
CME review article

This feature is supported by an unrestricted educational grant from AstraZeneca LP

Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature

Erik Letko, MD*; Dean N. Papalioidis, BS*; George N. Papalioidis, MD*; Yassine J. Daoud, BS*; A. Razzaque Ahmed, MD†; and C. Stephen Foster, MD*

Objective: To perform a comprehensive review of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Data Sources: A MEDLINE search was performed for the years 1975 to 2003 using the keywords *Stevens-Johnson syndrome* and *toxic epidermal necrolysis* to identify relevant articles published in English in peer-reviewed journals.

Study Selection: All clinical studies that reported on 4 or more patients, review articles, and experimental studies that concerned disease mechanisms were selected and further analyzed. Clinical reports that included fewer than 4 patients were selected only if they were believed to carry a significant message about disease mechanism or therapy.

Results: Stevens-Johnson syndrome and toxic epidermal necrolysis seem to be variants of the same disease with differing severities. A widely accepted consensus regarding diagnostic criteria and therapy does not exist at present. Despite the recent experimental studies, the pathogenic mechanisms of these diseases remain unknown. Although progress in survival through early hospitalization in specialized burn units has been made, the prevalence of life-long disability from the ocular morbidity of Stevens-Johnson syndrome and toxic epidermal necrolysis has remained unchanged for the past 35 years. Further progress depends on modification of the acute phase of the disease rather than continuation of supportive care. The available published evidence indicates that a principal problem in the pathogenesis is immunologic and that immunomodulatory intervention with short-term, high-dose intravenous steroids or intravenous immunoglobulin holds the most promise for effective change in survival and long-term morbidity.

Conclusions: The results of this review call for a widely accepted consensus on diagnostic criteria for Stevens-Johnson and toxic epidermal necrolysis and multicenter collaboration in experimental studies and clinical trials that investigate disease mechanisms and novel therapeutic interventions, respectively.

Ann Allergy Asthma Immunol. 2005;94:419–436.

Off-label disclosure: Drs Letko, G. N. Papalioidis, Ahmed, and Foster and Messrs D. N. Papalioidis and Daoud have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Drs Letko, G. N. Papalioidis, Ahmed, and Foster and Messrs D. N. Papalioidis and Daoud have indicated that in the last 12 months they have not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker's bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

Instructions for CME credit

1. Read the CME review article in this issue carefully and complete the activity by answering the self-assessment examination questions on the form on page
2. To receive CME credit, complete the entire form and submit it to the ACAAI office within 1 year after receipt of this issue of the *Annals*.

* Department of Ophthalmology, Uveitis and Immunology Service, The Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.

† Department of Medicine, New England Baptist Hospital, and Department of Oral Medicine and Diagnostic Sciences, Harvard School of Dental Medicine, Boston, Massachusetts.

Dr Foster is currently with The Ocular Immunology and Uveitis Foundation, Massachusetts Eye Research and Surgery Institute, Boston, MA.

None of the authors have financial interests in any of the medications or products mentioned in this article.

Yassine J. Daoud is the recipient of the Doris Duke Charitable Foundation and Harvard Medical School PASTEUR Clinical Research Fellowship.

Received for publication April 21, 2004.

Accepted for publication in revised form June 21, 2004.

INTRODUCTION

Stevens and Johnson described 2 patients, 8- and 7-year-old boys, with “an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis” in 1922.¹ Both patients had been misdiagnosed by primary care physicians as having hemorrhagic measles. Erythema multiforme (EM), originally described by von Hebra in 1866, had been part of the differential diagnosis in both cases but was excluded because of the “character of skin lesions, the lack of subjective symptoms, the prolonged high fever, and the terminal heavy crusting.” Despite leukopenia in both cases, Stevens and Johnson suspected an infec-

tious disease of unknown origin as a cause of the signs and symptoms. Thomas suggested in 1950 considering EM in 2 categories: erythema multiforme minor (von Hebra) and erythema multiforme major (EMM).² The eponymous term *Stevens-Johnson syndrome* (SJS) has been used as a synonym for EMM since 1983. Bastuji-Garin et al³ in 1993 and Roujeau⁴ in 1994 proposed that EMM and SJS are 2 distinct disorders. They suggested that the term *EM* should be restricted to patients with acraly distributed typical targets or raised edematous papules, with or without mucosal involvement. This clinical picture is in accordance with the original description by von Hebra. They further proposed that the term *SJS* should be used for a syndrome characterized by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric maculae that are different from classic target skin lesions. According to this clinical classification, EMM and SJS could be 2 distinct disorders with similar mucosal erosions but different patterns of cutaneous lesions. This hypothesis is further supported by a strong correlation between clinical classification and the probable cause.⁵

Additionally, some investigators propose that SJS and toxic epidermal necrolysis (TEN) are the same disease but of different severities and suggest using a unifying classification of "acute disseminated epidermal necrosis"⁶ or "exanthematic necrolysis."⁷ A strong argument against this unifying concept was that infection with herpes simplex virus had been described as a frequent cause of SJS or EMM but not of TEN. However, recent reports⁸ indicate that herpes simplex virus infection has not been strongly related to SJS and suggest that SJS and TEN, based on clinical manifestations and pathologic test results, are severity variants of the same disease, which differs from EM.^{5,8}

The purpose of this study is to provide a comprehensive review of SJS and TEN and to provide evidence that supports the idea that these 2 entities are variants of the same disease with differing severities. We performed a MEDLINE search for the years 1975 to 2003 using the keywords *Stevens-Johnson syndrome* and *toxic epidermal necrolysis* to identify relevant articles published in English in peer-reviewed journals. All clinical studies that reported on 4 or more patients, review articles, and experimental studies that concerned disease mechanisms were selected and further analyzed. Clinical reports that included fewer than 4 patients were selected only if they were believed to carry a significant message about disease mechanism or therapy.

STEVENS-JOHNSON SYNDROME

Classification

Since the report of Stevens and Johnson, various authors have published different diagnostic criteria for SJS (Table 1) or TEN (Table 2), but there is still no universally accepted definition, and the reports throughout the literature still refer to various criteria or create their own diagnostic criteria. Moreover, in some reports the diagnostic criteria are either

missing or not clear (Table 1). Hence, diagnosis of SJS made by one author may be different from that made by another. In particular, the diagnosis of SJS is usually admixed with EM, EMM, or TEN. Regrettably, these differences cause difficulties in attempts to evaluate, interpret, and compare the data on SJS and related diseases. Recent reports are encouraging, since they describe the correlation between clinical and histologic findings in SJS and EM and thus differentiate these 2 entities.^{3,57}

Epidemiology

The incidence of SJS is estimated to be between 1.1¹⁵ and 7.1¹⁶ cases per million person-years (Table 3). The differences in incidence reported in the literature might be caused by different inclusion criteria. Strom et al¹⁶ used as an inclusion criterion a discharge code that included several diagnoses, including erythema iris, herpes iris, and staphylococcal scalded skin syndrome (SSSS), in addition to SJS and TEN. The report from Germany¹⁵ may have expressed the incidence of SJS with higher accuracy, since the authors included in their study only the individuals diagnosed as having SJS or TEN.

The mean age of patients with SJS was 25 years in one large series.¹⁵ The mean age has been as high as 47 years in smaller series of patients.^{22,25} Interestingly, the average extent of skin detachment increases with higher average age (Tables 1 and 3). The proportion of females has been estimated between 33%²⁵ and 62%.⁵¹ The largest series reports 39.9% of females in a group of 315 patients with SJS.⁵⁷

Etiology

Various etiologic factors have been implicated as causes of SJS. These include infection, vaccination, drugs, systemic diseases, physical agents, and food.⁸ Drugs are the most commonly blamed (Table 4). Recent reports^{5,8} linked SJS to the use of drugs rather than to other etiologic factors, confirming this by close correlation between clinical pattern and etiologic factor. Antibiotics are the most common alleged cause of SJS, followed by analgesics, cough and cold medication, nonsteroidal anti-inflammatory drugs (NSAIDs), psychoepileptics, and antigout drugs.¹⁵ However, other drugs can be involved in the pathogenesis of SJS as well.^{9,15} Individuals with antigens HLA-Bw44,^{26,61} a part of HLA-B12,⁶² and HLA-DQB1*0601²⁴ may be more susceptible to developing SJS.

