

Stevens Johnson Syndrome

by Stephanie Harper, M.D.

Stevens Johnson Syndrome (SJS) is a rare vesiculobullous disease characterized by an acute cutaneous eruption that involves the skin and mucosal membranes. The condition was first described in 1922 as a generalized cutaneous eruption with inflamed buccal mucosa and purulent conjunctivitis. The two patients in the initial report went on to have visually significant ocular residua due to severe keratopathy despite resolution of the cutaneous manifestations. Thus, the authors, Dr. Stevens and Dr. Johnson, concluded that "this condition deserves to be considered a definite entity" (1).

Stevens Johnson Syndrome is a member of a spectrum of inflammatory vesiculobullous diseases. At the most benign end of the spectrum lies Erythema Multiforme Minor (EM- minor), which is characterized by an acute cutaneous eruption usually without mucosal membrane involvement. In Erythema Multiforme Major, or Stevens Johnson Syndrome, the acute exanthem includes erosive involvement of 2 or more mucosal surfaces. The most commonly involved surface is the oral mucosa. The conjunctiva is the next most commonly involved mucosal surface, occurring in up to 50% of patients. Toxic Epidermal Necrolysis (TEN) is the most severe vesiculobullous disease along this spectrum. It is characterized by mucosal and cutaneous lesions that involve greater than 20 % of the body surface area in the first 24 hours. In addition, the skin in TEN has been noted to peel off in sheets of greater than 3 cm, unlike SJS, in which sheets of skin peel off in less than 3 cm sections. TEN and SJS are typically accompanied by systemic features such as fever, arthralgia, and malaise; EM minor is not. While tenderness is more frequently reported in TEN patients, it is not restricted to this group. There have been attempts by some authors to reclassify these disorders into smaller groups based on cutaneous lesion descriptions, lesion patterns and responses to steroid therapy etc. We however will continue to use the above outlined classic categories since there is no widely agreed upon new grouping system.

Epidemiology

Because SJS is a rare condition, estimates of its incidence and prevalence are challenging. Hospital record reviews have provided the most useful information. The records of patients hospitalized between 1972 and 1986 with a diagnosis of EM-minor, SJS and TEN from a large urban area in the United States were reviewed and the incidence of hospitalization for one of these conditions was 4.2 per 106 person-year (2). The incidence of hospitalization for TEN alone was 0.5 per 106 person-years. A study of hospitalized cases from the Federal Republic of Germany found an annual risk of 0.93 per million for TEN and 1. 1 per million for SJS (3). Between 1990 and 1992, the incidence of SJS and TEN was calculated to be 1.89 per million inhabitants in Western Germany and Berlin (4).

The more severe disease forms, SJS and TEN, affect patients early or late in life. In the study from Germany, of 259 TEN patients, the average age was 63 years, as compared to 25 years in SJS. Interestingly, although most report no sex predilection, this group found that women were more likely to have TEN and men SJS. Consistent results have been obtained in the US and the risks defined as 7.0 per 106 person-years for those less than 20 and 9.4 per 106person-years for those greater than 60 years of age. The lowest risk is in patients between 20 and 64 years of age, 4.6 per 106 person-years. The conditions affect all races.

Etiology

The cause of EM-minor, SJS and TEN is unknown. These diseases have been associated with drug therapy, infectious agents and malignancy (5,6). Medication usage is most commonly associated with TEN, with up to 80% of TEN cases being attributed to drug therapy. SJS and EM-minor are also associated with medications, in up to 57% and 23% of cases respectively (Table 1). Antibiotics are the medications that appear to have the strongest associations, with sulfonamides and beta-lactam antibiotics topping the list. Other antibiotics, nonsteroidal anti-inflammatory agents and anticonvulsants have also been implicated in this spectrum of disease as have topical and systemic ocular medications. It has been suggested that the medications serve as haptens and facilitate deposition of complexes in tissues and vessels with a resulting

immunologic reaction.

