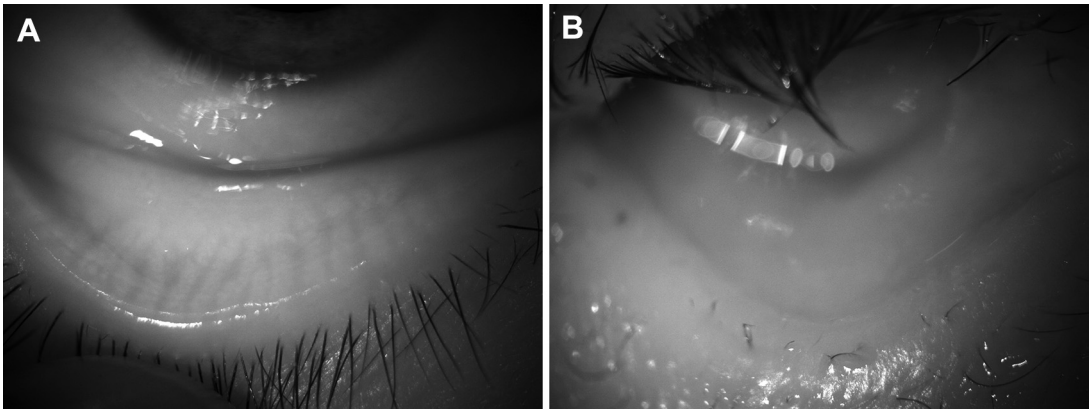

Figure 7. Meibography of (A) normal eyelid and (B) post SJS/TEN eyelid with meibomian gland dropout.

Table 1. Windows of opportunity for ophthalmic intervention in the SJS/TEN patient

SJS/TEN: Phase of disease	Exam finding
Acute	Ocular surface/eyelid margin epithelial defect Pseudomembrane formation
Chronic	Posterior eyelid margin keratinization Trichiasis/distichiasis Tear deficiency Persistent epithelial defect

(Each finding should trigger an intervention to mitigate likely further vision loss.)

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.[2,14,48,73,74] 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.[48] 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.[14] 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).[73] 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.[74]

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.[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 Table 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.[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

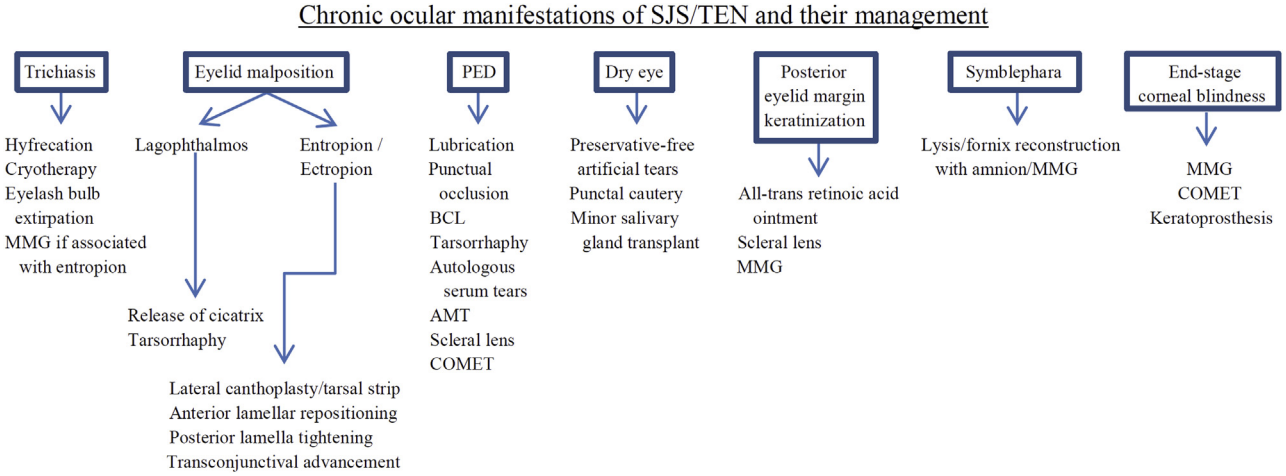

Figure 8. Management of chronic ocular manifestations of SJS/TEN. MMG: mucous membrane graft. PED: persistent (corneal) epithelial defect; BCL: bandage contact lens; AMT: amniotic membrane transplantation; COMET: cultivated oral mucosal epithelial transplantation.

Table 2. Suggested initial management of acute ocular SJS/TEN based on simple clinical grading system*

Grade	Grade defined	Management
0	No ocular involvement	AT 4x/day
1	Conjunctival hyperemia	Moxi 3x/day Pred 6x/day FML 6x/day AT every hour as feasible
2	Ocular surface/eyelid margin epithelial defect or pseudomembrane formation	Use above therapies, plus consider AMT
3	Ocular surface/eyelid margin epithelial defect and pseudomembrane formation	Use above therapies, plus consider AMT

* Adapted from reference 71.

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.

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.[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,[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.[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.[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 pseudomembranes or membranes. Supportive treatment included preservative-free artificial tears and ointments, daily examinations, and forniceal 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.[109]) Processed amnion has very low immunogenicity.[76,121] The anti-inflammatory mechanism of action of amnion may be due in part to promotion of leukocyte apoptosis and down-regulation of inflammatory cytokines released by activated lymphocytes and macrophages.[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.[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

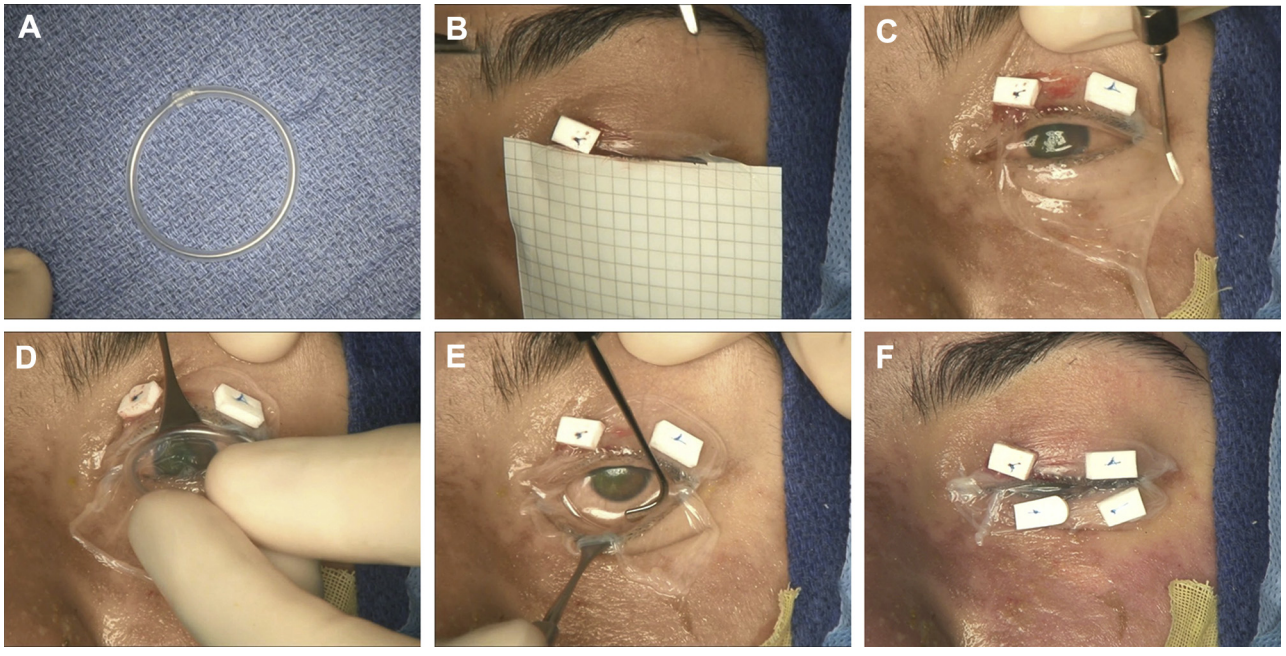

Figure 9. Amniotic membrane transplantation in SJS/TEN. A. A symblepharon ring is constructed from intravenous (IV) extension tubing, with one end of the tube cut so as to fit over the other end of the tube and adjusted to reach all fornices without preventing eyelid closure once in place. B. All eyelashes 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.

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.[30,31] 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),[46,118,128] 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.[111] 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.[46,118] 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.[41] 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®.[46] 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.[118] 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,[129-131] hemorrhage beneath the amnion, and detachment of the membrane.[6] 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.[130] 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.[130] 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,[129,131] as in the Good Tissue Banking Practices set forth by the U.S. Food and Drug Administration.[130]

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.[17,21] 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.[51] 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.[51,132,133] 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.[51] In 27 patients with chronic ocular sequelae from SJS/TEN in four published case series, systemic immunosuppressive therapy was used successfully, albeit without controls.[51,132,134,135] 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.[132,133,136] 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.[56,137]

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.[138] Of all of the agents mentioned above, oral mycophenolate is perhaps the best tolerated.[136]

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 tarsoconjunctival 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,[139] 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.[3,4,24] The aqueous tear film is reduced in SJS/TEN by scarring of the lacrimal ducts and possibly by primary inflammation of the lacrimal gland.[140,141] Goblet cell density in the conjunctiva is reduced after SJS/TEN and does not fully recover.[1] 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.[15,16,19,23] Topical cyclosporine appears to improve goblet cell density in patients with dry eye[142-146] and graft-versus-host-disease.[147] 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.[148] 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.[55] 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.[21] 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,[21,149,150] although the duration of effect, and potential deleterious consequences of saliva on ocular surface epithelium[151] remain to be determined. Anecdotal reports also suggest improvement in clinical signs and symptoms with the application of topical, autologous, serum-derived eye drops.[65,152,153]

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.[154] 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.[65,152,155-159] Autologous cultivated oral mucosal epithelial transplantation (**COMET**) has been used to promote re-epithelialization in recalcitrant cases.[160]

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.[19] 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.[31] Eyelid margin ulceration in the acute phase of SJS/TEN destroys the mucocutaneous junction with resultant overgrowth of the keratinized epithelium onto the tarsal conjunctiva.[19,20] 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.[19,20,161] 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,[68,69,162,163] 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.[21,35-37,44,47,61,164-166] 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.[35-37,47] 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).[21,35,37] 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.[35]

In eyes with symblepharon, fornix reconstruction may be required prior to lens fitting.[19] 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),[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

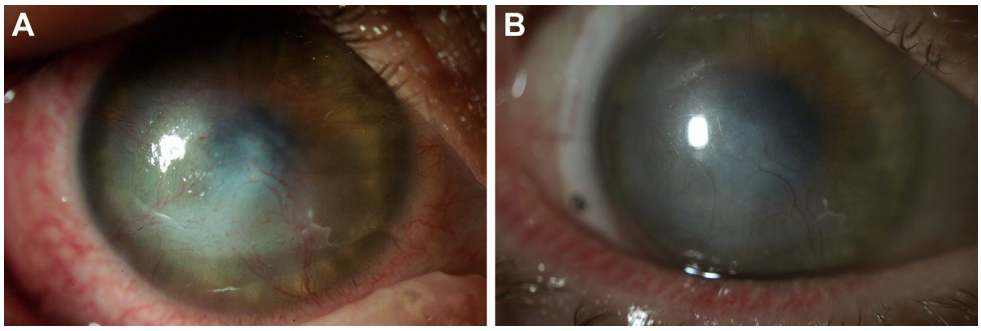

Figure 10. Chronic SJS/TEN with corneal opacity (A) at initiation and (B) after 5 months of daily PROSE treatment, showing improved corneal clarity.

(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.[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,[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

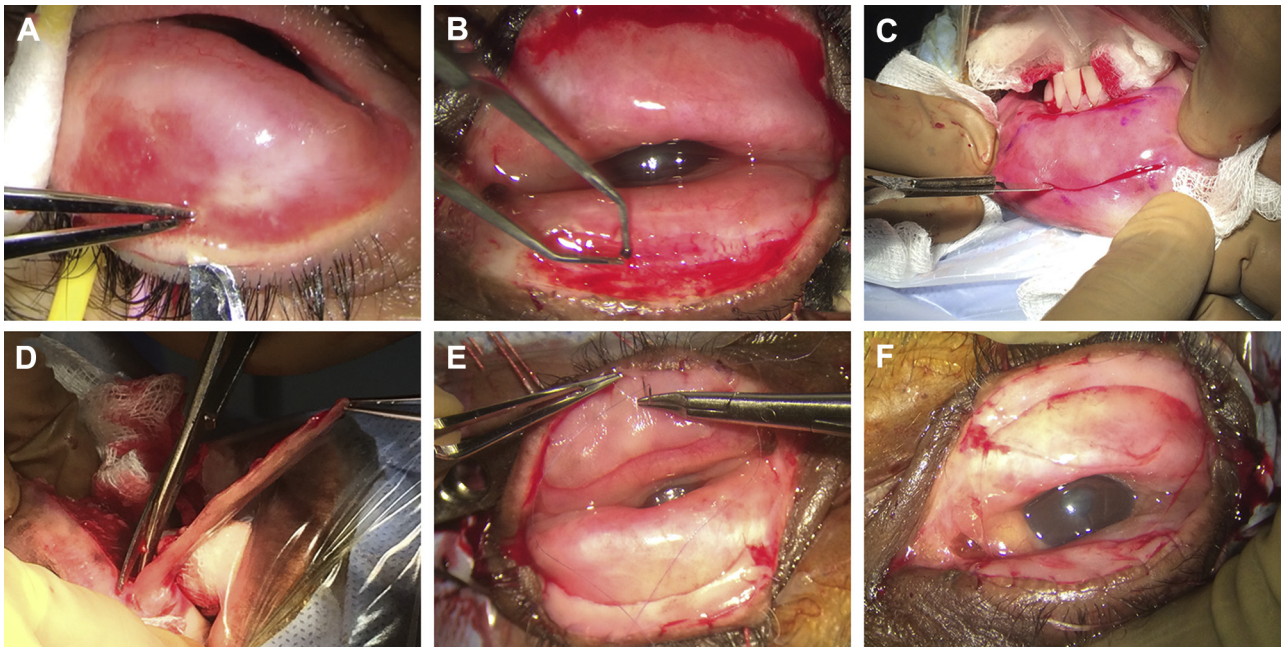

Figure 11. Labial mucous membrane graft to the eyelids for eyelid margin and tarsal keratinization. A. First, the keratinized portion of the tarsal conjunctiva is sharply excised. B. Bipolar cautery is applied at the base beneath the excised mucosa. C. The labial mucosa is incised at predetermined and 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.

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.[150] 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.[149]

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.[137] 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.[169]

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.[159] 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.[66] Therefore, SJS/TEN patients are not candidates for limbal autografts.[170] Keratolimbal allografts, although initially reported to have promise,[63,65,66,171-175] 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.[56,173,176] The use of living-related limbal allografts was not successful in one study with two SJS/TEN patients with severe ocular surface disease,[177] and in another study showed a marginally improved ocular surface in two of ten eyes in patients with SJS/TEN.[56] However, one study suggested that keratolimbal allografts in SJS/TEN do not undergo rejection at a higher rate than for other conditions,[178] and occasional single case reports of success with keratolimbal allograft in SJS/TEN have been published.[174,175] 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.[179] 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,[180-182] but not others.[183,184]

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[21,55]; MMG to treat posterior eyelid margin keratinatinization[20,149,167,168]; amnion with or without MMG[18,21,22,40,62,65,94,106,185] or COMET[42,152,176-183] 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.[21] COMET was used in 6 of these eyes to reduce postoperative 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.[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.[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.[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.[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).[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,[42,186,209] while others have advocated against it.[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.[209,227] A retrospective case series by Sayegh and coworkers[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.[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

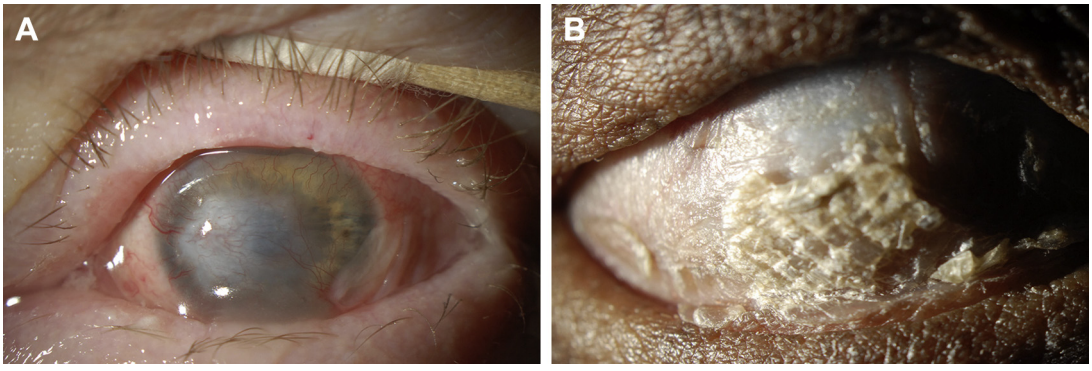

Figure 12. Severe corneal sequelae of SJS/TEN. A. Dense corneal neovascularization and opacity in a wet, blinking eye. B. Complete ocular surface keratinization in an eye devoid of aqueous tears.

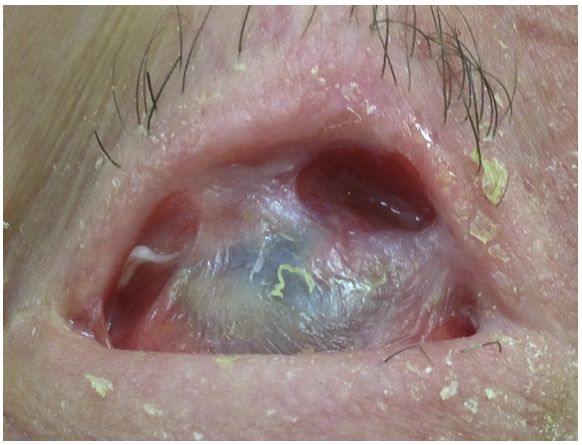

Figure 13. Xerotic, keratinized eye with symblephara. Only a Boston type II or osteo-odonto keratoprosthesis should be considered for visual rehabilitation.

of over 4 years postoperative.[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.[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.[50,191,194,198,205,206] Because only a few centers worldwide 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.

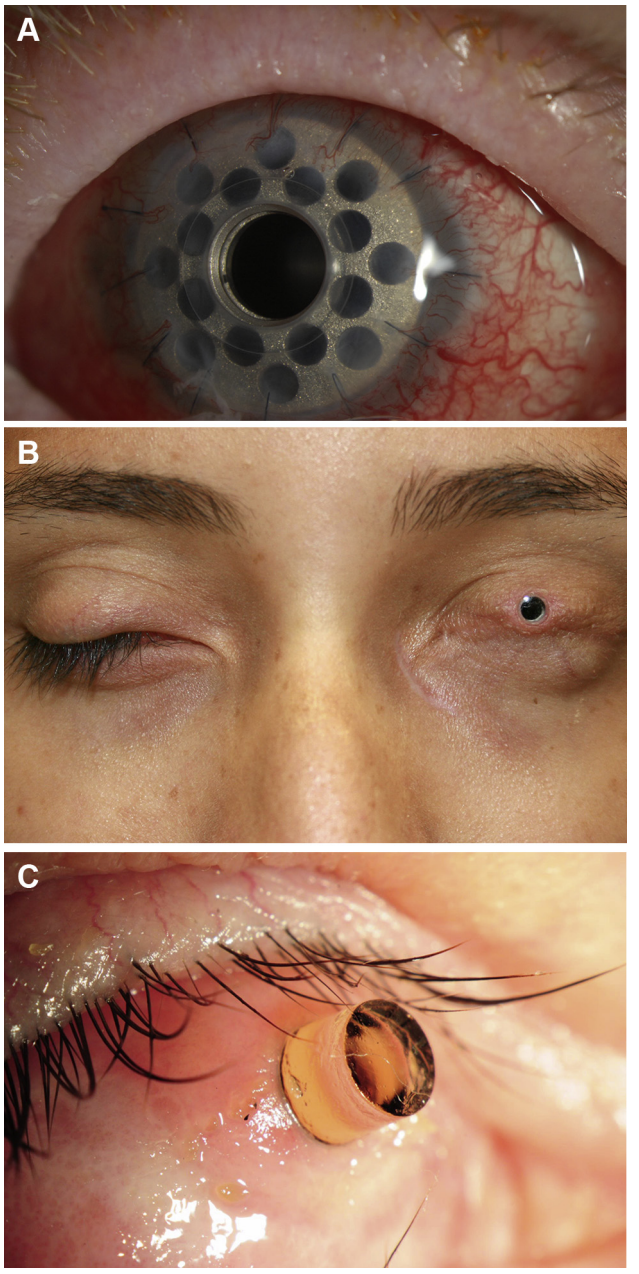

Figure 14. Keratoprosthesis implantation in patients post SJS/TEN. (A) Boston keratoprosthesis type I. (B) Boston keratoprosthesis type II. (C) Osteo-odonto-keratoprosthesis. This image is taken from an oblique view.

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.

