Analysis of the Acute Ophthalmic Manifestations of the Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Disease Spectrum

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Purpose: To evaluate the epidemiology, possible etiologic factors, complications encountered, and treatment administered to a group of patients with ocular involvement in the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum who were seen at two large tertiary referral centers over a 34-year period.

Methods: Hospital records from 1960 to 1994 at the Massachusetts General Hospital and Shriners Hospital for Crippled Children were reviewed for patients with erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Only patients fulfilling specific clinical diagnostic criteria and those who received a diagnosis by a dermatologist were included in the review.

Results: A total of 366 patients with erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis were identified. Drugs were the most commonly identified etiologic factor in all three conditions; sulfonamides were the most frequently identified agents. Eighty-nine patients (24%) had ocular manifestations at the time of their acute hospital stay. Ocular involvement was seen in 9% of patients with erythema multiforme, in 69% with Stevens-Johnson syndrome, and in 50% with toxic epidermal necrolysis. The ocular problems were more severe in patients with both Stevens-Johnson syndrome and toxic epidermal necrolysis. There was no significant difference between the number of patients who were treated with systemic steroids and those who were not ($P = 0.42$).

Conclusion: The erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum remains an important cause of severe visual loss in a significant number of patients. Systemic steroids used during the acute phase of the disease appear to have no effect on the development of ocular manifestations. Studies on the acute immunopathogenic mechanisms occurring in these diseases are warranted if more effective therapies are to be found. *Ophthalmology 1995;102:1669–1676*

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Ferdinand von Hebra[1] generally is credited with the first recognition of erythema multiforme in 1866. He described a self-limiting cutaneous syndrome, usually lasting less than 1 month but often recurrent, characterized by round erythematous skin lesions with frequent, concentric color changes. In 1922, Stevens and Johnson[2] described a more severe acute febrile illness in two boys, which they characterized as "a new eruptive fever with stomatitis and ophthalmia." Subsequently, the term *Stevens-Johnson syndrome* has been applied to this mucocutaneous syndrome, which most observers now agree represents a more severe form of von Hebra's erythema multiforme.[3] In 1950, Thomas[4] suggested the division of erythema multiforme into two forms: erythema multiforme minor (von Hebra) and erythema multiforme major (Stevens-Johnson).

In 1956, Lyell[5] described a clinical condition characterized by extensive epidermal loss, which he termed *toxic epidermal necrolysis.* It subsequently became apparent that extensive epidermal necrosis eventually developed in some patients with severe Stevens-Johnson syndrome, and target-like lesions, often adjacent to areas of full-thickness skin loss, developed in many patients with toxic epidermal necrolysis.[6,7] In addition, similar drugs have been implicated as a cause of both Stevens-Johnson syndrome and toxic epidermal necrolysis.[8] Accordingly, many observers now classify toxic epidermal necrolysis as the most severe form of the erythema multiforme/Stevens-Johnson syndrome spectrum.

Although ocular involvement in erythema multiforme minor is rare, at least two mucosal sites (most commonly, oral and conjunctival) in Stevens-Johnson syndrome, by definition, are involved.[9] Similarly, mucosal involvement is present in virtually all patients with toxic epidermal necrolysis, most often in the mouth and eyes.[10] The primary purpose of this report is to describe the etiologic factors implicated, treatment administered, and complications encountered in a group of patients with ocular involvement secondary to the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum, which was diagnosed over a 34-year period at two large tertiary referral centers during the patients' hospital stay.

Materials and Methods

The inpatient medical records of the Massachusetts General Hospital and Shriners Hospital for Crippled Children for the years 1960 to 1994 were reviewed for patients with erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

The criteria used for diagnosis of erythema multiforme minor were as follows: (1) an acute self-limited inflammatory disease of the skin; (2) characteristic target skin lesions typically distributed in a symmetric manner on the extremities; (3) either no mucosal, or one mucosal surface involved; and (4) lacking a distinct prodromal phase.

