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REVIEW

Ophthalmic Aspects of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A Narrative Review

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ABSTRACT

The aim of our review article was to summarize the current literature on Stevens–Johnson syndrome (SJS) and its severe form, toxic epidermal necrolysis (TEN). SJS/TEN is a serious, rare multi-system, immune-mediated, mucocutaneous disease with a significant mortality rate that can lead to severe ocular surface sequelae and even to bilateral blindness. Restoration of the ocular surface in acute and chronic SJS/TEN is challenging. There are only limited local or systemic treatment options for SJS/TEN. Early diagnosis, timely amniotic membrane transplantation and aggressive topical management in acute SJS/TEN are necessary to prevent long-term, chronic ocular complications. Although the primary aim of acute care is to save the life of the patient, ophthalmologists should regularly examine patients already in the acute phase, which should also be followed by systematic ophthalmic examination in the chronic phase. Herein, we summarize actual knowledge on the epidemiology, aetiology, pathology, clinical appearance and treatment of SJS/TEN.

Keywords: Corneal blindness; Stevens–Johnson syndrome; Toxic epidermal necrolysis

Key Summary Points

Stevens–Johnson syndrome and toxic epidermal necrolysis may have devastating ocular sequelae.

Ophthalmologists should examine patients already in the acute phase.

Timely amniotic membrane transplantation as a patch combined with conformer, symblepharon ring or ProKera can prevent severe chronic complications.

To date, there are only limited local or systemic treatment options for ocular complications of Stevens–Johnson syndrome and toxic epidermal necrolysis.

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INTRODUCTION

Stevens–Johnson syndrome (SJS) and its severe form, toxic epidermal necrolysis (TEN), represent the ends of a clinical spectrum of inflammatory, vesiculobullous skin and mucous membrane diseases [1]. These are considered to be delayed-type hypersensitivity reactions (type IV hypersensitivity) caused by drugs or infections. SJS and TEN classification is based on the extent of skin and mucous membrane involvement [2].

The course of the disease can be divided into acute and chronic stages. The acute phase can be characterized by epidermal necrolysis and sloughing. Acute SJS/TEN represents a medical, dermatological and even ophthalmic emergency, and can be a life-threatening condition [3]. Early recognition and appropriate local and systemic interventions are essential for survival and in avoiding corneal blindness. Early recognition of ophthalmic signs and appropriate management are also crucial in preventing serious ocular complications in the chronic stage [4]. Nevertheless, ophthalmologists mainly encounter people with SJS/TEN in the chronic phase, as patients with SJS/TEN primarily receive intensive dermatological (and burn unit) care in the acute phase; thus, ophthalmic examination is lacking in most cases [5]. Differentiation between SJS and TEN may be difficult in the chronic stage, as skin lesions are already healed at that timepoint. Management of repeat exacerbations of SJS/TEN in the chronic phase can be even more challenging, and is therefore very often inefficient [6].

This review article summarizes previously published studies and knowledge on ocular complications and their diagnosis and management in SJS/TEN. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

SJS and TEN incidence varies by geographic region. These are rare and unpredictable diseases [7]. SJS and TEN appear in all races, ages and sexes. The annual incidence of SJS/TEN (per million people) is reported to be 0.93 in Germany [8], 5.76 in the UK [9] and 12.35 in the USA [10]. In contrast, the incidence of SJS/TEN in Africa is 100× higher than that in industrialized countries, since SJS/TEN is more common in people with human immunodeficiency virus (HIV) infection [11]. The incidence also rises with increasing age [4]. The incidence of SJS/TEN is at least 30× higher in cancer patients, which may also draw attention to the possible role of the immune system in the development of SJS/TEN [12]. Additionally, female sex is associated with a 1.5× increase in the prevalence of SJS/TEN, and pregnancy is associated with a 14× increase compared with the entire population [7, 11]. Acute ocular signs of SJS/TEN affect 50–80% of patients [13, 14], and severe early ocular complications affect approximately 50% of people with SJS/TEN [15]. Almost 90% of people with SJS/TEN have some chronic ocular disease following the acute stage [16]. In Europe, the overall lethality of SJS/TEN is estimated to be 34%, with 24% in SJS and 49% in TEN [17].

AETIOLOGY

The main aetiological factors are medicines (75%). The other 25% can be caused by viral and *Mycoplasma pneumoniae* infections, and can be idiopathic [18].

The most frequent pharmacological triggers are antibiotics (53.2%), anticonvulsants (35.7%), non-steroidal anti-inflammatory drugs (NSAIDs; 15.9%) and anti-neoplastic agents [12, 19]. SJS/TEN occurs most frequently following fluoroquinolone (8.5%), antitubercular (5.7%), penicillin (5.4%) and sulphonamide (3.1%) intake. Among anti-epileptics, carbamazepine and phenytoin are the most common causative agents. Paracetamol (6.2%), nimesulide (2.8%), diclofenac (2.1%) and ibuprofen (1.0%) have been reported to be the most common NSAIDs associated with subsequent SJS/TEN. Severe ocular complications due to SJS/TEN are thought to be associated with cold medicines [20]. However, there may be a large

overlap between cold medicine-related and idiopathic SJS/TEN. For this reason, some authors consider SJS/TEN induced by cold medicines to be idiopathic [21].