REFERENCES

1. Lopez-Garcia JS, Rivas Jara L, Garcia-Lozano CI, et al. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. *Ophthalmology* 2011;118:265-71
2. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology* 1995;102:1669-76
3. Gueudry J, Roujeau JC, Binaghi M, et al. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2009;145:157-62
4. Yip LW, Thong BY, Lim J, et al. Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. *Allergy* 2007;62:527-31
5. Chang YS, Huang FC, Tseng SH, et al. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. *Cornea* 2007;26:123-9
6. Fu Y, Gregory DG, Sippel KC, et al. The ophthalmologist's role in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ocul Surf* 2010;8:193-203
7. Sotozono C, Ueta M, Koizumi N, et al. Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. *Ophthalmology* 2009;116:685-90
8. Morales ME, Purdue GF, Verity SM, et al. Ophthalmic manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis and relation to SCORTEN. *Am J Ophthalmol* 2010;150:505-510.e1
9. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol* 1987;123:1160-5
10. Correia O, Chosidow O, Saiag P, et al. Evolving pattern of drug-induced toxic epidermal necrolysis. *Dermatology* 1993;186:32-7
11. Oplatek A, Brown K, Sen S, et al. Long-term follow-up of patients treated for toxic epidermal necrolysis. *J Burn Care Res* 2006;27:26-33
12. Isawi H, Dhaliwal DK. Corneal melting and perforation in Stevens Johnson syndrome following topical bromfenac use. *J Cataract Refract Surg* 2007;33:1644-6
13. Sachdev R, Bansal S, Sinha R, et al. Bilateral microbial keratitis in highly active antiretroviral therapy-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a case series. *Ocul Immunol Inflamm* 2011;19:343-5
14. Kim KH, Park SW, Kim MK, Wee WR. Effect of age and early intervention with a systemic steroid, intravenous immunoglobulin or amniotic membrane transplantation on the ocular outcomes of patients with Stevens-Johnson syndrome. *Korean J Ophthalmol* 2013;27:331-40
15. Alsuhaibani AH, Carter KD, Abramoff MD, Nerad JA. Utility of meibography in the evaluation of meibomian glands morphology in normal and diseased eyelids. *Saudi J Ophthalmol* 2011;25:61-6
16. Sotozono C, Ang LP, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. *Ophthalmology* 2007;114:1294-302
17. Arstikaitis MJ. Ocular aftermath of Stevens-Johnson syndrome. *Arch Ophthalmol* 1973;90:376-9
18. Tseng SC, Di Pascuale MA, Liu DT, et al. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. *Ophthalmology* 2005;112:896-903
19. Di Pascuale MA, Espana EM, Liu DT, et al. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. *Ophthalmology* 2005;112:904-12
20. Iyer G, Pillai VS, Srinivasan B, et al. Mucous membrane grafting for lid margin keratinization in Stevens-Johnson syndrome: results. *Cornea* 2010;29:146-51
21. Iyer G, Srinivasan B, Agarwal S, et al. Comprehensive approach to ocular consequences of Stevens Johnson Syndrome - the aftermath of a systemic condition. *Graefes Arch Klin Exper Ophthalmol* 2014;252:457-67
22. Fu Y, Liu J, Tseng SC. Oral mucosal graft to correct lid margin pathologic features in cicatricial ocular surface diseases. *Am J Ophthalmol* 2011;152:600-608.e1
23. Wall V, Yen MT, Yang MC, et al. Management of the late ocular sequelae of Stevens-Johnson syndrome. *Ocul Surf* 2003;1:192-201
24. Magina S, Lisboa C, Leal V, et al. Dermatological and ophthalmological sequels in toxic epidermal necrolysis. *Dermatology* 2003;207:33-6
25. Kaido M, Yamada M, Sotozono C, et al. The relation between visual performance and clinical ocular manifestations in Stevens-Johnson syndrome. *Am J Ophthalmol* 2012;154:499-511.e1
26. Nelson JD, Wright JC. Conjunctival goblet cell densities in ocular surface disease. *Arch Ophthalmol* 1984;102:1049-51
27. Ralph RA. Conjunctival goblet cell density in normal subjects and in dry eye syndromes. *Invest Ophthalmol* 1975;14:299-302
28. Vera LS, Gueudry J, Delcampe A, et al. In vivo confocal microscopic evaluation of corneal changes in chronic Stevens-Johnson syndrome and toxic epidermal necrolysis. *Cornea* 2009;28:401-7
29. Shay E, Kheirkhah A, Liang L, et al. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Surv Ophthalmol* 2009;54:686-96
30. Gregory DG. The ophthalmologic management of acute Stevens-Johnson syndrome. *Ocul Surf* 2008;6:87-95
31. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology* 2011;118:908-14
32. Lin A, Patel N, Yoo D, et al. Management of ocular conditions in the burn unit: thermal and chemical burns and Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Burn Care Res* 2011;32:547-60
33. Hsu M, Jayaram A, Verner R, et al. Indications and outcomes of amniotic membrane transplantation in the management of acute stevens-johnson syndrome and toxic epidermal necrolysis: a case-control study. *Cornea* 2012;31:1394-402
34. Ciralsky JB, Sippel KC, Gregory DG. Current ophthalmologic treatment strategies for acute and chronic Stevens-Johnson syndrome and toxic epidermal necrolysis. *Curr Opin Ophthalmol* 2013;24:321-8
35. Papakostas TD, Le HG, Chodosh J, Jacobs DS. Prosthetic replacement of the ocular surface ecosystem as treatment for ocular surface disease in patients with a history of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Ophthalmology* 2015;122:248-53
36. Sotozono C, Yamauchi N, Maeda S, Kinoshita S. Tear exchangeable limbal rigid contact lens for ocular sequelae resulting from Stevens-Johnson syndrome or toxic epidermal necrolysis. *Am J Ophthalmol* 2014;158:983-993.e1
37. Heur M, Bach D, Theophanous C, Chiu GB. Prosthetic replacement of the ocular surface ecosystem scleral lens therapy for patients with ocular symptoms of chronic Stevens-Johnson syndrome. *Am J Ophthalmol* 2014;158:49-54

38. Ciralsky JB, Sippel KC. Prompt versus delayed amniotic membrane application in a patient with acute Stevens-Johnson syndrome. *Clin Ophthalmol* 2013;7:1031-4
39. Sotozono C, Inatomi T, Nakamura T, et al. Visual improvement after cultivated oral mucosal epithelial transplantation. *Ophthalmology* 2013;120:193-200
40. Kheirkhah A, Ghaffari R, Kaghazkanani R, et al. A combined approach of amniotic membrane and oral mucosa transplantation for fornix reconstruction in severe symblepharon. *Cornea* 2013;32:155-60
41. Tomlins PJ, Parulekar MV, Rauz S. "Triple-TEN" in the treatment of acute ocular complications from toxic epidermal necrolysis. *Cornea* 2013;32:365-9
42. Pujari S, Siddique SS, Dohlman CH, Chodosh J. The Boston keratoprosthesis type II: the Massachusetts Eye and Ear Infirmary experience. *Cornea* 2011;30:1298-303
43. Sejpal K, Yu F, Aldave AJ. The Boston keratoprosthesis in the management of corneal limbal stem cell deficiency. *Cornea* 2011;30:1187-94
44. Rathi VM, Mandathara PS, Dumpati S, et al. Boston ocular surface prosthesis: an Indian experience. *Indian J Ophthalmol* 2011;59:279-81
45. Iyer G, Pillai VS, Srinivasan B, et al. Modified osteo-odonto keratoprosthesis—the Indian experience—results of the first 50 cases. *Cornea* 2010;29:771-6
46. Shammas MC, Lai EC, Sarkar JS, et al. Management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. *Am J Ophthalmol* 2010;149:203-213.e2
47. Tougeron-Brousseau B, Delcampe A, Gueudry J, et al. Vision-related function after scleral lens fitting in ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol* 2009;148:852-859.e2
48. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol* 2009;147:1004-11. 11 e1
49. Fukuda M, Hamada S, Liu C, Shimomura Y. Osteo-odonto-keratoprosthesis in Japan. *Cornea* 2008;27(Suppl 1):S56-61
50. Tan DT, Tay AB, Theng JT, et al. Keratoprosthesis surgery for end-stage corneal blindness in Asian eyes. *Ophthalmology* 2008;115:503-510.e3
51. De Rojas MV, Dart JK, Saw VP. The natural history of Stevens-Johnson syndrome: patterns of chronic ocular disease and the role of systemic immunosuppressive therapy. *Br J Ophthalmol* 2007;91:1048-53
52. Kobayashi A, Yoshita T, Sugiyama K, et al. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. *Ophthalmology* 2006;113:126-32
53. Falcinelli G, Falsini B, Taloni M, Colliardo P. Modified osteo-odonto-keratoprosthesis for treatment of corneal blindness: long-term anatomical and functional outcomes in 181 cases. *Arch Ophthalmol* 2005;123:1319-29
54. Nishida K, Yamato M, Hayashida Y, et al. Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *N Engl J Med* 2004;351:1187-96
55. Kaido M, Goto E, Dogru M, Tsubota K. Punctal occlusion in the management of chronic Stevens-Johnson syndrome. *Ophthalmology* 2004;111:895-900
56. Gomes JA, Santos MS, Ventura AS, et al. Amniotic membrane with living related corneal limbal/conjunctival allograft for ocular surface reconstruction in Stevens-Johnson syndrome. *Arch Ophthalmol* 2003;121:1369-74
57. Geerling G, Liu CS, Dart JK, et al. Sight and comfort: complex procedures in end-stage Stevens-Johnson syndrome. *Eye* 2003;17:89-91
58. Shimazaki J, Aiba M, Goto E, et al. Transplantation of human limbal epithelium cultivated on amniotic membrane for the treatment of severe ocular surface disorders. *Ophthalmology* 2002;109:1285-90
59. John T, Foulks GN, John ME, et al. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. *Ophthalmology* 2002;109:351-60
60. Koizumi N, Inatomi T, Suzuki T, et al. Cultivated corneal epithelial transplantation for ocular surface reconstruction in acute phase of Stevens-Johnson syndrome. *Arch Ophthalmol* 2001;119:298-300
61. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol* 2000;130:25-32
62. Honavar SG, Bansal AK, Sangwan VS, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome. *Ophthalmology* 2000;107:975-9
63. Tsubota K, Satake Y, Kaido M, et al. Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation. *N Engl J Med* 1999;340:1697-703
64. Tseng SC, Prabhasawat P, Barton K, et al. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. *Arch Ophthalmol* 1998;116:431-41
65. Tsubota K, Satake Y, Ohyama M, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *Am J Ophthalmol* 1996;122:38-52
66. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. *Trans Am Ophthalmol Soc* 1996;94:677-743
67. Mannor GE, Mathers WD, Wolfley DE, Martinez JA. Hard-palate mucosa graft in Stevens-Johnson syndrome. *Am J Ophthalmol* 1994;118:786-91
68. Soong HK, Martin NF, Wagoner MD, et al. Topical retinoid therapy for squamous metaplasia of various ocular surface disorders. A multicenter, placebo-controlled double-masked study. *Ophthalmology* 1988;95:1442-6
69. Tseng SC, Maumenee AE, Stark WJ, et al. Topical retinoid treatment for various dry-eye disorders. *Ophthalmology* 1985;92:717-27
70. McCord Jr CD, Chen WP. Tarsal polishing and mucous membrane grafting for cicatricial entropion, trichiasis and epidermalization. *Ophthalmic Surg* 1983;14:1021-5
71. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol* 2015;160:228-37
72. Kalwerisky K, Davies B, Mihora L, et al. Use of the Boston Ocular Surface Prosthesis in the management of severe periorbital thermal injuries: a case series of 10 patients. *Ophthalmology* 2012;119:516-21
73. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye* 2005;19:846-53
74. Kim DH, Yoon KC, Seo KY, et al. The role of systemic immunomodulatory treatment and prognostic factors on chronic ocular complications in Stevens-Johnson syndrome. *Ophthalmology* 2015;122:254-64
75. Kompella VB, Sangwan VS, Bansal AK, et al. Ophthalmic complications and management of Stevens-Johnson syndrome at a tertiary eye care centre in south India. *Indian J Ophthalmol* 2002;50:283-6
76. Toda A, Okabe M, Yoshida T, Nikaido T. The potential of amniotic membrane/amnion-derived cells for regeneration of various tissues. *J Pharmacol Sci* 2007;105:215-28
77. Danforth D, Hull RW. The microscopic anatomy of the fetal membranes with particular reference to the detailed structure of the amnion. *Am J Obstetr Gynecol* 1958;75:536-47. discussion 48—50
78. Bourne GL. The microscopic anatomy of the human amnion and chorion. *Am J Obstetr Gynecol* 1960;79:1070-3

79. Prasad JK, Feller I, Thomson PD. Use of amnion for the treatment of Stevens-Johnson syndrome. *J Trauma* 1986;26:945-6
80. Kim JC, Tseng SC. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. *Cornea* 1995;14:473-84
81. Kim JC, Tseng SC. The effects on inhibition of corneal neovascularization after human amniotic membrane transplantation in severely damaged rabbit corneas. *Korean J Ophthalmol* 1995;9:32-46
82. Nakamura M, Naka M, Tatsumi Y, et al. Filtering bleb structure associated with long-term intraocular pressure control after amniotic membrane-assisted trabeculectomy. *Curr Eye Res* 2012;37:239-50
83. Tejwani S, Kolari RS, Sangwan VS, Rao GN. Role of amniotic membrane graft for ocular chemical and thermal injuries. *Cornea* 2007;26:21-6
84. Sangwan VS, Burman S, Tejwani S, et al. Amniotic membrane transplantation: a review of current indications in the management of ophthalmic disorders. *Indian J Ophthalmol* 2007;55:251-60
85. Tseng SC, Espana EM, Kawakita T, et al. How does amniotic membrane work? *Ocul Surf* 2004;2:177-87
86. Sippel KC, Ma JJ, Foster CS. Amniotic membrane surgery. *Curr Opin Ophthalmol* 2001;12:269-81
87. Grueterich M, Espana EM, Tseng SC. Ex vivo expansion of limbal epithelial stem cells: amniotic membrane serving as a stem cell niche. *Surv Ophthalmol* 2003;48:631-46
88. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. *Ocul Surf* 2004;2:201-11
89. Rahman I, Said DG, Maharajan VS, Dua HS. Amniotic membrane in ophthalmology: indications and limitations. *Eye* 2009;23:1954-61
90. Dua HS, Gomes JA, King AJ, Maharajan VS. The amniotic membrane in ophthalmology. *Surv Ophthalmol* 2004;49:51-77
91. Moore JE, Dua HS, Page AB, et al. Ocular surface reconstruction in LOGIC syndrome by amniotic membrane transplantation. *Cornea* 2001;20:753-6
92. Park EH, Korn TS, Vasani SN, Kikkawa DO. Autologous allogeneic amniotic membrane grafting in Stevens-Johnson syndrome. *Ophthal Plast Reconstr Surg* 2003;19:250-1
93. Atzori L, Peiretti E, Ferreli C, et al. Amniotic membrane transplantation in the surgical management of symblepharon following toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2006;20:214-6
94. Liu J, Sheha H, Fu Y, et al. Oral mucosal graft with amniotic membrane transplantation for total limbal stem cell deficiency. *Am J Ophthalmol* 2011;152:739-747.e1
95. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. *Ophthalmology* 2002;109:694-703
96. Tseng SC. Amniotic membrane transplantation for ocular surface reconstruction. *BiosciRep* 2001;21:481-9
97. Tseng SC. Amniotic membrane transplantation for persistent corneal epithelial defect. *Br J Ophthalmol* 2001;85:1400-1
98. Zhou S, Yuan J, Chen L, Chen J. Fresh versus preserved amniotic membrane transplantation for conjunctival surface reconstruction. *Yan Ke Xue Bao* 2008;24:39-43. Chinese
99. Santos MS, Gomes JA, Hofling-Lima AL, et al. Survival analysis of conjunctival limbal grafts and amniotic membrane transplantation in eyes with total limbal stem cell deficiency. *Am J Ophthalmol* 2005;140:223-30
100. Lopez-Garcia JS, Rivas L, Garcia-Lozano I. Severe limbal deficiency treated by combined limbal allograft and amniotic membrane transplantation. *Arch Soc Esp Oftalmol* 2005;80:405-12
101. Nava-Castaneda A, Tovila-Canales JL, Monroy-Serrano MH, et al. Comparative study of amniotic membrane transplantation, with and without simultaneous application of mitomycin C in conjunctival fornix reconstruction. *Arch Soc Esp Oftalmol* 2005;80:345-52. Spanish
102. Hick S, Demers PE, Brunette I, et al. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. *Cornea* 2005;24:369-77
103. Datta H, Sarkar K, Chatterjee PR. Amniotic membrane transplantation in ocular surface disorders. *J Indian Med Assoc* 2004;102:726-9
104. Zhou SY, Chen JQ, Chen LS, et al. Long-term results of amniotic membrane transplantation for conjunctival surface reconstruction. *Zhonghua Yan Ke Za Zhi* 2004;40:745-9. Chinese
105. Zhou SY, Chen JQ, Liu ZG, et al. A clinical study of amniotic membrane transplantation for severe eye burns at the acute stage. *Zhonghua Yan Ke Za Zhi* 2004;40:97-100. Chinese
106. Zhou S, Chen J, Xu L, et al. Fresh amniotic membrane transplantation for conjunctival surface reconstruction. *Yan Ke Xue Bao* 1999;15:169-73
107. Forbes J, Fetterolf DE. Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series. *J Wound Care* 2012;290:294-6
108. Kesting MR, Wolff KD, Nobis CP, Rohleder NH. Amniotic membrane in oral and maxillofacial surgery. *Oral Maxillofac Surg* 2014;18:153-64
109. Mamede AC, Carvalho MJ, Abrantes AM, et al. Amniotic membrane: from structure and functions to clinical applications. *Cell Tissue Res* 2012;349:447-58
110. Alsina-Gibert M, Pedregosa-Fauste S. Amniotic membrane transplantation in the treatment of chronic lower limb ulcers. *Actas Dermosifiliogr* 2012;103:608-13
111. Pruet CM, Queen JH, Kim G. Amnion doughnut: a novel method for sutureless fixation of amniotic membrane to the bulbar and palpebral conjunctiva in acute ocular-involving Stevens-Johnson syndrome. *Cornea* 2014;33:1240-4
112. Barua A, McKee HD, Barbara R, et al. Toxic epidermal necrolysis in a 15-month-old girl successfully treated with amniotic membrane transplantation. *J AAPOS* 2012;16:478-80
113. Foulks GN. Amniotic membrane therapy in the acute phase of toxic epidermal necrolysis. *J AAPOS* 2007;11:531
114. Hess TM, Chew HF. Successful treatment of acute ocular involvement in Stevens-Johnson syndrome with amniotic membrane transplantation: a case report. *Can J Ophthalmol* 2012;47:e44-6
115. Muqit MM, Ellingham RB, Daniel C. Technique of amniotic membrane transplant dressing in the management of acute Stevens-Johnson syndrome. *Br J Ophthalmol* 2007;91:1536
116. Ricardo JR, Barros SL, Santos MS, et al. Amniotic membrane transplantation for severe acute cases of chemical ocular burn and Stevens-Johnson syndrome. *Arq Bras Oftalmol* 2009;72:215-20. Portuguese
117. Schwartz R, Avello E, Palisson F. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous immunoglobulin and amniotic membranes. *Arch Dermatol* 2008;144:724-6
118. Shay E, Khadem JJ, Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrolysis. *Cornea* 2010;29:359-61
119. Tandon A, Cackett P, Mulvihill A, Fleck B. Amniotic membrane grafting for conjunctival and lid surface disease in the acute phase of toxic epidermal necrolysis. *J AAPOS* 2007;11:612-3
120. Warkad VU, Sahu SK, Das S. Amniotic membrane grafting in the management of acute toxic epidermal necrolysis/Stevens Johnson syndrome. *Am J Ophthalmol* 2011;151:381-2. author reply 2
121. Miki T, Lehmann T, Cai H, et al. Stem cell characteristics of amniotic epithelial cells. *Stem Cells* 2005;23:1549-59

122. Park WC, Tseng SC. Modulation of acute inflammation and keratocyte death by suturing, blood, and amniotic membrane in PRK. *Invest Ophthalmol Vis Sci* 2000;41:2906-14
123. Bauer D, Wasmuth S, Hermans P, et al. On the influence of neutrophils in corneas with necrotizing HSV-1 keratitis following amniotic membrane transplantation. *Exp Eye Res* 2007;85:335-45
124. Li W, He H, Kawakita T, et al. Amniotic membrane induces apoptosis of interferon-gamma activated macrophages in vitro. *Exp Eye Res* 2006;82:282-92
125. Park CY, Kohanim S, Zhu L, et al. Immunosuppressive property of dried human amniotic membrane. *Ophthalmic Res* 2009;41:112-3
126. Hao Y, Ma DH, Hwang DG, et al. Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane. *Cornea* 2000;19:348-52
127. Kim JS, Kim JC, Na BK, et al. Amniotic membrane patching promotes healing and inhibits proteinase activity on wound healing following acute corneal alkali burn. *Exp Eye Res* 2000;70:329-37
128. Kolomeyer AM, Do BK, Tu Y, Chu DS. Placement of ProKera in the management of ocular manifestations of acute Stevens-Johnson syndrome in an outpatient. *Eye Contact Lens* 2013;39:e7-11
129. Aghayan HR, Goodarzi P, Baradaran-Rafii A, et al. Bacterial contamination of amniotic membrane in a tissue bank from Iran. *Cell Tissue Bank* 2013;14:401-6
130. Marangon FB, Alfonso EC, Miller D, et al. Incidence of microbial infection after amniotic membrane transplantation. *Cornea* 2004;23:264-9
131. Al-Kharashi S, Al-Khawaja A, Gonnah el S, et al. Microbial keratitis after amniotic membrane transplantation. *Int Ophthalmol* 2005;26:73-6
132. Chan LS, Soong HK, Foster CS, et al. Ocular cicatricial pemphigoid occurring as a sequela of Stevens-Johnson syndrome. *JAMA* 1991;266:1543-6
133. Fania L, Giannico MI, Fasciani R, et al. Ocular mucous membrane pemphigoid after Lyell syndrome: occasional finding or predisposing event? *Ophthalmology* 2012;119:688-93
134. Radford CF, Rauz S, Williams GP, et al. Incidence, presenting features, and diagnosis of cicatrising conjunctivitis in the United Kingdom. *Eye* 2012;26:1199-208
135. Balkrishnan C, Sharma V, Vyas A. Immunosuppressive therapy in inflammatory ocular surface disease post Steven Johnson syndrome. *Indian J Ophthalmol* 2011;59:69-70
136. Saw VP, Dart JK, Rauz S, et al. Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology* 2008;115:253-61
137. Frizon L, Araujo MC, Andrade L, et al. Evaluation of conjunctival bacterial flora in patients with Stevens-Johnson Syndrome. *Clinics* 2014;69:168-72
138. Dart JKG SV. *Immune Modulation in Ocular Mucous MembranePemphigoid*. Berlin Heidelberg, Springer, 2014
139. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: is it real? *Ocul Surf* 2009;7:28-40
140. Roujeau JC, Phlippoteau C, Koso M, et al. Sjogren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985;1:609-11
141. Roujeau JC, Phlippoteau C, Koso M, et al. Ocular sequelae and sicca syndrome following Lyell's syndrome. *Ann Dermatol Venereol* 1985;112:883-8. French
142. Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Arch Ophthalmol* 2002;120:330-7
143. Moon JW, Lee HJ, Shin KC, et al. Short term effects of topical cyclosporine and viscoelastic on the ocular surfaces in patients with dry eye. *Korean J Ophthalmol* 2007;21:189-94
144. Pflugfelder SC, De Paiva CS, Villarreal AL, Stern ME. Effects of sequential artificial tear and cyclosporine emulsion therapy on conjunctival goblet cell density and transforming growth factor-beta2 production. *Cornea* 2008;27:64-9
145. Sahli E, Hosal BM, Zilelioglu G, et al. The effect of topical cyclosporine A on clinical findings and cytological grade of the disease in patients with dry eye. *Cornea* 2010;29:1412-6
146. Demiryay E, Yaylali V, Cetin EN, Yildirim C. Effects of topical cyclosporine a plus artificial tears versus artificial tears treatment on conjunctival goblet cell density in dysfunctional tear syndrome. *Eye Contact Lens* 2011;37:312-5
147. Wang Y, Ogawa Y, Dogru M, et al. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. *Bone Marrow Transplant* 2008;41:293-302
148. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. *J Ocul Pharmacol Ther* 2013;29:372-7
149. Sant' Anna AE, Hazarbassanov RM, de Freitas D, Gomes JA. Minor salivary glands and labial mucous membrane graft in the treatment of severe symblepharon and dry eye in patients with Stevens-Johnson syndrome. *Br J Ophthalmol* 2012;96:234-9
150. Marinho DR, Burmann TG, Kwitko S. Labial salivary gland transplantation for severe dry eye due to chemical burns and Stevens-Johnson syndrome. *Ophthal Plast Reconstr Surg* 2010;26:182-4
151. Leibovitch I, Hoyama E, Limawararut V, et al. Novel technique to control hypersecretion from a transplanted autologous submandibular salivary gland for keratoconjunctivitis sicca. *Cornea* 2006;25:1251-3
152. Phasukkijwatana N, Lertrit P, Liammongkolkul S, Prabhasawat P. Stability of epitheliotrophic factors in autologous serum eye drops from chronic Stevens-Johnson syndrome dry eye compared to non-autoimmune dry eye. *Curr Eye Res* 2011;36:775-81
153. Quinto GG, Campos M, Behrens A. Autologous serum for ocular surface diseases. *Arq Bras Oftalmol* 2008;71:47-54
154. Lau B, Mutyala D, Dhaliwal D. A case report of doxycycline-induced Stevens-Johnson syndrome. *Cornea* 2011;30:595-7
155. Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. *Saudi J Ophthalmol* 2014;28:168-72
156. Ciralsky JB, Chapman KO, Rosenblatt MI, et al. Treatment of refractory persistent corneal epithelial defects: A standardized approachusing continuous wear PROSE therapy. *Ocul Immunol Inflamm* 2015;23:219-24
157. Erdem E, Yagmur M, Harbiyeli I, et al. Umbilical cord blood serum therapy for the management of persistent corneal epithelial defects. *Int J Ophthalmol* 2014;7:807-10
158. Watson SL, Geerling G, Dart JK. Clinical study of therapeutic ocular surface medium for persistent epithelial defect. *Ophthalmic Res* 2014;51:82-7
159. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol* 2013;156:1095-101
160. Sotozono C, Inatomi T, Nakamura T, et al. Cultivated oral mucosal epithelial transplantation for persistent epithelial defect in severe ocular surface diseases with acute inflammatory activity. *Acta Ophthalmol* 2014;92:e447-53
161. Cher I. Blink-related microtrauma: when the ocular surface harms itself. *Clin Experiment Ophthalmol* 2003;31:183-90
162. Tseng SC. Topical retinoid treatment for dry eye disorders. *Trans Ophthalmol Soc U K* 1985;104(Pt 4):489-95
163. Chan RY, Foster CS. A step-wise approach to ocular surface rehabilitation in patients with ocular inflammatory disease. *Int Ophthalmol Clin* 1999;39:83-108