Stevens-Johnson syndrome was defined to include the following: (1) a serious mucocutaneous illness with characteristic target-like lesions; (2) bullae and extensive areas of necrosis; (3) a prominent acute prodrome; and (4) involvement of at least two mucosal sites.

Toxic epidermal necrolysis was defined according to the following criteria: (1) widespread mucocutaneous painful edematous skin lesions; (2) positive Nikolsky sign (epidermal loss with lateral shearing force); (3) presence of prodromal symptoms of fever, cough, headache, and malaise; (4) prominent mucus membrane involvement; and (5) exclusion of the staphylococcal scalded skin syndrome.

Only those patients who met the criteria outlined above, with a clinical diagnosis made by a dermatologist, were included in the analysis. In many cases, a skin biopsy had been performed early in the course of the disease. If the biopsy findings were inconsistent with a diagnosis of erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis, the patient was not included in the review, regardless of the clinical impression of the involved physician. Charts were reviewed for epidemiologic parameters, possible etiologic factors, disease complications, and treatment modalities used.

Because drugs are the most widely considered etiologic factor in these diseases, an accurate drug history usually was recorded carefully by the admitting physician. Three groups of patients can be identified when considering the role of drugs in the etiology of this disease spectrum.[11] In the first group, the syndrome appears in the absence of any drugs. Also included in this group are patients who were given drugs after all the diagnostic criteria for erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis were met. The second group consists of patients in whom drugs were administered for symptoms unlike the prodromal symptoms of erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis. In the third group, a drug was given after prodromal symptoms similar to erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis appeared. For the purposes of the current report, a drug etiology was considered possible for patients in groups 2 and 3. A drug was considered to have a possible causal relation to the condition only if it had been taken close enough before the onset of symptoms (i.e., 15 days). If the reaction showed signs of regression during continued administration of the drug, a causal relation was considered unlikely.

All patients who were believed to have an ocular complication at the time of their acute admission had been seen by an ophthalmologist; therefore, results of a detailed ocular examination were included in the records. Many patients with no clinically obvious ocular disease also had an ophthalmology consult. The severity of ocular involvement was classified as mild, moderate, or severe. Mild involvement was defined as complications requiring routine eye care with full resolution of signs and symptoms before hospital discharge. Examples of patients in this category included those with with lid edema, conjunctival injection, and chemosis who received either prophylactic topical antibiotics and/or lubricants. Moderate involve-

Table 1. Comparison of Epidemiologic Data in Patients with Ocular Complications of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

	Erythema Multiforme	Stevens-Johnson Syndrome	Toxic Epidermal Necrolysis
No. of patients	22	37	30
Mean age (yrs)	41	32	35
Sex (% female)	55	62	60
Biopsy positive (%)	45	60	83
Mortality rate (%)	0	3	27
Cases with possible drug involvement (%)	23	51	80
Cases of unknown etiology (%)	64	30	13

ment included specific ocular complications that required specific treatment and normal vision and near complete resolution of all active disease on discharge. For example, patients in this category had conjunctival membrane formation, corneal epithelial loss of greater than 30%, evidence of corneal ulceration, or corneal infiltrates. Severe complications included sight-threatening disease, ongoing ocular inflammation with reduced vision, and the need for specific, ongoing eye care after discharge. Patients in this category had conjunctival fornix foreshortening, symblepharon formation, and ongoing active corneal disease at the time of discharge. In more than 90% of patients, our classification of ocular severity was in agreement with the ophthalmologists' prognostic assessment at the time of patient discharge.

Follow-up information for a minimum of 3 months on the ocular status of patients was available in the records of 78 (88%) of the 89 patients with ocular manifestations. No attempts were made to obtain long-term (>3 months) follow-up on patients.