SJS/TEN caused by infections is rare. Nevertheless, viral infections are more frequent causes of SJS/TEN in children and young adults than medications [18]. Only case reports and small sample-size case series are available in the literature on the association between infection and SJS/TEN. *Mycoplasma pneumoniae*, coxsackievirus A6 and COVID-19 have been reported to cause SJS/TEN [22, 23]. A microbiological study reported that higher germ counts of *Pseudomonas* spp., *Streptococcus* ssp., *Acinetobacter* ssp. and *Staphylococcus* spp. can be observed in people with SJS/TEN [24].

Several authors are assuming a revised classification for SJS/TEN in children. They suggest distinguishing between medicine-induced SJS/TEN (drug-induced epidermal necrolysis; DEN) and infection-caused SJS/TEN (reactive infectious mucocutaneous eruption; RIME) in children because DEN and RIME have differing therapeutic strategies. Management strategies should focus on medicine withdrawal at DEN and on treatment of infection at RIME [25, 26].

PATHOPHYSIOLOGY

Genetic predisposition is suspected, as SJS/TEN does not develop in all patients taking the above-mentioned drugs [15]. SJS/TEN is supposed to be associated with changes in the innate immune system; however, the pathophysiology of SJS/TEN has only been partly explored until now.

The acute phase of SJS/TEN is thought to be a T-cell-mediated type IV hypersensitivity reaction [7], where the exogenous factor causes an abnormal immune reaction with extensive keratinocyte apoptosis [27]. Drugs and infections are perceived by T-cell receptors, which lead to CD8 + , cytotoxic T-cell and natural killer (NK) cell-mediated keratinocyte apoptosis.

Cytotoxic mediators, such as perforin, granzyme B, Fas ligand, tumour necrosis factor alpha and granulysin, seem to have an important role in keratinocyte death [28]. Chung et al. revealed that granulysin is a key mediator in disseminated keratinocyte apoptosis. Similar to graft-versus-host disease, granulysin is also expressed in SJS/TEN skin lesions. Another similarity is that in both graft-versus-host disease and SJS/TEN, the dermis is populated by CD4-positive T cells and the epidermis with CD8-positive T cells [29].

Histocompatibility loci are frequently analysed to determine whether there is a connection between human leucocyte antigens (HLA) and SJS/TEN.

HLA-B* 1508, HLA-B* 1511, HLA-B* 1518 and HLA-B* 3101 have a strong association with carbamazepine-induced SJS/TEN, and HLA-B* 1502 presumably increases the risk of carbamazepine-, phenytoin- and oxacarbazepine-induced SJS/TEN [30, 31].

The HLA-B* 12 genotype has an important role in oxicam- and sulfonamide-induced SJS/TEN [32].

It is presumed that HLA-B* 5801 has an association with allopurinol-induced SJS/TEN. Moreover, the HLA-B* 5801 genotype, together with HLA-B75 or DR13 homozygosity, further enhances the danger of allopurinol-induced SJS/TEN [33].

Other studies reported an association between HLA-A* 0206 and NSAID- and acetaminophen-induced SJS/TEN. Furthermore, the HLA-A* 0206 genotype with prostaglandin-E receptor 3 single nucleotide polymorphism evolves a synergistic impact in the evocation of NSAID-induced SJS/TEN, with severe ocular complications [14].

Genetic variants of cytochrome P450 2C are also thought to be related to SJS/TEN [28].

CLINICAL MANIFESTATION

Acute Phase

The acute phase of SJS/TEN develops 4–28 days after the triggering event [34]. SJS/TEN begins with a prodrome of fever, cough, rhinorrhea, anorexia and malaise. This is followed by the acute phase with inflammation and ulcerations of the oral, genital, ocular and anal mucosa 1–3 days later [3, 5]. Acute SJS/TEN can be

recognized by the inflammation of at least two mucous membranes [4]. The acute phase takes place within 2 weeks after the appearance of SJS/TEN and is characterized by excessive epidermal and keratinocyte necrosis. Skin lesions appear as erythaematous maculas or atypical targetoid lesions, bullae, erosions and ulcers on the trunk [19].

Differentiation between SJS and TEN is based on the affected total body surface area (BSA): SJS with < 10% BSA, SJS/TEN overlap with 10–30% BSA and TEN with > 30% BSA involvement [35]. The most frequently found ocular symptoms (Fig. 1) are bilateral conjunctivitis and corneal epithelial defects. Widespread eyelid margin necrosis, meibomitis, epithelial loss of the conjunctiva and pseudomembrane/membrane development can lead to symblepharon formation, and corneal erosions may result in corneal ulceration and perforation [36].

The most common ophthalmic complaints of patients with acute SJS/TEN are visual impairment, eye pain and photophobia. The severity of ocular sequelae does not always correspond to the severity of cutaneous lesions or systemic disease [37].