164. Siqueira AC, Santos MS, Farias CC, et al. Scleral contact lens for ocular rehabilitation in patients with Stevens-Johnson syndrome. *Arq Bras Oftalmol* 2010;73:428-32. Portuguese
165. Gungor I, Schor K, Rosenthal P, Jacobs DS. The Boston Scleral Lens in the treatment of pediatric patients. *J AAPOS* 2008;12:263-7
166. Pullum K, Buckley R. Therapeutic and ocular surface indications for scleral contact lenses. *Ocul Surf* 2007;5:40-8
167. Haefliger IO, Vysniauskiene I, Pimentel AR, et al. Free autologous buccal mucosal graft transplantation to treat ocular complications after toxic epidermal necrolysis: case report. *Klin Monbl Augenheilkd* 2004;221:395-7
168. Koreen IV, Taich A, Elner VM. Anterior lamellar recession with buccal mucous membrane grafting for cicatricial entropion. *Ophthal Plast Reconstr Surg* 2009;25:180-4
169. Tugal-Tutkun I, Akova YA, Foster CS. Penetrating keratoplasty in cicatrizing conjunctival diseases. *Ophthalmology* 1995;102:576-85
170. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. *Ophthalmology* 1989;96:709-22. discussion 22—23
171. Tsubota K, Shimazaki J. Surgical treatment of children blinded by Stevens-Johnson syndrome. *Am J Ophthalmol* 1999;128:573-81
172. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. *Cornea* 1994;13:389-400
173. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. *Ophthalmology* 2002;109:1159-66
174. Tsubota K, Shimmura S, Shinozaki N, et al. Clinical application of living-related conjunctival-limbal allograft. *Am J Ophthalmol* 2002;133:134-5
175. Nordlund ML, Holland EJ, Kersten RC. Ocular surface reconstruction in a patient with complete ankyloblepharon resulting from stevens-johnson syndrome. *Arch Ophthalmol* 2004;122:934-5
176. Samson CM, Nduaguba C, Baltatzis S, Foster CS. Limbal stem cell transplantation in chronic inflammatory eye disease. *Ophthalmology* 2002;109:862-8
177. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P. Limbal allografting from related live donors for corneal surface reconstruction. *Ophthalmology* 1999;106:822-8
178. Ang AY, Chan CC, Biber JM, Holland EJ. Ocular surface stem cell transplantation rejection: incidence, characteristics, and outcomes. *Cornea* 2013;32:229-36
179. Iyer G, Srinivasan B, Agarwal S, et al. Treatment modalities and clinical outcomes in ocular sequelae of Stevens-Johnson syndrome over 25 years- a paradigm shift. *Cornea* 2016;35:46-50
180. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of autologous serum-derived cultivated corneal epithelial equivalents for the treatment of severe ocular surface disease. *Ophthalmology* 2006;113:1765-72
181. Ang LP, Sotozono C, Koizumi N, et al. A comparison between cultivated and conventional limbal stem cell transplantation for Stevens-Johnson syndrome. *Am J Ophthalmol* 2007;143:178-80
182. Shimazaki J, Higa K, Morito F, et al. Factors influencing outcomes in cultivated limbal epithelial transplantation for chronic cicatricial ocular surface disorders. *Am J Ophthalmol* 2007;143:945-53
183. Shortt AJ, Bunce C, Levis HJ, et al. Three-year outcomes of cultured limbal epithelial allografts in aniridia and Stevens-Johnson syndrome evaluated using the Clinical Outcome Assessment in Surgical Trials assessment tool. *Stem Cells Transl Med* 2014;3:265-75
184. Kim JT, Chun YS, Song KY, Kim JC. The effect of in vivo grown corneal epithelium transplantation on persistent epithelial defects with limbal stem cell deficiency. *J Korean Med Sci* 2008;23:502-8
185. Solomon A, Espana EM, Tseng SC. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. *Ophthalmology* 2003;110:93-100
186. Dohlman CH, Terada H. Keratoprosthesis in pemphigoid and Stevens-Johnson syndrome. *Adv Exp Med Biol* 1998;438:1021-5
187. Geerling G, Liu CS, Collin JR, Dart JK. Costs and gains of complex procedures to rehabilitate end stage ocular surface disease. *Br J Ophthalmol* 2002;86:1220-1
188. Liu C, Paul B, Tandon R, et al. The osteo-odonto-keratoprosthesis (OOKP). *Semin Ophthalmol* 2005;20:113-28
189. Stoiber J, Grabner G. Clinical management of severe ocular surface disease. *Klin Monbl Augenheilkd* 2005;222:533-51. German
190. Fukuda M, Nakao A, Hamada S, et al. A case of severe Stevens-Johnson syndrome successfully treated by osteo-odonto-keratoprosthesis surgery. *Japan J Ophthalmol* 2005;49:423-4
191. Liu C, Okera S, Tandon R, et al. Visual rehabilitation in end-stage inflammatory ocular surface disease with the osteo-odonto-keratoprosthesis: results from the UK. *Br J Ophthalmol* 2008;92:1211-7
192. Pinar-Sueiro S, Etxebarria-Ecenarro J, Gibelalde A, et al. Successful Boston keratoprosthesis in a patient with Lyell's syndrome. *Arch Soc Esp Oftalmol* 2009;84:635-40. Spanish
193. Reddy SC, Tajunisah I, Tan DT. Osteo-odonto keratoprosthesis in Stevens-Johnson syndrome: a case report. *Int J Ophthalmol* 2011;4:212-5
194. De La Paz MF, De Toledo JA, Charoenrook V, et al. Impact of clinical factors on the long-term functional and anatomic outcomes of osteo-odonto-keratoprosthesis and tibial bone keratoprosthesis. *Am J Ophthalmol* 2011;151:829-839.e1
195. Guell JL, Arcos E, Gris O, et al. Outcomes with the Boston Type 1 Keratoprosthesis at Instituto de Microcirugia Ocular IMO. *Saudi J Ophthalmol* 2011;25:281-4
196. Ament JD, Stryjewski TP, Pujari S, et al. Cost effectiveness of the type II Boston keratoprosthesis. *Eye* 2011;25:342-9
197. Basu S, Taneja M, Narayanan R, et al. Short-term outcome of Boston Type 1 keratoprosthesis for bilateral limbal stem cell deficiency. *Indian J Ophthalmol* 2012;60:151-3
198. Tan A, Tan DT, Tan XW, Mehta JS. Osteo-odonto keratoprosthesis: systematic review of surgical outcomes and complication rates. *Ocul Surf* 2012;10:15-25
199. Huang Y, Dong Y, Wang L, et al. Long-term outcomes of MICOF keratoprosthesis in the end stage of autoimmune dry eyes: an experience in China. *Br J Ophthalmol* 2012;96:28-33
200. Koller B, Neuhann T, Neuhann I. Results with the Boston keratoprosthesis. *Der Ophthalmologe* 2012;109:454-61. German
201. Kang JJ, de la Cruz J, Cortina MS. Visual outcomes of Boston keratoprosthesis implantation as the primary penetrating corneal procedure. *Cornea* 2012;31:1436-40
202. de la Paz MF, Stoiber J, de Rezende Couto Nascimento V, et al. Anatomical survival and visual prognosis of Boston type I keratoprosthesis in challenging cases. *Graefes Arch Klin Exp Ophthalmol* 2014;252:83-90
203. Dong D, Tan A, Mehta JS, et al. Cost-effectiveness of osteo-odonto keratoprosthesis in Singapore. *Am J Ophthalmol* 2014;157:78-84.e2
204. Basu S, Sureka S, Shukla R, Sangwan V. Boston type 1 based keratoprosthesis (Auro Kpro) and its modification (LVP Kpro) in chronic Stevens Johnson syndrome. *BMJ Case Rep* 2014:2014
205. Michael R, Charoenrook V, de la Paz MF, et al. Long-term functional and anatomical results of osteo- and osteoodonto-keratoprosthesis. *Graefes Arch Klin Exp Ophthalmol* 2008;246:1133-7
206. Marchi V, Ricci R, Pecorella I, et al. Osteo-odonto-keratoprosthesis. Description of surgical technique with results in 85 patients. *Cornea* 1994;13:125-30
207. Nouri M, Terada H, Alfonso EC, et al. Endophthalmitis after keratoprosthesis: incidence, bacterial causes, and risk factors. *Arch Ophthalmol* 2001;119:484-9

208. Yaghouti F, Nouri M, Abad JC, et al. Keratoprosthesis: preoperative prognostic categories. *Cornea* 2001;20:19-23
209. Sayegh RR, Ang LP, Foster CS, Dohlman CH. The Boston keratoprosthesis in Stevens-Johnson syndrome. *Am J Ophthalmol* 2008;145:438-44
210. Bradley JC, Hernandez EG, Schwab IR, Mannis MJ. Boston type 1 keratoprosthesis: the university of california davis experience. *Cornea* 2009;28:321-7
211. Ciralsky J, Papaliodis GN, Foster CS, et al. Keratoprosthesis in autoimmune disease. *Ocul Immunol Inflamm* 2010;18:275-80
212. Munoz-Gutierrez G, Alvarez de Toledo J, Barraquer RI, et al. Post-surgical visual outcome and complications in Boston type 1 keratoprosthesis. *Arch Soc Esp Oftalmol* 2013;88:56-63
213. Parthasarathy A, Aung T, Oen FT, Tan DT. Endoscopic cyclophotocoagulation for the management of advanced glaucoma after osteo-odonto-keratoprosthesis surgery. *Clin Experiment Ophthalmol* 2008;36:93-4
214. Yu JF, Huang YF. Glaucoma with modified osteo-odonto keratoprosthesis. *Cornea* 2012;31:1214. author reply -5
215. Yu JF, Huang YF. Characteristics of endophthalmitis with Boston keratoprosthesis. *Cornea* 2012;31:594
216. Robert MC, Moussally K, Harissi-Dagher M. Review of endophthalmitis following Boston keratoprosthesis type 1. *Br J Ophthalmol* 2012;96:776-80
217. Chan CC, Holland EJ. Infectious keratitis after Boston type 1 keratoprosthesis implantation. *Cornea* 2012;31:1128-34
218. Chan CC, Holland EJ. Infectious endophthalmitis after Boston type 1 keratoprosthesis implantation. *Cornea* 2012;31:346-9
219. Basu S, Pillai VS, Sangwan VS. Mucosal complications of modified osteo-odonto keratoprosthesis in chronic Stevens-Johnson syndrome. *Am J Ophthalmol* 2013;156:867-873.e2
220. Iyer G, Srinivasan B, Agarwal S, et al. Glaucoma in modified osteo-odonto-keratoprosthesis eyes: role of additional stage 1A and Ahmed glaucoma drainage device-technique and timing. *Am J Ophthalmol* 2015;159:482-9
221. Iyer G, Srinivasan B, Agarwal S, Rachapalle SR. Laminar resorption in modified osteo-odonto-keratoprosthesis procedure: a cause for concern. *Am J Ophthalmol* 2014;158:263-269.e2
222. Forlini M, Adabache-Guel T, Bratu A, et al. Endoscopic cyclophotocoagulation in refractory glaucoma after osteo-odonto-keratoprosthesis in Stevens-Johnson syndrome: a case report. *Retin Cases Brief Rep* 2014;8:193-6
223. de Oliveira LA, Pedreira Magalhaes F, Hirai FE, de Sousa LB. Experience with Boston keratoprosthesis type 1 in the developing world. *Can J Ophthalmol* 2014;49:351-7
224. Robert MC, Dohlman CH. A review of corneal melting after Boston Keratoprosthesis. *Semin Ophthalmol* 2014;29:349-57
225. Sawatari Y, Perez VL, Parel JM, et al. Oral and maxillofacial surgeons' role in the first successful modified osteo-odonto-keratoprosthesis performed in the United States. *J Oral Maxillofac Surg* 2011;69:1750-6
226. Gomaa A, Comyn O, Liu C. Keratoprostheses in clinical practice - a review. *Clin Experiment Ophthalmol* 2010;38:211-24
227. Durand ML, Dohlman CH. Successful prevention of bacterial endophthalmitis in eyes with the Boston keratoprosthesis. *Cornea* 2009;28:896-901

Analysis of Ocular Manifestation and Genetic Association of Allopurinol-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis in South Korea

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Purpose: To describe the clinical characteristics and genetic background of allopurinol-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in South Korea.

Methods: This is a prospective, noncomparative case series. Visual acuity, detailed medical history, ocular findings, and systemic manifestations of 5 patients (10 eyes) with allopurinol-induced SJS/TEN were recorded. The acute ocular involvement score and the chronic ocular manifestation score were graded on scales of 0–3 and 0–39, respectively, based on severity. Human leukocyte antigen (HLA) genotyping was also performed during the hospitalization.

Results: Three patients were diagnosed with SJS, and 2 with TEN. Mild ocular involvement with only conjunctival hyperemia (acute ocular involvement score ≤1) was present in all 10 eyes during the acute stage. Patients were treated with systemic steroids and topical antibiotics, steroids, and preservative-free artificial tears, with rinsing of the ocular surface, in the acute stages of SJS/TEN. In the final follow-up, none of the patients had developed severe chronic ocular complications (chronic ocular manifestation score ≤8), including keratinization, corneal conjunctivalization, mucocutaneous junction involvement, or symblepharon. One patient developed bilateral persistent epithelial defects 3 months after the disease onset, which healed after conservative treatment, leaving a bilateral central corneal haze. HLA genotyping showed that 4 of the 5 patients (80%) were positive for *HLA-B*58:01*.

Conclusions: Allopurinol-induced SJS/TEN might not cause serious acute or chronic complications of the ocular surface. In addition, our HLA genotyping results are consistent with previous studies reporting a strong association between *HLA-B*58:01* and allopurinol-induced SJS/TEN among Koreans.

Key Words: allopurinol, human leukocyte antigen, Stevens–Johnson syndrome, toxic epidermal necrolysis

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The Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute diseases of the skin and the mucosal surfaces throughout the body (eg, eye, lung, gastrointestinal, genitourinary system), characterized by the detachment and blistering of the skin epidermis and the mucosal epithelium.[1,2] The acute ocular complications of the SJS and TEN may occur along with the involvement of the skin, which frequently leads to late cicatricial sequelae. The chronic ocular surface complications can involve the eyelids, conjunctiva, cornea, and the tear film, resulting in visual deterioration and the worsening of the ocular surface health.[3–5]

It is well known that the SJS/TEN can be induced by various infections or classes of pharmacological agents, such as antibiotics, anticonvulsants, nonsteroidal antiinflammatory drugs, or allopurinol.[6–8] Moreover, human leukocyte antigen (HLA) types have recently been reported to be associated with the onset of SJS/TEN. The genetic predisposition to the disease seems to be specific for different ethnic groups. For instance, *HLA-B*15:02* exhibited a strong association with carbamazepine-induced SJS/TEN in Taiwanese Han Chinese patients.[9] However, in Japanese and European patients, *HLA-A*31:01* was strongly associated with carbamazepine-induced severe cutaneous adverse reactions (SCARs), including SJS/TEN.[10,11] We also recently reported that cold medicine (CM)-related SJS/TEN with severe mucosal involvement, including severe ocular surface complications (SOC), is associated with *HLA-A*02:06* in Japanese and Korean populations and with *HLA-B*44:03* in Indian and Brazilian populations.[12] Taken together, these reports suggest that the SJS/TEN induced by different drugs have different

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genetic susceptibilities; therefore, it is possible that different causative drug-induced SJS/TEN reactions have different pathogeneses and phenotypes.[13,14]

Allopurinol is a xanthine oxidase inhibitor commonly used for the treatment of gout and is known to be one of the drugs most frequently associated with SJS and TEN.[15] Recent studies have reported a strong association between allopurinol-induced SJS/TEN and the genetic marker, *HLA-B*58:01* in the Han Chinese, Thai, European, and Japanese populations.[16–19] To our knowledge, 2 studies to date have reported an association between allopurinol-induced SCARs and *HLA-B*58:01* in the Korean population.[20,21] However, no reports have evaluated the acute or chronic ocular complications in allopurinol-induced SJS/TEN patients.

In this study, we evaluated the acute and chronic ocular complications, and cutaneous and systemic manifestations along with HLA genotype, of allopurinol-induced SJS/TEN patients in tertiary referral ophthalmic centers.

MATERIALS AND METHODS

A prospective study on the SJS/TEN patients who were referred to the ophthalmology department of one of 3 tertiary referral centers [Chonnam National University Hospital (CNUH), Seoul National University Hospital (SNUH), and Yonsei University Hospital (YUH)] was conducted from January 2012 to May 2014. Institutional review board/ethics committee approval was obtained from the participating institutions, and the study protocol followed the guidelines of the Declaration of Helsinki. Prior informed consent to participate in this study was obtained in written form from all the patients.

The inclusion criteria were as follows: (1) dermatologist-diagnosed SJS/TEN in the acute phase based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and the involvement of at least 2 mucosal sites, including the ocular surface,[22,23] characterized by an epidermal detachment of $<$30% (SJS) and $>$30% (TEN) of the body surface area[24]; (2) the absence of a history of previous ophthalmic disease or ocular surgery; and (3) a follow-up period of at least 12 months.

Forty-three patients fulfilled the inclusion criteria during the study period, with 5 patients identified as having allopurinol-induced SJS/TEN (2 patients from CNUH, 1 from SNUH, and 2 from YUH). Allopurinol was considered as the possible causative agent if it had been taken shortly before the onset of the symptoms and signs, that is, within 2 weeks before the disease onset.[25] All the patients were subjected to a daily ophthalmological evaluation, including forniceal inspection, for the determination of the type, extent, and severity of the ocular involvement, by one of 3 cornea specialists (K.C.Y., M.K.K., or K.Y.S.), for as long as there was any significant ocular surface inflammation during the hospitalization. We collected demographic and clinical data on each patient. The patients' age, sex, best-corrected visual acuity (BCVA) both at disease onset and during the follow-up period, systemic and ocular manifestations and treatments, and the systemic and ocular sequelae were recorded on an itemized data collection form. Acute ocular involvement scores (AOS) were assigned based on the classification system proposed by Kim et al.[26] In brief, the AOS ranged from zero to three, depending on the presence of conjunctival hyperemia, pseudomembrane formation, and/or corneal epithelial erosion (0: no involvement; 1: conjunctival hyperemia; 2: pseudomembrane formation or corneal epithelial erosion; 3: pseudomembrane formation and corneal epithelial erosion). The systemic involvement in each patient was also graded using the acute systemic involvement score (ASS) developed by Kim et al.[26] ASS values ranged from zero to sixteen and were determined by the status of the oral or genital erythema, the extension degree of epidermal detachment, degree of liver dysfunction, and presence of fever, respiratory disturbance, total necrosis of epidermis, anemia, elevated serum C-reactive protein concentrations, kidney dysfunction, and pneumonia. Severe ocular and systemic involvement were defined as AOS $\geq$2 and ASS $\geq$8, respectively.

Chronic Ocular Surface Complication Evaluation and Follow-up

The BCVA and other ophthalmic parameters including the corneal and conjunctival status, limbal deficiency, tear volume, eyelid involvement, and symblepharon were investigated at each outpatient visit to the ophthalmology clinic after discharge. The tear volume was measured using the Schirmer I test.[27] A chronic ocular manifestation score (COMS) was assigned based on the involvement area or the severity of the above-mentioned factors, according to the grading system proposed by Sotozono et al.[25] Thirteen clinical signs of ocular complications of 3 ocular surface structures (cornea, conjunctiva, and eyelid) were graded on a scale of zero to three, depending on the severity of ocular involvement. The corneal complications consisted of superficial punctate keratopathy severity, extent of the epithelial defect, loss of the palisades of Vogt, and the presence and degree of conjunctivalization, corneal neovascularization, corneal opacification, and keratinization. The conjunctival complications included hyperemia and symblepharon. Eyelid complications included trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage. Severe chronic ocular manifestation was defined as having a COMS $\geq$13.

HLA Genotyping

The genotyping of the HLA-A, B, C, DRB1, and DQB1 alleles was performed as part of another study on the transethnic genetic associations of the SJS/TEN, using polymerase chain reaction assays, followed by hybridization with sequence-specific oligonucleotide probes using commercial bead-based typing kits (Wakunaga, Hiroshima, Japan).[12]

RESULTS

The demographics, clinical characteristics, and treatment plans of the 5 patients (3 male; 2 female) enrolled in this

study are summarized in Tables 1 and 2. The patients' age at the time of the SJS/TEN onset ranged from 47 to 78 years (average, 63.8 ± 13.5 years). Three patients were diagnosed as having the SJS and 2 as having TEN. Bilateral ocular involvement was noted in all of the patients in the acute phase of the disease. The AOS was ≤1 in both the eyes of all 5 patients (conjunctival hyperemia only, without corneal involvement). None of the patients showed severe ocular involvement. The initial BCVA was 20/40 or better in each eye. All the patients, except patient 2, had taken more than 1 medication because of their underlying illnesses, but those medications had been taken for more than 6 months without any changes in the dosage or dosing interval.

Ocular management consisted of the application of topical antibiotics, preservative-free artificial tears, and steroids, with rinsing of the ocular surface with sterile saline (2 times per day), for all the patients in the acute stage of the SJS/TEN. None of the patients underwent amniotic membrane transplantation or any other surgical procedures during the acute phase. The mean ASS was 7.6 ± 1.8 (range: 6–10). Two of the 5 patients showed severe systemic involvement. Each patient received systemic immunomodulatory treatment (steroids and/or intravenous immunoglobulin), depending on the dermatologist's or physician's recommendation. All the patients were administered systemic corticosteroids (prednisolone) intravenously at 1.0 mg/kg/d for 3 to 8 consecutive days, followed by the tapering off of the dosage. Patient 5 additionally received 1.0 g/kg intravenous immunoglobulin daily for 5 days. All the patients received systemic immunomodulatory treatment within 7 days of disease onset.

Blood sampling and genomic DNA analysis were performed during the hospitalization period; the results are shown in Table 3. Four patients (80%) were found to be positive for *HLA-B*58:01*; the remaining patient was positive for *HLA-B*51:01*. Four patients (80%) were positive for *HLA-DRB1*13:02* and *HLA-DQB1*06:09*. Three patients (60%) were positive for *HLA-A*33:03* and 2 (40%) for *HLA-A*02:01*. Genomic DNA analysis was performed on the other 38 patients with nonallopurinol-related SJS/TEN. Four of 38 patients (10.5%) were identified to have *HLA-B*58:01*.

No severe systemic complications were found, and there were no SJS/TEN recurrences during the follow-up period. The follow-up period ranged from 14 to 31 months (mean follow-up duration; 18.4 ± 7.2 months). During the follow-up period, all the patients showed a good clinical course without serious ocular or systemic complications with the exception of patient 3, who developed bilateral persistent epithelial defects 3 months after disease onset. He was treated with topical antibiotics, preservative-free artificial tears, autologous serum, and a bandage soft contact lens application. After receiving treatment for 2 weeks, his corneal lesions healed, but left a bilateral central haze. All the patients, with the exception of patient 3, retained a BCVA of 20/40 or better in each eye and demonstrated an intact ocular surface and a good tear meniscus. The mean COMS at the final follow-up visit was 3.3 ± 2.3 (range: 2–8).