Table I
IMPLICATED MEDICATIONS

Antibiotics	Others
Sulfonamides	Nonsteroidal Anti-inflammatory Drugs - Ibuprofen - Oxyphenbutazone - Naproxen - Diclofenac Sodium - Indomethacin
Beta-Lactams - Penicillins - Ciprofloxacin	Seizure Medications - Phenytoin Sodium - Carbamazepine - Phenobarbital
Aminoglycosides - Gentamycin	Diuretics - Furosemide - Methazolamide
Tetracycline - Doxycycline	Topical Ocular Medications - Scopolamine - Tropicamide - Sulfonamide

Herpes and the Mycoplasma are the organisms most notably associated with SJS. The Herpes virus has been isolated from a skin lesion in a patient with recurrent herpes-associated SJS. Other microbial associations include Streptococci, Yersinia, Adenovirus, and the measles virus. It has been postulated that an immunologic process directed against a viral or microbial antigen or a viral or microbial altered host antigen may mediate the disease process.

Ocular Manifestations

Ocular involvement occurs in a significant number of patients and the most severe form of disease occurs in those at the extreme end of the spectrum. Review of hospital records from the Massachusetts General Hospital and Shriners Hospital for Crippled Children between 1960 and 1994 reveal that 24 % of 366 patients had ocular manifestations at the time of their acute stay (7). Ocular manifestations can be classified as mild-lid edema, conjunctivitis, chemosis; moderate - conjunctival membranes, corneal epithelial loss and corneal ulceration; severe - perforation, cicatricial changes. Nine percent of patients with EM-minor had ocular manifestations. In comparison, ocular manifestations were much more common in the SJS (69%) and the TEN (50%) groups. The most sight threatening forms of eye disease were found in the SJS and TEN groups with twenty-seven percent of patients experiencing severe complications including, corneal melts and cicatricial changes. All patients with EM-minor had mild disease. Other authors have reported that up to 50% of patients with severe cutaneous disease develop severe ocular manifestations. (8)

The acute phase of disease is characterized primarily by eyelid involvement. The lids are typically swollen and erythematous. Soon thereafter, or coincident with this, the conjunctiva is inflamed. The conjunctivitis frequently parallels the skin findings, with bullae formation and eruption. Membrane or pseudomembrane formation then occurs (figure 1). The healing process can result in cicatricial changes which include symblepharon, ankyloblepharon, eyelid margin rotation, severe dry eye and conjunctivization of the cornea (**Figure 2**). Recurrent ocular inflammation can occur in patients with resolved acute ocular and systemic disease in the absence of systemic recurrence (9).