A grading system for ocular manifestations of acute SJS/TEN was developed by Gregory [38] (Table 1). The grading scheme is developed based on the epithelial defects at the eyelid margins, on the conjunctiva, and on the cornea. Ocular surface alterations in acute SJS/TEN result in devastating long-term complications.

Predicted mortality can be calculated with the SCORe of TEN (SCORTEN) [39] and ABCD-10 [40] methodologies. SCORTEN is a mathematical model that uses seven independent risk factors (age, malignancy, heart rate, epidermal detachment, serum urea, serum glucose and serum bicarbonate) to estimate the probability of mortality due to SJS/TEN [39]. ABCD-10 is a newer risk prediction model for predicting the mortality rate from SJS/TEN. The estimation is based on five risk factors: age, serum bicarbonate, cancer, dialysis and 10% body surface area. ABCD-10 uses 'dialysis before SJS/TEN' instead of SCORe's renal dysfunction at mortality prognostication [40]. SCORTEN has been proven to be superior to ABCD-10 in mortality rate estimation for SJS/TEN [41].

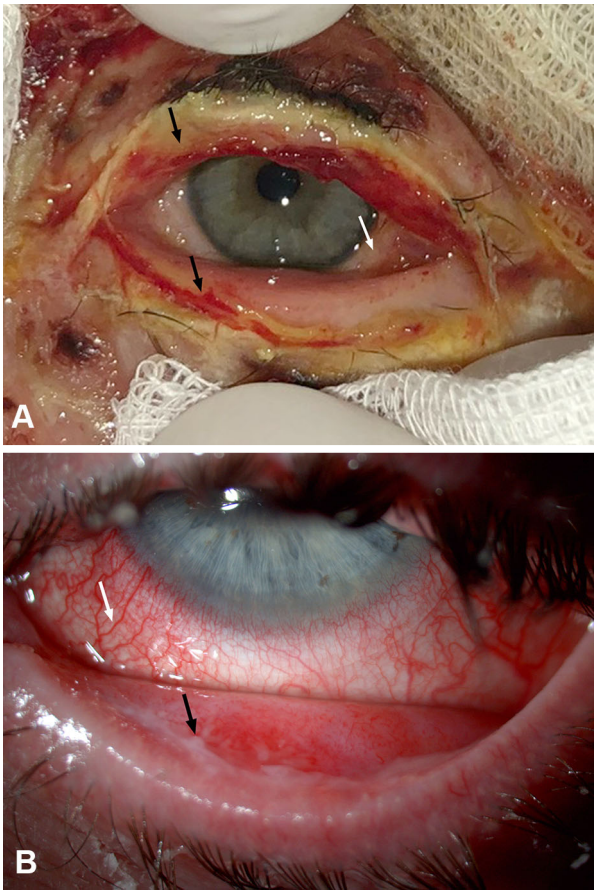

Fig. 1 Ocular signs of acute Stevens–Johnson syndrome/toxic epidermal necrolysis. **A** BA: widespread eyelid margin necrosis, WA: conjunctival chemosis; **B** BA: pseudomembrane development, WA: conjunctival hyperaemia. *BA* black arrow, *WA* white arrow

The most frequently isolated bacterium in the early acute phase of SJS/TEN is *Staphylococcus aureus*, while the most commonly isolated microbe that can lead to a prolonged hospital stay in SJS/TEN is *Pseudomonas aeruginosa* [6].

Chronic Phase

Chronic ocular sequelae may occur in 35–90% of people with SJS/TEN and may affect the eyelid, conjunctiva and cornea. Chronic SJS/TEN can be considered an aftermath of mechanical and physiological insults of the ocular surface [42]. There is no explicit zero point at which SJS/TEN can be considered chronic, but it generally starts between 3 and

Table 1 Grading scheme for ocular manifestations of acute Stevens–Johnson syndrome and toxic epidermal necrolysis developed by Gregory [38]

Location of the defect	Mild	Moderate	Severe	Very severe
Eye lid margin	No defect	FS < 30% of lid margin	FS > 30% of lid margin on one eyelid	FS > 30% of lid margin on two eyelids
Conjunctiva	Hyperaemia	FS < 1 cm of diameter	FS > 1 cm of diameter	FS > Multiple areas larger than 1 cm of diameter
Cornea	No defect	No defect	FS > larger than punctate erosions	FS > larger than punctate erosions

FS fluorescein staining

6 months following the acute phase, after stabilization of the ocular surface inflammation [43].

Sotozono et al. [13] evolved a three-category grading scheme for chronic ocular complications of SJS/TEN (Table 2) in 2007, using 13 clinical components based on eyelid, conjunctival and corneal involvement. Sharma et al. [34] developed a modified multi-step grading system for chronic ocular sequelae of SJS/TEN (Table 3) based on the grading scheme of Sotozono et al. in 2019, addressing the more severe cases in greater detail.

Chronic ocular sequelae of SJS/TEN (Fig. 2) are unpredictable and have poor correlation with acute SJS/TEN [27]. However, the severity of acute SJS/TEN is the best predictor for chronic eye complications [44].