The clinical course of patient 2 is described below. Patient 2 was selected to illustrate the representative features of the acute and chronic phases of allopurinol-induced SJS/TEN in our study.

Patient 2

A 47-year-old female was admitted with a 5-day history of high fever and blistering maculopapular rash involving her limbs, lips, and oral mucosa, which limited her ability to consume food and drink (Fig. 1). Conjunctival hyperemia and lid margin inflammation developed 4 days after admission. Topical moxifloxacin 0.5% (Vigamox, Alcon, Fort Worth, TX) 4 times per day, loteprednol etabonate 0.5% (Lotemax, Bausch & Lomb, Tampa, FL) 4 times per day, and hyaluronic acid 0.1% (Kynex, Alcon) 5 to 6 times per day were administered along with the rinsing of the ocular surface 2 times per day. The conjunctival and lid margin abnormalities resolved gradually with conservative treatment. The eye drops were gradually tapered over the treatment period, according to the

TABLE 1. Demographic and Clinical Characteristics of Allopurinol-Induced SJS and TEN Patients

Patient Number	Sex	Age (yrs)	Underlying Disease	Systemic Agent Taken Before the Onset of SJS/TEN	Diagnosis	Onset of Disease ~ Development of Ocular Complication (d)	Onset of Disease ~ Systemic Treatment Initiation (d)	Eyes	Initial BCVA (logMAR)	AOS
1	M	72	Gout	Allopurinol	SJS	8	6	Rt.	0.1	1
								Lt.	0.0	1
2	F	47	Gout, liver cirrhosis	Allopurinol	SJS	9	6	Rt.	0.1	1
								Lt.	0.0	1
3	M	71	Gout, HTN, DM	Allopurinol, losartan, glimepiride	SJS	8	7	Rt.	0.1	1
								Lt.	0.0	1
4	F	71	Gout, HTN	Allopurinol, amlodipine	TEN	9	5	Rt.	0.2	1
								Lt.	0.2	1
5	M	78	Gout, HTN, BPH	Allopurinol, olmesartan, alfuzosin	TEN	3	3	Rt.	0.3	1
								Lt.	0.2	1

BPH, benign prostate hyperplasia; DM, diabetes mellitus; F, female; HTN, hypertension; logMAR, logarithm of the minimum angle of resolution; Lt., left; M, male; Rt., right.

TABLE 2. Demographic and Clinical Characteristics of Allopurinol-Induced SJS and TEN Patients (Continued)

Ocular Treatment	ASS	Systemic Treatment	Final BCVA (logMAR)	COMS	Follow-up Period (mo)
Topical	7	Systemic steroids	0.1	2	14
Topical			0.0	2	
Topical	6	Systemic steroids	0.1	2	14
Topical			0.0	2	
Topical	6	Systemic steroids	0.5	7	18
Topical			1.0	8	
Topical	10	Systemic steroids	0.0	3	31
Topical			0.1	3	
Topical	9	Systemic steroids	0.3	2	15
Topical		+IVIG	0.2	2	

ASS, acute systemic involvement score; BCVA, best-corrected visual acuity; COMS, chronic ocular manifestation score; IVIG, intravenous immunoglobulin; logMAR, logarithm of the minimum angle of resolution.

ocular surface status. Systemic steroids were administered after admission at 1.0 mg/kg/d for 4 days. The patient was discharged after 18 days of hospitalization. At the 14-month follow-up, the patient had no dry eye symptoms. Both corneas were clear with a BCVA of 16/20 in the right eye and 20/20 in the left eye. No ocular surface sequelae had occurred.

DISCUSSION

Regarding the Japanese populations, we had reported that approximately 80% of the SJS/TEN patients with SOC had taken CMs (eg, nonsteroidal antiinflammatory drugs and multiingredient CMs) several days before the disease onset[13,23]; they were classified as CM-related SJS/TEN patients.[12,13,28] We had also previously reported that in Japan and Korea, *HLA-A*02:06* is significantly associated with CM-related SJS/TEN.

However, Ueta[14] reported that allopurinol-induced SJS/TEN might be rare among the Japanese SJS/TEN patients with SOC. The diagnosis of the SJS/TEN by ophthalmologists was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites, including the ocular surface.[13,23,28] As ophthalmologists usually encounter SJS/TEN patients in the chronic rather than the acute stages, it is possible that allopurinol-induced SJS/TEN may not have been accompanied by SOC in the chronic stage.

In this study, the ophthalmologists could prospectively examine the ocular complications in the allopurinol-induced SJS/TEN patients during the acute and chronic stages. In our case series, none of the patients developed any severe acute or chronic ocular complications, such as pseudomembrane, corneal epithelial defect, corneal opacification, mucocutaneous junction involvement (mucocutaneous junction irregularity),[25] or symblepharon formation, with the exception of patient 3, who developed a persistent corneal epithelial defect 3 months after the disease onset. Additionally, in accordance with the published classification system for the acute manifestations of the SJS/TEN developed by Kim et al,[26] none of the patients in our series had severe ocular damage from SJS/TEN in the acute stage. In contrast, according to a recent multicenter study in South Korea, severe ocular involvement was observed in 59 eyes (68.6%) during the acute stage of SJS/TEN[26]; the proportion of severe acute ocular involvement in patients with SJS/TEN was still relatively high among the patients treated with conventional steroids (63.8%) or intravenous steroid pulse therapy (66.7%), according to the subgroup analysis included in that study. Moreover, according to Kim et al,[26] acute and chronic ocular involvement correlated significantly with acute systemic involvement. However, in our case series, even the 2 patients with severe systemic involvement (ASS $\geq$8) showed only mild acute ocular involvement and chronic sequelae.

Serious ocular complications, such as corneal epithelial defects and pseudomembrane during the acute stage, and symblepharon, corneal opacification and conjunctival invasion onto the cornea during the chronic stage, are usually found in CM-related SJS/TEN with SOC.[12,13] However, our study showed that none of the 5 allopurinol-induced SJS/TEN patients exhibited serious complications of the ocular surface in either the acute or the chronic stages. This might suggest that allopurinol-induced SJS/TEN showed a phenotype different from that of CM-related SJS/TEN with SOC.

In addition, a previous study by Kang et al,[21] analyzing both the drug-induced hypersensitivity syndrome and the SJS/TEN together as SCAR, reported a strong positive relationship between *HLA-B*58:01* and allopurinol-induced SCARs in the Korean population. Another study on allopurinol hypersensitivity in the Korean population included only 2 cases of SJS; both were positive for *HLA-B*58:01*.[20] In our study, 4 of the 5 patients (80%) were *HLA-B*58:01* carriers. This proportion is fairly high, considering that the allelic frequency of *HLA-B*58:01* in the general Korean population is estimated to be 6.5%–6.8%.[29,30] In addition, the allelic frequency of *HLA-B*58:01* in the nonallopurinol-induced SJS/TEN cases is only 10.5% in our study. This finding is consistent with the previous reports showing a positive association between *HLA-B*58:01* allele and allopurinol-induced SJS/TEN in the Korean population.

TABLE 3. HLA Genotypes Among Allopurinol-Induced SJS and TEN Patients

Patient Number	HLA-A*	HLA-B*	HLA-C*	HLA-DRB1*	HLA-DQB1*
1	*02:01/24:02*	*51:01/51:01*	*14:02/15:02*	*04:10/09:01*	*03:03/04:02*
2	*33:03/33:03*	*58:01/58:01*	*03:02/03:02*	*03:01/13:02*	*02:01/06:09*
3	*11:01/24:02*	*40:06/58:01*	*04:01/08:01*	*04:05/13:02*	*03:03/06:09*
4	*02:10/33:03*	*40:06/58:01*	*03:02/08:01*	*12:01/13:02*	*03:02/06:09*
5	*02:01/33:03*	*15:01/58:01*	*03:02/03:03*	*04:05/13:02*	*04:01/06:09*

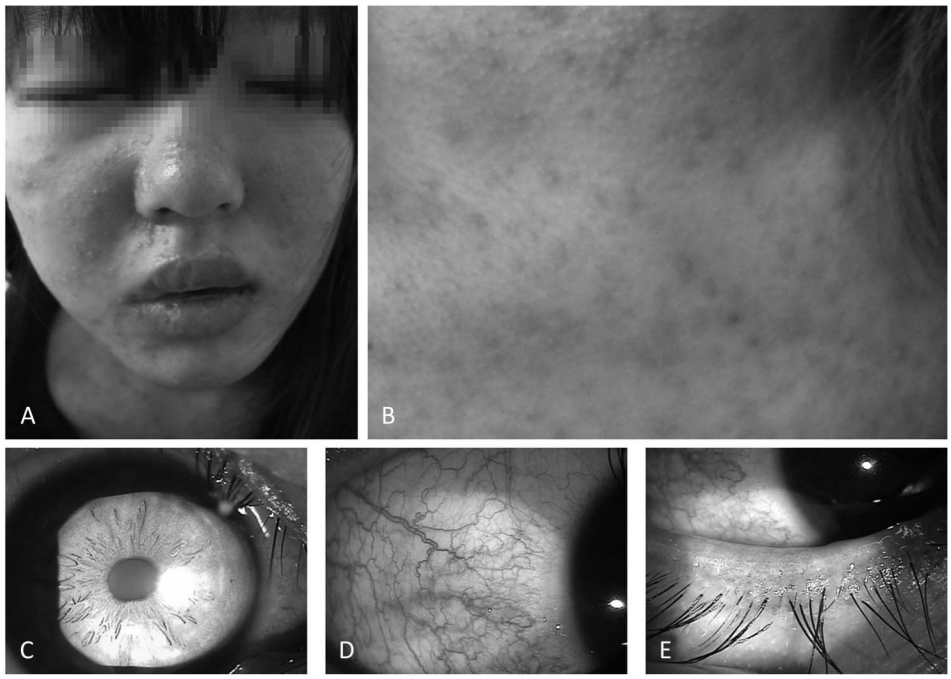

FIGURE 1. A and B, Clinical appearance of patient 2, 6 days after disease onset, showing a blistering maculopapular rash appears on the face and neck. C–E, Appearance of the right eye of patient 2, 10 days after disease onset, revealing mild conjunctival hyperemia with lid margin inflammation, accompanied by a clear corneal surface.

At the genetic level, the presence of *HLA-A*02:06* and the polymorphisms of several immune-related genes, including Toll-like receptor 3, interleukin-4 receptor, interleukin 13, and Fas ligands, have been associated with SJS/TEN with SOC.[22,31–33] Recently, it was proposed that various factors could affect the ocular outcome of the SJS/TEN caused by certain medications. As mentioned previously, *HLA-A*02:06* is a risk factor for CM-related SJS/TEN with SOC, but not for CM-related SJS/TEN without SOC, nor for CM-unrelated SJS/TEN with SOC.[13] We also reported that CM-related SJS/TEN with SOC is significantly associated with *HLA-A*02:06* not only in Japanese populations but also in Korean populations, and that *HLA-B*44:03* was significantly associated only with CM-related SJS/TEN with severe ocular complications in Indian and Brazilian populations.[12,13] Moreover, a recent analysis proved that certain types of causative medicines can affect the severity of the acute ocular involvement in the SJS/TEN patients.[34] These results suggest that different susceptibility alleles are involved in the development of allopurinol-induced SJS/TEN and CM-related SJS/TEN with SOC, which is consistent with our findings that allopurinol-induced SJS/TEN shows a phenotype different from that of CM-related SJS/TEN with SOC.

In our study, 4 patients were positive for *HLA-DRB1*13:02* and *HLA-DQB1*06:09* and 3 patients for *HLA-A*33:03*. In a recent study about the allelic and haplotypic frequencies of the HLA in the Korean population, *HLA-DRB1*13:02* was identified to be the second most common allele and *HLA-A*33:03* the third most common.[29,30] However, *HLA-DQB1*06:09* was found to be less common, with an allelic frequency of less than 5% in the Korean population.[29,30]

As for *HLA-A*33:03* and *HLA-DRB1*13:02*, the frequency of the former was found to be significantly higher in white allopurinol-induced SJS/TEN patients.[35] *HLA-DRB1*13:02* alone was not significantly associated with the development of the SJS/TEN in white patients; but, in conjunction with *HLA-B*58:01,* both the alleles, *HLA-A*33:03* and *HLA-DRB1*13:02*, behave as a strong risk factors for allopurinol-induced SJS/TEN in white patients.[35] However, the role of these genes in the development of SJS/TEN among the Korean population has not been identified yet. *HLA-DQB1*06:09* was found to be a significant risk factor for the development of aspirin-induced urticaria,[36] but its association with the development of SJS/TEN has not been identified in any population so far. Further studies with a larger number of patients are warranted to identify the relationship between the 3 genes and the development of the SJS/TEN in the Korean population.

This study has several limitations. The patients were identified from 3 different centers to present a small, noncomparative case series without statistical comparison because SJS and TEN are rare disease entities with an annual incidence of 0.4–6 cases per million.[37,38] A prospective, multicenter study with a controlled design and a longer follow-up period will be required in the future to address this limitation. In addition, our patients received systemic steroid treatment in the acute phase of SJS/TEN, and this might have played a role in decreasing the acute or chronic ocular complications to some extent. However, the systemic role of corticosteroids in SJS or TEN is still controversial. A previous small case series indicated that steroid pulse therapy in the acute phase prevented ocular complications,[39] whereas other studies indicated that systemic steroids neither beneficially affected the acute or chronic ocular damage nor improved the final visual outcome.[26,40,41]

Taking together the results of previous investigations and those of our study, we concluded that allopurinol-induced

SJS/TEN, with or without the *HLA-B*58:01* allele, might not cause severe complications of the ocular surface. Further study with larger sample sizes is warranted for the investigation of the ocular complications of allopurinol-induced SJS/TEN and the role of *HLA-B*58:01*.

REFERENCES

1. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology*. 2011;118:908–914.
2. Hsu M, Jayaram A, Verner R, et al. Indications and outcomes of amniotic membrane transplantation in the management of acute stevens-johnson syndrome and toxic epidermal necrolysis: a case-control study. *Cornea*. 2012;31:1394–1402.
3. Gueudry J, Roujeau JC, Binaghi M, et al. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol.* 2009;145:157–162.
4. Kaido M, Yamada M, Sotozono C, et al. The relation between visual performance and clinical ocular manifestations in Stevens-Johnson syndrome. *Am J Ophthalmol.* 2012;154:499–511.e1.
5. López-García JS, Rivas Jara L, García-Lozano CI, et al. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. *Ophthalmology*. 2011;118:265–271.
6. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol.* 2002;138:1019–1024.
7. Del Pozzo-Magana BR, Lazo-Langner A, Carleton B, et al. A systematic review of treatment of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Popul Ther Clin Pharmacol.* 2011;18:e121–e133.
8. Somkrua R, Eickman EE, Saokaew S, et al. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet.* 2011;12:118.
9. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428:486.
10. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med.* 2011;364:1134–1143.
11. Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet.* 2011;20:1034–1041.
12. Ueta M, Kannabiran C, Wakamatsu TH, et al. Trans-ethnic study confirmed independent associations of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe ocular surface complications. *Sci Rep.* 2014;4:5981.
13. Ueta M, Kaniwa N, Sotozono C, et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. *Sci Rep.* 2014;4:4862.
14. Ueta M. Ethnic differences in the association between human leukocyte antigen and Stevens-Johnson syndrome. *Eur Ophthalmic Rev.* 2009;3:15–18.
15. Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol.* 2008;58:25–32.
16. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A.* 2005;102:4134–4139.
17. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics*. 2008;9:1617–1622.
18. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics.* 2008;18:99–107.
19. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics.* 2009;19:704–709.
20. Jung JW, Song WJ, Kim YS, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant.* 2011;26:3567–3572.
21. Kang HR, Jee YK, Kim YS, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet Genomics.* 2011;21:303–307.
22. Ueta M, Sotozono C, Inatomi T, et al. Association of IL4R polymorphisms with Stevens-Johnson syndrome. *J Allergy Clin Immunol.* 2007;120:1457–1459.
23. Ueta M, Sotozono C, Nakano M, et al. Association between prostaglandin E receptor 3 polymorphisms and Stevens-Johnson syndrome identified by means of a genome-wide association study. *J Allergy Clin Immunol.* 2010;126:1218–1225.e10.
24. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–96.
25. Sotozono C, Ang LPK, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. *Ophthalmology*. 2007;114:1294–1302.
26. Kim DH, Yoon KC, Seo KY, et al. The role of systemic immunomodulatory treatment and prognostic factors on chronic ocular complications in stevens-johnson syndrome. *Ophthalmology*. 2015;122:254–264.
27. Lee HS, Ji YS, Yoon KC. Efficacy of hypotonic 0.18% sodium hyaluronate eye drops in patients with dry eye disease. *Cornea*. 2014;33:946–951.
28. Ueta M, Sawai H, Sotozono C, et al. IKZF1, a new susceptibility gene for cold medicine-related Stevens-Johnson syndrome/toxic epidermal necrolysis with severe mucosal involvement. *J Allergy Clin Immunol.* 2015;135:1538–1545.e17.
29. In JW, Roh EY, Oh S, et al. Allele and Haplotype frequencies of human leukocyte antigen-a, -B, -C, -DRB1, and -DQB1 from sequence-based DNA typing data in koreans. *Ann Lab Med.* 2015;35:429.
30. Lee KW, Oh DH, Lee C, et al. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens*. 2005;65:437–447.
31. Ueta M, Sotozono C, Inatomi T, et al. Association of combined IL-13/IL-4R signaling pathway gene polymorphism with Stevens-Johnson syndrome accompanied by ocular surface complications. *Invest Ophthalmol Vis Sci.* 2008;49:1809–1813.
32. Ueta M, Sotozono C, Inatomi T, et al. Association of Fas Ligand gene polymorphism with Stevens-Johnson syndrome. *Br J Ophthalmol.* 2008;92:989–991.
33. Ueta M, Tamiya G, Tokunaga K, et al. Epistatic interaction between Toll-like receptor 3 (TLR3) and prostaglandin E receptor 3 (PTGER3) genes. *J Allergy Clin Immunol.* 2012;129:1413–1416.e11.
34. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol.* 2015;160:228–237.e2.
35. Cristallo AF, Schroeder J, Citterio A, et al. A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Int J Immunogenet.* 2011;38:303–309.
36. Shimada-Sugimoto M, Otowa T, Miyagawa T, et al. Immune-related pathways including HLA-DRB1(*)13:02 are associated with panic disorder. *Brain Behav Immun.* 2015;46:96–103.
37. Yetiv JZ, Bianchine JR, Owen JA. Etiologic factors of the Stevens-Johnson syndrome. *South Med J.* 1980;73:599–602.
38. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* 1990;126:43–47.
39. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol.* 2009;147:1004–1011.
40. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye (Lond).* 2005;19:846–853.
41. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology*. 1995;102:1669–1676.

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,**

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Dr. Jacobs is an employee at the Boston Foundation for Sight, a nonprofit organization. Dr. Tseng has obtained a patent for the method of preparation and clinical uses of amniotic membrane and has licensed the right to Bio-Tissue, which procures, processes, and distributes preserved amniotic membrane for clinical and research uses. Dr. Chodosh is an employee of the Mass. Eye and Ear Infirmary, a non-profit hospital, which manufactures and distributes the Boston keratoprosthesis.

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OUTLINE

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**

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. 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.[1-5] Ocular involvement has been variably reported as worse in TEN,[3] comparable between SJS and TEN,[4] or worse in SJS than in TEN.[5] Diffuse cutaneous and oral mucosal damage was also reported as carrying a higher risk of damage to the eyes.[6,7] 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.[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.[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.[12,13] Meibomitis is common.[14-16]

Historically, acute ocular manifestations of SJS/TEN led to chronic ocular sequelae with visual significance in at least one-third of patients.[17] Chronic ocular complications of SJS/TEN are multifactorial in origin. Fusion between the bulbar and forniceal surfaces due to conjunctival ulcerations or conjunctival membrane formation acutely, or persistent inflammation later, causes permanent symblepharon and ankyloblepharon (Figure 3),[6] disrupting an already compromised tear film meniscus and inhibiting proper eyelid closure and blink, and sometimes restricting ocular motility.[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

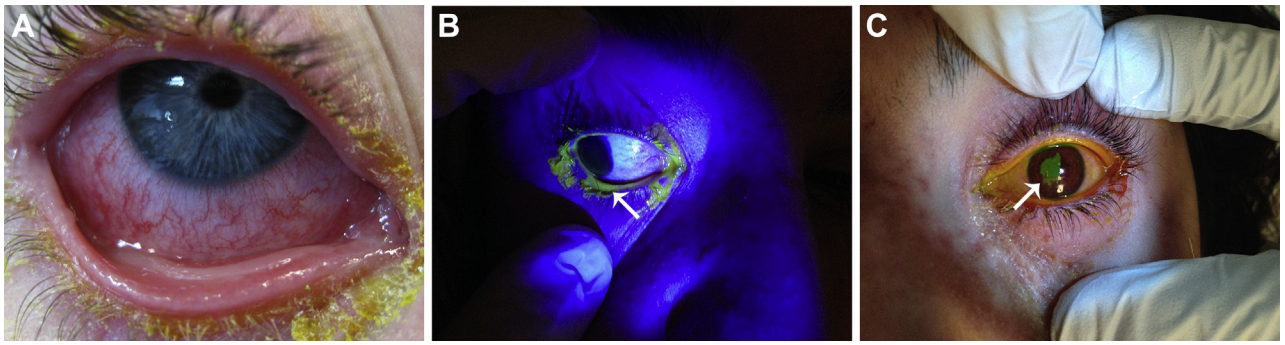

Figure 1. Ocular surface involvement in acute SJS/TEN. A. Conjunctival hyperemia and membrane. B. Eyelid margin sloughing (arrow) as evident with fluorescein staining under cobalt blue light. C. Corneal epithelial defect (arrow) stained with fluorescein.

vision and are correlated with development of late corneal blindness,[19] due at least in part to chronic limbal stem cell dysfunction (**LSCD**). If not removed, misdirected and/or distichiatic 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.[19-22]

Scarring in the fornices and in the lacrimal gland ducts cause severe aqueous tear deficiency and xerosis.[23] 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.[3,4,24] 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.[3] 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.[25] 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.[1,15,16,19,26,27] 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.[28] 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.[1]

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.[1] Di Pascuale and colleagues reported much higher rates in the SJS/TEN patients they studied. Seventy-one percent of

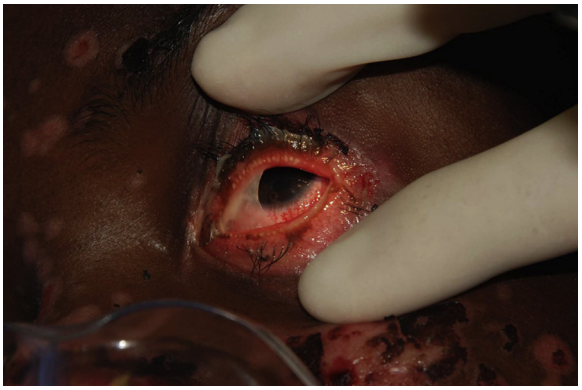

Figure 2. A pseudomembrane in acute SJS/TEN seen here spanning the upper and lower eyelids. Note also the meibomian gland inspissations on both eyelid margins.

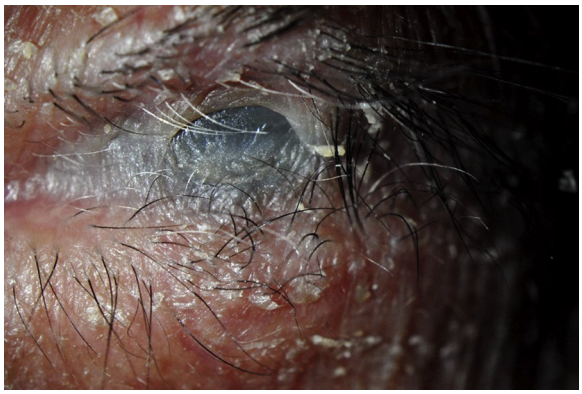

Figure 3. Ankyloblepharon in a patient years after acute SJS/TEN.