Results

A total of 366 patients with erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis were identified during the 34-year study period. In 89 (24%) of the 366 patients, ocular complications developed. Nine percent of patients with erythema multiforme, 69% of patients with Stevens-Johnson syndrome, and 50% of patients with toxic epidermal necrolysis had ocular involvement during their hospital stay. Only the 89 patients with ocular involvement are included in this report.

There were no major changes in the numbers of patients seen at 5 yearly intervals during the 34-year period of the review. The epidemiologic parameters of the 89 patients with ocular involvement are summarized in Table 1.

The sex distribution was approximately equal among the three conditions. One striking feature was the relatively high mortality rate (27%) in patients with toxic epidermal necrolysis. The most common cause of death in this group was septicemia (4 patients), respiratory failure (3 patients), and renal failure (1 patient).

The possible factors implicated in the diagnosis of the conditions are presented in Table 2. Drugs were the most commonly associated etiologic factor in all three conditions. There was a greater likelihood of a drug-associated etiology in patients whose disease was at the more severe end of the spectrum. A drug etiology was considered likely in 80% of patients with toxic epidermal necrolysis, compared with only 23% of patients with erythema multiforme (Table 3). In only one patient with Stevens-Johnson syndrome was mycoplasma infection considered a possible etiologic factor. No underlying etiologic factor was identified in 64% of patients with erythema multiforme. No major differences for sex and age distribution could be found when patients with drug-induced and nondrug-induced etiologies were compared.

Antibiotics were the most common agents implicated in all three conditions. Sulfonamides were the most frequently identified group of antibiotics and were implicated

Table 2. Etiologic Factors Implicated in Diagnosis in Patients with Ocular Manifestations

	Erythema Multiforme (n = 22)	Stevens-Johnson Syndrome (n = 37)	Toxic Epidermal Necrolysis (n = 30)
	No. of Patients (%)	*No. of Patients (%)*	*No. of Patients (%)*
Drug	5 (22.7)	19 (51.4)	24 (80)
Viral	1 (4.5)	5 (13.5)	2 (6.7)
Herpes	2 (9)	1 (2.7)	0 (0)
Mycoplasma	0 (0)	1 (2.7)	0 (0)
None	14 (63.8)	11 (29.7)	4 (13.3)

as possible etiologic factors in 30% of the patients with toxic epidermal necrolysis. The next most frequently encountered group of antibiotics were seizure medications, followed by the more recently developed nonsteroidal anti-inflammatory agents.

Of the 89 patients with ocular involvement, the oral cavity was the next most frequently involved mucosal site (Table 4). This was followed in order of decreasing frequency by genital and anal mucosal involvement and by pneumonitis. In two of the patients in the toxic epidermal necrolysis group, pneumonitis subsequently developed. These two patients died of respiratory failure.

A large number of patients in all three groups had a positive skin biopsy; 83% who had toxic epidermal necrolysis showed features consistent with the diagnosis on histopathologic examination. Features seen in patients with erythema multiforme/Stevens-Johnson syndrome included papillary dermal edema, endothelial swelling, and a lymphocytic perivascular infiltrate. Immunofluorescent studies done on a skin biopsy of a patient with Stevens-Johnson syndrome demonstrated the deposition of IgG around vessel walls and at the dermal–epidermal junction. Histopathologic features seen on skin biopsy in the early stage of toxic epidermal necrolysis included single epidermal cell necrosis of basal layers with little inflammatory infiltrate in the dermis. In the later stages, eosinophilic necrosis of the epidermis with cleavage of the dermal–epidermal junction was seen.