Eyelid complications include meibomian gland destruction, lid margin keratinization, entropion or ectropion development, trichiasis, lacrimal punctal occlusion and mucocutaneous junction involvement. It should be emphasized that most corneal sequelae can originate from lid margin keratinization [45].

Conjunctival complications may lead to persistent inflammation, hyperaemia, membrane formation, ulceration, scarring and squamous metaplasia. Obstruction of the ductal openings of the lacrimal gland due to conjunctival scarring and destruction of the goblet cells impair the tear film quality [3, 5]. All components of the tear film can be affected (mucin, aqueous and lipid layers) in chronic SJS/TEN, and their dysfunction may lead to severe dry eye, which is one of the most common ocular complications of the disease. Ocular surface scarring leads to ankyloblepharon and symblepharon formation with inadequate closure of the eyelids and limited ocular motility [37].

Microtraumas through the affected eyelids lead to long-term corneal complications, including loss of the palisades of Vogt, limbal stem cell deficiency, neovascularization, keratinization, conjunctivalization and corneal decompensation. Keratinization of the eyelid margin may lead to persistent or recurrent corneal epithelial defects, ulceration, stromal melting and corneal perforation [14]. The ocular surface in healthy eyes has a high diversity of microbiomes, with *Streptococcus* and *Lactobacillus* as the most prevalent bacteria. In contrast, the ocular surface in chronic SJS/TEN shows a lower bacterial diversity with a *Staphylococcus* predominance, and these bacteria can become easily pathogenic. Accordingly, the incidence of infective keratitis is higher in people with SJS/TEN than in persons with earlier severe ocular burns [46].

The combination of these processes may lead to blindness and loss of the eye. The end stage of chronic ocular SJS/TEN can be characterized by an entirely keratinized and dry ocular surface [4]. In total, 87% of people with chronic SJS/TEN have difficulties with driving at night or reading [47].

Table 2 Grading scheme for ocular manifestations of chronic Stevens–Johnson syndrome and toxic epidermal necrolysis developed by Sotozono et al. [13]

Location of the defect		Grade/score			
		0	1	2	3
Eye lid	Mucocutaneous junction involvement	No	Mild irregularity	Moderate irregularity	Severe irregularity
	Meibomian gland dysfunction	No	Whitish–yellow secret	Toothpaste-like secret	No expressible secret
	Punctal defect	No	Surgical punctal occlusion	One punctal occlusion by scarring	Upper and lower punctal occlusion by scarring
	Trichiasis	No	< 1/4 of lid margin	≥ 1/4 and < 2/4	≥ Half
Conjunctiva	Bulbar hyperaemia	No	Mild	Moderate	Severe
	Symblepharon	No	Cornea is not involved	< 50% corneal surface	≥ 50% corneal surface
Cornea	Conjunctivalization	No	< 3 clock hours of limbal involvement	3–6 clock hours of limbal involvement	> 6 clock hours of limbal involvement
	Loss of palisades of Vogt	No	< 6 clock hours of limbal involvement	6–12 clock hours of limbal involvement	Total limbal involvement
	Neovascularization	No	Corneal periphery is affected	Extends until the pupil margin	Extends to the central cornea
	Keratinization	No	< 1/4	≥ 1/4 and < 2/4	≥ Half
	Epithelial defect	No	< 25% of the surface	25–50% of the surface	> 50% of the surface
	Superficial punctate keratopathy	No	< 33% of the surface	33–66% of the surface	> 66% of the surface
	Opacification	No	Mild haze	Moderate haze	Severe haze

Diagnosis and Differential Diagnosis

SJS/TEN diagnosis must be based on clinical characteristics, but histological confirmation should always be performed. Histologically, SJS/TEN shows partial to full-thickness keratinocyte necrosis and slight lymphohistiocytic inflammation around the vessels [6].

Nevertheless, there are some other vesiculobullous and desquamating skin diseases that may have a similar appearance as SJS/TEN. The most important differential diagnostic entity is erythema multiforme major (EMM). Previously, SJS/TEN and EMM with similar histologic and clinical appearances were considered different presentations of a spectrum disease, but currently, both are considered two separate entities [48]. EMM may recur more often than SJS/TEN and affects only one mucosal surface in most cases; it is caused most commonly by *M. pneumoniae* and herpes simplex virus (HSV) [49]. EMM concerns mainly the facial and acral skin, while SJS/TEN predominantly involves the trunk [7].