Clinical Profile

SJS may present as a febrile illness (malaise, headache, cough, rhinorrhea) associated with prodromal target lesions (Fig 1) followed by skin detachment as a dominant clinical finding (Fig 2). Typical target lesions have 3 rings: a bright pink or red inner ring, a lighter pink outer ring, and a darker pink outermost ring. The shedding of nails and eruptive nevi are rare manifestations.⁶³ Mucous membrane involvement is reported to be between 92.3% and 100% of patients (Fig 3), and the frequency of visceral involvement (sloughing of gastrointestinal mucosa, tracheal or bronchial erosions, glo-

Table 1. Diagnostic Criteria for SJS

Diagnostic criteria	Year	Initial reference	Subsequent reference(s)
Generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis	1922	1	
(1) Acute, self-limited, or episodic course; (2) attack or episode 1–6 weeks; (3) symmetrically distributed, fixed (lasting > 7 days), discrete, round erythematous skin lesions; (4) concentric color changes in at least some lesions; (5) severe mucous involvement on at least 2 surfaces; (6) histopathology “compatible” (primarily mononuclear cell infiltrate, no leukocytoclastic vasculitis)	1983	9	10,11
(1) A self-limited or episodic cutaneous or mucocutaneous syndrome; (2) symmetrically distributed, round, erythematous skin lesions; (3) concentric color changes without blister formation in at least some of the lesions (target or iris lesion); (4) persistence of individual lesions for at least 7 days; (5) duration of entire episode fewer than 6 weeks; (6) no histopathologic findings diagnostic of another process, such as leukocytoclastic vasculitis or a viral vesicle	1984	12	13
(1) Individual lesions <3 cm in diameter (lesions may coalesce); (2) target (iris) lesions (typical or atypical); (3) mucous membrane involvement (at least 2); (4) fever; (5) biopsy specimen compatible with erythema multiforme; (6) <20% of the BSA involved in first 48 hours and >10% of the BSA involved	1990	14	
(1) A “targetlike” lesion; (2) involvement of the mucous membranes (at least 2); (3) fever; (4) biopsy specimen compatible with SJS	1991	15	
ICD-9-CM code 695.1*	1991	16	
(1) Skin detachment <10% and (2) flat atypical targets (ie, round lesions), reminiscent of EM but with only 2 zones and/or poorly defined border, nonpalpable with the exception of potential central blister†	1993	3	8,12,17–21
Extensive skin involvement consistent with EM and ulcerative lesions of at least 1 mucosal surface	1994	22	
(1) Serious mucocutaneous illness with characteristic targetlike lesions; (2) bullae and extensive areas of necrosis; (3) a prominent acute prodrome; (4) involvement of at least 2 mucosal sites	1995	23	
Widespread small blisters with skin detachment of less than 10% of the BSA	1995	19	
(1) Acute febrile illness with (2) characteristic target lesions each less than 3 cm in diameter; (3) involvement of at least 2 mucous membranes; and (4) less than 20% of BSA involved in the first 48 hours	1996	24	
Not specified		25–35	

Abbreviations: BSA, body surface area; EM, erythema multiforme; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; SJS, Stevens-Johnson syndrome.

* Discharge diagnosis of erythema iris, herpes iris, Lyell syndrome, staphylococcal scalded skin syndrome, SJS, and/or toxic epidermal necrolysis.

† SJS and toxic epidermal necrolysis overlap was defined as skin detachment between 10% and 30% of the BSA plus widespread macules or flat atypical targets.

merulonephritis, hepatitis) was estimated to be between 8.1% and 61.5% of the patients (Table 5).^{15,22,25,29} The clinical course of SJS does not differ from TEN. Nevertheless, studies that analyze the clinical course, particularly in patients with SJS, are limited.

Pathology and Immunology

The earliest histologic finding observed in skin lesions of patients with SJS is a perivascularitis of the superficial dermal vessels²⁷ associated with minimal dermal inflammatory cell infiltrate (usually mononuclear) and full-thickness necrosis of epidermis.^{66,67} The dermoepidermal junction shows changes that range from vacuolar alteration to subepidermal blister

formation.¹² The dermal infiltrate is superficial, mostly perivascular, with presence of erythrocytes and eosinophils.¹² Keratinocytes undergo perforin-mediated apoptosis.¹⁰

Early skin lesions from SJS patients examined by immunofluorescence demonstrated IgM and C3 deposits in the vascular walls in more than 75% of specimens.²⁷ Patients with recurrent SJS were noted to have IgG, IgA, IgD, C3, and C4 present in vascular walls.

Foster et al²⁷ observed numerous HLA-DR⁺ cells in the substantia propria, vessel walls, and epithelium of the conjunctiva from the SJS patients. In the epithelium, HLA-DR was present on Langerhans cells, macrophages, and activated

Table 2. Diagnostic Criteria for TEN

Diagnostic criteria	Year	Initial reference	Subsequent reference(s)
Erosive skin lesions on at least 10% of the BSA	1985	36	
(1) Widespread blisters with morbilliform or confluent erythema and associated skin tenderness; the area involved by erythema and blister formation should be noted; (2) the absence of target lesions; (3) sudden onset and generalization within 24 to 48 hours; and (4) the histologic findings of full-thickness epidermal confluent keratinocyte necrosis, leaving the cytoplasm of keratinocytes eosinophilic and glassy, and a minimal to absent dermal infiltrate	1987	37	13 (>50% of the BSA)
Necrolysis - areas of erythema in which Nikolsky sign is positive, uncovering raw dermis, detachment >10% of the BSA	1987	38	39
(1) Bullae or erosions on 20% of BSA or at least 3 different anatomic areas involved; (2) bullae or erosions develop on erythematous base; (3) staphylococcus scalded skin syndrome excluded; (4) occurs on non-sun-exposed skin; (5) skin peels off in >3-cm sheets (ie, not just erythema and desquamation as seen in exfoliative erythroderma); (6) mucous membrane involvement frequent; (7) tender skin within 48 hours of onset of rash; (8) fever; (9) biopsy specimen compatible with drug-induced TEN (basal necrosis) (biopsy performed within 48 hours of onset)	1989	40	14,15,41
Biopsy	1989	42	43-46
Area of epidermis detached >20%, skin biopsy	1990	47	
Sudden onset of epidermal separation affecting at least 20% of the BSA	1991	48	
(1) Explosive onset of widespread disease (80% to 100% skin involvement), with large sheets of erythema not preceded by focal or target lesions; (2) extreme pain associated with the skin lesions; (3) precipitation by drugs, with the onset after 1 to 4 days of drug therapy; (4) the peeling of large sheets of skin; (5) absence of immune reactants (IgM and C3) within the dermal blood vessels on immunofluorescent studies; (6) absence of blood vessel damage as assessed by <i>Ulex europaeus</i> I (UEA I) with L-fucose specificity; and (7) widespread epidermal necrosis	1991	49	
(1) Skin detachment >10% of the BSA; (2) no spots; (3) large epidermal sheets or (1) skin detachment >30% of the BSA; (2) spots; (3) macules (ie, nonpalpable, erythematous, or purpuric macules with irregular shape and size, often confluent, with or without blisters) or flat atypical targets (ie, round lesions reminiscent of EM but with only 2 zones and/or a poorly defined border, nonpalpable with the exception of potential central blister)*	1993	3	12,15,17-21,50
Necrolysis of all epidermal layers, confirmed by skin biopsy results, leading to erosions of at least 10% of the BSA	1993	51	
Widespread detachment of the epidermis, involving 30% or more of the BSA†	1995	19	
(1) Widespread mucocutaneous painful edematous skin lesions; (2) positive Nikolsky sign; (3) presence of prodromal symptoms of fever, cough, headache, and malaise; (4) prominent mucous membrane involvement; (5) exclusion of the staphylococcal scalded skin syndrome	1995	23	
Confluent often dark erythema, associated with the sudden onset of epidermal detachment, mucosal erythema, and ulcerations, confirmed by skin biopsy showing full-thickness epidermal necrosis and detachment	1998	52	
NR		32,51,53-60	

Abbreviations: BSA, body surface area; EM, erythema multiforme, NR, not reported; TEN, toxic epidermal necrolysis.

* Stevens-Johnson syndrome and TEN overlap was defined as skin detachment between 10% and 30% of the BSA plus widespread macules or flat atypical targets.

† Overlapping Stevens-Johnson syndrome and TEN skin detachment of 10% to 29% of the BSA.

Table 3. Incidence of SJS and TEN

Incidence of SJS				Incidence of TEN			
Location	Period	Annual incidence (per 1 million)	Reference	Location	Period	Annual incidence (per 1 million)	Reference
Michigan	1980–1983	7.1	16	Sweden	1964–1969	0.4	32
Minnesota	1980–1983	2.6	16	Seattle	1972–1986	0.5	14
Florida	1983	6.8	16	United States	1980–1984	<1	16
West Germany	1981–1985	1.1	15	West Germany	1981–1985	0.93	15
				France	1981–1985	1.2–1.3	47
				Italy	1984–1988	0.6	31
				Italy	1989	1.2	31

Abbreviations: SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis.

Table 4. Etiology of SJS and TEN

Source	No. of patients	Etiology		
		Drug	Infection	Unknown
SJS				
Patterson et al ²⁹	13	12	1	0
Porteous and Berger ¹³	5	3	0	2
Power et al ²³	37	19	7	11
Patterson et al ²²	13	12	1	0
Patterson et al ²⁵	15	13	2	0
Assier et al ⁵	33	28	0	5
Total No. (%)	135 (100)	98 (72.6)	14 (10.4)	23 (17.0)
TEN				
Porteous and Berger ¹³	3	2	0	1
Power et al ²³	30	24	2	4
Villada et al ⁵³	5	3	0	2
Guibal et al ⁵⁰	13	9	0	4
Mclvor et al ⁴⁵	12	10	0	2
Total No. (%)	63 (100)	48 (76.2)	2 (3.2)	13 (20.6)

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

T cells. On transmission electron microscopy, the conjunctivae of patients with episodic conjunctival inflammation revealed squamous epithelial metaplasia, vascular membrane zone disruption, reduplication, and thickening.²⁷ Nishida et al⁶⁸ suggested that epithelial hyperproliferation and transglutaminase 1 gene expression led to the pathologic keratinization of ocular surface epithelium.

Immune complexes in the serum have been reported by Wuepper et al²⁸ and others.⁶⁴ Two of 4 serum specimens each from different patients with SJS had a positive RAJI cell assay, indicating the presence of circulating immune complexes.⁷⁰

Treatment

There is no universally accepted, definitively effective, specific treatment for acute SJS other than supportive care. The studies that report on corticosteroid use in SJS patients^{22,25,29} include (based on the various diagnostic criteria) patients with TEN rather than SJS (Table 1). Kim et al⁷¹ suggested that treatment with glucocorticoids is associated with increased morbidity and mortality. It must be emphasized, however, that the steroid use in the patients who were the

subject of the report was often delayed in onset, was usually very prolonged in duration, and was moderate in dose; most of the deaths were secondary to infection.