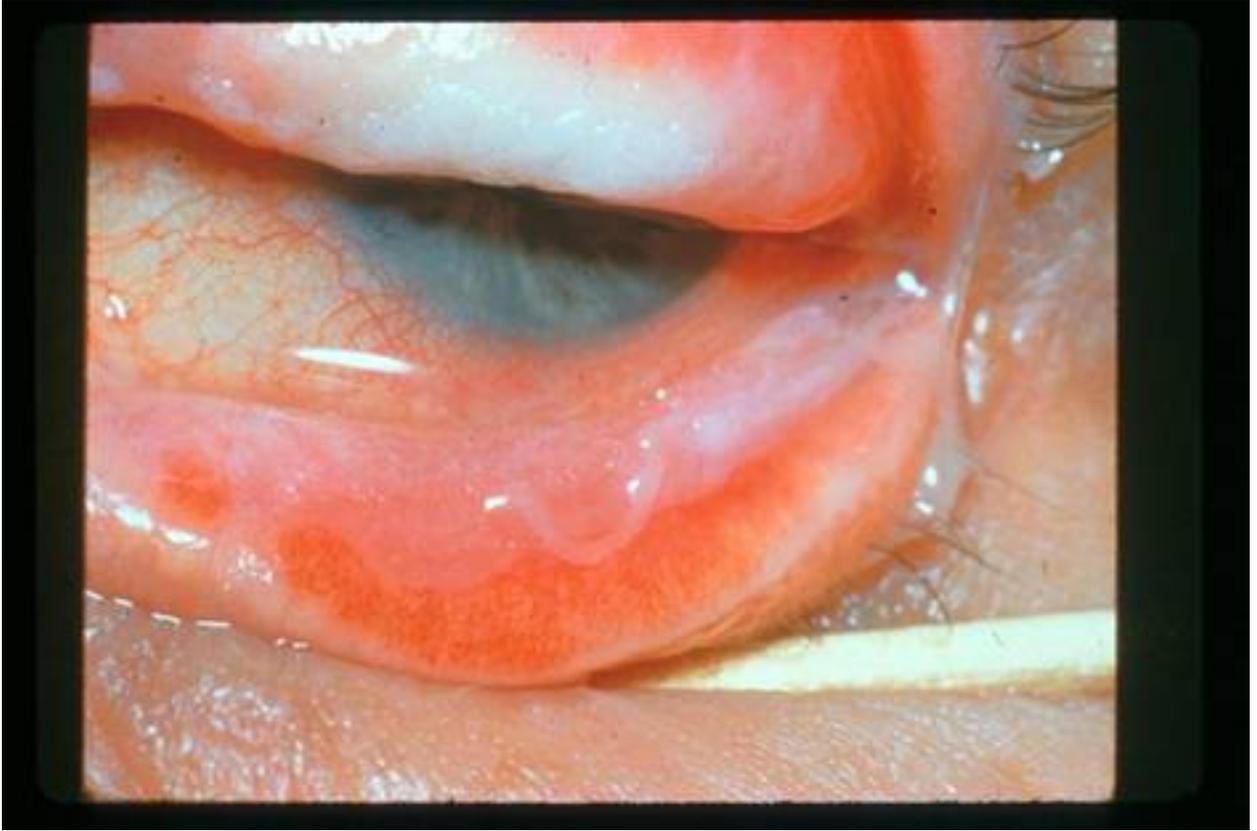


Figure 1. Ocular involvement in the acute phase of Stevens-Johnson syndrome. Note the presence of a pseudomembrane in the lower cul-de-sac.