Other differential diagnostic options that should be considered are staphylococcal scalded skin syndrome, acute generalized exanthaematous pustulosis, linear immunoglobulin (Ig)A

Table 3 Grading scheme for ocular manifestations of chronic Stevens–Johnson syndrome and toxic epidermal necrolysis developed by Sharma et al. [34]

Location of the defect		Grade/score					
		0	1	2	3	4	5
Eye lid	Mucocutaneous junction involvement	No	Mild irregularity	Moderate irregularity	Severe irregularity	Total symblepharon	Ankyloblepharon
	Meibomian gland dysfunction	No	Whitish–yellow secret	Toothpaste-like secret	No expressible secret	–	–
	Punctal defect	No	One punctal occlusion	Upper and lower punctal occlusion	–	–	–
Conjunctiva	Bulbar hyperaemia	No	$\leq 1/4$	$> 1/4$ and $\leq 2/4$	$> 2/4$ and $\leq 3/4$	4/4	Ankyloblepharon
	Bulbar keratinization	No	$\leq 1/4$	$> 1/4$ and $\leq 2/4$	$> 2/4$ and $\leq 3/4$	4/4	Ankyloblepharon
	Symblepharon	No	Cornea is not involved	$< 1/3$ corneal surface	1/3 to 2/3 corneal surface	$> 2/3$ corneal surface	Ankyloblepharon
Cornea	Conjunctivalization	No	≤ 3 clock hours of limbal involvement	3–6 clock hours of limbal involvement	6–9 clock hours of limbal involvement	> 9 clock hours of limbal involvement	Ankyloblepharon
	Loss of palisades of Vogt	No	≤ 3 clock hours of limbal involvement	3–6 clock hours of limbal involvement	6–9 clock hours of limbal involvement	> 9 clock hours of limbal involvement	Ankyloblepharon
	Neovascularization	No	≤ 3 clock hours of limbal involvement	3–6 clock hours of limbal involvement	6–9 clock hours of limbal involvement	> 9 clock hours of limbal involvement	Ankyloblepharon
	Keratinization	No	$\leq 1/4$	$> 1/4$ and $\leq 2/4$	$> 2/4$ and $\leq 3/4$	4/4	Ankyloblepharon
	Epithelial defect	No	Punctate erosions	Larger than punctate erosions	Not gradable due to the condition of the corneal surface	–	–
	Opacification	No	Very mild haze	Mild haze	Moderate haze	Severe haze	Ankyloblepharon