Ocular complications were minor in all patients with erythema multiforme. This contrasts with both the Ste-

Table 4. Mucosal Involvement in Patients with Ocular Manifestations

	Erythema Multiforme (n = 22)	Stevens-Johnson Syndrome (n = 37)	Toxic Epidermal Necrolysis (n = 30)
	No. of Patients	*No. of Patients*	*No. of Patients*
Conjunctival	22	37	30
Oral	0	36	27
Genital	0	16	15
Anal	0	5	8
Pneumonitis	0	3	4

Table 3. Drugs Associated with Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

	Erythema Multiforme	Stevens-Johnson Syndrome	Toxic Epidermal Necrolysis
	No. of Patients	*No. of Patients*	*No. of Patients*
Antibiotics			
Sulfonamides	0	4	9
Penicillins	4	4	1
Ciprofloxacin	0	0	2
Gentamicin	0	1	0
Seizure medications			
Phenytoin sodium	0	3	1
Carbamazepine	0	2	3
Pentobarbital	0	0	1
NSAIDs			
Naproxen	0	1	1
Piroxicam	0	1	0
Diflunisal	0	1	1
Ibuprofen	0	0	1
Thiazide diuretics			
Hydrochlorthiazide	1	0	0
Analgesics			
Oxycodone/acetaminophen	0	0	1
Others			
Furosemide	0	1	0
Glipizide	0	1	0
Reserpine	0	0	1
Hydralazine	0	0	1
Imipramine	0	0	1

NSAIDs = nonsteroidal anti-inflammatory drugs.

vens-Johnson syndrome and toxic epidermal necrolysis groups of patients. In each of these groups, severe complications developed in 27% of patients. The spectrum of ocular complications encountered is shown in Tables 5 and 6. Serious complications such as cicatrizing symblepharon formation and fornix foreshortening occurred in approximately 25% of patients with either Stevens-Johnson syndrome or toxic epidermal necrolysis (Fig 1). Two patients in either group also had corneal melts during their hospital stay. In two of these patients, one in each group, impending corneal perforation necessitated the application of tissue adhesive glue and a bandage contact lens. Both patients were discharged with the contact lenses in place and subsequently were followed as outpatients.

Conjunctival biopsies were performed on four patients with Stevens-Johnson syndrome during active ocular disease. Results of biopsy showed a subepithelial plasma cell and lymphocytic infiltrate, with the aggregation of lymphocytes around vessel walls (Fig 2, top left). Immunoperoxidase studies confirmed that the predominant infiltrating T cell was of the T-helper class (Fig 2, top right). Immunofluorescent studies demonstrated the deposition of immunoreactants in the walls of conjunctival vessels in four of the five patients (Fig 2, bottom). Immunoreactants detected included IgG, IgD, IgA, and the C3 and C4 components of complement.

Treatment modalities used during the period of acute ocular disease varied considerably (Table 7). All patients received topical antibiotics. Topical steroids were used in 18% of patients with erythema multiforme and in 57% of patients with Stevens-Johnson syndrome. Fornix sweeping was performed in none of the patients in the erythema multiforme group and in approximately one third of patients in both the Stevens-Johnson syndrome and toxic epidermal necrolysis groups. In all patients, the fornix sweeping was performed by an ophthalmologist using either a glass rod or a strabismus hook. None of the patients had a punctal occlusion procedure during their acute illness.

Figure 3 shows the percentage of patients receiving systemic steroids as part of their acute regimen. In those patients receiving steroids, the mean interval between starting steroids and the onset of symptoms was 2.5 days (range, 1–6 days). The mean dosage used was 54 mg prednisone (range, 20–150 mg). There was no statistically significant difference in the number of patients with ocular manifestations between those who were treated with systemic steroids and those who were not ($P = 0.42$, chi-square test). It also appears that the use of systemic steroids had no effect on the severity of the ocular involvement (Fig 2).