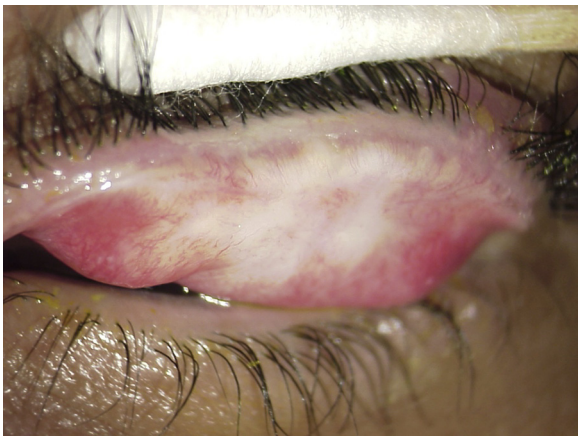

Figure 4. Tarsal conjunctival scarring and vertical shortening of the upper eyelid post- SJS/TEN. Eyelid everted for purpose of photograph.

patients had symblepharon and trichiasis, 52.2% had aqueous deficiency, and nearly all suffered from meibomian gland dysfunction and abnormal lipid tear layer.[19] In contrast, Chang and coworkers reported that only 6.7% of patients in their series had symblepharon and 3.3% had trichiasis.[5] Dry eye symptoms may be the most common patient complaint, affecting an estimated 46-59% of SJS/TEN survivors.[3,4,24] 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.[19] Sotozono and colleagues developed a severity grading for chronic ocular complications of SJS/TEN, including those affecting the cornea, conjunctiva, and eyelids.[16] 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.[16] 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.[1]

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.[6,20-23,29-70] Therefore, we propose a "windows of opportunity" algorithm for ophthalmic interventions (Table 1, Figure 8). 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,[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

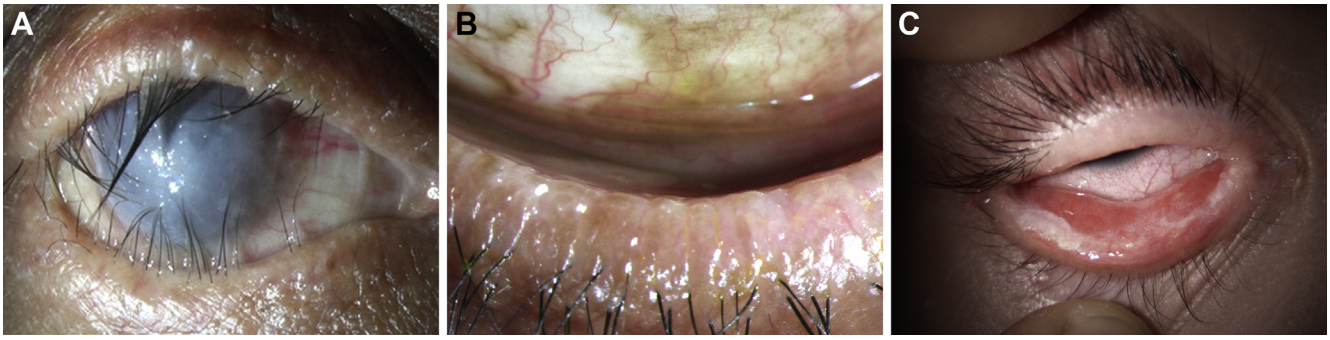

Figure 5. Structural eyelid changes after SJS/TEN. A. Trichiasis from cicatricial entropion. B. Meibomian gland atrophy. C. Eyelid margin keratinization.

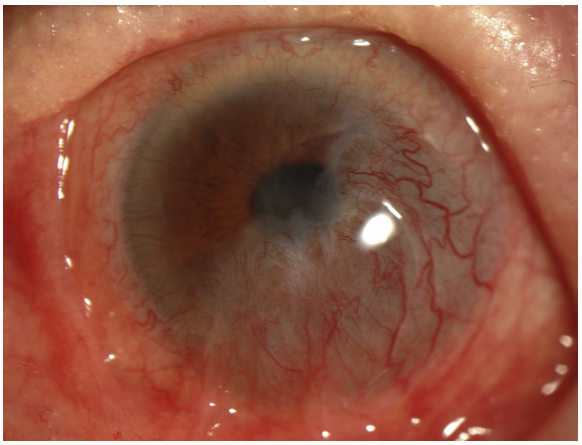

Figure 6. Loss of limbal palisades in patient post SJS/TEN. Note the 360 degrees of limbal vascularization, even where the fibrovascular pannus is absent.

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.[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[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 forniceal and tarsal conjunctival epithelial defects and early symblephara, which could be otherwise missed.[19] 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.[32,72] 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.

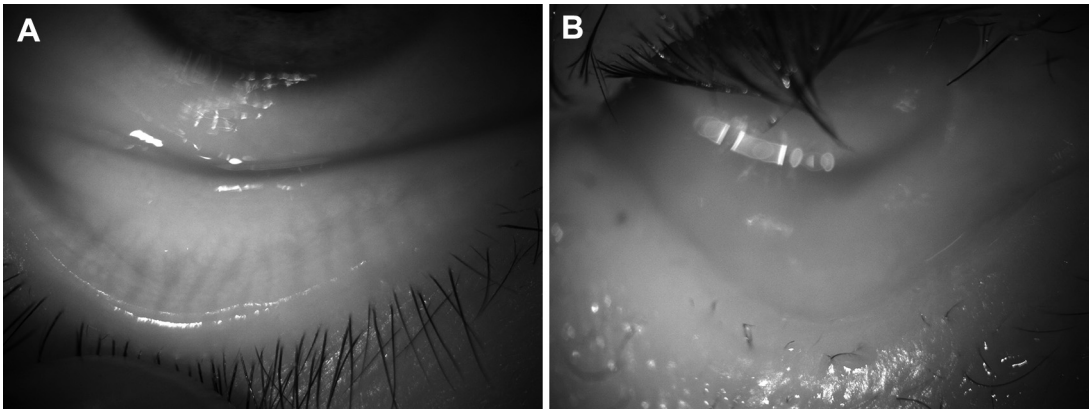

Figure 7. Meibography of (A) normal eyelid and (B) post SJS/TEN eyelid with meibomian gland dropout.

Table 1. Windows of opportunity for ophthalmic intervention in the SJS/TEN patient

SJS/TEN: Phase of disease	Exam finding
Acute	Ocular surface/eyelid margin epithelial defect Pseudomembrane formation
Chronic	Posterior eyelid margin keratinization Trichiasis/distichiasis Tear deficiency Persistent epithelial defect

(Each finding should trigger an intervention to mitigate likely further vision loss.)

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.[2,14,48,73,74] 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.[48] 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.[14] 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).[73] 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.[74]

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.[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 Table 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.[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

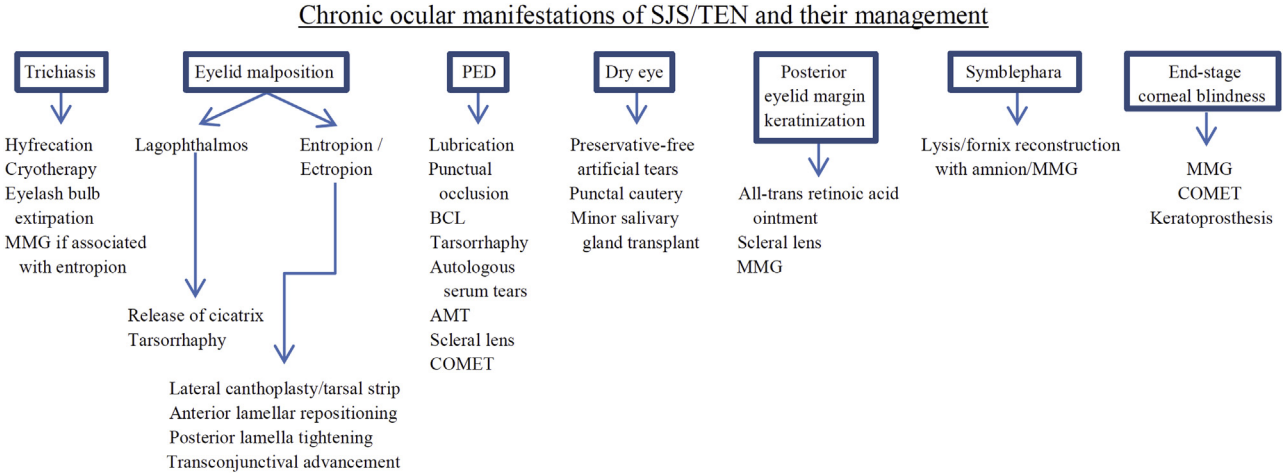

Figure 8. Management of chronic ocular manifestations of SJS/TEN. MMG: mucous membrane graft. PED: persistent (corneal) epithelial defect; BCL: bandage contact lens; AMT: amniotic membrane transplantation; COMET: cultivated oral mucosal epithelial transplantation.

Table 2. Suggested initial management of acute ocular SJS/TEN based on simple clinical grading system*

Grade	Grade defined	Management
0	No ocular involvement	AT 4x/day
1	Conjunctival hyperemia	Moxi 3x/day Pred 6x/day FML 6x/day AT every hour as feasible
2	Ocular surface/eyelid margin epithelial defect or pseudomembrane formation	Use above therapies, plus consider AMT
3	Ocular surface/eyelid margin epithelial defect and pseudomembrane formation	Use above therapies, plus consider AMT

* Adapted from reference 71.

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.

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.[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,[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.[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.[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 pseudomembranes or membranes. Supportive treatment included preservative-free artificial tears and ointments, daily examinations, and forniceal 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.[109]) Processed amnion has very low immunogenicity.[76,121] The anti-inflammatory mechanism of action of amnion may be due in part to promotion of leukocyte apoptosis and down-regulation of inflammatory cytokines released by activated lymphocytes and macrophages.[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.[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

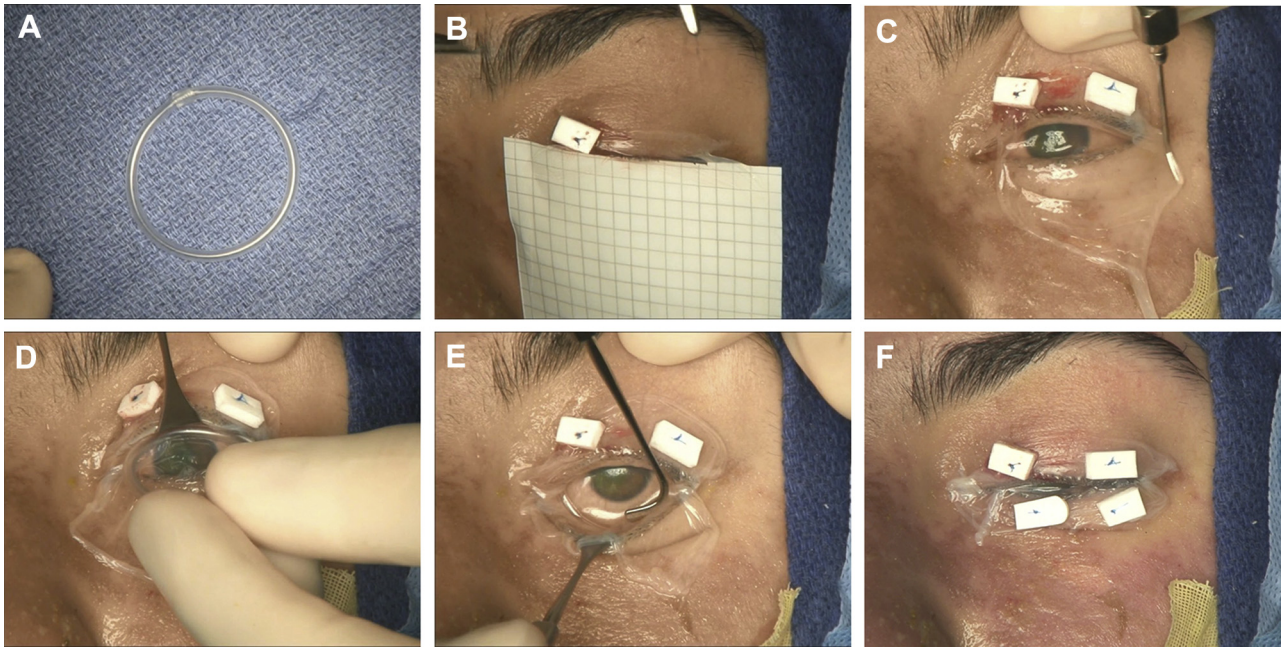

Figure 9. Amniotic membrane transplantation in SJS/TEN. A. A symblepharon ring is constructed from intravenous (IV) extension tubing, with one end of the tube cut so as to fit over the other end of the tube and adjusted to reach all fornices without preventing eyelid closure once in place. B. All eyelashes 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.

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.[30,31] 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),[46,118,128] 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.[111] 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.[46,118] 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.[41] 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®.[46] 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.[118] 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,[129-131] hemorrhage beneath the amnion, and detachment of the membrane.[6] 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.[130] 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.[130] 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,[129,131] as in the Good Tissue Banking Practices set forth by the U.S. Food and Drug Administration.[130]

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.[17,21] 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.[51] 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.[51,132,133] 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.[51] In 27 patients with chronic ocular sequelae from SJS/TEN in four published case series, systemic immunosuppressive therapy was used successfully, albeit without controls.[51,132,134,135] 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.[132,133,136] 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.[56,137]

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.[138] Of all of the agents mentioned above, oral mycophenolate is perhaps the best tolerated.[136]

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 tarsoconjunctival 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,[139] 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.[3,4,24] The aqueous tear film is reduced in SJS/TEN by scarring of the lacrimal ducts and possibly by primary inflammation of the lacrimal gland.[140,141] Goblet cell density in the conjunctiva is reduced after SJS/TEN and does not fully recover.[1] 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.[15,16,19,23] Topical cyclosporine appears to improve goblet cell density in patients with dry eye[142-146] and graft-versus-host-disease.[147] 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.[148] 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.[55] 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.[21] 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,[21,149,150] although the duration of effect, and potential deleterious consequences of saliva on ocular surface epithelium[151] remain to be determined. Anecdotal reports also suggest improvement in clinical signs and symptoms with the application of topical, autologous, serum-derived eye drops.[65,152,153]

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.[154] 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.[65,152,155-159] Autologous cultivated oral mucosal epithelial transplantation (**COMET**) has been used to promote re-epithelialization in recalcitrant cases.[160]

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.[19] 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.[31] Eyelid margin ulceration in the acute phase of SJS/TEN destroys the mucocutaneous junction with resultant overgrowth of the keratinized epithelium onto the tarsal conjunctiva.[19,20] 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.[19,20,161] 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,[68,69,162,163] 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.[21,35-37,44,47,61,164-166] 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.[35-37,47] 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).[21,35,37] 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.[35]

In eyes with symblepharon, fornix reconstruction may be required prior to lens fitting.[19] 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),[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

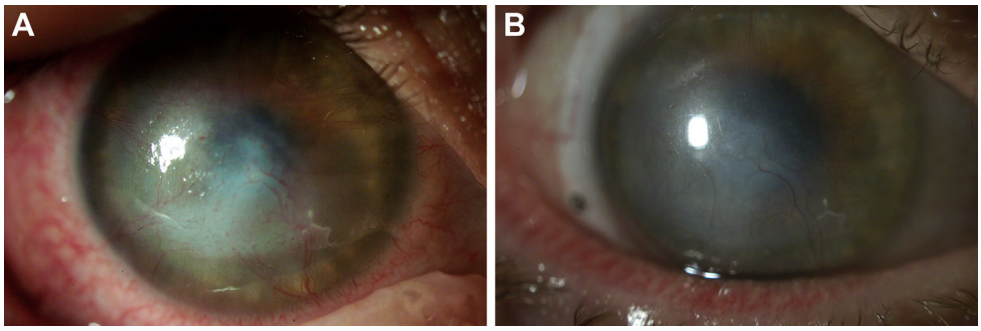

Figure 10. Chronic SJS/TEN with corneal opacity (A) at initiation and (B) after 5 months of daily PROSE treatment, showing improved corneal clarity.

(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.[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,[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

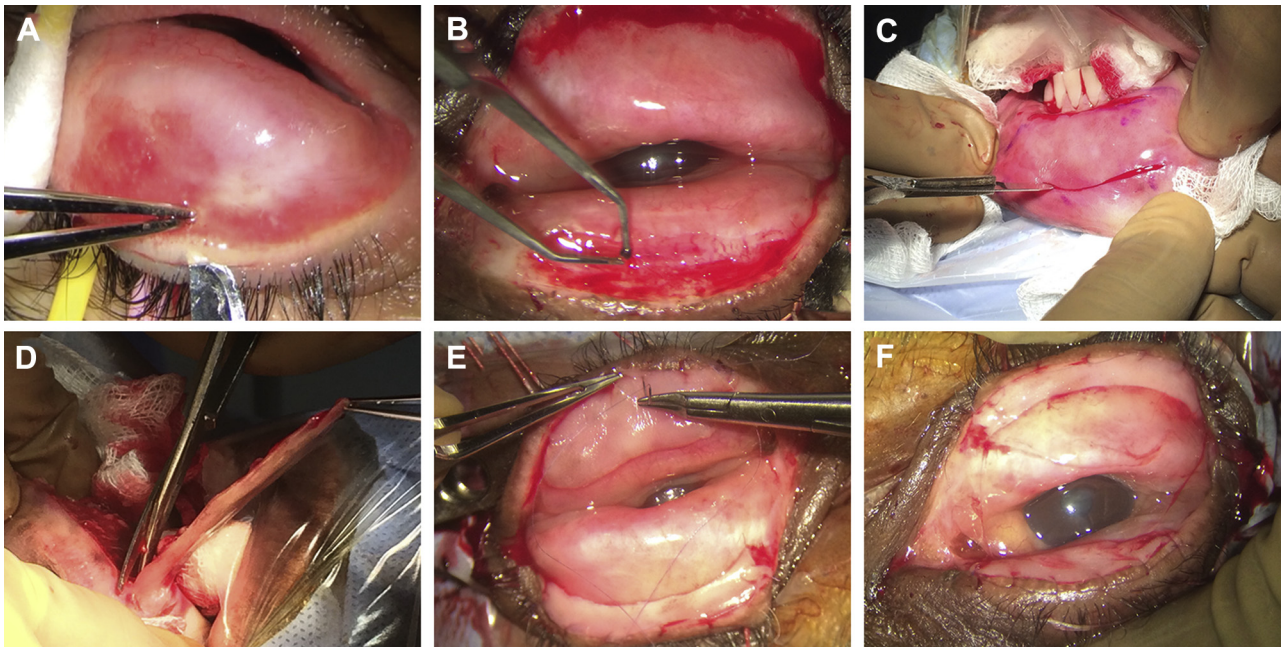

Figure 11. Labial mucous membrane graft to the eyelids for eyelid margin and tarsal keratinization. A. First, the keratinized portion of the tarsal conjunctiva is sharply excised. B. Bipolar cautery is applied at the base beneath the excised mucosa. C. The labial mucosa is incised at predetermined and 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.

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.[150] 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.[149]

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.[137] 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.[169]

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.[159] 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.[66] Therefore, SJS/TEN patients are not candidates for limbal autografts.[170] Keratolimbal allografts, although initially reported to have promise,[63,65,66,171-175] 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.[56,173,176] The use of living-related limbal allografts was not successful in one study with two SJS/TEN patients with severe ocular surface disease,[177] and in another study showed a marginally improved ocular surface in two of ten eyes in patients with SJS/TEN.[56] However, one study suggested that keratolimbal allografts in SJS/TEN do not undergo rejection at a higher rate than for other conditions,[178] and occasional single case reports of success with keratolimbal allograft in SJS/TEN have been published.[174,175] 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.[179] 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,[180-182] but not others.[183,184]

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[21,55]; MMG to treat posterior eyelid margin keratinatinization[20,149,167,168]; amnion with or without MMG[18,21,22,40,62,65,94,106,185] or COMET[42,152,176-183] 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.[21] COMET was used in 6 of these eyes to reduce postoperative 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.[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.[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.[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.[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).[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,[42,186,209] while others have advocated against it.[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.[209,227] A retrospective case series by Sayegh and coworkers[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.[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

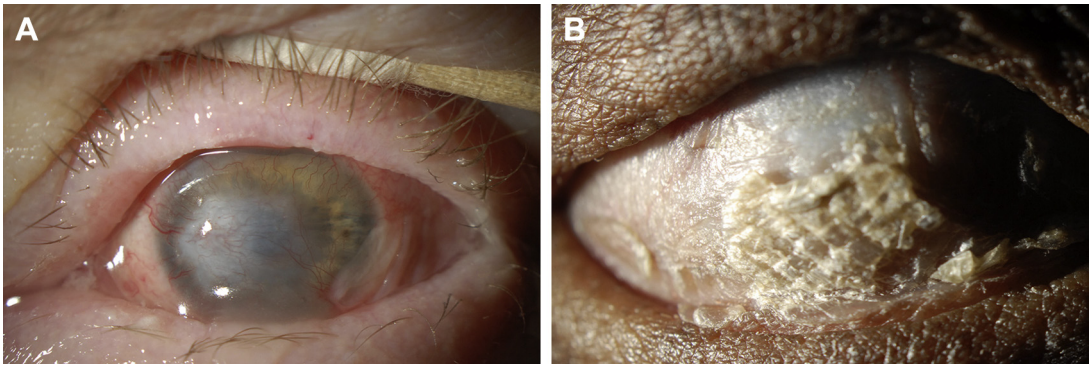

Figure 12. Severe corneal sequelae of SJS/TEN. A. Dense corneal neovascularization and opacity in a wet, blinking eye. B. Complete ocular surface keratinization in an eye devoid of aqueous tears.

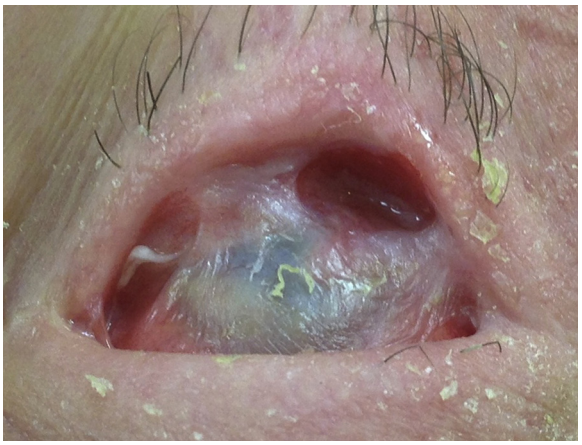

Figure 13. Xerotic, keratinized eye with symblephara. Only a Boston type II or osteo-odonto keratoprosthesis should be considered for visual rehabilitation.

of over 4 years postoperative.[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.[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.[50,191,194,198,205,206] Because only a few centers worldwide 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.