In striking contrast to the observations of Kim et al,⁷¹ Patterson et al²² reported a spectacular success rate with short-term use of high-dose corticosteroids. They reviewed records of 67 patients with SJS in whom systemic corticosteroid therapy was initiated between day 0 and 22 of the onset of symptoms. Sixty-six patients recovered; 1 died of reasons unrelated to SJS or steroid therapy. The authors concluded that prompt treatment with very high-dose systemic (intravenous) corticosteroids for a relatively brief period improves the outcomes of patients with SJS.

The number of studies other than sporadic case reports that show the effect of intravenous immunoglobulin (IVIG) in patients with SJS is limited.^{72–75} The amount of IVIG used in these reports varied from 1.5 to 2 g/kg administered in a single infusion. Although retrospective studies^{72–74} suggested that IVIG may be effective in halting the progression of SJS and TEN, a prospective noncomparative study showed no benefit on mortality rate or progression of the disease. These

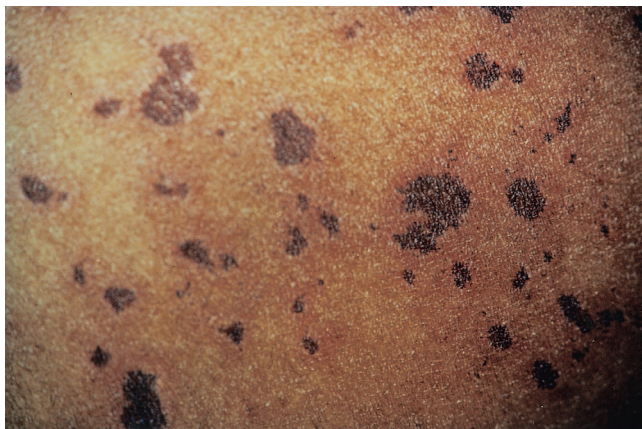


Figure 1. Prodrromal target lesions.



Figure 3. Mucous membrane lesions.



Figure 2. Skin detachment.

controversial data warrant a multicenter prospective randomized trial to address the efficacy of IVIG in patients with SJS and TEN. Symptomatic treatment of the patients with SJS does not differ from that of TEN patients.

Complications

The complications most commonly encountered in SJS include hypovolemia due to fluid losses by lack of an intact skin barrier and infection by similar mechanism. Aside from skin manifestations, mucosal ulcerations may similarly occur in the trachea or bronchi, potentially compromising the patient's airway and oxygenation. Pneumothorax⁷⁶ and bronchiolitis obliterans³⁰ may occur in patients with SJS secondary to sloughing of the bronchial epithelium and need for mechanical ventilation for respiratory support. Mucosal erosions can develop in the gastrointestinal tract, and biopsy specimens of the lesions show intraepithelial inflammatory cells and necrosis of epithelial cells, similar to the features of SJS skin lesions.⁷⁷ Gastrointestinal symptoms may manifest as dysphagia, odynophagia, dyspepsia, and bloody diarrhea. Endoscopy in patients with bloody diarrhea reveals features similar to pseudomembranous colitis, with pathosis resembling the in-

testinal lesions that occur in graft-vs-host disease.⁷⁸ Hepatitis, myocardial injury, and hematologic complications have also been reported.⁶³ Proteinuria, hematuria, and azotemia may occur as a consequence of glomerulonephritis.^{47,79–81} A small subset of SJS patients experience episodic recurrent conjunctivitis after recovery from the acute phase.²⁷

Mortality

The mortality rate has been reported to be between 1% and 3%. Patient age and extent of skin detachment are proposed as the main prognostic factors.⁴⁷ A recent study⁸² suggests that the long-held intuitive, logical hypothesis that early withdrawal of any causative drug may decrease mortality in patients with SJS is probably correct. Controversies in the use of systemic medications, including steroids, during the acute phase of SJS persist. Because of limited data, it is not clear what the effect (if any) of systemic steroids on mortality is.

TOXIC EPIDERMAL NECROLYSIS

History

Ruskin first described a condition similar to TEN in 1948,⁸³ and in 1956 Lyell⁸⁴ reported on 4 more patients who had acute rash followed by skin detachment and mucous membrane involvement and proposed the name TEN. Lyell⁸⁵ also postulated that a circulating toxin caused the damage to the epidermis. It was shown later that 2 of Lyell's patients with TEN actually had SSSS. Both TEN and SSSS can be difficult to distinguish from each other clinically (Table 6), and histopathologic analysis of the skin remains the main tool for discrimination between the two.

Classification

Several authors have proposed diagnostic criteria for SJS and TEN, although none is universally accepted (Tables 1 and 2). Recent reports suggest that TEN and SJS are the same disorder of different severities and should, therefore, comprise a unifying name.^{6,7} In some reports, the terms *TEN* and *SJS* are used as synonyms.^{86,87}

Table 5. Clinical Profile of Patients With SJS and TEN

Source	No. of patients	Female, %	Average age, y	Skin detachment, %	Mucous membrane involvement, % of patients	Visceral involvement, % of patients
SJS						
Patterson et al ²⁹	13	53	39	77	100	53.8
Power et al ²³	37	62	32	NS	100	8.1
Schopf et al ¹⁵	315	39.9	25	NS	NS	NS
Patterson et al ²²	13	38	47	71	92.3	61.5
Patterson et al ²⁵	15	33	47	77	93.3	46.7
TEN						
Guibal et al ⁵⁰	13	54	44.2	40.2	100	NS
Guillaume et al ⁶⁴	87	63	45.8	38.9	96.5	NS
Jones et al ⁴²	9	67	12.7	60.0	NS	NS
Patterson et al ²⁹	13	54	34.3	76.9	100	53.8
Goens et al ⁶⁵	10	80	39.2	NS	NS	NS
Schopf et al ¹⁵	259	64.3	64	NS	NS	NS

Abbreviations: NS, not specified; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 6. Characteristics of SJS and TEN

Characteristic	SJS	TEN
Epidemiology		
Incidence per million person-years	1.1–7.1	0.4–1.2
Age range, y	25–47	46–63
Proportion of females, range, %	33–62	61.3–64.3
Etiology, %		
Drugs	72.6	76.2
Infection	10.4	3.2
Unknown	17.0	20.6
Pathology		
Epidermis	Full-thickness necrosis Apoptosis of keratinocytes	Full-thickness necrosis Apoptosis of keratinocyte
Dermis	Mild infiltrate	Mild infiltrate
Association with HLA antigens	HLA-B12 HLA-Bw44 HLA-DQB*0601	HLA-B12
Clinical profile, %		
Extent of skin detachment	<50	>10
Mucous membrane involvement	92.3–100	96.5–100
Visceral involvement	8.1–61.5	53.8
Mortality	1–3	10–70

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Epidemiology

TEN has been observed worldwide in all races.⁸⁸ The incidence of TEN is reported to be between 0.4 and 1.3 cases per million person-years (Table 3). Interestingly, there has been a recent increase in incidence. TEN can occur in all age groups, including newborns and elderly patients.^{43,64,89} The mean age of patients with TEN is reported to be between 46⁴⁷ and 63 years.¹⁵ The proportion of females is estimated to be between 61.3%⁴³ and 64.3%.¹⁵

One study reported on the overall incidence of SJS, SJS/TEN overlap, and TEN, because these diseases were viewed

as a spectrum of the same clinical entity.¹² The incidence was estimated at 1.17, 1.53, and 1.89 for 1990, 1991, and 1992, respectively. The data are essentially a sum of the incidences in separate epidemiologic reports on SJS¹⁵ and TEN.^{14–16,31,32,82} As stated by the authors, the increase in overall incidence reflected the acceptance of a registry that was used for the study rather than a real increase in the incidence of these diseases. A recently established case-population surveillance network (Euronet) in Western Europe may provide more accurate epidemiologic data on SJS and TEN in the future.¹⁷

Table 7. Incidence of Drugs Associated With Toxic Epidermal Necrolysis

Source	No. of patients	Incidence, %				
		Antibiotics	Psychoepileptics	NSAIDs	Analgesics	Antigout drugs
Schopf et al ¹⁵	216	42	11	19	23	15
Roujeau et al ⁴⁷	195	29	NR	33	5.4	NR

Abbreviations: NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs.

Etiology

A distinction was made between TEN and SSSS after the initial report by Lyell,⁸⁴ and it is generally accepted that TEN is usually a drug reaction.⁸⁵ This is also supported by the fact that readministration of the suspect drug can cause the recurrence of TEN.^{90–92} However, in some patients, the origin of TEN remains unknown. Based on the scanty reports of infectious etiology, it is unclear whether there is a real relation between TEN and infection.^{86,89,93,94}

Antibiotics are the most frequent cause of TEN followed by NSAIDs and analgesics (Table 7). Anticonvulsants are reported in 18% of drug-induced cases of TEN.⁸⁸ A case-control study conducted in several European countries estimated the risk of SJS or TEN associated with medication use (Table 7) and concluded that the use of antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol were statistically associated with greater risk (but none of these drugs had risk greater than 5 cases per million users per week).^{18,19}

Importantly, food additives,^{95,96} fumigants,^{47,97} and contact with chemicals^{77,98–101} are also described as causative factors of TEN. Thus, in general, chemicals in various forms, drugs or otherwise, may cause TEN. This should be kept in mind when attempting to determine the etiology in patients for whom the trigger for TEN is not immediately apparent; detailed history may reveal the causative agent. This information is also of obvious importance for manufacturers.