Table 5. Severity of Ocular Involvement

	Erythema Multiforme (n = 22)	Stevens–Johnson Syndrome (n = 37)	Toxic Epidermal Necrolysis (n = 30)
	No. of Patients (%)	*No. of Patients (%)*	*No. of Patients (%)*
Mild	22 (100)	20 (54)	12 (40)
Moderate	0 (0)	7 (19)	10 (33)
Severe	0 (0)	10 (27)	8 (27)

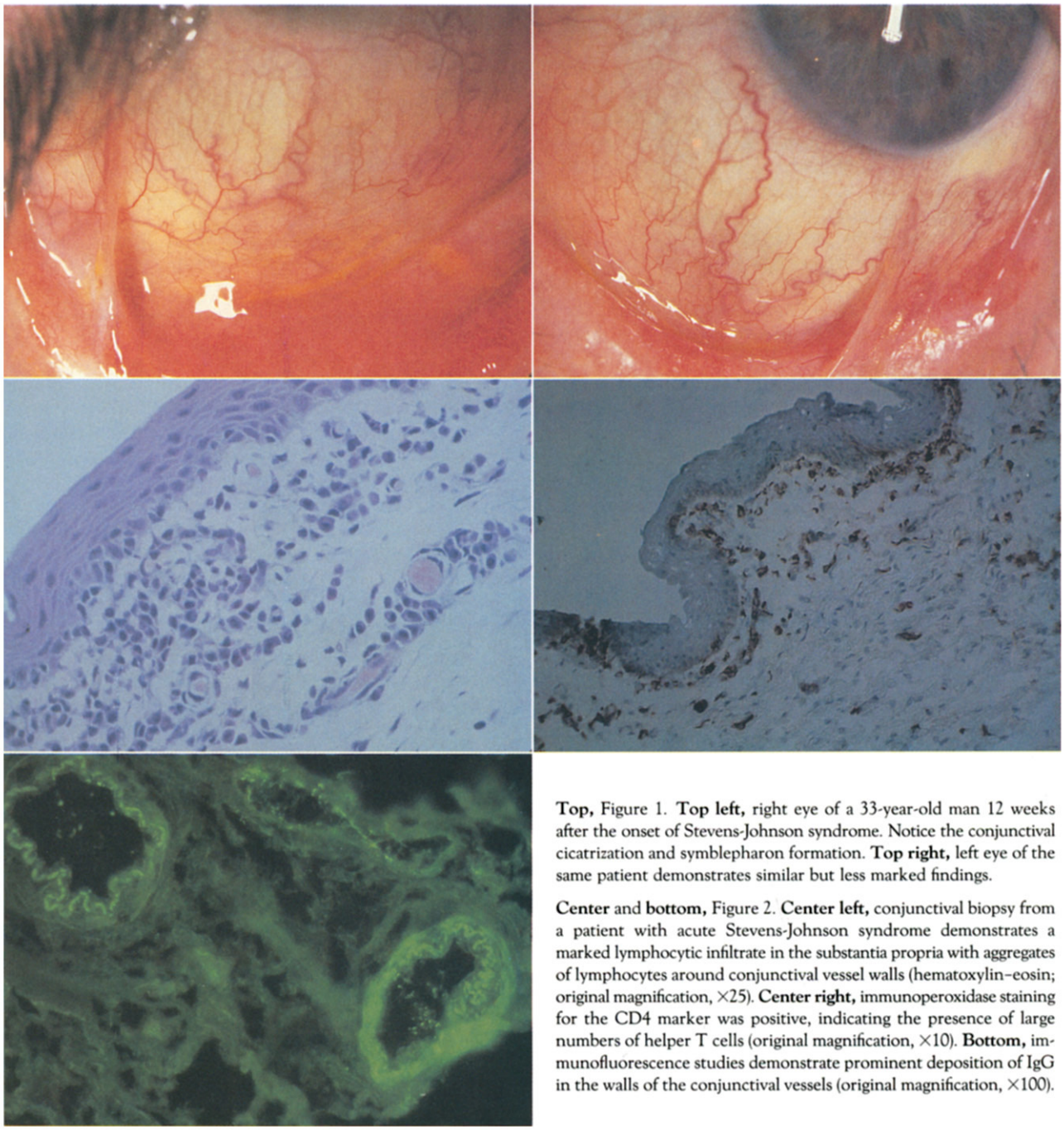
Discussion

The purpose of the current review was to evaluate the epidemiology, possible etiologic factors, complications encountered, and treatment administered to a group of patients with ocular complications secondary to the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease complex seen at two large tertiary referral centers. Of 366 patients, 89 (24%) were seen over a 34-year period and had ocular manifestations during their acute hospital stay. These figures are in agreement with previously reported smaller series.[11–14] In more than 50% of patients in the Stevens-Johnson syndrome and toxic epidermal necrolysis groups, ocular complications developed, and there was a tendency for the nature of the complications in these groups to be more severe (Tables 5 and 6).