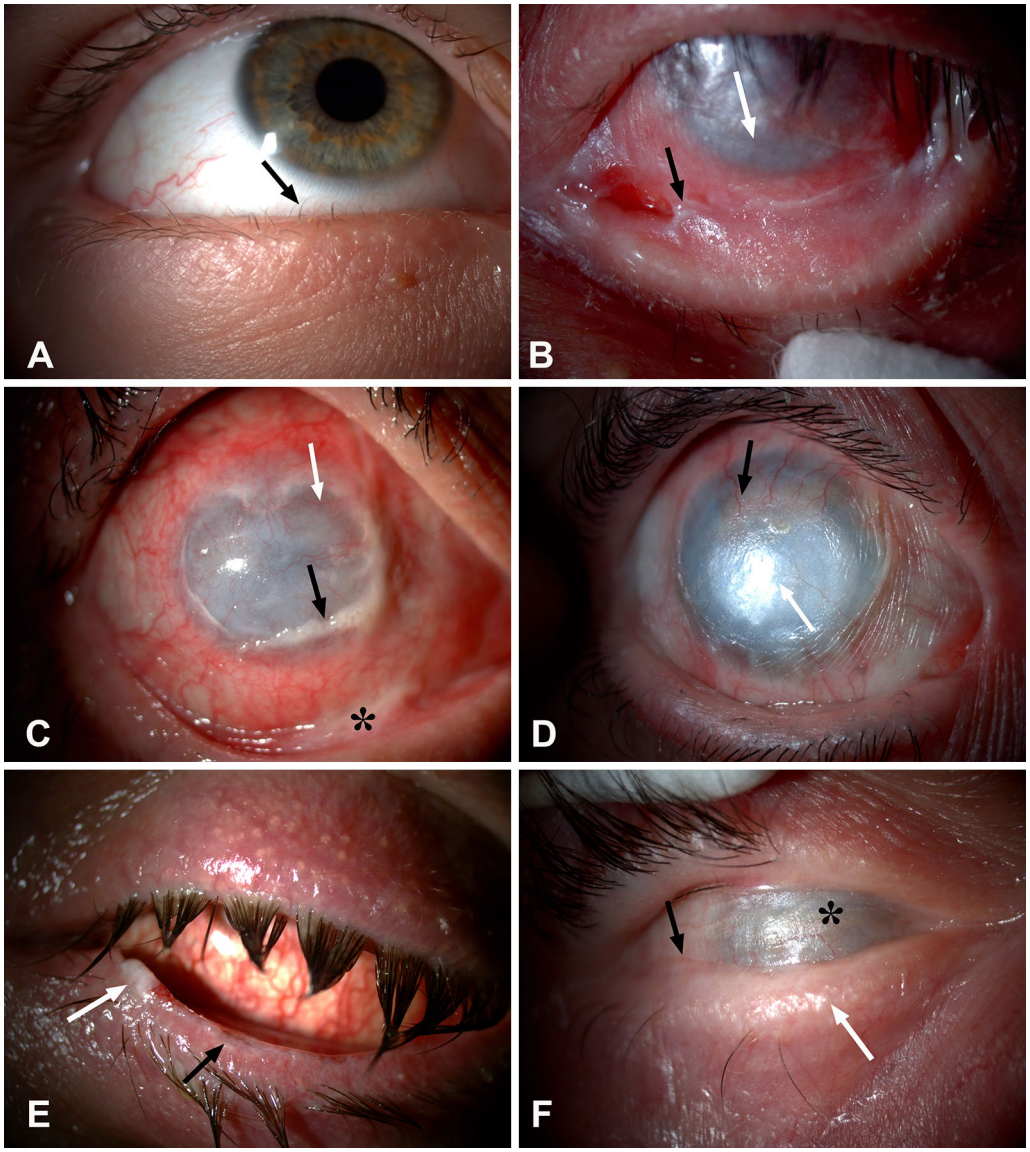

Fig. 2 Chronic ocular sequelae of Stevens–Johnson syndrome/toxic epidermal necrolysis. **A** BA: trichiasis; **B** BA: symblepharon, WA: corneal keratinization; **C** BA: conjunctivalization of the cornea, WA: corneal neovascularization, S: symblepharon; **D** BA: corneal neovascularization, WA: corneal keratinization; **E** BA: meibomian gland destruction, WA: lid margin keratinization; **F** BA: symblepharon, WA: meibomian gland destruction, S: corneal keratinization. *BA* black arrow, *WA* white arrow, *S* star

bullous dermatosis, pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid and acute graft-versus-host disease. Therefore, the most important differential diagnostic step is to visit a dermatologist [50].

MANAGEMENT

Acute SJS/TEN

The management of acute SJS/TEN is multidisciplinary and starts with the discontinuation or suppression of the causative factor [51].

Medical history is essential to explore the cause of the disease, as the first symptoms typically appear within 1–8 weeks after starting taking the causative drug [7, 52].

All people with acute SJS/TEN should be managed first in a burn unit or intensive care unit. The most important general aspects of medical attendance are to manage nutritional, electrolyte and fluid imbalances; to maintain respiratory and renal function; and to control infection, as well as to assure analgesia [6]. Dermatological, ophthalmic, gynaecological, urological and nephrological consultation may be necessary in the early phase [53], depending on the patient's needs. Ophthalmic examination is necessary at admission or within 1–-2 days after SJS/TEN diagnosis [54].

Cornerstones of acute ophthalmic care are to inhibit the immune response on the ocular surface and to prevent chronic ocular sequelae. Waiting for skin biopsy results should not delay eye care. Ophthalmic care of acute SJS/TEN should be initiated based on the clinical signs [43]. Daily eye examinations should be performed, as ocular inflammation can evolve rapidly [37].

Eyelid margins should be managed with a combination of antibiotic–steroid ointment (tobramycin 0.3%/dexamethasone 1%) 4–6 times daily [38].

Mild and moderate SJS/TEN cases should be treated with levofloxacin 0.5–1.5% or moxifloxacin 0.5% eye drops three to four times a day, with topical corticosteroid (dexamethasone 1% or prednisolone acetate 1%) eye drops two to six times daily and cyclosporine 0.05–0.09% drops two to four times daily, depending on the severity [4, 14, 43]. The use of preservative-free topical lubricants is also recommended to protect the ocular surface, which should be instilled every hour. Topical lubricants could also be replaced by autologous serum eye drops. The removal of ocular surface membranes and pseudomembranes is recommended with a glass rod in all patients [42]. Healing of smaller corneal epithelial defects can be promoted by fitting soft therapeutic contact lenses [5].

Severe and extremely severe cases should be managed similarly to moderate cases with topical drops and ointment. In addition, all patients must undergo thorough removal of inflammatory debris and amniotic membrane transplantation (AMT) as a patch, combined with conformer, symblepharon ring or ProKera use within the first 10 days. AMT for acute SJS/TEN was first reported by John et al. in 2002 [55]. The amniotic membrane patch must cover the entire ocular surface, the fornix, the tarsal conjunctiva and the eyelid margins [56]. AMT prevents eye surface ruination, inhibits inflammation and hastens re-epithelization. AMT reduces the risk of chronic ophthalmic complications, such as limbal stem cell deficiency, corneal haze, ankyloblepharon, symblepharon or other eyelid sequelae. People with acute SJS/TEN are frequently medically unstable; therefore, AMT in general anaesthesia may be unfeasible. Thus, AMT should be performed bedside with local anaesthesia [42]. The AMT could be fixated to a conformer using 10/0 nylon sutures, and this complex could be inserted under the eyelids. In addition, the suture-less AMT technique with cyanoacrylate glue has been described by Shanbhag et al. [57]. Suture-less AMT is more feasible under local anaesthesia and causes less discomfort. Generally, the amniotic membrane dissolves in several weeks, and topical therapy should be further continued [42]. An eye check-up should occur on the fourth day and then every week following AMT [4]. Complications of AMT in people with SJS/TEN are extremely rare [58].

In the case of extremely severe acute SJS/TEN, the presence of large de-epithelized ocular surface areas and ocular surface inflammation, a repeat AMT should be performed 7–14 days following the first AMT [44].