TEN has also been observed in an animal model of acute graft-vs-host disease without any drug administration.^{102,103} The incidence of TEN in patients infected with human immunodeficiency virus¹⁰⁴ and in patients following bone marrow transplantation¹⁰⁵ is higher than in the general population. Multiple drug exposure and immune- or infection-induced response may account for this phenomenon. Individuals with the HLA-B12 antigen are at significantly higher risk of developing TEN.¹⁰⁶

Clinical Profile

Fever and constitutional symptoms are present in all patients⁶ 2 to 3 days before the rash, often resembling an upper respiratory tract infection (malaise, fever, rhinitis, and anorexia).¹⁰⁷ Other prodromal signs and symptoms may occur: conjunctivitis (32%), pharyngitis (25%), and pruritus (28%).¹⁰⁸ The prodrome lasts from 1 day to as long as 3 weeks.¹⁰⁹ Yetiv et al⁶¹ proposed that fever might be related to infection rather than to an inciting drug, but other data sug-

gest that antibiotics and not infection probably cause the reaction.¹⁹

The acute phase of TEN lasts for approximately 8 to 12 days and is characterized by persistent fever, mucositis, and generalized epidermal sloughing⁶ (Fig 4). The skin lesions begin as a painful or burning eruption, usually starting symmetrically on the face and thorax and spreading to the entire body.⁸⁸ Denudation and erosions of mucous membranes precede epidermal necrolysis.¹¹⁰ Mucositis can occur on conjunctival,²³ buccal,¹¹¹ tracheal, bronchial,¹⁰⁷ pharyngeal, esophageal, nasal, anal, vaginal,⁴⁴ and perineal mucosae.¹⁰⁹ Urethritis may lead to urinary retention.¹¹² Mucous membrane involvement is present in nearly all patients^{86,113} (Table 6).

The skin involvement is significant. The epidermis is sloughed in large sheets that produce a dark red, oozing dermis.⁴⁷ The initial lesions may be targetoid or morbilliform, although classic target lesions are usually absent³⁸; the target lesions are typical of SJS and do not present in patients with TEN.³ The erythematous skin lesions of TEN demonstrate the Nikolsky sign (slipping of the superficial skin layer induced by slight rubbing pressure).¹⁰⁸ Areas of involved skin are tender and painful.^{6,112} The dermis remains undamaged.¹¹⁴ The usual course is an intense erythema that progresses rapidly to epidermolysis and stops in 2 to 3 days.¹¹² In 1 of 7 patients, however, 100% loss of epidermis in less than 24 hours occurs.^{6,110} This has been called *d'emblee* or full-blown TEN.⁶ The scalp is usually spared.^{6,110}

Dermatologic recovery from TEN typically takes 1 to 3 weeks, depending on the extent of skin detachment. Obviously, those with more extensive denudation may require longer periods for reepithelialization (at times up to 3–6 months). This period is necessary for the mucous membranes and skin to reepithelialize.⁶ Rarely, the necrolysis can recur in areas that began to heal.¹¹⁰ The healing of the skin is faster on the anterior thorax than in intertriginous areas and the back.¹¹⁰ Mucosal lesions usually require a longer time to heal. The glans penis may require as long as 2 months to reepithelialize.¹¹⁰ Long-term episodic conjunctivitis that results in damage to the ocular surface with symblepharon formation may follow the acute phase of TEN.^{23,27}

The skin heals without scarring unless infection develops.⁸⁸ After healing of the skin, disturbance in pigmentation is reported in 88%.⁶ Nails may be shed, and an abnormal or absent regrowth may ensue.^{6,85}

Mucous membrane lesions may persist for months after the acute attack. The healing of mucous membranes can result in scar formation, resembling cicatricial pemphigoid or lichen planus.⁶ Phimosis,¹¹⁵ vaginal synechiae,^{115,116} esophageal stenosis,^{85,117,118} and ocular symblephara²⁷ may result. Ocular sequelae, potentially leading to blindness, are some of the more serious consequences of TEN.

Pathology, Pathophysiology, and Immunology

Bullous lesions in TEN result from complete epidermal necrosis with development of a subepidermal blister underlined by a sparse mononuclear cell infiltrate.¹⁵ Epithelial shedding occurs in skin, oropharynx, and esophagus, all sites where Langerhans cells have been documented in normal tissues.¹¹⁹ A quantitative difference between the infiltration and the prominent epidermal destruction is the major histologic difference between TEN and SJS.¹⁵

Histopathologic and immunohistochemical studies of the earliest TEN lesions are characterized by abundant macrophage infiltration of the dermis and epidermis, numerous dermal dendrocytes with a plump aspect, and abundant deposits of tumor necrosis factor α (TNF- α) in the epidermis.¹⁵ Another study⁹² showed that T lymphocytes were the predominant cells.⁵³ A synergistic activity of these cells is likely responsible for the epidermal destruction.^{41,49} The controversy regarding migration of macrophages with endogenous peroxidase-positive granules in the epidermis may be caused by different ages of the biopsy specimens.^{53,54}

TEN is characterized by a cell-poor infiltrate in which macrophages and dendrocytes predominate, with a strong immunoreactivity for TNF- α .¹⁵ CD4⁺ T lymphocytes predominate in the dermis, whereas CD8⁺ T cells predominate in the epidermis.^{41,53,120} The dermoepidermal junction and epidermis is infiltrated mostly by CD8⁺ T lymphocytes as well.¹¹⁹ Necrotic keratinocytes, vacuolar alteration, epidermal blistering, and superficial, mostly perivascular dermal infiltrate with the presence of erythrocytes and eosinophils were described.¹² C3 and IgG deposits at the dermoepidermal junction and around small dermal vessels were interpreted to be the result of a nonspecific exudative phenomenon.¹²¹

The immunologically activated state characteristic of TEN is underscored by HLA-DR expression on keratinocytes.^{53,122} Miyauchi et al⁹⁶ proposed that skin lesions of TEN may be produced by CD8⁺ T cells that recognize major histocompatibility complex 1 modified by an antigen or by those that recognize an antigen that is restricted by major histocompatibility complex 1.¹²⁰

The death of keratinocytes in TEN was shown to be apoptotic.¹²³ Apoptosis is mediated by Fas-FasL interactions.⁵² Perforin¹²⁴ and TNF- α ,⁴¹ other mediators of apoptosis, are present in the epidermis of the patients with TEN as well. Other studies have demonstrated that mucosal epithelium, particularly in the conjunctiva and intestine,¹²⁵ undergo apoptosis.

Macrophages or keratinocytes present in the skin could be responsible for releasing TNF- α ⁴¹; the exact origin of the

TNF- α is not clear. TNF- α may induce skin alteration either directly by intrinsic cell damage or indirectly by activation of other cells.⁴¹ Nitric oxide has also been implicated as another potential mediating agent at the molecular level. Nitric oxide can cause apoptosis and necrosis, and elevated levels of inducible nitric oxide synthase have been detected by reverse-transcription polymerase chain reaction at the lower epidermis and upper dermis of TEN and SJS patients.¹²⁶

Electron microscopic studies of the skin of TEN patients revealed necrotic keratinocytes with nuclear disintegration and dendritic cells with the nuclear chromatin configuration of T lymphocytes. These findings, including the presence of keratinocyte blebs and membrane defects with cytoplasmic processes from the lymphoid cells, suggested the involvement of T-lymphocyte-mediated cytolysis of drug-altered target keratinocytes in TEN.

The hematologic disturbances observed in patients with TEN were reported by Goens et al in 1986.⁶⁵ Lymphopenia, with a decrease in the CD4/CD8 ratio, is present in peripheral blood.⁵⁴ Granulocytopenia has a prognostic value according to one study.⁵⁵ Patients with neutropenia or leukopenia (defined as a white blood cell count of less than 1,000/mm³) had a poor prognosis, with all but 1 patient in the study with leukopenia dying. The number of HLA-DR⁺ mononuclear cells and the number of HLA-DR antigens, mainly on monocytes, are decreased in the acute phase and are increased after recovery compared with healthy controls.⁵¹ Serum levels of interleukin 6 are increased in the acute phase.⁵¹

Elevated serum amylase levels were reported in several studies.^{36,127,128} Both salivary¹²⁸ and pancreatic¹²⁷ origins of the amylases were suggested. Parotitis was first clinically documented in TEN patients by Lyell⁸⁵ and histologically confirmed later by Roujeau et al.¹²⁹ A few cases of pancreatitis were reported as well.^{36,128,130} A correlation between hyperamylasemia and ocular sequelae was observed by Chosidow et al.³⁶ It was suggested that hyperamylasemia may reflect the severity of mucous membrane involvement and may have a predictive value of post-TEN sicca syndrome.¹²⁹

Peripheral blood lymphopenia, especially of CD4⁺ T lymphocytes, is associated with a high lymphocytic cellularity of the blister fluid, with predominance of antigen primed CD8⁺ CD29⁺ T lymphocytes.¹²⁷ Increased serum and blister fluid levels of creatine kinase in patients with TEN have also been reported.^{131,132} The origin of the creatine kinase in serum and blister fluid remains unknown (but is possibly from keratinocytes).^{131,132} Interleukin 6 in blister fluid¹³³ and elevated levels of matrix metalloproteinase 2 (MMP2) were observed.¹³⁴ Compared with patients with other blistering diseases (bullous pemphigoid, thermal burns), a significantly higher amount of MMP2 was found in TEN blister fluid, emphasizing the potential role MMP2 may play in the specific inflammatory reaction of TEN.¹³⁴

Skin tests have shown a delayed hypersensitivity reaction to ampicillin in a patient with TEN following ampicillin ingestion.¹²⁵ The lack of lymphocyte response to native drug