The acute phase of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum usually persists for 2 to 6 weeks.[15] Initially, the eyelids may be swollen, erythematous, and encrusted. The conjunctiva is hyperemic, and distinct bullae may occur, although these are rarely visualized. After the acute vesicular stage, a concomitant conjunctivitis typically appears; its severity usually parallels that of the skin eruption. More severe conjunctival involvement can result in a pseudomembranous or membranous conjunctivitis.[16] The conjunctiva of such patients may heal, leaving scar tissue, symblepharon, or ankyloblepharon.[17] Late complications of the cicatrizing process may include entropion with trichiasis, lagophthalmos, and probably most importantly a severe dry eye syndrome.

Recurrences of erythema multiforme can occur, and in many instances these are associated with herpes simplex virus infection.[18,19] Recurrences of Stevens-Johnson syndrome/toxic epidermal necrolysis also may occur, particularly in the skin and oral mucosa.[20] We previously reported a small subset of patients with Stevens-Johnson syndrome with recurrent episodes of conjunctival inflammation not associated with external factors.[21] Results of histopathologic examination of conjunctival biopsies in these patients showed an underlying perivasculitis.

A feature of the current report is the high amount of skin biopsies performed on the patients. This probably reflects the nature of the care they received with the early involvement of a dermatologist in virtually all cases. The clinical diagnosis in these patients can be difficult; therefore, a skin biopsy that demonstrates features consistent with the diagnosis can be extremely helpful. Drugs are the most frequent precipitating factors in the development of erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis in the majority of patients.[22] All at-



Top, Figure 1. **Top left,** right eye of a 33-year-old man 12 weeks after the onset of Stevens-Johnson syndrome. Notice the conjunctival cicatrization and symblepharon formation. **Top right,** left eye of the same patient demonstrates similar but less marked findings.

Center and **bottom,** Figure 2. **Center left,** conjunctival biopsy from a patient with acute Stevens-Johnson syndrome demonstrates a marked lymphocytic infiltrate in the substantia propria with aggregates of lymphocytes around conjunctival vessel walls (hematoxylin–eosin; original magnification, ×25). **Center right,** immunoperoxidase staining for the CD4 marker was positive, indicating the presence of large numbers of helper T cells (original magnification, ×10). **Bottom,** immunofluorescence studies demonstrate prominent deposition of IgG in the walls of the conjunctival vessels (original magnification, ×100).

tempts at making a definitive diagnosis should be undertaken because possible exposure to the implicated agent in the future could be lethal.

Antibiotics have remained the most commonly identified etiologic agents in these conditions. The sulfonamides still remain the most common type of antibiotic associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. Seizure medications were the next most frequently identified agents. It is to be expected that the profile of implicated agents will change as prescribing habits change and new agents become available. It is interesting to note that the nonsteroidal anti-inflammatory agents were implicated in three patients with both Stevens-Johnson syndrome and toxic epidermal necrolysis, and the quinilone antibiotic ciprofloxacin was identified in two patients with toxic epidermal necrolysis in this report.

