The ROYAL COLLEGE of OPHTHALMOLOGISTS

focus

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Management of Ocular involvement of Steven Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis Syndrome (TENS)

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Steven Johnson Syndrome (SJS) and its more severe form, Toxic Epidermal Necrolysis Syndrome (TENS) are rare, drug-induced, immune-mediated acute blistering, necrotic diseases of the skin and mucous membranes with life-threatening complications including sepsis, respiratory dysfunction, gastrointestinal ulceration, significant ocular morbidity and potential multiple organ failure.[1,2] The most frequent precipitant drugs are anti-convulsants, NSAIDS and antibiotics, although no causal drug may be identified in up to 30% of cases.[3,4]

SJS/TENS is a disease severity spectrum. Skin detachment of less than 10% of total body surface area (TBSA) is classified as SJS, 10% to 30% TBSA skin detachment as SJS/TENS overlap, and >30 % TBSA skin detachment as TENS.[5] Mortality, ranges from 1%-5% in SJS rising to 25%-40% in TENS. Ocular involvement with inflammatory de-epithelization of the ocular surface is seen in 50%-81%.[5]

Remarkably, despite extensive skin loss, the skin recovery is usually complete and without dysfunction (apart from hyperpigmentary changes). However, when there is ocular involvement, the acute destructive ocular inflammation is followed by cicatrizing sequalae in 20%-75% of the SJS/TEN survivors. This can result in lifelong severe debilitating dry eye and blindness.

Thus, the focus is on acute management with the goal of controlling the acute inflammatory reaction, restoration of an intact ocular surface, and prevention of chronic and blinding sequalae.[5]

Grading of acute ocular involvement

The acute pathology includes inflammation and denudation of the entire ocular surface including the lid margin, bulbar and palpebral conjunctiva. Lid margin staining is often the earliest sign and should be carefully looked for. The conjunctiva appears congested, oedematous and may have pseudomembranes over the palpebral surface. Bulbar conjunctival staining is an important sign. Defects larger than 1cm should prompt amniotic membrane transplantation. In the initial stages, denuded epithelial cells may form pseudo synechiae that are easily breakable manually or with saline washes. Corneal staining and frank epithelial defects are not seen until two to three weeks after the onset of skin detachment and blistering. These corneal epithelial defects may become persistent and may be complicated by stromal inflammation or infection. Early cicatrizing changes with loss of luster of conjunctival epithelium and symblephera may be seen within a few weeks of onset.

The severe acute inflammatory process has a destructive effect on limbal stem cells and the conjunctival goblet cells. This is responsible for the devastating cicatrizing sequalae of the disease.

Destruction of the conjunctival goblet cells and obliteration of the secretory lacrimal gland ducts leads to severe ocular surface dryness.

The conjunctival surface may undergo squamous metaplasia and develop symblephera, ankyloblephera and fornix shortening.

Limbal stem cell deficiency manifests as conjunctivalisation, vascularization and opacification of the cornea. Persistent corneal epithelial defects may be complicated by ulceration, corneal melt with descemetocele formation, perforation, secondary infection and blindness.

Obliteration of meibomian orifices contributes to severe dry eye and keratinization of the lid margin, which perpetuates corneal microtrauma leading to lid wiper keratopathy. Fornix shortening leads to entropion, trichiasis, deficiency in lid closure and blinking, collectively aggravating the corneal complications.[6]

Management of ocular involvement in SJS/TENS

SJS/TENS patients need multi-disciplinary input from dermatologists, microbiologists, burns surgeons, gynaecologists, urologists and ophthalmologists. Patients with TENS (>30% skin loss) require management in a specialised burns centre with intensive care facilities. First-line treatment includes prompt removal of the offending drug, management of skin loss, fluid balance, temperature maintenance, pain relief and supportive care to minimize complications - most notably sepsis.

Ophthalmologists should be involved within 24 hours of suspicion of SJS/TENS and provide daily reviews during the acute phase that can last for two to six weeks. Although examining intubated patients in the intensive care unit can be challenging, a portable slit lamp assisted by saline irrigations, removal of membranes, lid retraction using Desmarres retractors, and fluorescein staining allow meticulous evaluation. The extent of involvement of the lid, conjunctiva and cornea must be serially documented. (Table 1)

Three-pronged approach for ocular SJS/TENS management

1. Intensive topical lubricants and steroids
2. Amniotic Membrane Transplantation (AMT)
3. Systemic immunosuppression

Intensive topical treatment

Patients require a high frequency of eye drops round the clock and intensive care staff play a key role in the acute phase of the illness.