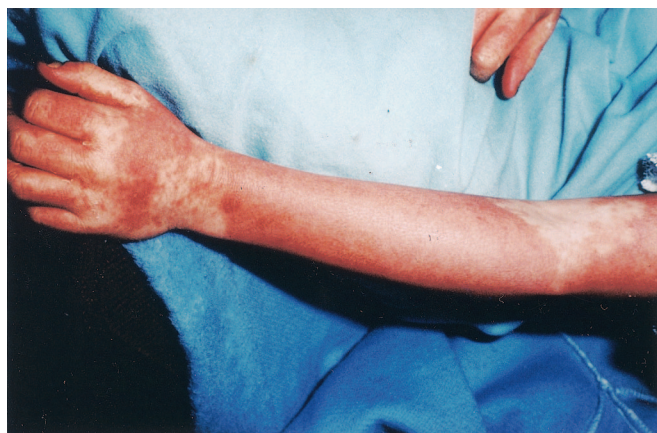


Figure 4. General epidermal sloughing.

and the positive skin test result suggest that the immune response may be directed at drug-modified epidermal cells.¹³⁵

TEN patients can be distinguished from controls by exposure of their lymphocytes to oxidative drug metabolites generated by a murine hepatic microsomal system *in vitro*.^{135,136} and Friedman et al¹³⁵ suggested that probably both immune hypersensitivity reactions and reactions mediated by toxic intermediates generated as a result of impaired or altered drug metabolism are involved in the pathogenesis of TEN. The defect in metabolism is highly specific for drugs.^{20,138} For example, the toxic-reactive metabolite has been identified as hydroxylamine for sulfonamides,¹³⁹ and for anticonvulsants and amineptin the toxic-reactive metabolite seems to be an arene oxide.¹⁴⁰ Deficiency of glutathione transferase- μ , which is present in 50% of the population, and additional factors, particularly a qualitative deficiency of some other enzymes, may play a role in the pathogenesis of TEN.¹³⁵

It has been shown that the toxin-mediating SSSS causes intraepidermal cleavage, which is responsible for skin peeling and bullae formation.¹⁴¹ Another study⁴³ showed that in patients with TEN, drugs bind to intercellular epidermal protein. These findings suggest that similar pathogenic mechanisms in the epidermal cleavage in SSSS and TEN may be involved. Cells separated from their surroundings are susceptible to apoptosis. Whether this is a mechanism-inducing apoptosis of keratinocytes in patients with TEN is not clear yet.

Treatment

The treatment of patients with TEN is, in general, most appropriately provided in intensive care units or burn centers,¹⁴² since these patients are or have the potential to be extremely ill and require specialized care (mechanical ventilation, pressors for blood pressure support, appropriate wound care). There is no definite specific treatment for TEN. Thus, most of the patients are treated symptomatically and supportively. The principles of emergency treatment of patients with TEN are similar to the treatment of patients with extensive thermal burns.¹⁴² Fluid management is provided by macromolecules and saline solutions during the first 24

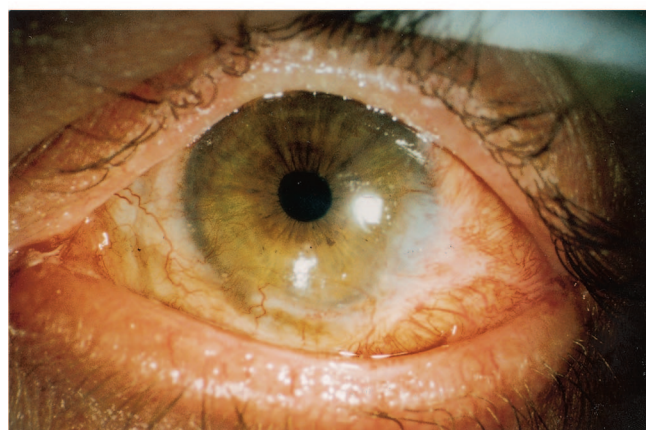
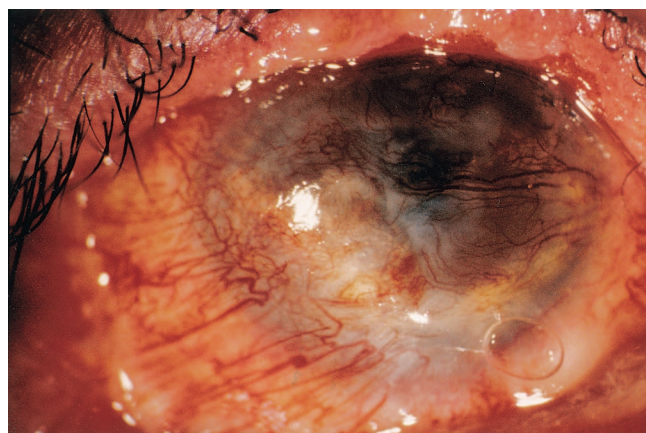


Figure 5. Limbal stem cell transplantation before surgery (top) and 6 months after surgery (bottom).

hours.¹⁴³ Phosphate repletion is necessary in the presence of hypophosphatemia.^{143,145} The fluid resuscitation requirement is usually less than in patients with burns that cover the same body surface area.^{37,112} Oral intake of fluids provided by a nasogastric tube can sometimes be started after the second day, thus decreasing intravenous fluid requirements, which can be progressively tapered and discontinued, usually in approximately 2 weeks.⁸⁸

Parenteral nutrition is necessary to replace the protein loss in this hypercatabolic state and to promote healing of cutaneous lesions.^{146,147} Because of impaired glycoregulation, intravenous insulin therapy may be required.¹⁴⁴ Patients with TEN are at high risk of infection. Therefore, sterile handling and/or reverse-isolation nursing care is essential to decrease the risk of nosocomial infection.^{37,143} Cultures of blood, catheters, and gastric and urinary tubes must be routinely performed. Because of the frequent association between TEN and sulfonamide exposure, silver sulfadiazine, commonly used in burn units, is avoided and replaced by another antiseptic, such as 0.5% silver nitrate and 0.05% chlorhexidine, to paint and bathe affected skin areas.⁸⁸ Prophylactic antibiotics are not recommended.^{139,140,148} The diagnosis of sepsis is

Table 8. Specific Treatment for TEN

Treatment	No. of patients	No. of dead patients	Reference
Steroids	13	4	50
IVIg	10	0	53
Cyclophosphamide	5	0	49
Plasmapheresis	5	0	156
Steroids	15	10	44
Symptomatic	15	5	44
Steroids	13	0	29
Plasmapheresis	5	1	48
Plasmapheresis	6	0	39
Thalidomide	12	10*	70
Plasmapheresis	7	0	17
Cyclosporin	11	0	157
Plasmapheresis	8	1	158

Abbreviations: IVIG, intravenous immunoglobulin; TEN, toxic epidermal necrolysis.

* Study stopped because of high mortality.

difficult, and the decision about whether to administer systemic antibiotics must be carefully considered. Increase in the number of bacteria cultured from the skin, sudden decrease in temperature, and deterioration of the patient's condition may be the first signs of infection, indicating the need for initiation of antibiotic therapy. The choice of antibiotic is usually based on the bacteria present on the skin.¹¹⁶ Because of the impaired pharmacokinetics, similar to that of burn patients, the administration of high doses may be required to reach therapeutic levels.¹⁴⁹ Therefore, monitoring of serum levels is necessary to adjust the dosage of the antibiotic.

Other general measures include increasing environmental temperature in the room to 30°C to 32°C to reduce caloric loss through the skin. Fluidized air beds are recommended if a large portion of the skin on the patient's backside is involved: the use of heat shields and infrared lamps help to reduce heat loss.^{112,116}

Anticoagulation with heparin or low-molecular-weight heparin for the duration of hospitalization is recommended⁸⁸ due to the risk of deep vein thrombosis and pulmonary emboli in immobile patients. Antacids reduce the incidence of gastric bleeding. Pulmonary care includes aerosols, bronchial aspiration, and physical therapy.⁸⁸ Tranquilizers are used to the extent limited by the respiratory status.

Several approaches for skin care have been suggested. Some authors recommend extensive debridement of nonviable epidermis³³ followed by immediate cover with biologic dressings, such as porcine cutaneous xenografts, cryopreserved cutaneous allografts, and amnion- or collagen-based skin substitutes.^{37,56,112,150,151} Others recommend leaving in place the involved epidermis that has not yet peeled off and use of biologic dressings only on raw dermis.⁸⁸ Skin allotransplantation reduces pain, minimizes fluid loss, improves heat control, and prevents bacterial infection.⁵⁶ Hyperbaric oxygen can also improve healing.¹⁵²

Treatment of ocular involvement in the acute phase requires topical lubricants, steroid drops, and regular release of

symblepharon.²³ Conjunctivitis may cause severe damage to the ocular surface, leading to symblepharon formation, lid margin keratinization, and limbal stem cell deficiency.^{27,153} Corneal ulcers, corneal neovascularization, and infectious complications may develop.