The effect of systemic anti-inflammatory therapies is still a subject of debate. The published data on adjunctive therapies in acute SJS/TEN are equivocal. To date, there is no available evidence regarding whether systemic corticosteroid, intravenous immunoglobulin (IVIG), plasmapheresis, systemic cyclosporine, tumour necrosis factor (TNF) inhibitors or cyclophosphamide have advantageous effects on visual outcome and chronic eye sequelae in SJS/TEN [59]. Moreover, the use of these systemic

therapeutic possibilities includes severe systemic risks [43].

A larger meta-analysis has not found any statistically significant positive effect of systemic corticosteroid monotherapy [60]. Interestingly, people taking systemic corticosteroids for other diseases still develop SJS/TEN [61]. Moreover, corticosteroids seem to be associated with higher rates of mortality and infections [62]. Therefore, many experts advise against the use of systemic corticosteroids as monotherapy for people with acute SJS/TEN [28].

Nevertheless, a 3-day course of high-dose pulsed corticosteroid (1.5 mg/kg/day) appeared to improve the mortality rate and visual outcome [50], with no systemic complications [37].

IVIG is a commonly administered, first-line therapy for acute SJS/TEN. IVIG down-regulates Fas-mediated keratinocyte apoptosis [63]. Nevertheless, in the largest published treatment series, there was no significant mortality benefit compared with the SCORTEN-predicted mortality using IVIG treatment [28]. Other studies have shown that IVIG monotherapy can lead to longer hospital stays [64] and increase mortality [50]. In addition, IVIG does not seem to decrease the severity of chronic ocular sequelae [65], and acute renal failure – which is the most severe complication – may occur [66].

Nevertheless, combining IVIG with high-dose pulsed steroid treatment (500–-1000 mg/day for 4 days) has been shown to restrain ocular complications when administered within 4 days of SJS/TEN onset [67].

Plasmapheresis removes non-dialysable pathogenic agents from the plasma. The method is relatively safe. Several case reports and series are available in the literature, reporting controversial results [50]. The only available prospective study, published by Han et al., showed that people with acute SJS/TEN had a lower severity of illness scores in the chronic phase following plasmapheresis [68]. However, there is no evidence that plasmapheresis has any significant effect on mortality or reepithelization [69].

Cyclosporin A has an immunosuppressive effect and can inhibit apoptosis [70]. Cyclosporin A (4 mg/kg/day) may have a mortality benefit compared with the SCORTEN-predicted mortality, and delays the progression of the disease [28]. Nevertheless, it can be associated with severe side effects such as neutropenia, nephropathy, pneumonia and leucoencephalopathy [71].

TNF inhibitors may inhibit keratinocyte apoptosis. Unfortunately, administration of thalidomide in SJS/TEN had to be stopped during the first trial as it increased mortality [72]. In contrast, infliximab and etanercept have promising prospects, as they may hamper progression, induce skin reepithelization and seem to decrease mortality [28, 50].

Cyclophosphamide can facilitate re-epithelization. However, its usage also had to be discontinued in people with acute SJS/TEN due to its higher mortality rate [73].

Chronic SJS/TEN

The management of chronic ocular sequelae of SJS/TEN is based on prevention of ocular surface irritation, treatment of the complications and visual rehabilitation [4]. The first follow-up examination should occur within 4 weeks after release from the hospital and should be performed every 2–4 months repeatedly in the first year and every 6 months thereafter [74].

Ocular surface dryness can be managed from several aspects. Replacement of the aqueous layer with preservative-free artificial tears is frequently a first-line therapy [75]. Autologous serum eye drops contain several ingredients similar to natural tears, such as vitamin A, fibronectin and epidermal growth factor [76]. In addition, topical cyclosporine improves goblet cell density [77]. Meibomian gland dysfunction should be treated with daily eye lid hygiene. Depending on the ocular surface inflammation, topical steroid eye drops and antibiotics can be used [78]. Oral azithromycin or doxycycline may add to the management of inflammation [79].

It is important to avoid any surgical procedures in chronic SJS/TEN, unless it is definitely inevitable. If the lacrimal drainage system is intact, lacrimal punctal occlusion using punctal plugs or cautery may help in controlling ocular surface dryness [43].

In cases of severe dry eye, salivary gland transplantation can be performed either from the submandibular or minor salivary glands. Nevertheless, it has limited popularity as it may often be accompanied by excessive tearing, and this type of surgery has low reproducibility [78]. Epiphora is rarely observed following minor salivary gland transplantation compared with submandibular gland transplantation [80].

Before any surgical procedures for visual rehabilitation, it is essential to manage eyelid abnormalities. To protect the ocular surface, keratin must be removed from the eyelid margins. Ectropion and entropion can be treated with eye lid surgery, trichiasis and distichiasis with epilation, cryotherapy and extirpation [74].