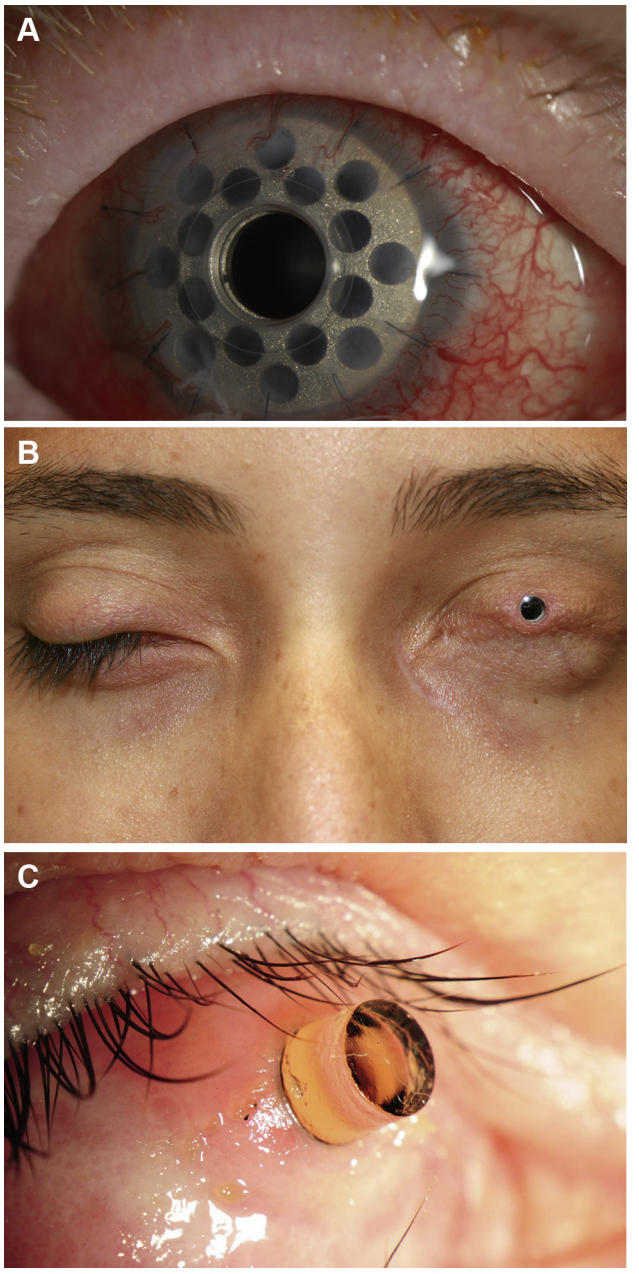

Figure 14. Keratoprosthesis implantation in patients post SJS/TEN. (A) Boston keratoprosthesis type I. (B) Boston keratoprosthesis type II. (C) Osteo-odonto-keratoprosthesis. This image is taken from an oblique view.

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.

REFERENCES

1. Lopez-Garcia JS, Rivas Jara L, Garcia-Lozano CI, et al. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. *Ophthalmology* 2011;118:265-71
2. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology* 1995;102:1669-76
3. Gueudry J, Roujeau JC, Binaghi M, et al. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2009;145:157-62
4. Yip LW, Thong BY, Lim J, et al. Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. *Allergy* 2007;62:527-31
5. Chang YS, Huang FC, Tseng SH, et al. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. *Cornea* 2007;26:123-9
6. Fu Y, Gregory DG, Sippel KC, et al. The ophthalmologist's role in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ocul Surf* 2010;8:193-203
7. Sotozono C, Ueta M, Koizumi N, et al. Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. *Ophthalmology* 2009;116:685-90
8. Morales ME, Purdue GF, Verity SM, et al. Ophthalmic manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis and relation to SCORTEN. *Am J Ophthalmol* 2010;150:505-510.e1
9. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol* 1987;123:1160-5
10. Correia O, Chosidow O, Saiag P, et al. Evolving pattern of drug-induced toxic epidermal necrolysis. *Dermatology* 1993;186:32-7
11. Oplatek A, Brown K, Sen S, et al. Long-term follow-up of patients treated for toxic epidermal necrolysis. *J Burn Care Res* 2006;27:26-33
12. Isawi H, Dhaliwal DK. Corneal melting and perforation in Stevens Johnson syndrome following topical bromfenac use. *J Cataract Refract Surg* 2007;33:1644-6
13. Sachdev R, Bansal S, Sinha R, et al. Bilateral microbial keratitis in highly active antiretroviral therapy-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a case series. *Ocul Immunol Inflamm* 2011;19:343-5
14. Kim KH, Park SW, Kim MK, Wee WR. Effect of age and early intervention with a systemic steroid, intravenous immunoglobulin or amniotic membrane transplantation on the ocular outcomes of patients with Stevens-Johnson syndrome. *Korean J Ophthalmol* 2013;27:331-40
15. Alsuhaibani AH, Carter KD, Abramoff MD, Nerad JA. Utility of meibography in the evaluation of meibomian glands morphology in normal and diseased eyelids. *Saudi J Ophthalmol* 2011;25:61-6
16. Sotozono C, Ang LP, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. *Ophthalmology* 2007;114:1294-302
17. Arstikaitis MJ. Ocular aftermath of Stevens-Johnson syndrome. *Arch Ophthalmol* 1973;90:376-9
18. Tseng SC, Di Pascuale MA, Liu DT, et al. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. *Ophthalmology* 2005;112:896-903
19. Di Pascuale MA, Espana EM, Liu DT, et al. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. *Ophthalmology* 2005;112:904-12
20. Iyer G, Pillai VS, Srinivasan B, et al. Mucous membrane grafting for lid margin keratinization in Stevens-Johnson syndrome: results. *Cornea* 2010;29:146-51
21. Iyer G, Srinivasan B, Agarwal S, et al. Comprehensive approach to ocular consequences of Stevens Johnson Syndrome - the aftermath of a systemic condition. *Graefes Arch Klin Exper Ophthalmol* 2014;252:457-67
22. Fu Y, Liu J, Tseng SC. Oral mucosal graft to correct lid margin pathologic features in cicatricial ocular surface diseases. *Am J Ophthalmol* 2011;152:600-608.e1
23. Wall V, Yen MT, Yang MC, et al. Management of the late ocular sequelae of Stevens-Johnson syndrome. *Ocul Surf* 2003;1:192-201
24. Magina S, Lisboa C, Leal V, et al. Dermatological and ophthalmological sequels in toxic epidermal necrolysis. *Dermatology* 2003;207:33-6
25. Kaido M, Yamada M, Sotozono C, et al. The relation between visual performance and clinical ocular manifestations in Stevens-Johnson syndrome. *Am J Ophthalmol* 2012;154:499-511.e1
26. Nelson JD, Wright JC. Conjunctival goblet cell densities in ocular surface disease. *Arch Ophthalmol* 1984;102:1049-51
27. Ralph RA. Conjunctival goblet cell density in normal subjects and in dry eye syndromes. *Invest Ophthalmol* 1975;14:299-302
28. Vera LS, Gueudry J, Delcampe A, et al. In vivo confocal microscopic evaluation of corneal changes in chronic Stevens-Johnson syndrome and toxic epidermal necrolysis. *Cornea* 2009;28:401-7
29. Shay E, Kheirkhah A, Liang L, et al. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Surv Ophthalmol* 2009;54:686-96
30. Gregory DG. The ophthalmologic management of acute Stevens-Johnson syndrome. *Ocul Surf* 2008;6:87-95
31. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology* 2011;118:908-14
32. Lin A, Patel N, Yoo D, et al. Management of ocular conditions in the burn unit: thermal and chemical burns and Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Burn Care Res* 2011;32:547-60
33. Hsu M, Jayaram A, Verner R, et al. Indications and outcomes of amniotic membrane transplantation in the management of acute stevens-johnson syndrome and toxic epidermal necrolysis: a case-control study. *Cornea* 2012;31:1394-402
34. Ciralsky JB, Sippel KC, Gregory DG. Current ophthalmologic treatment strategies for acute and chronic Stevens-Johnson syndrome and toxic epidermal necrolysis. *Curr Opin Ophthalmol* 2013;24:321-8
35. Papakostas TD, Le HG, Chodosh J, Jacobs DS. Prosthetic replacement of the ocular surface ecosystem as treatment for ocular surface disease in patients with a history of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Ophthalmology* 2015;122:248-53
36. Sotozono C, Yamauchi N, Maeda S, Kinoshita S. Tear exchangeable limbal rigid contact lens for ocular sequelae resulting from Stevens-Johnson syndrome or toxic epidermal necrolysis. *Am J Ophthalmol* 2014;158:983-993.e1
37. Heur M, Bach D, Theophanous C, Chiu GB. Prosthetic replacement of the ocular surface ecosystem scleral lens therapy for patients with ocular symptoms of chronic Stevens-Johnson syndrome. *Am J Ophthalmol* 2014;158:49-54

38. Ciralsky JB, Sippel KC. Prompt versus delayed amniotic membrane application in a patient with acute Stevens-Johnson syndrome. *Clin Ophthalmol* 2013;7:1031-4
39. Sotozono C, Inatomi T, Nakamura T, et al. Visual improvement after cultivated oral mucosal epithelial transplantation. *Ophthalmology* 2013;120:193-200
40. Kheirkhah A, Ghaffari R, Kaghazkanani R, et al. A combined approach of amniotic membrane and oral mucosa transplantation for fornix reconstruction in severe symblepharon. *Cornea* 2013;32:155-60
41. Tomlins PJ, Parulekar MV, Rauz S. "Triple-TEN" in the treatment of acute ocular complications from toxic epidermal necrolysis. *Cornea* 2013;32:365-9
42. Pujari S, Siddique SS, Dohlman CH, Chodosh J. The Boston keratoprosthesis type II: the Massachusetts Eye and Ear Infirmary experience. *Cornea* 2011;30:1298-303
43. Sejpal K, Yu F, Aldave AJ. The Boston keratoprosthesis in the management of corneal limbal stem cell deficiency. *Cornea* 2011;30:1187-94
44. Rathi VM, Mandathara PS, Dumpati S, et al. Boston ocular surface prosthesis: an Indian experience. *Indian J Ophthalmol* 2011;59:279-81
45. Iyer G, Pillai VS, Srinivasan B, et al. Modified osteo-odonto keratoprosthesis—the Indian experience—results of the first 50 cases. *Cornea* 2010;29:771-6
46. Shammas MC, Lai EC, Sarkar JS, et al. Management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. *Am J Ophthalmol* 2010;149:203-213.e2
47. Tougeron-Brousseau B, Delcampe A, Gueudry J, et al. Vision-related function after scleral lens fitting in ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol* 2009;148:852-859.e2
48. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol* 2009;147:1004-11. 11 e1
49. Fukuda M, Hamada S, Liu C, Shimomura Y. Osteo-odonto-keratoprosthesis in Japan. *Cornea* 2008;27(Suppl 1):S56-61
50. Tan DT, Tay AB, Theng JT, et al. Keratoprosthesis surgery for end-stage corneal blindness in Asian eyes. *Ophthalmology* 2008;115:503-510.e3
51. De Rojas MV, Dart JK, Saw VP. The natural history of Stevens-Johnson syndrome: patterns of chronic ocular disease and the role of systemic immunosuppressive therapy. *Br J Ophthalmol* 2007;91:1048-53
52. Kobayashi A, Yoshita T, Sugiyama K, et al. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. *Ophthalmology* 2006;113:126-32
53. Falcinelli G, Falsini B, Taloni M, Colliardo P. Modified osteo-odonto-keratoprosthesis for treatment of corneal blindness: long-term anatomical and functional outcomes in 181 cases. *Arch Ophthalmol* 2005;123:1319-29
54. Nishida K, Yamato M, Hayashida Y, et al. Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *N Engl J Med* 2004;351:1187-96
55. Kaido M, Goto E, Dogru M, Tsubota K. Punctal occlusion in the management of chronic Stevens-Johnson syndrome. *Ophthalmology* 2004;111:895-900
56. Gomes JA, Santos MS, Ventura AS, et al. Amniotic membrane with living related corneal limbal/conjunctival allograft for ocular surface reconstruction in Stevens-Johnson syndrome. *Arch Ophthalmol* 2003;121:1369-74
57. Geerling G, Liu CS, Dart JK, et al. Sight and comfort: complex procedures in end-stage Stevens-Johnson syndrome. *Eye* 2003;17:89-91
58. Shimazaki J, Aiba M, Goto E, et al. Transplantation of human limbal epithelium cultivated on amniotic membrane for the treatment of severe ocular surface disorders. *Ophthalmology* 2002;109:1285-90
59. John T, Foulks GN, John ME, et al. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. *Ophthalmology* 2002;109:351-60
60. Koizumi N, Inatomi T, Suzuki T, et al. Cultivated corneal epithelial transplantation for ocular surface reconstruction in acute phase of Stevens-Johnson syndrome. *Arch Ophthalmol* 2001;119:298-300
61. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol* 2000;130:25-32
62. Honavar SG, Bansal AK, Sangwan VS, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome. *Ophthalmology* 2000;107:975-9
63. Tsubota K, Satake Y, Kaido M, et al. Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation. *N Engl J Med* 1999;340:1697-703
64. Tseng SC, Prabhasawat P, Barton K, et al. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. *Arch Ophthalmol* 1998;116:431-41
65. Tsubota K, Satake Y, Ohyama M, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *Am J Ophthalmol* 1996;122:38-52
66. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. *Trans Am Ophthalmol Soc* 1996;94:677-743
67. Mannor GE, Mathers WD, Wolfley DE, Martinez JA. Hard-palate mucosa graft in Stevens-Johnson syndrome. *Am J Ophthalmol* 1994;118:786-91
68. Soong HK, Martin NF, Wagoner MD, et al. Topical retinoid therapy for squamous metaplasia of various ocular surface disorders. A multicenter, placebo-controlled double-masked study. *Ophthalmology* 1988;95:1442-6
69. Tseng SC, Maumenee AE, Stark WJ, et al. Topical retinoid treatment for various dry-eye disorders. *Ophthalmology* 1985;92:717-27
70. McCord Jr CD, Chen WP. Tarsal polishing and mucous membrane grafting for cicatricial entropion, trichiasis and epidermalization. *Ophthalmic Surg* 1983;14:1021-5
71. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol* 2015;160:228-37
72. Kalwerisky K, Davies B, Mihora L, et al. Use of the Boston Ocular Surface Prosthesis in the management of severe periorbital thermal injuries: a case series of 10 patients. *Ophthalmology* 2012;119:516-21
73. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye* 2005;19:846-53
74. Kim DH, Yoon KC, Seo KY, et al. The role of systemic immunomodulatory treatment and prognostic factors on chronic ocular complications in Stevens-Johnson syndrome. *Ophthalmology* 2015;122:254-64
75. Kompella VB, Sangwan VS, Bansal AK, et al. Ophthalmic complications and management of Stevens-Johnson syndrome at a tertiary eye care centre in south India. *Indian J Ophthalmol* 2002;50:283-6
76. Toda A, Okabe M, Yoshida T, Nikaido T. The potential of amniotic membrane/amnion-derived cells for regeneration of various tissues. *J Pharmacol Sci* 2007;105:215-28
77. Danforth D, Hull RW. The microscopic anatomy of the fetal membranes with particular reference to the detailed structure of the amnion. *Am J Obstetr Gynecol* 1958;75:536-47. discussion 48—50
78. Bourne GL. The microscopic anatomy of the human amnion and chorion. *Am J Obstetr Gynecol* 1960;79:1070-3

79. Prasad JK, Feller I, Thomson PD. Use of amnion for the treatment of Stevens-Johnson syndrome. *J Trauma* 1986;26:945-6
80. Kim JC, Tseng SC. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. *Cornea* 1995;14:473-84
81. Kim JC, Tseng SC. The effects on inhibition of corneal neovascularization after human amniotic membrane transplantation in severely damaged rabbit corneas. *Korean J Ophthalmol* 1995;9:32-46
82. Nakamura M, Naka M, Tatsumi Y, et al. Filtering bleb structure associated with long-term intraocular pressure control after amniotic membrane-assisted trabeculectomy. *Curr Eye Res* 2012;37:239-50
83. Tejwani S, Kolari RS, Sangwan VS, Rao GN. Role of amniotic membrane graft for ocular chemical and thermal injuries. *Cornea* 2007;26:21-6
84. Sangwan VS, Burman S, Tejwani S, et al. Amniotic membrane transplantation: a review of current indications in the management of ophthalmic disorders. *Indian J Ophthalmol* 2007;55:251-60
85. Tseng SC, Espana EM, Kawakita T, et al. How does amniotic membrane work? *Ocul Surf* 2004;2:177-87
86. Sippel KC, Ma JJ, Foster CS. Amniotic membrane surgery. *Curr Opin Ophthalmol* 2001;12:269-81
87. Grueterich M, Espana EM, Tseng SC. Ex vivo expansion of limbal epithelial stem cells: amniotic membrane serving as a stem cell niche. *Surv Ophthalmol* 2003;48:631-46
88. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. *Ocul Surf* 2004;2:201-11
89. Rahman I, Said DG, Maharajan VS, Dua HS. Amniotic membrane in ophthalmology: indications and limitations. *Eye* 2009;23:1954-61
90. Dua HS, Gomes JA, King AJ, Maharajan VS. The amniotic membrane in ophthalmology. *Surv Ophthalmol* 2004;49:51-77
91. Moore JE, Dua HS, Page AB, et al. Ocular surface reconstruction in LOGIC syndrome by amniotic membrane transplantation. *Cornea* 2001;20:753-6
92. Park EH, Korn TS, Vasani SN, Kikkawa DO. Autologous allogeneic amniotic membrane grafting in Stevens-Johnson syndrome. *Ophthal Plast Reconstr Surg* 2003;19:250-1
93. Atzori L, Peiretti E, Ferreli C, et al. Amniotic membrane transplantation in the surgical management of symblepharon following toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2006;20:214-6
94. Liu J, Sheha H, Fu Y, et al. Oral mucosal graft with amniotic membrane transplantation for total limbal stem cell deficiency. *Am J Ophthalmol* 2011;152:739-747.e1
95. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. *Ophthalmology* 2002;109:694-703
96. Tseng SC. Amniotic membrane transplantation for ocular surface reconstruction. *BiosciRep* 2001;21:481-9
97. Tseng SC. Amniotic membrane transplantation for persistent corneal epithelial defect. *Br J Ophthalmol* 2001;85:1400-1
98. Zhou S, Yuan J, Chen L, Chen J. Fresh versus preserved amniotic membrane transplantation for conjunctival surface reconstruction. *Yan Ke Xue Bao* 2008;24:39-43. Chinese
99. Santos MS, Gomes JA, Hofling-Lima AL, et al. Survival analysis of conjunctival limbal grafts and amniotic membrane transplantation in eyes with total limbal stem cell deficiency. *Am J Ophthalmol* 2005;140:223-30
100. Lopez-Garcia JS, Rivas L, Garcia-Lozano I. Severe limbal deficiency treated by combined limbal allograft and amniotic membrane transplantation. *Arch Soc Esp Oftalmol* 2005;80:405-12
101. Nava-Castaneda A, Tovila-Canales JL, Monroy-Serrano MH, et al. Comparative study of amniotic membrane transplantation, with and without simultaneous application of mitomycin C in conjunctival fornix reconstruction. *Arch Soc Esp Oftalmol* 2005;80:345-52. Spanish
102. Hick S, Demers PE, Brunette I, et al. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. *Cornea* 2005;24:369-77
103. Datta H, Sarkar K, Chatterjee PR. Amniotic membrane transplantation in ocular surface disorders. *J Indian Med Assoc* 2004;102:726-9
104. Zhou SY, Chen JQ, Chen LS, et al. Long-term results of amniotic membrane transplantation for conjunctival surface reconstruction. *Zhonghua Yan Ke Za Zhi* 2004;40:745-9. Chinese
105. Zhou SY, Chen JQ, Liu ZG, et al. A clinical study of amniotic membrane transplantation for severe eye burns at the acute stage. *Zhonghua Yan Ke Za Zhi* 2004;40:97-100. Chinese
106. Zhou S, Chen J, Xu L, et al. Fresh amniotic membrane transplantation for conjunctival surface reconstruction. *Yan Ke Xue Bao* 1999;15:169-73
107. Forbes J, Fetterolf DE. Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series. *J Wound Care* 2012;290:294-6
108. Kesting MR, Wolff KD, Nobis CP, Rohleder NH. Amniotic membrane in oral and maxillofacial surgery. *Oral Maxillofac Surg* 2014;18:153-64
109. Mamede AC, Carvalho MJ, Abrantes AM, et al. Amniotic membrane: from structure and functions to clinical applications. *Cell Tissue Res* 2012;349:447-58
110. Alsina-Gibert M, Pedregosa-Fauste S. Amniotic membrane transplantation in the treatment of chronic lower limb ulcers. *Actas Dermosifiliogr* 2012;103:608-13
111. Pruet CM, Queen JH, Kim G. Amnion doughnut: a novel method for sutureless fixation of amniotic membrane to the bulbar and palpebral conjunctiva in acute ocular-involving Stevens-Johnson syndrome. *Cornea* 2014;33:1240-4
112. Barua A, McKee HD, Barbara R, et al. Toxic epidermal necrolysis in a 15-month-old girl successfully treated with amniotic membrane transplantation. *J AAPOS* 2012;16:478-80
113. Foulks GN. Amniotic membrane therapy in the acute phase of toxic epidermal necrolysis. *J AAPOS* 2007;11:531
114. Hess TM, Chew HF. Successful treatment of acute ocular involvement in Stevens-Johnson syndrome with amniotic membrane transplantation: a case report. *Can J Ophthalmol* 2012;47:e44-6
115. Muqit MM, Ellingham RB, Daniel C. Technique of amniotic membrane transplant dressing in the management of acute Stevens-Johnson syndrome. *Br J Ophthalmol* 2007;91:1536
116. Ricardo JR, Barros SL, Santos MS, et al. Amniotic membrane transplantation for severe acute cases of chemical ocular burn and Stevens-Johnson syndrome. *Arq Bras Oftalmol* 2009;72:215-20. Portuguese
117. Schwartz R, Avello E, Palisson F. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous immunoglobulin and amniotic membranes. *Arch Dermatol* 2008;144:724-6
118. Shay E, Khadem JJ, Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrolysis. *Cornea* 2010;29:359-61
119. Tandon A, Cackett P, Mulvihill A, Fleck B. Amniotic membrane grafting for conjunctival and lid surface disease in the acute phase of toxic epidermal necrolysis. *J AAPOS* 2007;11:612-3
120. Warkad VU, Sahu SK, Das S. Amniotic membrane grafting in the management of acute toxic epidermal necrolysis/Stevens Johnson syndrome. *Am J Ophthalmol* 2011;151:381-2. author reply 2
121. Miki T, Lehmann T, Cai H, et al. Stem cell characteristics of amniotic epithelial cells. *Stem Cells* 2005;23:1549-59