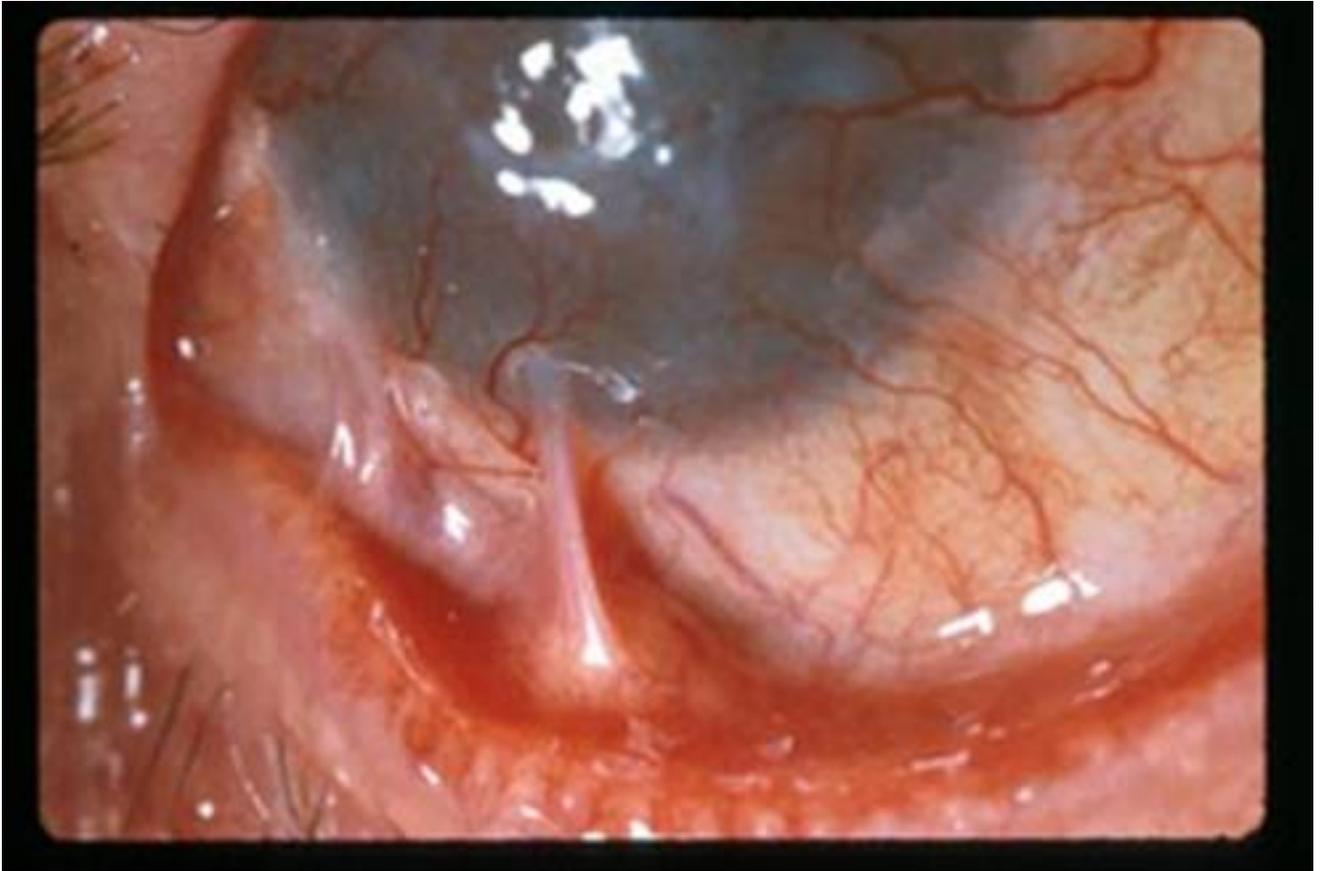


Figure 2. Total conjunctivalization of the cornea with symblepharon formation in a late stage of Stevens-Johnson Syndrome. Note not only the obvious focal symblepharon arms adherent to the cornea, but the broader symblepharon resulting in foreshortening of the inferior fornix.

Ocular involvement in SJS has been associated with the presence of certain class I and class II MHC antigens. In a study of 23 patients with ocular complications HLA-DQB 1 *0601 was found in 17% as compared to 3% of controls (10). The relative risk of ocular disease in this group was 7.2. The frequency of the HLA-Bw44 antigen was found to be increased in white patients with SJS and ocular involvement as compared to controls (11). It was found in 66.7% of SJS patients and 20.4% of controls. The presence of these alleles in a disproportionate number of SJS patients with ocular involvement lends support to the concept of immunologic susceptibility to the development of SJS.

Immunopathologic Observations in Ocular Disease

Conjunctival biopsies from patients with active ocular disease show subepithelial plasma cell and lymphocyte infiltration. Lymphocytes are also seen to aggregate around vessel walls. The predominant infiltrating lymphocyte is the T helper cell. Immunoreactant deposition in vessel walls, immunoglobulin and complement components, is another prominent feature (**Figure 3**).