The use of scleral contact lenses protects the corneal surface from micro-traumas caused by keratinized eyelid margins and misdirected eyelashes, and therefore supports the healing of corneal epithelial defects. In addition to scleral contact lenses, the prosthetic replacement of the ocular surface ecosystem (PROSE) device is a promising treatment option in patients with chronic SJS/TEN, and has beneficial features similar to those of scleral lenses. PROSE is a scleral prosthetic device that can be used in people with highly irregular ocular surfaces [37].

Other aims of scleral contact lenses and PROSE are to reduce photophobia and mask corneal irregular astigmatism. Overnight wear of scleral lenses is not recommended as it may enhance the risk of microbial keratitis. Soft and rigid contact lenses are not appropriate as they do not ensure enough fluid-filled space between the posterior surface of the contact lens and the anterior surface of the cornea. However, considerable symblephara may hamper the use of scleral contact lenses [42].

In patients with symblepharon, lid margin keratinization and reconstruction of conjunctival surfaces and lid margins with mucous membrane grafting (MMG) can be a solution. Keratinized tarsal and bulbar conjunctiva can be replaced with autologous buccal or labial mucosa, which can be fixed either with Vicryl sutures or with fibrin glue. MMG has been reported to be sufficient in stabilizing the ocular surface and improving visual function [81]. Moreover, MMG seems to have a beneficial effect on corneal neovascularization, haze formation and corneal reepithelialization [19]. MMG can be combined with AMT for fornix restoration [74]. MMG combined with scleral contact lens use is an optimal treatment method in chronic SJS/TEN.

MMG addresses lid margin-related keratopathy, even overnight, while wearing scleral contact lenses, and PROSE is not recommended. Early use of MMG in conjunction with scleral contact lens use may have synergistic effects, can prevent the development of limbal stem cell deficiency and persistent corneal epitheliopathy, and is effective in preservation and improvement of visual acuity. MMG may also improve the compliance of children in wearing rigid contact lenses and PROSE [42, 82, 83].

Persistent corneal epithelial defects can be treated with AMT [84]. Penetrating keratoplasty (PK) may help in urgent cases, such as corneal perforation, advanced thinning or ulceration [43], but is not suitable for people with SJS/TEN as PK does not facilitate the regeneration of corneal epithelial stem cells. Limbal stem cell transplantation (LSCT) is a general surgical intervention for limbal stem cell deficiency. However, it has been reported that allogenic LSCT has a poorer success rate for people with chronic SJS/TEN than for persons who suffered ocular burn [4, 85]. Graft failure is a frequent complication of LSCT in people with SJS/TEN, as patients with SJS/TEN have severe ocular comorbidities (ocular surface inflammation, serious dry eye, eye lid margin and epithelial abnormalities) preoperatively [36]. Therefore, allogenic LSCT is not the recommended procedure for chronic SJS/TEN, even with immunosuppression. Since SJS/TEN affects both eyes, autologous LSCT is not a possibility [37].

Since 2002, autologous cultivated oral mucosal epithelial transplantation (COMET) has been developed for reconstruction of the corneal surface in people with chronic SJS/TEN as it promotes post-operative corneal re-epithelialization and stabilizes the corneal surface in the long term. Additionally, after COMET patients do not need immunosuppression after surgery [86]. For COMET, autologous mucosal

epithelial cells are gathered from the buccal mucosa and seeded on an amniotic membrane, first in vitro [87]. These cultivated cells are later used for ocular surface reconstruction. Sotozono et al. reported that better postoperative visual acuity is achievable in people with chronic SJS/TEN using COMET than with LSCT [88].

Keratoprosthesis is suitable for the replacement of an opaque cornea. Keratoprosthesis implantation is actually regarded as a safe and effective treatment option for patients with severe limbal stem cell deficiency and corneal surface disease, where further PK, LSCT or COMET are deemed likely to fail [89]. Keratoprosthesis implantation is a suitable procedure for visual rehabilitation in special cases of corneal blindness, and it has been proven to be more effective than PK with or without LSCT. Boston type I keratoprosthesis is used in cases of unchanged eyelid function, while xerotic ocular surfaces are only suitable for Boston type II keratoprosthesis and osteo-odonto-keratoprosthesis (OOKP) implantation [90]. Nevertheless, unfortunately, compared with other ocular surface diseases, SJS/TEN is associated with a higher post-operative complication rate of ulceration, corneal melting and endophthalmitis, as well as worse visual prognosis following keratoprosthesis surgery, than other autoimmune-based disorders [43].

It is important to note that referral of patients with severe chronic SJS/TEN to a clinical psychologist may provide great support to the patients [4].

CONCLUSIONS

SJS/TEN are rare multisystem diseases with severe ocular surface sequelae, which can lead to bilateral blindness. Careful examination and adequate aggressive ophthalmic management in the acute phase are essential to prevent or moderate chronic SJS/TEN. Restoration of the ocular surface in SJS/TEN remains challenging. If necessary, AMT should be performed in the acute stage at the earliest possibility to prevent chronic complications. PROSE combined with MMG should be the standard management technique for lid margin keratinization in people with chronic SJS/TEN. Randomized studies are needed to determine the best therapies for patients with acute and chronic SJS/TEN.

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