Follow-up data on the ocular status of patients in the current report were limited to 3 months after the onset of the acute illness. Nevertheless, in this relatively short period of time, severe ocular complications developed in a significant number of patients. These figures may, in fact, be a conservative estimate, because a compromised

Table 6. Range of Ocular Complications

Complication (severity)	Erythema Multiforme (n = 22) No. (%)	Stevens-Johnson Syndrome (n = 37) No. (%)	Toxic Epidermal Necrolysis (n = 30) No. (%)
Conjunctivitis (mild)	22 (100)	37 (100)	30 (100)
Conjunctival pseudomembrane (mild)	4 (18)	18 (49)	18 (60)
Conjunctival membrane (moderate)	0	6 (16)	4 (13)
Fornix foreshortening (severe)	0	9 (24)	8 (27)
Symblepharon formation (severe)	0	7 (19)	5 (17)
Corneal epithelial defect (mild/moderate)	0	16 (43)	15 (50)
Corneal ulceration (moderate/severe)	0	2 (5)	2 (7)

tear film may have resulted in some of those patients classified as having moderate disease during their acute illness and would have been at risk for further associated complications at a later date. In addition, the extent of the cicatrizing process may not have become fully evident at the 3-month period.

There is no specific treatment for patients with erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis with the exception of general supportive measures and discontinuation of nonessential drugs. Current evidence would suggest that treating these patients with systemic corticosteroids in the setting of a burn center offers no improvement in overall survival.[23] In the current study, we show that systemic corticosteroids had no effect on the incidence or the severity of ocular manifestations.

Topical antibiotic and steroid usage, frequent lubrication, early lysis of symblepharon, and the occasional use of therapeutic soft contact lenses are common modalities of treatment used in patients with ocular manifestations of these diseases. However, the efficacy of such local treatment in managing these patients has never been evaluated in a prospective manner.

We are aware that a retrospective study of this nature has its limitations. There may be some underestimation of cases, or misinterpretation of data due to insufficient documentation. Some of the etiologies considered to be nondrug-induced and some considered to be drug induced might have been classified erroneously, despite careful review of all available medical records. Patients with milder symptoms treated only in the outpatient department, which are likely to be more frequent, are not included in this report. Nevertheless, it has enabled us to examine the demographic background of these diseases, their complication rates, treatment modalities used, and the relative etiologic significance of various classes of drugs.

The outlook for patients with ocular complications secondary to the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis syndrome probably has changed only slightly over the last 30 years.[13] It is essential that we better understand the cellular and molecular events that contribute early to ocular surface dis-

Table 7. Treatment Modalities Used during Acute Ocular Disease

	Erythema Multiforme (n = 22) No. of Patients (%)	Stevens-Johnson Syndrome (n = 37) No. of Patients (%)	Toxic Epidermal Necrolysis (n = 30) No. of Patients (%)
Topical antibiotics	22 (100)	37 (100)	30 (100)
Topical steroids	4 (18)	21 (57)	14 (47)
Lubricants	5 (23)	15 (41)	17 (57)
Fornix sweeping	0	13 (35)	10 (33)

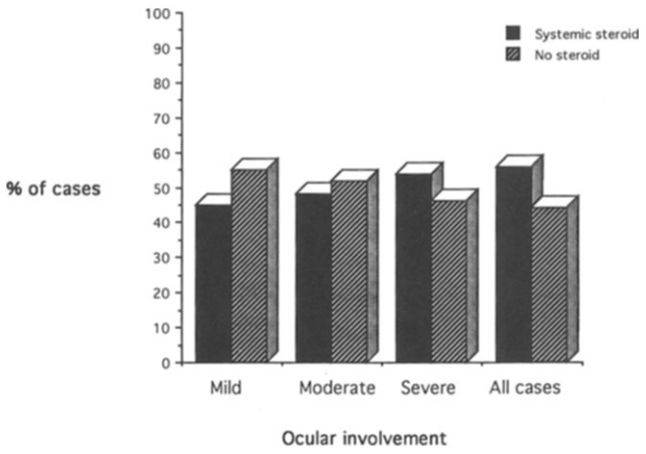


Figure 3. Relation between systemic steroid usage and severity of ocular involvement.

tress. Studying the acute immunopathogenic mechanisms that occur in these diseases may help improve the prognosis for these patients.

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