122. Park WC, Tseng SC. Modulation of acute inflammation and keratocyte death by suturing, blood, and amniotic membrane in PRK. *Invest Ophthalmol Vis Sci* 2000;41:2906-14
123. Bauer D, Wasmuth S, Hermans P, et al. On the influence of neutrophils in corneas with necrotizing HSV-1 keratitis following amniotic membrane transplantation. *Exp Eye Res* 2007;85:335-45
124. Li W, He H, Kawakita T, et al. Amniotic membrane induces apoptosis of interferon-gamma activated macrophages in vitro. *Exp Eye Res* 2006;82:282-92
125. Park CY, Kohanim S, Zhu L, et al. Immunosuppressive property of dried human amniotic membrane. *Ophthalmic Res* 2009;41:112-3
126. Hao Y, Ma DH, Hwang DG, et al. Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane. *Cornea* 2000;19:348-52
127. Kim JS, Kim JC, Na BK, et al. Amniotic membrane patching promotes healing and inhibits proteinase activity on wound healing following acute corneal alkali burn. *Exp Eye Res* 2000;70:329-37
128. Kolomeyer AM, Do BK, Tu Y, Chu DS. Placement of ProKera in the management of ocular manifestations of acute Stevens-Johnson syndrome in an outpatient. *Eye Contact Lens* 2013;39:e7-11
129. Aghayan HR, Goodarzi P, Baradaran-Rafii A, et al. Bacterial contamination of amniotic membrane in a tissue bank from Iran. *Cell Tissue Bank* 2013;14:401-6
130. Marangon FB, Alfonso EC, Miller D, et al. Incidence of microbial infection after amniotic membrane transplantation. *Cornea* 2004;23:264-9
131. Al-Kharashi S, Al-Khawaja A, Gonnah el S, et al. Microbial keratitis after amniotic membrane transplantation. *Int Ophthalmol* 2005;26:73-6
132. Chan LS, Soong HK, Foster CS, et al. Ocular cicatricial pemphigoid occurring as a sequela of Stevens-Johnson syndrome. *JAMA* 1991;266:1543-6
133. Fania L, Giannico MI, Fasciani R, et al. Ocular mucous membrane pemphigoid after Lyell syndrome: occasional finding or predisposing event? *Ophthalmology* 2012;119:688-93
134. Radford CF, Rauz S, Williams GP, et al. Incidence, presenting features, and diagnosis of cicatrising conjunctivitis in the United Kingdom. *Eye* 2012;26:1199-208
135. Balkrishnan C, Sharma V, Vyas A. Immunosuppressive therapy in inflammatory ocular surface disease post Steven Johnson syndrome. *Indian J Ophthalmol* 2011;59:69-70
136. Saw VP, Dart JK, Rauz S, et al. Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology* 2008;115:253-61
137. Frizon L, Araujo MC, Andrade L, et al. Evaluation of conjunctival bacterial flora in patients with Stevens-Johnson Syndrome. *Clinics* 2014;69:168-72
138. Dart JKG SV. *Immune Modulation in Ocular Mucous MembranePemphigoid*. Berlin Heidelberg, Springer, 2014
139. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: is it real? *Ocul Surf* 2009;7:28-40
140. Roujeau JC, Phlippoteau C, Koso M, et al. Sjogren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985;1:609-11
141. Roujeau JC, Phlippoteau C, Koso M, et al. Ocular sequelae and sicca syndrome following Lyell's syndrome. *Ann Dermatol Venereol* 1985;112:883-8. French
142. Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Arch Ophthalmol* 2002;120:330-7
143. Moon JW, Lee HJ, Shin KC, et al. Short term effects of topical cyclosporine and viscoelastic on the ocular surfaces in patients with dry eye. *Korean J Ophthalmol* 2007;21:189-94
144. Pflugfelder SC, De Paiva CS, Villarreal AL, Stern ME. Effects of sequential artificial tear and cyclosporine emulsion therapy on conjunctival goblet cell density and transforming growth factor-beta2 production. *Cornea* 2008;27:64-9
145. Sahli E, Hosal BM, Zilelioglu G, et al. The effect of topical cyclosporine A on clinical findings and cytological grade of the disease in patients with dry eye. *Cornea* 2010;29:1412-6
146. Demiryay E, Yaylali V, Cetin EN, Yildirim C. Effects of topical cyclosporine a plus artificial tears versus artificial tears treatment on conjunctival goblet cell density in dysfunctional tear syndrome. *Eye Contact Lens* 2011;37:312-5
147. Wang Y, Ogawa Y, Dogru M, et al. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. *Bone Marrow Transplant* 2008;41:293-302
148. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. *J Ocul Pharmacol Ther* 2013;29:372-7
149. Sant' Anna AE, Hazarbassanov RM, de Freitas D, Gomes JA. Minor salivary glands and labial mucous membrane graft in the treatment of severe symblepharon and dry eye in patients with Stevens-Johnson syndrome. *Br J Ophthalmol* 2012;96:234-9
150. Marinho DR, Burmann TG, Kwitko S. Labial salivary gland transplantation for severe dry eye due to chemical burns and Stevens-Johnson syndrome. *Ophthal Plast Reconstr Surg* 2010;26:182-4
151. Leibovitch I, Hoyama E, Limawararut V, et al. Novel technique to control hypersecretion from a transplanted autologous submandibular salivary gland for keratoconjunctivitis sicca. *Cornea* 2006;25:1251-3
152. Phasukkijwatana N, Lertrit P, Liammongkolkul S, Prabhasawat P. Stability of epitheliotrophic factors in autologous serum eye drops from chronic Stevens-Johnson syndrome dry eye compared to non-autoimmune dry eye. *Curr Eye Res* 2011;36:775-81
153. Quinto GG, Campos M, Behrens A. Autologous serum for ocular surface diseases. *Arq Bras Oftalmol* 2008;71:47-54
154. Lau B, Mutyala D, Dhaliwal D. A case report of doxycycline-induced Stevens-Johnson syndrome. *Cornea* 2011;30:595-7
155. Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. *Saudi J Ophthalmol* 2014;28:168-72
156. Ciralsky JB, Chapman KO, Rosenblatt MI, et al. Treatment of refractory persistent corneal epithelial defects: A standardized approachusing continuous wear PROSE therapy. *Ocul Immunol Inflamm* 2015;23:219-24
157. Erdem E, Yagmur M, Harbiyeli I, et al. Umbilical cord blood serum therapy for the management of persistent corneal epithelial defects. *Int J Ophthalmol* 2014;7:807-10
158. Watson SL, Geerling G, Dart JK. Clinical study of therapeutic ocular surface medium for persistent epithelial defect. *Ophthalmic Res* 2014;51:82-7
159. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol* 2013;156:1095-101
160. Sotozono C, Inatomi T, Nakamura T, et al. Cultivated oral mucosal epithelial transplantation for persistent epithelial defect in severe ocular surface diseases with acute inflammatory activity. *Acta Ophthalmol* 2014;92:e447-53
161. Cher I. Blink-related microtrauma: when the ocular surface harms itself. *Clin Experiment Ophthalmol* 2003;31:183-90
162. Tseng SC. Topical retinoid treatment for dry eye disorders. *Trans Ophthalmol Soc U K* 1985;104(Pt 4):489-95
163. Chan RY, Foster CS. A step-wise approach to ocular surface rehabilitation in patients with ocular inflammatory disease. *Int Ophthalmol Clin* 1999;39:83-108

164. Siqueira AC, Santos MS, Farias CC, et al. Scleral contact lens for ocular rehabilitation in patients with Stevens-Johnson syndrome. *Arq Bras Oftalmol* 2010;73:428-32. Portuguese
165. Gungor I, Schor K, Rosenthal P, Jacobs DS. The Boston Scleral Lens in the treatment of pediatric patients. *J AAPOS* 2008;12:263-7
166. Pullum K, Buckley R. Therapeutic and ocular surface indications for scleral contact lenses. *Ocul Surf* 2007;5:40-8
167. Haefliger IO, Vysniauskiene I, Pimentel AR, et al. Free autologous buccal mucosal graft transplantation to treat ocular complications after toxic epidermal necrolysis: case report. *Klin Monbl Augenheilkd* 2004;221:395-7
168. Koreen IV, Taich A, Elner VM. Anterior lamellar recession with buccal mucous membrane grafting for cicatricial entropion. *Ophthal Plast Reconstr Surg* 2009;25:180-4
169. Tugal-Tutkun I, Akova YA, Foster CS. Penetrating keratoplasty in cicatrizing conjunctival diseases. *Ophthalmology* 1995;102:576-85
170. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. *Ophthalmology* 1989;96:709-22. discussion 22—23
171. Tsubota K, Shimazaki J. Surgical treatment of children blinded by Stevens-Johnson syndrome. *Am J Ophthalmol* 1999;128:573-81
172. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. *Cornea* 1994;13:389-400
173. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. *Ophthalmology* 2002;109:1159-66
174. Tsubota K, Shimmura S, Shinozaki N, et al. Clinical application of living-related conjunctival-limbal allograft. *Am J Ophthalmol* 2002;133:134-5
175. Nordlund ML, Holland EJ, Kersten RC. Ocular surface reconstruction in a patient with complete ankyloblepharon resulting from stevens-johnson syndrome. *Arch Ophthalmol* 2004;122:934-5
176. Samson CM, Nduaguba C, Baltatzis S, Foster CS. Limbal stem cell transplantation in chronic inflammatory eye disease. *Ophthalmology* 2002;109:862-8
177. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P. Limbal allografting from related live donors for corneal surface reconstruction. *Ophthalmology* 1999;106:822-8
178. Ang AY, Chan CC, Biber JM, Holland EJ. Ocular surface stem cell transplantation rejection: incidence, characteristics, and outcomes. *Cornea* 2013;32:229-36
179. Iyer G, Srinivasan B, Agarwal S, et al. Treatment modalities and clinical outcomes in ocular sequelae of Stevens-Johnson syndrome over 25 years- a paradigm shift. *Cornea* 2016;35:46-50
180. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of autologous serum-derived cultivated corneal epithelial equivalents for the treatment of severe ocular surface disease. *Ophthalmology* 2006;113:1765-72
181. Ang LP, Sotozono C, Koizumi N, et al. A comparison between cultivated and conventional limbal stem cell transplantation for Stevens-Johnson syndrome. *Am J Ophthalmol* 2007;143:178-80
182. Shimazaki J, Higa K, Morito F, et al. Factors influencing outcomes in cultivated limbal epithelial transplantation for chronic cicatricial ocular surface disorders. *Am J Ophthalmol* 2007;143:945-53
183. Shortt AJ, Bunce C, Levis HJ, et al. Three-year outcomes of cultured limbal epithelial allografts in aniridia and Stevens-Johnson syndrome evaluated using the Clinical Outcome Assessment in Surgical Trials assessment tool. *Stem Cells Transl Med* 2014;3:265-75
184. Kim JT, Chun YS, Song KY, Kim JC. The effect of in vivo grown corneal epithelium transplantation on persistent epithelial defects with limbal stem cell deficiency. *J Korean Med Sci* 2008;23:502-8
185. Solomon A, Espana EM, Tseng SC. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. *Ophthalmology* 2003;110:93-100
186. Dohlman CH, Terada H. Keratoprosthesis in pemphigoid and Stevens-Johnson syndrome. *Adv Exp Med Biol* 1998;438:1021-5
187. Geerling G, Liu CS, Collin JR, Dart JK. Costs and gains of complex procedures to rehabilitate end stage ocular surface disease. *Br J Ophthalmol* 2002;86:1220-1
188. Liu C, Paul B, Tandon R, et al. The osteo-odonto-keratoprosthesis (OOKP). *Semin Ophthalmol* 2005;20:113-28
189. Stoiber J, Grabner G. Clinical management of severe ocular surface disease. *Klin Monbl Augenheilkd* 2005;222:533-51. German
190. Fukuda M, Nakao A, Hamada S, et al. A case of severe Stevens-Johnson syndrome successfully treated by osteo-odonto-keratoprosthesis surgery. *Japan J Ophthalmol* 2005;49:423-4
191. Liu C, Okera S, Tandon R, et al. Visual rehabilitation in end-stage inflammatory ocular surface disease with the osteo-odonto-keratoprosthesis: results from the UK. *Br J Ophthalmol* 2008;92:1211-7
192. Pinar-Sueiro S, Etxebarria-Ecenarro J, Gibelalde A, et al. Successful Boston keratoprosthesis in a patient with Lyell's syndrome. *Arch Soc Esp Oftalmol* 2009;84:635-40. Spanish
193. Reddy SC, Tajunisah I, Tan DT. Osteo-odonto keratoprosthesis in Stevens-Johnson syndrome: a case report. *Int J Ophthalmol* 2011;4:212-5
194. De La Paz MF, De Toledo JA, Charoenrook V, et al. Impact of clinical factors on the long-term functional and anatomic outcomes of osteo-odonto-keratoprosthesis and tibial bone keratoprosthesis. *Am J Ophthalmol* 2011;151:829-839.e1
195. Guell JL, Arcos E, Gris O, et al. Outcomes with the Boston Type 1 Keratoprosthesis at Instituto de Microcirugia Ocular IMO. *Saudi J Ophthalmol* 2011;25:281-4
196. Ament JD, Stryjewski TP, Pujari S, et al. Cost effectiveness of the type II Boston keratoprosthesis. *Eye* 2011;25:342-9
197. Basu S, Taneja M, Narayanan R, et al. Short-term outcome of Boston Type 1 keratoprosthesis for bilateral limbal stem cell deficiency. *Indian J Ophthalmol* 2012;60:151-3
198. Tan A, Tan DT, Tan XW, Mehta JS. Osteo-odonto keratoprosthesis: systematic review of surgical outcomes and complication rates. *Ocul Surf* 2012;10:15-25
199. Huang Y, Dong Y, Wang L, et al. Long-term outcomes of MICOF keratoprosthesis in the end stage of autoimmune dry eyes: an experience in China. *Br J Ophthalmol* 2012;96:28-33
200. Koller B, Neuhann T, Neuhann I. Results with the Boston keratoprosthesis. *Der Ophthalmologe* 2012;109:454-61. German
201. Kang JJ, de la Cruz J, Cortina MS. Visual outcomes of Boston keratoprosthesis implantation as the primary penetrating corneal procedure. *Cornea* 2012;31:1436-40
202. de la Paz MF, Stoiber J, de Rezende Couto Nascimento V, et al. Anatomical survival and visual prognosis of Boston type I keratoprosthesis in challenging cases. *Graefes Arch Klin Exp Ophthalmol* 2014;252:83-90
203. Dong D, Tan A, Mehta JS, et al. Cost-effectiveness of osteo-odonto keratoprosthesis in Singapore. *Am J Ophthalmol* 2014;157:78-84.e2
204. Basu S, Sureka S, Shukla R, Sangwan V. Boston type 1 based keratoprosthesis (Auro Kpro) and its modification (LVP Kpro) in chronic Stevens Johnson syndrome. *BMJ Case Rep* 2014:2014
205. Michael R, Charoenrook V, de la Paz MF, et al. Long-term functional and anatomical results of osteo- and osteoodonto-keratoprosthesis. *Graefes Arch Klin Exp Ophthalmol* 2008;246:1133-7
206. Marchi V, Ricci R, Pecorella I, et al. Osteo-odonto-keratoprosthesis. Description of surgical technique with results in 85 patients. *Cornea* 1994;13:125-30
207. Nouri M, Terada H, Alfonso EC, et al. Endophthalmitis after keratoprosthesis: incidence, bacterial causes, and risk factors. *Arch Ophthalmol* 2001;119:484-9

208. Yaghouti F, Nouri M, Abad JC, et al. Keratoprosthesis: preoperative prognostic categories. *Cornea* 2001;20:19-23
209. Sayegh RR, Ang LP, Foster CS, Dohlman CH. The Boston keratoprosthesis in Stevens-Johnson syndrome. *Am J Ophthalmol* 2008;145:438-44
210. Bradley JC, Hernandez EG, Schwab IR, Mannis MJ. Boston type 1 keratoprosthesis: the university of california davis experience. *Cornea* 2009;28:321-7
211. Ciralsky J, Papaliodis GN, Foster CS, et al. Keratoprosthesis in autoimmune disease. *Ocul Immunol Inflamm* 2010;18:275-80
212. Munoz-Gutierrez G, Alvarez de Toledo J, Barraquer RI, et al. Post-surgical visual outcome and complications in Boston type 1 keratoprosthesis. *Arch Soc Esp Oftalmol* 2013;88:56-63
213. Parthasarathy A, Aung T, Oen FT, Tan DT. Endoscopic cyclophotocoagulation for the management of advanced glaucoma after osteo-odonto-keratoprosthesis surgery. *Clin Experiment Ophthalmol* 2008;36:93-4
214. Yu JF, Huang YF. Glaucoma with modified osteo-odonto keratoprosthesis. *Cornea* 2012;31:1214. author reply -5
215. Yu JF, Huang YF. Characteristics of endophthalmitis with Boston keratoprosthesis. *Cornea* 2012;31:594
216. Robert MC, Moussally K, Harissi-Dagher M. Review of endophthalmitis following Boston keratoprosthesis type 1. *Br J Ophthalmol* 2012;96:776-80
217. Chan CC, Holland EJ. Infectious keratitis after Boston type 1 keratoprosthesis implantation. *Cornea* 2012;31:1128-34
218. Chan CC, Holland EJ. Infectious endophthalmitis after Boston type 1 keratoprosthesis implantation. *Cornea* 2012;31:346-9
219. Basu S, Pillai VS, Sangwan VS. Mucosal complications of modified osteo-odonto keratoprosthesis in chronic Stevens-Johnson syndrome. *Am J Ophthalmol* 2013;156:867-873.e2
220. Iyer G, Srinivasan B, Agarwal S, et al. Glaucoma in modified osteo-odonto-keratoprosthesis eyes: role of additional stage 1A and Ahmed glaucoma drainage device-technique and timing. *Am J Ophthalmol* 2015;159:482-9
221. Iyer G, Srinivasan B, Agarwal S, Rachapalle SR. Laminar resorption in modified osteo-odonto-keratoprosthesis procedure: a cause for concern. *Am J Ophthalmol* 2014;158:263-269.e2
222. Forlini M, Adabache-Guel T, Bratu A, et al. Endoscopic cyclophotocoagulation in refractory glaucoma after osteo-odonto-keratoprosthesis in Stevens-Johnson syndrome: a case report. *Retin Cases Brief Rep* 2014;8:193-6
223. de Oliveira LA, Pedreira Magalhaes F, Hirai FE, de Sousa LB. Experience with Boston keratoprosthesis type 1 in the developing world. *Can J Ophthalmol* 2014;49:351-7
224. Robert MC, Dohlman CH. A review of corneal melting after Boston Keratoprosthesis. *Semin Ophthalmol* 2014;29:349-57
225. Sawatari Y, Perez VL, Parel JM, et al. Oral and maxillofacial surgeons' role in the first successful modified osteo-odonto-keratoprosthesis performed in the United States. *J Oral Maxillofac Surg* 2011;69:1750-6
226. Gomaa A, Comyn O, Liu C. Keratoprostheses in clinical practice - a review. *Clin Experiment Ophthalmol* 2010;38:211-24
227. Durand ML, Dohlman CH. Successful prevention of bacterial endophthalmitis in eyes with the Boston keratoprosthesis. *Cornea* 2009;28:896-901

Analysis of Ocular Manifestation and Genetic Association of Allopurinol-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis in South Korea

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Purpose: To describe the clinical characteristics and genetic background of allopurinol-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in South Korea.

Methods: This is a prospective, noncomparative case series. Visual acuity, detailed medical history, ocular findings, and systemic manifestations of 5 patients (10 eyes) with allopurinol-induced SJS/TEN were recorded. The acute ocular involvement score and the chronic ocular manifestation score were graded on scales of 0–3 and 0–39, respectively, based on severity. Human leukocyte antigen (HLA) genotyping was also performed during the hospitalization.

Results: Three patients were diagnosed with SJS, and 2 with TEN. Mild ocular involvement with only conjunctival hyperemia (acute ocular involvement score ≤1) was present in all 10 eyes during the acute stage. Patients were treated with systemic steroids and topical antibiotics, steroids, and preservative-free artificial tears, with rinsing of the ocular surface, in the acute stages of SJS/TEN. In the final follow-up, none of the patients had developed severe chronic ocular complications (chronic ocular manifestation score ≤8), including keratinization, corneal conjunctivalization, mucocutaneous junction involvement, or symblepharon. One patient developed bilateral persistent epithelial defects 3 months after the disease onset, which healed after conservative treatment, leaving a bilateral central corneal haze. HLA genotyping showed that 4 of the 5 patients (80%) were positive for *HLA-B*58:01*.

Conclusions: Allopurinol-induced SJS/TEN might not cause serious acute or chronic complications of the ocular surface. In addition, our HLA genotyping results are consistent with previous studies reporting a strong association between *HLA-B*58:01* and allopurinol-induced SJS/TEN among Koreans.

Key Words: allopurinol, human leukocyte antigen, Stevens–Johnson syndrome, toxic epidermal necrolysis

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The Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute diseases of the skin and the mucosal surfaces throughout the body (eg, eye, lung, gastrointestinal, genitourinary system), characterized by the detachment and blistering of the skin epidermis and the mucosal epithelium.[1,2] The acute ocular complications of the SJS and TEN may occur along with the involvement of the skin, which frequently leads to late cicatricial sequelae. The chronic ocular surface complications can involve the eyelids, conjunctiva, cornea, and the tear film, resulting in visual deterioration and the worsening of the ocular surface health.[3–5]

It is well known that the SJS/TEN can be induced by various infections or classes of pharmacological agents, such as antibiotics, anticonvulsants, nonsteroidal antiinflammatory drugs, or allopurinol.[6–8] Moreover, human leukocyte antigen (HLA) types have recently been reported to be associated with the onset of SJS/TEN. The genetic predisposition to the disease seems to be specific for different ethnic groups. For instance, *HLA-B*15:02* exhibited a strong association with carbamazepine-induced SJS/TEN in Taiwanese Han Chinese patients.[9] However, in Japanese and European patients, *HLA-A*31:01* was strongly associated with carbamazepine-induced severe cutaneous adverse reactions (SCARs), including SJS/TEN.[10,11] We also recently reported that cold medicine (CM)-related SJS/TEN with severe mucosal involvement, including severe ocular surface complications (SOC), is associated with *HLA-A*02:06* in Japanese and Korean populations and with *HLA-B*44:03* in Indian and Brazilian populations.[12] Taken together, these reports suggest that the SJS/TEN induced by different drugs have different

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genetic susceptibilities; therefore, it is possible that different causative drug-induced SJS/TEN reactions have different pathogeneses and phenotypes.[13,14]

Allopurinol is a xanthine oxidase inhibitor commonly used for the treatment of gout and is known to be one of the drugs most frequently associated with SJS and TEN.[15] Recent studies have reported a strong association between allopurinol-induced SJS/TEN and the genetic marker, *HLA-B*58:01* in the Han Chinese, Thai, European, and Japanese populations.[16–19] To our knowledge, 2 studies to date have reported an association between allopurinol-induced SCARs and *HLA-B*58:01* in the Korean population.[20,21] However, no reports have evaluated the acute or chronic ocular complications in allopurinol-induced SJS/TEN patients.

In this study, we evaluated the acute and chronic ocular complications, and cutaneous and systemic manifestations along with HLA genotype, of allopurinol-induced SJS/TEN patients in tertiary referral ophthalmic centers.

MATERIALS AND METHODS

A prospective study on the SJS/TEN patients who were referred to the ophthalmology department of one of 3 tertiary referral centers [Chonnam National University Hospital (CNUH), Seoul National University Hospital (SNUH), and Yonsei University Hospital (YUH)] was conducted from January 2012 to May 2014. Institutional review board/ethics committee approval was obtained from the participating institutions, and the study protocol followed the guidelines of the Declaration of Helsinki. Prior informed consent to participate in this study was obtained in written form from all the patients.

The inclusion criteria were as follows: (1) dermatologist-diagnosed SJS/TEN in the acute phase based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and the involvement of at least 2 mucosal sites, including the ocular surface,[22,23] characterized by an epidermal detachment of $<$30% (SJS) and $>$30% (TEN) of the body surface area[24]; (2) the absence of a history of previous ophthalmic disease or ocular surgery; and (3) a follow-up period of at least 12 months.

Forty-three patients fulfilled the inclusion criteria during the study period, with 5 patients identified as having allopurinol-induced SJS/TEN (2 patients from CNUH, 1 from SNUH, and 2 from YUH). Allopurinol was considered as the possible causative agent if it had been taken shortly before the onset of the symptoms and signs, that is, within 2 weeks before the disease onset.[25] All the patients were subjected to a daily ophthalmological evaluation, including forniceal inspection, for the determination of the type, extent, and severity of the ocular involvement, by one of 3 cornea specialists (K.C.Y., M.K.K., or K.Y.S.), for as long as there was any significant ocular surface inflammation during the hospitalization. We collected demographic and clinical data on each patient. The patients' age, sex, best-corrected visual acuity (BCVA) both at disease onset and during the follow-up period, systemic and ocular manifestations and treatments, and the systemic and ocular sequelae were recorded on an itemized data collection form. Acute ocular involvement scores (AOS) were assigned based on the classification system proposed by Kim et al.[26] In brief, the AOS ranged from zero to three, depending on the presence of conjunctival hyperemia, pseudomembrane formation, and/or corneal epithelial erosion (0: no involvement; 1: conjunctival hyperemia; 2: pseudomembrane formation or corneal epithelial erosion; 3: pseudomembrane formation and corneal epithelial erosion). The systemic involvement in each patient was also graded using the acute systemic involvement score (ASS) developed by Kim et al.[26] ASS values ranged from zero to sixteen and were determined by the status of the oral or genital erythema, the extension degree of epidermal detachment, degree of liver dysfunction, and presence of fever, respiratory disturbance, total necrosis of epidermis, anemia, elevated serum C-reactive protein concentrations, kidney dysfunction, and pneumonia. Severe ocular and systemic involvement were defined as AOS $\geq$2 and ASS $\geq$8, respectively.