1. **Lubricants:** Preservative-free lubricants (eg, Sodium Hyaluronate 0.2% or Carmellose 1%) are administered hourly day and night.[7] Serum eye drops can be used as an alternative in severe cases.
2. **Steroids:** Preservative free steroids (Dexamethasone 0.1%) are administered typically every one to two hours day and night. Frequency is determined upon the level of inflammation. Close monitoring of the eyes for infection and intraocular pressure rise is paramount. Ciclosporin (0.1%) eye drops may be used once a day alongside topical steroids.[8]
3. **Antibiotics:** Prophylactic preservative free antibiotic (Chloramphenicol 0.5% or a fluoroquinolone like Moxifloxacin or Levofloxacin in case of corneal epithelial defects) are used four times a day. The antibiotic may need to be tailored based on eye swabs, contact lens culture or corneal scrape culture sensitivity.

Lagophthalmos may be seen temporarily while patients are mechanically ventilated or when the skin lesions develop crusting. Lubricating ointments (such as Xailin night or Vitamin A) or chloramphenicol ointment is used to prevent exposure keratopathy (when a contact lens has not been inserted along with AMT).

In some cases (specifically SJS) patients are ambulatory and able to safely tolerate oral steroids. The ocular involvement is limited to mild non-progressive conjunctival inflammation and mild lid margin de epithelization. These cases can be treated with lubricant and steroid eye drops and oral prednisolone and monitored carefully for signs of progression.

Amniotic membrane transplant (AMT)

There is robust evidence that AMT performed within 10 days of rash onset reduces the destructive inflammation and thus minimises long-term cicatrizing sequelae thereby preserving vision.[5,9] The amniotic membrane is used as a biological dressing to:

- provide a mechanical barrier between the inflamed, denuded mucosal surfaces thereby minimizing adhesions.
- promote healing and re-epithelisation of the denuded areas by supplying a scaffold for the migration of epithelial cells.[10]
- provide an anti-inflammatory effect and anti-scarring effect
- supply limbal stem cells[9]

AMT is recommended for patients exhibiting eyelid margin involvement (>1/3 length), pseudomembranes, conjunctival epithelial defects (>1cm), and intense conjunctival inflammation within four to seven days from the index day.[11,12] It is crucial to perform AMT promptly since corneal indicators such as epithelial defects may only become apparent two to three weeks after the onset of the rash. Waiting for corneal signs before considering AMT could thus miss the early therapeutic window to effectively reduce the ocular surface inflammation.

Inflammation and/or sloughing of epithelium involves the entire surface including the cornea, bulbar and palpebral conjunctiva and eyelid margins and thus the amnion should cover the ocular surface in its entirety.[10] Cryopreserved amnion (at least 5 x 5cm) is placed epithelial side up over the ocular surface, gently pushed with a muscle hook into the depth of the fornices and sutured in place. The amnion edges are draped over the lid margin and sutured onto the eyelid skin surface (Fig 1). The placement of the amnion is generally unobstructed by eyelashes, as they are frequently shed during the acute phase.

Various techniques have been described for bedside application of amnion, utilising sutureless methods or glue. In unstable patients or while awaiting cryopreserved amnion, a dry amnion disc can also be employed. However, it is important to note that this approach may not adequately cover the fornix and lid margin. The dry amnion technique can prove beneficial in managing persistent epithelial defects later during the acute illness.

The amnion gets variably absorbed in seven to 14 days. Based on the level of ongoing inflammation and denudation, a repeat AMT may be needed every ten to 14 days.[13]

Having a layer of amnion over the corneal surface makes corneal examination challenging, however it should still be possible to monitor for corneal melt and infection.