Treatment of chronic consequences may require reconstruction of the ocular surface with mucous membrane grafting, amniotic membrane transplantation, and limbal stem cell transplantation (Fig 5). The use of gas permeable scleral contact lenses significantly improves subjective symptoms and visual acuity.¹⁵⁴ Keratoprosthesis may be the procedure of last resort in case of severe damage to the ocular surface.¹⁵⁵

Several specific therapeutic approaches have been used in the treatment of patients with TEN (Table 8). The use of systemic corticosteroids is controversial. The rationale for use of corticosteroids is based on the concept that TEN is a delayed-type immunologic reaction.¹⁵⁹ One report suggests that prompt short-term corticosteroid therapy appears to be a strategic key to minimize damage from TEN.¹⁶⁰ Corticosteroids have also been recommended by other authors.^{161,162} However, 2 studies^{44,71} from the 1980s have suggested that treatment with glucocorticosteroids is associated with increased morbidity and mortality. A death rate of 66% caused by infection in steroid-treated patients compared with 33% in those without steroids suggested an iatrogenic source of mortality.⁴⁴ The authors stated that steroids enhanced the risk of sepsis, increased protein catabolism, and delayed epithelialization. The results of the study by Guibal et al⁵⁰ showed that long-term steroid therapy may delay the onset of TEN, but it does not halt its progression. Moreover, TEN can occur in patients who undergo long-term glucocorticosteroid therapy.^{42,50,112,163,164} Based on these observations, one could conclude that treatment of TEN with corticosteroids is detrimental. However, we find the work of Patterson and associates especially compelling and believe that the issue of steroid therapy for acute SJS and TEN should be revisited with a multicenter randomized clinical trial comparing short-term,

high-dose intravenous steroids vs placebo in the care of patients hospitalized in burn care units with documented low nosocomial infection rates. Based on observations of Patterson et al, the study should theoretically be limited to those who present early (eg, within 20 days) after the onset of the exanthem.

Plasmapheresis has been reported to be effective in several studies of the acute care of patients with TEN.^{39,48,156,165,166} However, one report¹⁵⁸ showed that there was no difference in mortality, length of stay in hospital, or time to reepithelialization between a group of patients treated with plasmapheresis and a group treated symptomatically. The mechanism by which the effect of plasmapheresis is mediated remains speculative. Removal of a toxin, such as drug, drug metabolite, cytotoxic mediators, or antibodies, is a possible explanation. Importantly, in 2 studies^{156,166} that reported on 12 patients treated with plasmapheresis, ocular sequelae have not been observed after follow-up as long as 8 years.

Thalidomide is a potent inhibitor of TNF- α in vitro and in vivo.^{167,168} Treatment with thalidomide was used in a double-blind, randomized, placebo-controlled study of TEN patients.⁷⁰ However, the mortality rate in patients who received thalidomide was so high compared with that of the control group that the study had to be stopped. The authors hypothesized that the increase in mortality was related to a paradoxical increase in serum concentration of TNF- α .

After Viard et al⁵² published data on their in vivo experiments and clinical experience on the use of IVIG in a group of 10 patients with TEN, several other investigators^{169–173} used IVIG in treatment of acute TEN. In vitro studies of Viard et al⁵² showed that up-regulation of keratinocyte FasL expression is the critical trigger for keratinocyte destruction during TEN and that IVIG is likely to involve inhibition of Fas-mediated keratinocyte death by naturally occurring Fas-blocking antibodies in IVIG preparations.⁵² Other effects of IVIG may involve inhibition of inflammatory cytokines and neutralization of a toxin (hypothetically involved in TEN). The clinical benefit of IVIG for acute TEN was observed in several other studies,^{75,169–173} but Bachot et al⁷⁵ reported less optimistic data. Well-designed prospective randomized trials are needed to address the benefit, or a lack of it, in decreasing mortality rate and halting the progression of acute TEN.

Scanty reports exist on use of immunosuppressive drugs, such as cyclophosphamide⁴⁹ and cyclosporine,^{174,175} in the treatment of patients with TEN. TEN is an acute, fulminant disease that requires immediate treatment, the effect of which must begin no later than several hours after the onset of first symptoms. Cyclophosphamide or cyclosporine and other immunosuppressive drugs require more than 1 month to begin to have a therapeutic effect. It is noteworthy that in patients with skin loss, the kinetics of drugs is impaired, and reaching the therapeutic serum levels requires higher doses than in other patients. The potential damage to the liver and kidneys associated with TEN should also be considered when contemplating the use of immunosuppressive drugs. Furthermore, not only an immune-mediated response but also the presence of

a toxin is suspected to be involved in TEN. Taken together, these considerations suggest to us that the use of such treatment in the acute phase of TEN should probably be avoided.

Complications

Potential respiratory complications of TEN include lung infiltrates, pleural effusion, recurrent pneumothoraces, and respiratory failure.⁴⁵ A few cases of expectoration of cylindric bronchial casts have been reported.^{58,85} Postmortem examination of a respiratory tract showed polypoid masses of organizing granulation tissue (concentric whorls of fibroblasts) in the bronchiolar lumen.⁴⁵ Tracheal and bronchial erosions have been observed on autopsy.⁸⁸ A persistent significant reduction in diffusion capacity for carbon monoxide may occur as a consequence of lung involvement.⁴⁵

Mucosal erosions also occur in the gastrointestinal tract.^{85,94,117,125,145,175–177} The malpighian epithelium of the esophagus is the most commonly involved, leading to dysphagia and, eventually, bleeding.⁸⁸ Intestinal resection has been performed in a patient with severe chronic diarrhea.⁸⁸

Hepatitis is present in approximately 10%^{38,130} of patients, with approximately half of the patients with TEN demonstrating an increase of serum aminotransferase levels. Drug-induced liver damage and damage from sepsis or shock are speculated.⁸⁸ An increase in serum levels of amylases can also occur,^{36,128,178} and a few cases of frank acute pancreatitis have been reported as well.^{127,129,178,179}

Prerenal azotemia or acute tubular necrosis, the most common renal problems, result from hemodynamic alterations.⁸⁸ A case of glomerulonephritis has been reported as well.⁸¹

Other potential complications include coagulopathy, alopecia, and hypertrophic scarring.⁴² Long-term complications after recovery from the acute phase is reported in 45% of patients with TEN.^{38,47} Sicca syndrome develops in approximately 40% of patients,¹²⁹ and some meet the diagnostic criteria¹⁸⁰ for Sjögren syndrome.¹²⁹ One factor that showed a reduction in mortality was early referral of patients to the burn unit (≤ 7 days), mainly because of a lower frequency of septicemia and better prognosis quod vitam if septicemia developed.³⁴

Mortality

Death has been reported in 10% to 70% of patients according to various published series.^{38,48} Age and extent of skin detachment are the main prognostic factors.⁴⁷ In one study, only 1 death was reported among 35 children younger than 16 years compared with 44 deaths (51%) of 87 cases in patients older than 60 years.⁴⁷ As with SJS, early withdrawal of causative drug use may decrease mortality in patients with TEN.⁸² Currently, advances in care for burn patients in the past decades represent the major progress in treatment of acute SJS and TEN. Despite this, the standard medical therapy remains controversial and mortality continues to be high. The most common causes of death include sepsis, pulmonary edema, pulmonary embolism, gastrointestinal hemorrhage,⁴⁷ recurrent pneumothoraces,⁴⁵ and hypovolemia.³⁸

CONCLUSIONS

Our review of the literature leads us to conclude that SJS and TEN are variants of the same disease with differing severities. Further, we conclude that although progress has been made as far as survival is concerned through early hospitalization in specialized burn units, the prevalence of life-long disability from the ocular morbidity of SJS and TEN has remained unchanged during the past 35 years. We believe that any progress in this matter depends on modification of the acute phase of the disease rather than continuation of supportive care. We are persuaded by the available published evidence that a principal problem in the pathogenesis is immunologic and that immunomodulatory intervention with short-term, high-dose intravenous steroid or IVIG holds the most promise for effecting change and making progress in this matter. Regrettably, developing consensus and implementing appropriate studies on this seem extraordinarily difficult.

REFERENCES

1. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia: report of two cases in children. *Am J Dis Child*. 1922;24:526–533.
2. Thomas BA. The so-called Stevens-Johnson syndrome. *BMJ*. 1950;1:1393–1397.
3. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1993;129:92–96.
4. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994;102:28S–30S.
5. Assier H, Bastuji-Garin S, Revuz J, et al. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol*. 1995;131:539–543.
6. Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of sixty cases. *J Am Acad Dermatol*. 1985;13:623–635.
7. Lyell A. Requiem for toxic epidermal necrolysis. *Br J Dermatol*. 1990;122:837–846.
8. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol*. 1997;24:726–729.
9. Huff JC, Weston WL, Tonnesen MG, et al. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983;8:763–775.
10. Inachi S, Mizutani H, Shimizu M. Epidermal apoptotic cell death in erythema multiforme and Stevens-Johnson syndrome: contribution of perforin-positive cell infiltration. *Arch Dermatol*. 1997;133:845–849.
11. Ting HC, Adam BA. Erythema multiforme: response to corticosteroid. *Dermatologica*. 1984;169:175–178.
12. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 1996;135:6–11.
13. Porteous DM, Berger TG. Severe cutaneous reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol*. 1991;127:740–741.
14. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol*. 1990;126:43–47.
15. Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol*. 1991;127:839–842.
16. Strom BL, Carson JL, Halpern AC. A population-based study of Stevens-Johnson syndrome: incidence and antecedent drug exposure. *Arch Dermatol*. 1991;127:831–838.
17. Capella D, Laporte JR, Vidal X, et al. European network for the case-population surveillance of rare diseases (Euronet): a prospective feasibility study. *Eur J Clin Pharmacol*. 1998;53:299–302.
18. Kaufman DW. Epidemiologic approaches to the study of toxic epidermal necrolysis. *J Invest Dermatol*. 1994;102:31S–33S.
19. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333:1600–1607.
20. Wolkenstein P, Charue D, Laurent P, et al. Metabolic predisposition to cutaneous adverse drug reactions: role in toxic epidermal necrolysis caused by sulfonamides and anticonvulsants. *Arch Dermatol*. 1995;131:544–551.
21. Rzany B, Mockenhaupt M, Baur S, et al. Epidemiology of erythema exudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990–1992): structure and results of a population-based registry. *J Clin Epidemiol*. 1996;49:769–773.
22. Patterson R, Miller M, Kaplan M, et al. Effectiveness of early therapy with corticosteroids in Stevens-Johnson syndrome: experience with 41 cases and a hypothesis regarding pathogenesis. *Ann Allergy*. 1994;73:27–34.
23. Power WJ, Ghoraiishi M, Foster CS, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. *Ophthalmology*. 1995;102:1669–1676.
24. Power WJ, Saidman SL, Zhang DS, et al. HLA typing in patients with ocular manifestation of Stevens-Johnson syndrome. *Ophthalmology* 1996;103:1406–1409.
25. Patterson R, Grammer L, Greenberger PA, et al. Stevens-Johnson syndrome (SJS): effectiveness of corticosteroids in management and recurrent SJS. *Allergy Proc*. 1992;13:89–95.
26. Mondino BJ, Brown SI, Biglan AW, et al. HLA antigens in Stevens-Johnson syndrome with ocular involvement. *Arch Ophthalmol*. 1982;100:1453–1454.
27. Foster CS, Fong LP, Azar D, et al. Episodic conjunctival inflammation after Stevens-Johnson syndrome. *Ophthalmology*. 1988;95:453–462.
28. Wuepper KD, Watson PA, Kazmierowski JA. Immune complexes in erythema multiforme and the Stevens-Johnson syndrome. *J Invest Dermatol*. 1980;64:368–371.
29. Patterson R, Dykewicz MS, Gonzales A, et al. Erythema multiforme and Stevens-Johnson syndrome: descriptive and therapeutic controversy. *Chest*. 1990;98:331–336.
30. Tsuroda N, Iwanaga T, Sairo T, et al. Rapidly progressive bronchiolitis obliterans associated with Stevens-Johnson syndrome. *Chest*. 1990;98:243–245.