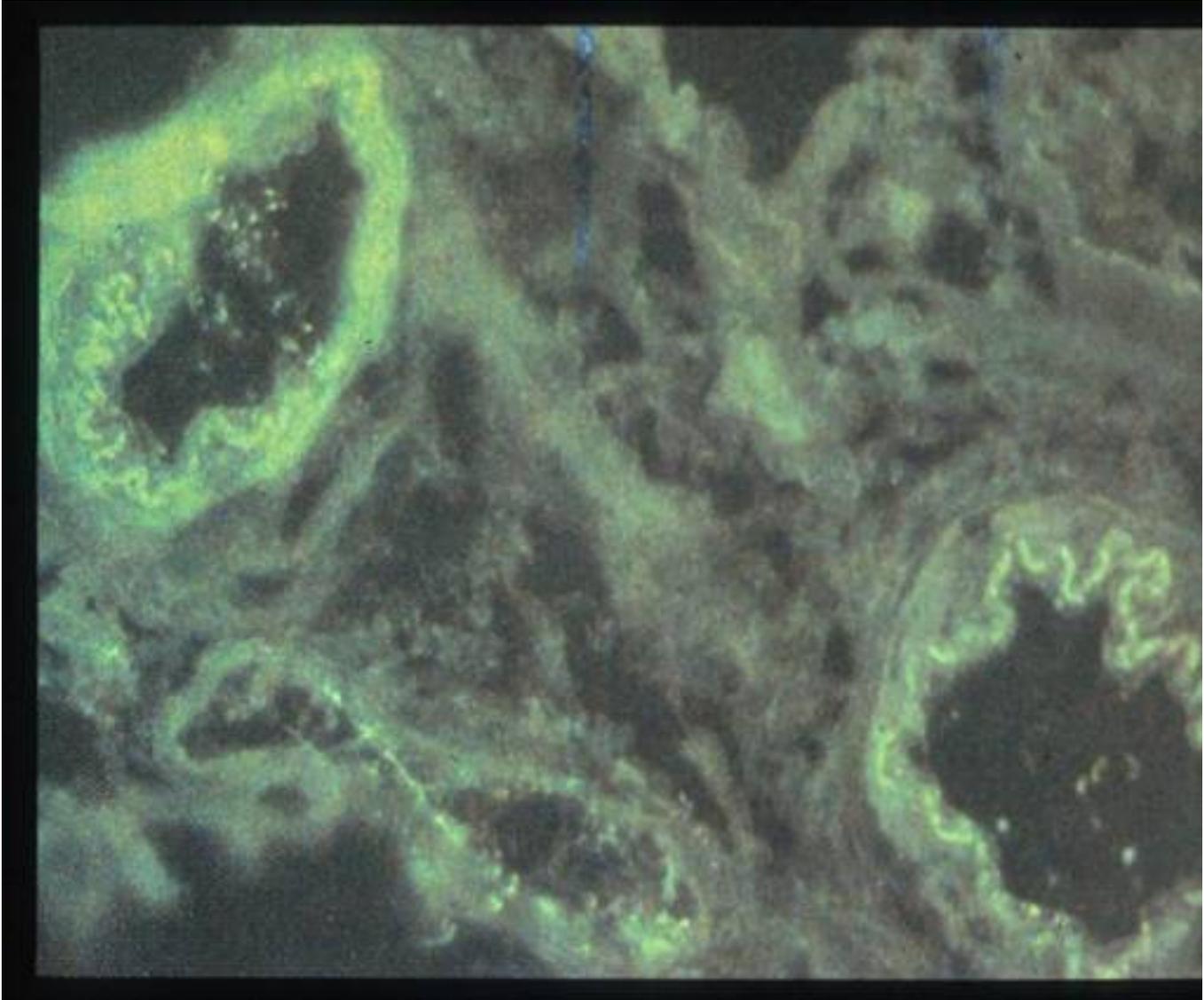


Figure 3. Immunohistochemistry of a conjunctival specimen from a patient with TEN.

DIFFERENTIAL DIAGNOSIS

EM-minor, SJS and TEN represent a spectrum of disease. Distinguishing the most severe forms from EM-minor should be performed because it has both prognostic and therapeutic implications. Another entity that results in skin sloughing is staphylococcal scalded skin syndrome. This condition is characterized by extensive erythema and skin sloughing. It occurs in young children. There is intense pain, rarely mucosal membrane involvement and less systemic toxicity. It results from toxins released by the staphylococcal organism. Recognizing this condition rapidly is imperative because it is cured with antibiotic therapy. Other conditions that cause exfoliation are toxic shock syndrome and Kawasaki's disease.

The differential for cicatrizing disease is vast (Table II). Distinguishing between these entities can frequently be done by taking a careful history. Other diagnostic adjuncts include cultures, biopsy with histologic, immunofluorescent and immunoperoxidase evaluations.