Systemic immunosuppression

The role of systemic corticosteroids and intravenous immunoglobulins (IVIG) is subject to debate. Older literature suggested no change in mortality, while more recent evidence reports the beneficial effect of systemic steroids, ciclosporin and etanercept on mortality. [1,14,15,16]

There is a paucity of literature on systemic immunosuppression for ocular morbidity. Recent case series recommend [1,17,18] starting pulse intravenous methylprednisolone (500mg - 1 g intravenous for three days) at the disease onset. This was followed by tapering dosage of oral steroids. It demonstrated reduction in complications and minimizing limbal stem cell loss. Higher steroid dose may be needed later in the course of the disease (week 3) as ocular inflammation lasts longer than cutaneous inflammation.[17] Tear film cytokines have also been shown to remain high in the second week as compared to serum levels.[19]

The dose of systemic steroids needs to be tailored as per the level of ocular surface inflammation. Systemic steroids have potential significant systemic implications, and the decision is made with the multidisciplinary team comprising of dermatologists, microbiologists and burns surgeons, taking into consideration the systemic status, risk of infection, extent of skin de-epithelization and the SCORTEN (prognostic score for mortality ranging from 0-5 with a predicted mortality of >60% of SCORTEN scores of 4 or more. One point is scored for each of the following: age ≥40 years, heart rate ≥120/min, presence of cancer/hematologic malignancy, >10% body surface area involvement, raised blood urea nitrogen (>28 mg/dL), serum bicarbonate <20 mmol/L, serum glucose level > 14 mmol/). The patient should be closely monitored with body temperature, biochemistry, blood cultures, swabs from skin and mucous membranes. Rarely SJS/TENS can be caused by viral infections and thus caution is advised while the patient is on steroid treatment.[17]

Other drugs to be considered on a case-by-case basis:

Cyclopentolate eye drops 1% can be used to reduce pain and photophobia in presence of a corneal epithelial defect. Oral Vitamin C 1g three times a day and oral Doxycycline 100mg once a day may be useful to prevent corneal melt.

Conclusions

- Acute intensive ocular care in SJS/TENS is critical to minimize the devastating long term sequalae.
- Destructive inflammation involves the entire ocular surface, and most crucially, the limbal stem cells.
- The three-pronged approach for managing acute SJS/TENS consists of intensive topical lubricants and steroids, early amniotic membrane transplantation and systemic steroids.
- The window of opportunity to modulate the immune response lies even before corneal changes are clinically apparent.
- The entire ocular surface needs to be covered with amnion and the procedure repeated as necessary.
- A multidisciplinary approach is essential to adequately and safely treat these patients with systemic steroids.

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Fig 1:

a) Severe lid margin involvement and pseudomembranes over palpebral conjunctiva

b) Severe bulbar de-epithelization and inflammation with minimal corneal involvement: AMT indicated.

c) Complete coverage of the ocular surface, fornices and lid margins with amnion

d) Retractor used to monitor fornices.

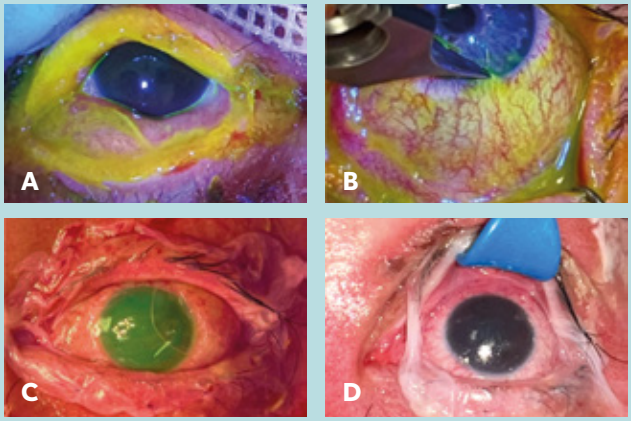

Table 1: Grading for acute ocular manifestations of SJS/TENS developed by Gregory[11,20]

	Severity of eye involvement			
Area involved	Mild	Moderate	Severe	Extremely severe
Lid margin	No stain	Stain <1/3 of lid margin length	Stain >1/3 of lid margin length on at least one lid	Stain >1/3 of lid margin length on more than one lid
Conjunctiva	Hyperemia, without stain	Stain + <1 cm in greatest diameter	Stain + > 1cm	Multiple areas of stain >1 cm
Cornea	No stain	No stain	Any epithelial defect more than punctate staining	Any epithelial defect more than punctate staining