Chronic Ocular Surface Complication Evaluation and Follow-up

The BCVA and other ophthalmic parameters including the corneal and conjunctival status, limbal deficiency, tear volume, eyelid involvement, and symblepharon were investigated at each outpatient visit to the ophthalmology clinic after discharge. The tear volume was measured using the Schirmer I test.[27] A chronic ocular manifestation score (COMS) was assigned based on the involvement area or the severity of the above-mentioned factors, according to the grading system proposed by Sotozono et al.[25] Thirteen clinical signs of ocular complications of 3 ocular surface structures (cornea, conjunctiva, and eyelid) were graded on a scale of zero to three, depending on the severity of ocular involvement. The corneal complications consisted of superficial punctate keratopathy severity, extent of the epithelial defect, loss of the palisades of Vogt, and the presence and degree of conjunctivalization, corneal neovascularization, corneal opacification, and keratinization. The conjunctival complications included hyperemia and symblepharon. Eyelid complications included trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage. Severe chronic ocular manifestation was defined as having a COMS $\geq$13.

HLA Genotyping

The genotyping of the HLA-A, B, C, DRB1, and DQB1 alleles was performed as part of another study on the transethnic genetic associations of the SJS/TEN, using polymerase chain reaction assays, followed by hybridization with sequence-specific oligonucleotide probes using commercial bead-based typing kits (Wakunaga, Hiroshima, Japan).[12]

RESULTS

The demographics, clinical characteristics, and treatment plans of the 5 patients (3 male; 2 female) enrolled in this

study are summarized in Tables 1 and 2. The patients' age at the time of the SJS/TEN onset ranged from 47 to 78 years (average, 63.8 ± 13.5 years). Three patients were diagnosed as having the SJS and 2 as having TEN. Bilateral ocular involvement was noted in all of the patients in the acute phase of the disease. The AOS was ≤1 in both the eyes of all 5 patients (conjunctival hyperemia only, without corneal involvement). None of the patients showed severe ocular involvement. The initial BCVA was 20/40 or better in each eye. All the patients, except patient 2, had taken more than 1 medication because of their underlying illnesses, but those medications had been taken for more than 6 months without any changes in the dosage or dosing interval.

Ocular management consisted of the application of topical antibiotics, preservative-free artificial tears, and steroids, with rinsing of the ocular surface with sterile saline (2 times per day), for all the patients in the acute stage of the SJS/TEN. None of the patients underwent amniotic membrane transplantation or any other surgical procedures during the acute phase. The mean ASS was 7.6 ± 1.8 (range: 6–10). Two of the 5 patients showed severe systemic involvement. Each patient received systemic immunomodulatory treatment (steroids and/or intravenous immunoglobulin), depending on the dermatologist's or physician's recommendation. All the patients were administered systemic corticosteroids (prednisolone) intravenously at 1.0 mg/kg/d for 3 to 8 consecutive days, followed by the tapering off of the dosage. Patient 5 additionally received 1.0 g/kg intravenous immunoglobulin daily for 5 days. All the patients received systemic immunomodulatory treatment within 7 days of disease onset.

Blood sampling and genomic DNA analysis were performed during the hospitalization period; the results are shown in Table 3. Four patients (80%) were found to be positive for *HLA-B*58:01*; the remaining patient was positive for *HLA-B*51:01*. Four patients (80%) were positive for *HLA-DRB1*13:02* and *HLA-DQB1*06:09*. Three patients (60%) were positive for *HLA-A*33:03* and 2 (40%) for *HLA-A*02:01*. Genomic DNA analysis was performed on the other 38 patients with nonallopurinol-related SJS/TEN. Four of 38 patients (10.5%) were identified to have *HLA-B*58:01*.

No severe systemic complications were found, and there were no SJS/TEN recurrences during the follow-up period. The follow-up period ranged from 14 to 31 months (mean follow-up duration; 18.4 ± 7.2 months). During the follow-up period, all the patients showed a good clinical course without serious ocular or systemic complications with the exception of patient 3, who developed bilateral persistent epithelial defects 3 months after disease onset. He was treated with topical antibiotics, preservative-free artificial tears, autologous serum, and a bandage soft contact lens application. After receiving treatment for 2 weeks, his corneal lesions healed, but left a bilateral central haze. All the patients, with the exception of patient 3, retained a BCVA of 20/40 or better in each eye and demonstrated an intact ocular surface and a good tear meniscus. The mean COMS at the final follow-up visit was 3.3 ± 2.3 (range: 2–8).

The clinical course of patient 2 is described below. Patient 2 was selected to illustrate the representative features of the acute and chronic phases of allopurinol-induced SJS/TEN in our study.

Patient 2

A 47-year-old female was admitted with a 5-day history of high fever and blistering maculopapular rash involving her limbs, lips, and oral mucosa, which limited her ability to consume food and drink (Fig. 1). Conjunctival hyperemia and lid margin inflammation developed 4 days after admission. Topical moxifloxacin 0.5% (Vigamox, Alcon, Fort Worth, TX) 4 times per day, loteprednol etabonate 0.5% (Lotemax, Bausch & Lomb, Tampa, FL) 4 times per day, and hyaluronic acid 0.1% (Kynex, Alcon) 5 to 6 times per day were administered along with the rinsing of the ocular surface 2 times per day. The conjunctival and lid margin abnormalities resolved gradually with conservative treatment. The eye drops were gradually tapered over the treatment period, according to the

TABLE 1. Demographic and Clinical Characteristics of Allopurinol-Induced SJS and TEN Patients

Patient Number	Sex	Age (yrs)	Underlying Disease	Systemic Agent Taken Before the Onset of SJS/TEN	Diagnosis	Onset of Disease ~ Development of Ocular Complication (d)	Onset of Disease ~ Systemic Treatment Initiation (d)	Eyes	Initial BCVA (logMAR)	AOS
1	M	72	Gout	Allopurinol	SJS	8	6	Rt.	0.1	1
								Lt.	0.0	1
2	F	47	Gout, liver cirrhosis	Allopurinol	SJS	9	6	Rt.	0.1	1
								Lt.	0.0	1
3	M	71	Gout, HTN, DM	Allopurinol, losartan, glimepiride	SJS	8	7	Rt.	0.1	1
								Lt.	0.0	1
4	F	71	Gout, HTN	Allopurinol, amlodipine	TEN	9	5	Rt.	0.2	1
								Lt.	0.2	1
5	M	78	Gout, HTN, BPH	Allopurinol, olmesartan, alfuzosin	TEN	3	3	Rt.	0.3	1
								Lt.	0.2	1

BPH, benign prostate hyperplasia; DM, diabetes mellitus; F, female; HTN, hypertension; logMAR, logarithm of the minimum angle of resolution; Lt., left; M, male; Rt., right.

TABLE 2. Demographic and Clinical Characteristics of Allopurinol-Induced SJS and TEN Patients (Continued)

Ocular Treatment	ASS	Systemic Treatment	Final BCVA (logMAR)	COMS	Follow-up Period (mo)
Topical	7	Systemic steroids	0.1	2	14
Topical			0.0	2	
Topical	6	Systemic steroids	0.1	2	14
Topical			0.0	2	
Topical	6	Systemic steroids	0.5	7	18
Topical			1.0	8	
Topical	10	Systemic steroids	0.0	3	31
Topical			0.1	3	
Topical	9	Systemic steroids	0.3	2	15
Topical		+IVIG	0.2	2	

ASS, acute systemic involvement score; BCVA, best-corrected visual acuity; COMS, chronic ocular manifestation score; IVIG, intravenous immunoglobulin; logMAR, logarithm of the minimum angle of resolution.

ocular surface status. Systemic steroids were administered after admission at 1.0 mg/kg/d for 4 days. The patient was discharged after 18 days of hospitalization. At the 14-month follow-up, the patient had no dry eye symptoms. Both corneas were clear with a BCVA of 16/20 in the right eye and 20/20 in the left eye. No ocular surface sequelae had occurred.

DISCUSSION

Regarding the Japanese populations, we had reported that approximately 80% of the SJS/TEN patients with SOC had taken CMs (eg, nonsteroidal antiinflammatory drugs and multiingredient CMs) several days before the disease onset[13,23]; they were classified as CM-related SJS/TEN patients.[12,13,28] We had also previously reported that in Japan and Korea, *HLA-A*02:06* is significantly associated with CM-related SJS/TEN.

However, Ueta[14] reported that allopurinol-induced SJS/TEN might be rare among the Japanese SJS/TEN patients with SOC. The diagnosis of the SJS/TEN by ophthalmologists was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites, including the ocular surface.[13,23,28] As ophthalmologists usually encounter SJS/TEN patients in the chronic rather than the acute stages, it is possible that allopurinol-induced SJS/TEN may not have been accompanied by SOC in the chronic stage.

In this study, the ophthalmologists could prospectively examine the ocular complications in the allopurinol-induced SJS/TEN patients during the acute and chronic stages. In our case series, none of the patients developed any severe acute or chronic ocular complications, such as pseudomembrane, corneal epithelial defect, corneal opacification, mucocutaneous junction involvement (mucocutaneous junction irregularity),[25] or symblepharon formation, with the exception of patient 3, who developed a persistent corneal epithelial defect 3 months after the disease onset. Additionally, in accordance with the published classification system for the acute manifestations of the SJS/TEN developed by Kim et al,[26] none of the patients in our series had severe ocular damage from SJS/TEN in the acute stage. In contrast, according to a recent multicenter study in South Korea, severe ocular involvement was observed in 59 eyes (68.6%) during the acute stage of SJS/TEN[26]; the proportion of severe acute ocular involvement in patients with SJS/TEN was still relatively high among the patients treated with conventional steroids (63.8%) or intravenous steroid pulse therapy (66.7%), according to the subgroup analysis included in that study. Moreover, according to Kim et al,[26] acute and chronic ocular involvement correlated significantly with acute systemic involvement. However, in our case series, even the 2 patients with severe systemic involvement (ASS $\geq$8) showed only mild acute ocular involvement and chronic sequelae.

Serious ocular complications, such as corneal epithelial defects and pseudomembrane during the acute stage, and symblepharon, corneal opacification and conjunctival invasion onto the cornea during the chronic stage, are usually found in CM-related SJS/TEN with SOC.[12,13] However, our study showed that none of the 5 allopurinol-induced SJS/TEN patients exhibited serious complications of the ocular surface in either the acute or the chronic stages. This might suggest that allopurinol-induced SJS/TEN showed a phenotype different from that of CM-related SJS/TEN with SOC.

In addition, a previous study by Kang et al,[21] analyzing both the drug-induced hypersensitivity syndrome and the SJS/TEN together as SCAR, reported a strong positive relationship between *HLA-B*58:01* and allopurinol-induced SCARs in the Korean population. Another study on allopurinol hypersensitivity in the Korean population included only 2 cases of SJS; both were positive for *HLA-B*58:01*.[20] In our study, 4 of the 5 patients (80%) were *HLA-B*58:01* carriers. This proportion is fairly high, considering that the allelic frequency of *HLA-B*58:01* in the general Korean population is estimated to be 6.5%–6.8%.[29,30] In addition, the allelic frequency of *HLA-B*58:01* in the nonallopurinol-induced SJS/TEN cases is only 10.5% in our study. This finding is consistent with the previous reports showing a positive association between *HLA-B*58:01* allele and allopurinol-induced SJS/TEN in the Korean population.

TABLE 3. HLA Genotypes Among Allopurinol-Induced SJS and TEN Patients

Patient Number	HLA-A*	HLA-B*	HLA-C*	HLA-DRB1*	HLA-DQB1*
1	*02:01/24:02*	*51:01/51:01*	*14:02/15:02*	*04:10/09:01*	*03:03/04:02*
2	*33:03/33:03*	*58:01/58:01*	*03:02/03:02*	*03:01/13:02*	*02:01/06:09*
3	*11:01/24:02*	*40:06/58:01*	*04:01/08:01*	*04:05/13:02*	*03:03/06:09*
4	*02:10/33:03*	*40:06/58:01*	*03:02/08:01*	*12:01/13:02*	*03:02/06:09*
5	*02:01/33:03*	*15:01/58:01*	*03:02/03:03*	*04:05/13:02*	*04:01/06:09*

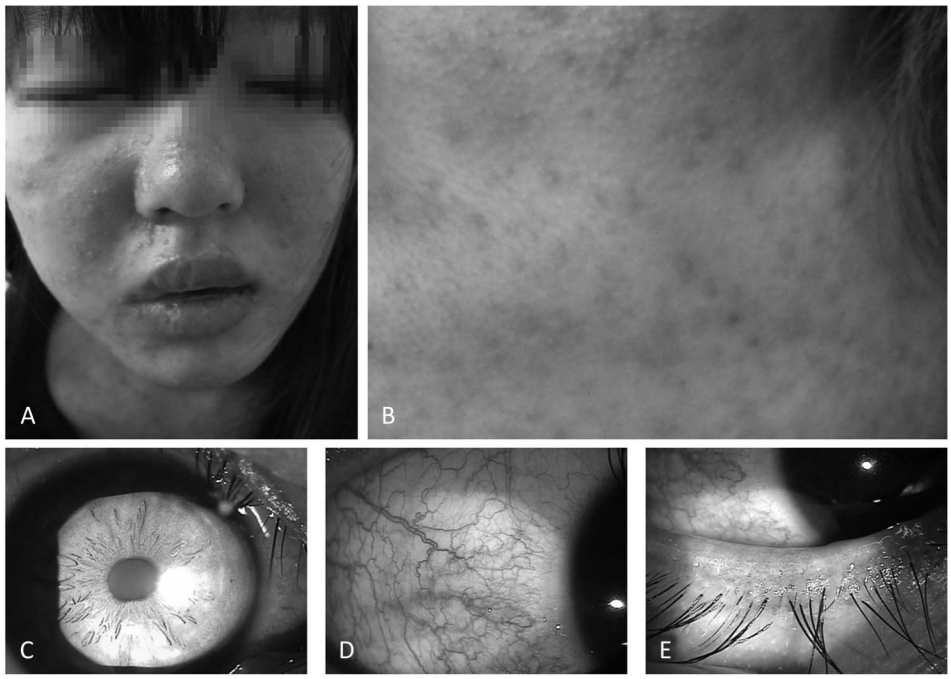

FIGURE 1. A and B, Clinical appearance of patient 2, 6 days after disease onset, showing a blistering maculopapular rash appears on the face and neck. C–E, Appearance of the right eye of patient 2, 10 days after disease onset, revealing mild conjunctival hyperemia with lid margin inflammation, accompanied by a clear corneal surface.

At the genetic level, the presence of *HLA-A*02:06* and the polymorphisms of several immune-related genes, including Toll-like receptor 3, interleukin-4 receptor, interleukin 13, and Fas ligands, have been associated with SJS/TEN with SOC.[22,31–33] Recently, it was proposed that various factors could affect the ocular outcome of the SJS/TEN caused by certain medications. As mentioned previously, *HLA-A*02:06* is a risk factor for CM-related SJS/TEN with SOC, but not for CM-related SJS/TEN without SOC, nor for CM-unrelated SJS/TEN with SOC.[13] We also reported that CM-related SJS/TEN with SOC is significantly associated with *HLA-A*02:06* not only in Japanese populations but also in Korean populations, and that *HLA-B*44:03* was significantly associated only with CM-related SJS/TEN with severe ocular complications in Indian and Brazilian populations.[12,13] Moreover, a recent analysis proved that certain types of causative medicines can affect the severity of the acute ocular involvement in the SJS/TEN patients.[34] These results suggest that different susceptibility alleles are involved in the development of allopurinol-induced SJS/TEN and CM-related SJS/TEN with SOC, which is consistent with our findings that allopurinol-induced SJS/TEN shows a phenotype different from that of CM-related SJS/TEN with SOC.

In our study, 4 patients were positive for *HLA-DRB1*13:02* and *HLA-DQB1*06:09* and 3 patients for *HLA-A*33:03*. In a recent study about the allelic and haplotypic frequencies of the HLA in the Korean population, *HLA-DRB1*13:02* was identified to be the second most common allele and *HLA-A*33:03* the third most common.[29,30] However, *HLA-DQB1*06:09* was found to be less common, with an allelic frequency of less than 5% in the Korean population.[29,30]

As for *HLA-A*33:03* and *HLA-DRB1*13:02*, the frequency of the former was found to be significantly higher in white allopurinol-induced SJS/TEN patients.[35] *HLA-DRB1*13:02* alone was not significantly associated with the development of the SJS/TEN in white patients; but, in conjunction with *HLA-B*58:01,* both the alleles, *HLA-A*33:03* and *HLA-DRB1*13:02*, behave as a strong risk factors for allopurinol-induced SJS/TEN in white patients.[35] However, the role of these genes in the development of SJS/TEN among the Korean population has not been identified yet. *HLA-DQB1*06:09* was found to be a significant risk factor for the development of aspirin-induced urticaria,[36] but its association with the development of SJS/TEN has not been identified in any population so far. Further studies with a larger number of patients are warranted to identify the relationship between the 3 genes and the development of the SJS/TEN in the Korean population.

This study has several limitations. The patients were identified from 3 different centers to present a small, noncomparative case series without statistical comparison because SJS and TEN are rare disease entities with an annual incidence of 0.4–6 cases per million.[37,38] A prospective, multicenter study with a controlled design and a longer follow-up period will be required in the future to address this limitation. In addition, our patients received systemic steroid treatment in the acute phase of SJS/TEN, and this might have played a role in decreasing the acute or chronic ocular complications to some extent. However, the systemic role of corticosteroids in SJS or TEN is still controversial. A previous small case series indicated that steroid pulse therapy in the acute phase prevented ocular complications,[39] whereas other studies indicated that systemic steroids neither beneficially affected the acute or chronic ocular damage nor improved the final visual outcome.[26,40,41]

Taking together the results of previous investigations and those of our study, we concluded that allopurinol-induced

SJS/TEN, with or without the *HLA-B*58:01* allele, might not cause severe complications of the ocular surface. Further study with larger sample sizes is warranted for the investigation of the ocular complications of allopurinol-induced SJS/TEN and the role of *HLA-B*58:01*.

REFERENCES

1. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology*. 2011;118:908–914.
2. Hsu M, Jayaram A, Verner R, et al. Indications and outcomes of amniotic membrane transplantation in the management of acute stevens-johnson syndrome and toxic epidermal necrolysis: a case-control study. *Cornea*. 2012;31:1394–1402.
3. Gueudry J, Roujeau JC, Binaghi M, et al. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol.* 2009;145:157–162.
4. Kaido M, Yamada M, Sotozono C, et al. The relation between visual performance and clinical ocular manifestations in Stevens-Johnson syndrome. *Am J Ophthalmol.* 2012;154:499–511.e1.
5. López-García JS, Rivas Jara L, García-Lozano CI, et al. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. *Ophthalmology*. 2011;118:265–271.
6. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol.* 2002;138:1019–1024.
7. Del Pozzo-Magana BR, Lazo-Langner A, Carleton B, et al. A systematic review of treatment of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Popul Ther Clin Pharmacol.* 2011;18:e121–e133.
8. Somkrua R, Eickman EE, Saokaew S, et al. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet.* 2011;12:118.
9. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428:486.
10. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med.* 2011;364:1134–1143.
11. Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet.* 2011;20:1034–1041.
12. Ueta M, Kannabiran C, Wakamatsu TH, et al. Trans-ethnic study confirmed independent associations of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe ocular surface complications. *Sci Rep.* 2014;4:5981.
13. Ueta M, Kaniwa N, Sotozono C, et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. *Sci Rep.* 2014;4:4862.
14. Ueta M. Ethnic differences in the association between human leukocyte antigen and Stevens-Johnson syndrome. *Eur Ophthalmic Rev.* 2009;3:15–18.
15. Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol.* 2008;58:25–32.
16. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A.* 2005;102:4134–4139.
17. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics*. 2008;9:1617–1622.
18. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics.* 2008;18:99–107.
19. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics.* 2009;19:704–709.
20. Jung JW, Song WJ, Kim YS, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant.* 2011;26:3567–3572.
21. Kang HR, Jee YK, Kim YS, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet Genomics.* 2011;21:303–307.
22. Ueta M, Sotozono C, Inatomi T, et al. Association of IL4R polymorphisms with Stevens-Johnson syndrome. *J Allergy Clin Immunol.* 2007;120:1457–1459.
23. Ueta M, Sotozono C, Nakano M, et al. Association between prostaglandin E receptor 3 polymorphisms and Stevens-Johnson syndrome identified by means of a genome-wide association study. *J Allergy Clin Immunol.* 2010;126:1218–1225.e10.
24. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–96.
25. Sotozono C, Ang LPK, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. *Ophthalmology*. 2007;114:1294–1302.
26. Kim DH, Yoon KC, Seo KY, et al. The role of systemic immunomodulatory treatment and prognostic factors on chronic ocular complications in stevens-johnson syndrome. *Ophthalmology*. 2015;122:254–264.
27. Lee HS, Ji YS, Yoon KC. Efficacy of hypotonic 0.18% sodium hyaluronate eye drops in patients with dry eye disease. *Cornea*. 2014;33:946–951.
28. Ueta M, Sawai H, Sotozono C, et al. IKZF1, a new susceptibility gene for cold medicine-related Stevens-Johnson syndrome/toxic epidermal necrolysis with severe mucosal involvement. *J Allergy Clin Immunol.* 2015;135:1538–1545.e17.
29. In JW, Roh EY, Oh S, et al. Allele and Haplotype frequencies of human leukocyte antigen-a, -B, -C, -DRB1, and -DQB1 from sequence-based DNA typing data in koreans. *Ann Lab Med.* 2015;35:429.
30. Lee KW, Oh DH, Lee C, et al. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens*. 2005;65:437–447.
31. Ueta M, Sotozono C, Inatomi T, et al. Association of combined IL-13/IL-4R signaling pathway gene polymorphism with Stevens-Johnson syndrome accompanied by ocular surface complications. *Invest Ophthalmol Vis Sci.* 2008;49:1809–1813.
32. Ueta M, Sotozono C, Inatomi T, et al. Association of Fas Ligand gene polymorphism with Stevens-Johnson syndrome. *Br J Ophthalmol.* 2008;92:989–991.
33. Ueta M, Tamiya G, Tokunaga K, et al. Epistatic interaction between Toll-like receptor 3 (TLR3) and prostaglandin E receptor 3 (PTGER3) genes. *J Allergy Clin Immunol.* 2012;129:1413–1416.e11.
34. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol.* 2015;160:228–237.e2.
35. Cristallo AF, Schroeder J, Citterio A, et al. A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Int J Immunogenet.* 2011;38:303–309.
36. Shimada-Sugimoto M, Otowa T, Miyagawa T, et al. Immune-related pathways including HLA-DRB1(*)13:02 are associated with panic disorder. *Brain Behav Immun.* 2015;46:96–103.
37. Yetiv JZ, Bianchine JR, Owen JA. Etiologic factors of the Stevens-Johnson syndrome. *South Med J.* 1980;73:599–602.
38. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* 1990;126:43–47.
39. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol.* 2009;147:1004–1011.
40. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye (Lond).* 2005;19:846–853.
41. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology*. 1995;102:1669–1676.