Table II
CICATRIZING CONJUNCTIVITIES

Differential Diagnosis
Cicatrizing Pemphigoid
Atopic Keratoconjunctivitis
Ocular Rosacea
Chemical Burns
Scleroderma
<i>Corynebacterium diphtheriae</i> Conjunctivitis
Intraepithelial Epithelioma
Squamous Cell Carcinoma
Sarcoidosis
Trachoma
Adenovirus Conjunctivitis
Trauma

Treatment

Prognosis

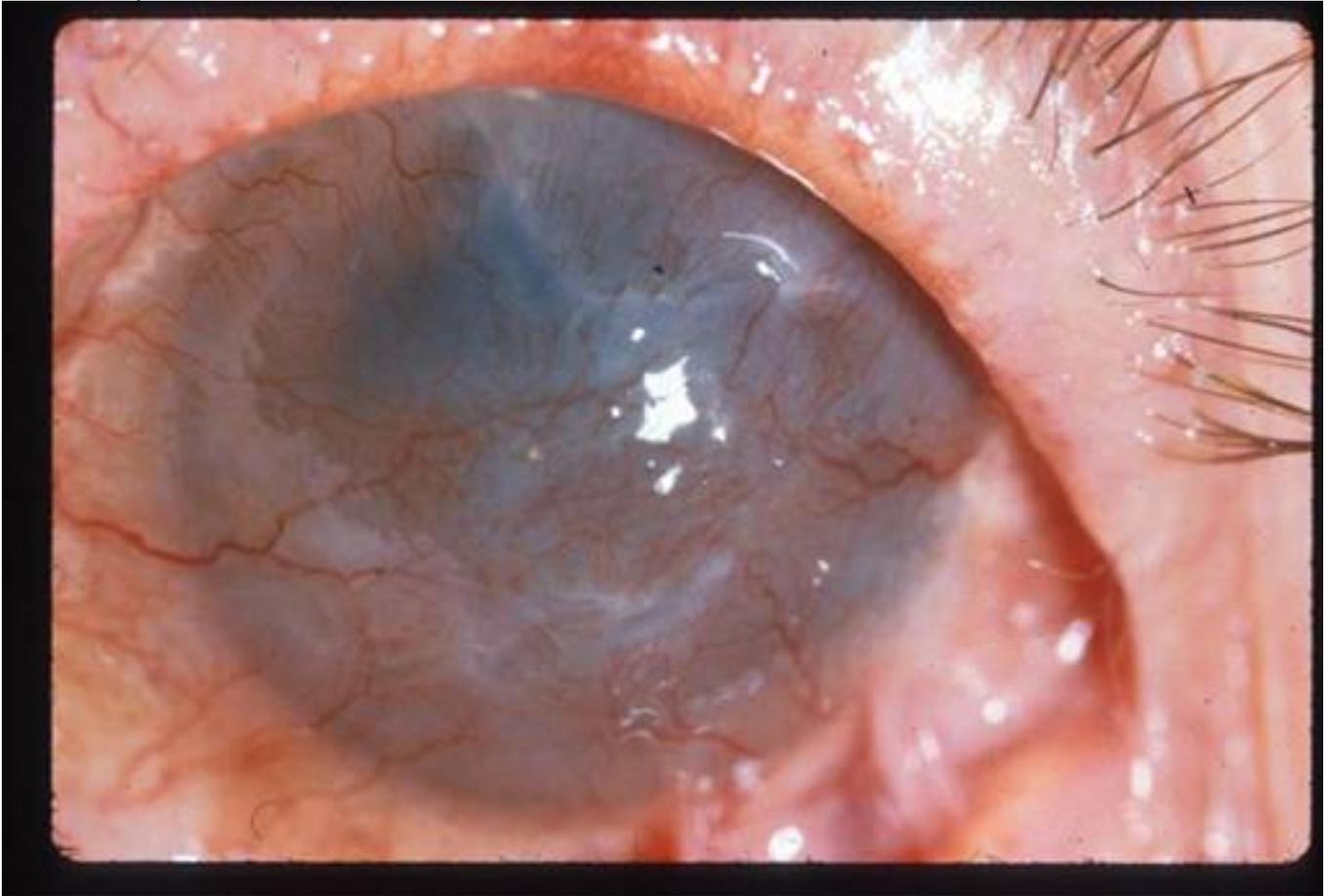
Systemic Disease

Treatment of the systemic manifestations of SJS and TEN is currently supportive in many parts of the world. Patients are best cared for in units that specialize in burn management since the most severe complications for this group of patients relate to the absence of the protective function of the skin. The highest mortality rate is seen in patients with the most severe disease. For TEN patients it can approach 27% at centers that specialize in burn care (7). Causes of death include septicemia, respiratory and renal failure. The rate of death in SJS patients is approximately 3%. Survival is excellent in EM-minor.