31. Naldi L, Locati F, Marchesi L, et al. Incidence of toxic epidermal necrolysis in Italy. *Arch Dermatol.* 1990;126:1103-1104.
32. Bottiger LE, Strandberg I, Westerholm B. Drug induced febrile mucocutaneous syndrome. *Acta Med Scand.* 1975;198:229-233.
33. Marvin JA, Heimbach DM, Engraw LH, et al. Improved treatment of the Stevens-Johnson syndrome. *Arch Surg.* 1984;119:601-605.
34. McGee T, Munster A. Toxic epidermal necrolysis syndrome: mortality reduced with early referral to regional burn center. *Plast Reconstr Surg.* 1998;102:1018-1022.
35. Singer L, Brook U, Romen M, et al. Vitamin A in Stevens-Johnson syndrome. *Ann Ophthalmol.* 1989;21:209-210.
36. Chosidow O, Zohra EW, Devanlay M, et al. Hyperamylasemia in toxic epidermal necrolysis. *Arch Dermatol.* 1993;129:792-793.
37. Pruitt BA. Burn treatment for the unburned. *JAMA.* 1987;257:2207-2208.
38. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol.* 1987;123:1160-1165.
39. Egan CA, Grant WJ, Morris SE, et al. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol.* 1999;40:458-461.
40. Stern RS, Chan HL. Usefulness of case report literature in determining drugs responsible for toxic epidermal necrolysis. *J Am Acad Dermatol.* 1989;21:317-322.
41. Paquet P, Nikkels A, Arrese JE, et al. Macrophages and tumor necrosis factor α in toxic epidermal necrolysis. *Arch Dermatol.* 1994;130:605-608.
42. Jones WG, Halebian P, Madden M, et al. Drug-induced toxic epidermal necrolysis in children. *J Pediatr Surg.* 1989;24:167-170.
43. Stein KM, Schlappner LA, Heaton CL, et al. Demonstration of basal cell immunofluorescence in drug-induced toxic epidermal necrolysis. *Br J Dermatol.* 1972;86:246-252.
44. Halebian PH, Corder VJ, Madden MR, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg.* 1986;204:503-512.
45. McIvor RA, Zaidi J, Peters WJ, et al. Acute and chronic respiratory complications of toxic epidermal necrolysis. *J Burn Care Rehabil.* 1996;17:237-240.
46. Manzella J, Hall CB, Green JL, McMeekin TO. Toxic epidermal necrolysis in childhood: differentiation from staphylococcal scaled skin syndrome. *Pediatrics.* 1980;66:291-294.
47. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981-1985. *Arch Dermatol.* 1990;126:37-42.
48. Sakellariou G, Koukoudis P, Karpouzas J, et al. Plasma exchange (PE) treatment in drug-induced toxic epidermal necrolysis (TEN). *Int J Artif Org.* 1991;14:634-638.
49. Heng M, Allen S. Efficacy of cyclophosphamide in toxic epidermal necrolysis. *J Am Acad Dermatol.* 1991;25:778-786.
50. Guibal F, Bastuji-Garin S, Chosidow O, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol.* 1995;131:669-672.
51. Bagot M, Charue D, Heslan M, et al. Impaired antigen presentation in toxic epidermal necrolysis. *Arch Dermatol.* 1993;129:721-727.
52. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science.* 1998;282:490-493.
53. Villada G, Roujeau JC, Clerici T, et al. Immunopathology of toxic epidermal necrolysis: keratinocytes, HLA-DR expression, Langerhans cells, mononuclear cells: an immunopathologic study of five cases. *Arch Dermatol.* 1992;128:50-53.
54. Roujeau J, Dubertret L, Moritz S, et al. Involvement of macrophages in the pathology of toxic epidermal necrolysis. *Br J Dermatol.* 1985;113:425-430.
55. Westly ED, Wechsler HL. Toxic epidermal necrolysis: granulocytic leukopenia as a prognostic indicator. *Arch Dermatol.* 1984;120:721-726.
56. Birchall N, Langdon R, Cuono C, et al. Toxic epidermal necrolysis: an approach to management using cryopreserved allograft skin. *J Am Acad Dermatol.* 1987;16:368-372.
57. Paquet P, Pierard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am J Dermatopathol.* 1997;19:127-132.
58. Bjornberg A. Fifteen cases of toxic epidermal necrolysis (Lyell). *Acta Dermatovener (Stockholm).* 1973;53:149-152.
59. Adzik NS, Kim SH, Bondoc CC, et al. Management of toxic epidermal necrolysis in a pediatric burn center. *Am J Dis Child.* 1985;139:499-502.
60. Breathnach SM, McGibbon DH, Ive FA, et al. Carbamazepine ("Tegretol") and toxic epidermal necrolysis: report of three cases with histopathological observations. *Clin Exp Dermatol.* 1982;7:585-591.
61. Yetiv JZ, Bianchine JR, Owen JA. Etiologic factors of the Stevens-Johnson syndrome. *South Med J.* 1980;73:599-602.
62. Nomenclature for factors of the HLA system 1980. *Eur J Immunol.* 1981;11:350-352.
63. Huff JC, Weston WL, Carr RI. Mixed cryoglobulinemia, ¹²⁵I C1q binding and skin immunofluorescence in erythema multiforme. *J Invest Dermatol.* 1980;74:375-378.
64. Guillaume JC, Roujeau JC, Revuz J, et al. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol.* 1987;123:1166-1170.
65. Goens J, Song M, Fondou P, et al. Haematological disturbance and immune mechanisms in toxic epidermal necrolysis. *Br J Dermatol.* 1986;114:255-259.
66. Orfanos CE, Schaumburg-Lever G, Lever WF. Dermal and epidermal types of erythema multiforme: a histopathologic study of 24 cases. *Arch Dermatol.* 1974;109:682-688.
67. Howland WW, Golitz LE, Weston WL, et al. Erythema multiforme: clinical, histopathologic, and immunologic study. *J Am Acad Dermatol.* 1984;10:438-446.
68. Nishida K, Yamanishi K, Yamada K, et al. Epithelial hyperproliferation and transglutaminase 1 gene expression in Stevens-Johnson syndrome conjunctiva. *Am J Pathol.* 1999;154:331-336.
69. Elias PM, Fritsch P, Epstein EH. Staphylococcal scalded skin syndrome: clinical features, pathogenesis, and recent microbiological and biochemical developments. *Arch Dermatol.* 1977;113:207-219.
70. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomized comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet.* 1998;352:1586-1589.
71. Kim PS, Goldfarb IW, Gaisford JC, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a pathophysiologic