Ocular Disease

As mentioned previously, 27 to 50 percent of patients have been found to progress to severe ocular disease. Treatment of ocular disease usually begins with aggressive lubrication of the ocular surface. As inflammation and cicatricial changes ensue, topical steroids, symblepharon lysis and topical retinoid therapy may be employed. Maintenance of ocular integrity can be achieved through the use of adhesive glues, lamellar grafts and penetrating keratoplasty. Visual rehabilitation can be considered once the eye has been quiet for at least 3 months. Long-term management frequently involves treatment of trichitic lashes and eyelid margin repair for distichiasis, entropion and ectropion. Scleral contact lenses, mucosal membrane grafts, limbal stem cell transplants and amniotic membrane grafting may be required. Immunomodulating therapy may halt the immunologic dysregulation and resulting inflammatory consequences. Recent reports suggest that IV-Ig may provide an alternative therapeutic modality, with or without

the use of systemic steroids.



References

1. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia. *American Journal of Diseases of Children*. 1922; : 526-533.
2. Chan H, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis. *Archives of Dermatology*. 1990; 126:43-47.
3. Schopf E, Stuhmer A, Rzany B, et al. Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome. *Archives of Dermatology*. 1991; 127:839-842.
4. Rzany B, Mockenhaupt M, Baur S, et al. Epidemiology of erythema multiforme majus, Stevens-Johnson syndrome, and Toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. *Journal of Clinical Epidemiology*. 1996; 49:769-773.
5. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: critical review of characteristics, diagnostic criteria and causes. *Journal of the American Academy of Dermatology*. 1983;8:763-775.
6. Britz M, Sibulkin D. Recurrent erythema multiforme and herpes genitalis (type 2). *Journal of the American Medical Association*. 1975;233:812-813.
7. Power WJ, Ghoraishi M, Merayo-Llodes 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.
8. Arstikaitis MJ. Ocular aftermath of Stevens-Johnson syndrome. *Archives of Ophthalmology*. 1973;90: 376-379.
9. Foster CS, Fong LP, Azar D, et al. Episodic conjunctival inflammation after Stevens-Johnson

syndrome. Ophthalmology. 1987;95:453-462.

10. Power WJ, Saidman SL, Zhang DS, et al. HLA-typing in patients with ocular manifestations of Stevens-Johnson syndrome. Ophthalmology. 1996;103:1406-1409.

11. Mondino BJ, Brown SI, Biglan AW. HLA antigens in Stevens-Johnson syndrome with ocular involvement. Archives of Ophthalmology. 1982;100:1453-1454.

Review Questions for Stevens Johnson Syndrome

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1. Acute inflammatory vesiculobullous disease of unknown etiology include (note all correct answers):

- A. SJS
- B. EM-minor
- C. Staphylococcal Scalded Skin Syndrome
- D. TEN

2. SJS is the most severe form of diseases along the spectrum of acute inflammatory vesiculobullous eruptions. True or False

3. The severe forms of disease (SJS, TEN) appear to be most common in middle aged patients. True or False

4. Systemic phenomena such as fever are less common in:

- A. SJS
- B. EM-minor
- C. TEN

5. The most common drug association is with what class of medications:

- A. Anticonvulsants
- B. Antibiotics
- C. Nonsteroidal antiinflammatory drugs
- D. Beta Blockers

6. Ophthalmic medications associated with SJS are:

- A. Methazolamide
- B. Scopolamine
- C. Tropicamide
- D. Proparacaine

7. Ocular manifestations are most common in:

- A. TEN
- B. EM-minor
- C. SJS

8. Ocular involvement is not associated with class H MHC antigens. True or False

9. Cytotoxic T cells are the predominant lymphocyte found infiltrating conjunctival biopsy specimens. True or False

10. Antibiotic therapy is standard therapy for SJS and TEN patients. True or False

ANSWERS

1. A,B,D

2. False

3. False

4.B

5.B

6. A,B,C,D

7. SJS

8. False

9. False

10. False