- review with recommendations for a treatment protocol. *J Burn Care Rehabil.* 1983;4:91–100.
72. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pediatrics.* 2003;112:1430–1436.
73. Morici MV, Galen WK, Shetty AK, et al. Intravenous immunoglobulin therapy for children with Stevens-Johnson syndrome. *J Rheumatol.* 2000;27:2494–2497.
74. Prins C, Vittorio C, Padilla RS, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology.* 2003;207:96–99.
75. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol.* 2003;139:33–36.
76. Broadbent RV. Stevens-Johnson disease presenting with pneumothorax. *Rocky Mt Med J.* 1967;167:69–72.
77. Zweibaum B, Cohen H, Chandrasoma P. Gastrointestinal involvement complicating Stevens-Johnson syndrome. *Gastroenterology.* 1986;91:469–474.
78. Bloom H, Lowel TWI. Erythema multiforme with renal and myocardial injury. *Proc R Soc Med.* 1964;57:175.
79. Comaish JS, Kerr DNS. Erythema multiforme and nephritis. *BMJ.* 1961;2:84.
80. Onadeko BO. A review of Stevens-Johnson syndrome at the University College Hospital, Ibadan. *West Afr Med J.* 1970;19:142.
81. Krumlovsky FA, Del Greco F, Herdson PB, et al. Renal disease associated with toxic epidermal necrolysis (Lyell's disease) (Lyell's disease) *Am J Med.* 1974;57:817–825.
82. Garcia DI, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* 2000;136:323–327.
83. Arnold HL Jr, Odom RB, James WD. Contact dermatitis; drug eruptions. In: *Andrews' Diseases of the Skin: Clinical Dermatology.* 8th ed. Philadelphia, PA: WB Saunders; 1990:128–130.
84. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Br J Dermatol.* 1956;68:355–361.
85. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a re-appraisal. *Br J Dermatol.* 1979;100:69–86.
86. Rasmussen JE. Toxic epidermal necrolysis: a review of 75 cases in children. *Arch Dermatol.* 1975;111:1135–1139.
87. Amon RB, Dimond RL. Toxic epidermal necrolysis: rapid differentiation between staphylococcal and drug-induced disease. *Arch Dermatol.* 1975;111:1433–1437.
88. Roujeau JC, Chosidow O, Saiag P, et al. Toxic epidermal necrolysis (Lyell syndrome). *Am J Acad Dermatol.* 1990;23:1039–1058.
89. Hawk RJ, Storer JS, Daum RS. Toxic epidermal necrolysis in a 6-week year old infant. *Pediatr Dermatol.* 1985;2:197–200.
90. Pegram PS, Mountz JD, O'Bar PR. Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med.* 1972;141:1677–1678.
91. Schmidt D, Kluge W. Fatal toxic epidermal necrolysis following reexposure to phenytoin: a case report. *Epilepsia.* 1983;24:440–443.
92. Dreyfuss DA, Gottlieb LJ, Wilkerson DK, et al. Survival after a second episode of toxic epidermal necrolysis. *Ann Plast Surg.* 1988;20:146–147.
93. De Groot R, Oranje AP, Vuzeski VD, et al. Toxic epidermal necrolysis probably due to *Klebsiella pneumoniae* sepsis. *Dermatologica.* 1984;169:88–90.
94. Rasmussen JE. Toxic epidermal necrolysis. *Med Clin North Am.* 1980;64:901–920.
95. Lyell A. A review of toxic epidermal necrolysis in Britain. *Br J Dermatol.* 1967;79:662–671.
96. Callaway JL, Tate WE. Toxic epidermal necrolysis caused by "gin and tonic" [letter]. *Arch Dermatol.* 1974;109:909.
97. Ramider GF, Davis JH, Ackerman AB. Fumigant-induced toxic epidermal necrolysis. *Arch Dermatol.* 1974;110:103–104.
98. Thompson JA, Wansker BA. A case of contact dermatitis, erythema multiforme, and toxic epidermal necrolysis. *J Am Acad Dermatol.* 1981;5:666–669.
99. Foged EK. Toxic epidermal necrolysis from oil lamp fuel. *Contact Dermatitis.* 1984;11:135–136.
100. Phoon WH, Chan MOY, Rajan VS, et al. Stevens-Johnson syndrome associated with occupational exposure to trichloroethylene. *Contact Dermatitis.* 1984;10:270–276.
101. Valsecchi R, Cassina P, Cainelli T. Contact toxic epidermal necrolysis. *Contact Dermatitis.* 1987;16:277.
102. Billingham RE, Streilein JW. Toxic epidermal necrolysis and homologous disease in hamsters. *Arch Dermatol.* 1968;98:528–539.
103. Streilein JW, Billingham RE. An analysis of graft-vs-host disease in Syrian hamsters, I: the epidermolytic syndrome: description and studies on its procurement. *J Exp Med.* 1970;132:163–180.
104. Saiag P, Caumes E, Chosidow O, et al. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol.* 1992;26:567–574.
105. Villada G, Roujeau JC, Cordonnier C, et al. Toxic epidermal necrolysis after bone marrow transplantation: study of nine cases. *J Am Acad Dermatol.* 1990;23:870–875.
106. Roujeau JC, Huynh TN, Bracq C, et al. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol.* 1987;123:1171–1173.
107. Dolan PA, Flowers FP, Araujo OE, et al. Toxic epidermal necrolysis. *J Emerg Med.* 1989;7:65–69.
108. Becker DS. Toxic epidermal necrolysis. *Lancet.* 1998;351:1417–1419.
109. Prendiville JS, Hebert AA, Greenwald MJ, et al. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr.* 1989;115:881–887.
110. Revuz J, Roujeau JC, Guillaume JC, et al. Treatment of toxic epidermal necrolysis. *Arch Dermatol.* 1987;123:1156–1158.
111. Cohen SG, Glick M, Schaeffer VH. Toxic epidermal necrolysis. *Spec Care Dentist.* 1989;9:6–9.
112. Heimbach DM, Engray LH, Marvin JA, et al. Toxic epidermal necrolysis: a step forward in treatment. *JAMA.* 1987;257:2171–2175.
113. Snyder RA, Elias PM. Toxic epidermal necrolysis and staphylococcal scalded skin syndrome. *Dermatol Clin.* 1983;1:235–248.
114. Avakian R, Flowers FP, Araujo OE, et al. Toxic epidermal necrolysis: a review. *J Am Acad Dermatol.* 1991;25:69–79.

115. Management of toxic epidermal necrolysis [editorial]. *Lancet*. 1984;2:1250–1252.
116. Meneux E, Wolkenstein P, Haddad B, et al. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol*. 1998;91:283–287.
117. Herman TE, Kushner DC, Cleveland RH. Esophageal stricture secondary to drug-induced toxic epidermal necrolysis. *Pediatr Radiol*. 1984;14:439–440.
118. Barrera JE, Meyers AD, Hartford EC. Hypopharyngeal stenosis and dysphagia complicating toxic epidermal necrolysis. *Arch Otolaryngol Head Neck Surg*. 1998;124:1375–1376.
119. Correia O, Delgado L, Ramos JP, et al. Cutaneous T-cell recruitment in toxic epidermal necrolysis: further evidence of CD8+ lymphocyte involvement. *Arch Dermatol*. 1993;129:466–468.
120. Miyauchi H, Hosokawa H, Akaeda T, et al. T-cell subsets in drug-induced toxic epidermal necrolysis: possible pathogenic mechanism induced by CD8-positive T cells. *Arch Dermatol*. 1991;127:851–855.
121. Merot Y, Saurat JH. Clues to pathogenesis of toxic epidermal necrolysis. *Int J Dermatol*. 1985;24:165–168.
122. Merot Y, Gravalles E, Guillen FJ, et al. Lymphocyte subsets and Langerhans' cells in toxic epidermal necrolysis. *Arch Dermatol*. 1986;22:455–458.
123. Paul C, Wolkenstein CP, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. *Br J Dermatol*. 1996;134:710–714.
124. Posadas SJ, Torres MJ, Mayorga C, Juarez C, Blanca M. Gene expression levels of cytokine profile and cytotoxic markers in non-immediate reactions to drugs. *Blood Cells Mol Dis*. 2002;29:179–189.
125. Sugimoto Y, Mizutani H, Sato T, et al. Toxic epidermal necrolysis with severe gastrointestinal mucosal cell death: a patient who excreted long tubes of dead intestinal epithelium. *J Dermatol*. 1998;25:533–538.
126. Lerner L, Qureshi A, Reddy B, et al. Nitric oxide synthase in toxic epidermal necrolysis and Stevens-Johnson syndrome. *J Invest Derm*. 2000;114:196–199.
127. Tagami H, Tatsuta K, Iwatski K, Yamada M. Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. *Arch Dermatol*. 1983;119:910–913.
128. Tatnall FM, Dodd HJ, Sarkany I, et al. Elevated serum amylase in a case of toxic epidermal necrolysis. *Br J Dermatol*. 1985;113:629–630.
129. Roujeau JC, Koso M, Andre C, et al. Sjögren syndrome after drug-induced toxic epidermal necrolysis. *Lancet*. 1985;16:609–611.
130. Klein SM. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol*. 1983;10:512–513.
131. Zemtsov A. The cellular source of creatine kinase in patients with toxic epidermal necrolysis. *Br J Dermatol*. 1995;132:487–488.
132. Caux F, Chosidow O, Philippon C, et al. Increased serum and blister fluid levels of creatinine kinase in patients with toxic epidermal necrolysis. *Br J Dermatol*. 1994;130:337–341.
133. O'Garra A. Interleukins and the immune system 1. *Lancet*. 1989;1:943–946.
134. Paquet P, Nusgens B, Pierard G, et al. Gelatinases in drug-induced toxic epidermal necrolysis. *Eur J Clin Invest*. 1998;28:528–532.
135. Friedman PS, Strickland I, Pirmohamed M, et al. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. *Arch Dermatol*. 1994;130:598–604.
136. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. *J Clin Invest*. 1988;82:1826–1832.
137. Pirmohamed M, Graham A, Roberts P, et al. Carbamazepine-hypersensitivity: assessment of clinical and *in vitro* chemical cross-reactivity with phenytoin and oxcarbazepine. *Br J Clin Pharmacol*. 1991;32:741–749.
138. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *Br J Clin Pharmacol*. 1992;34:377–395.
139. Rieder MJ, Uetrecht J, Shear NH, et al. Diagnosis of sulfonamide hypersensitivity reactions by in vitro "rechallenge" with hydroxylamine metabolites. *Ann Intern Med*. 1989;110:286–289.
140. Larrey D, Berson A, Habersetzer F, et al. Genetic predisposition to drug hepatotoxicity: role in hepatitis caused by amineptin, a tricyclic antidepressant. *Hepatology*. 1989;10:168–173.
141. Cribier B, Piemont Y, Grosshans E, et al. Staphylococcal scalded skin syndrome in adults: a clinical review illustrated with a new case. *J Am Acad Dermatol*. 1994;319–324.
142. Demling RH, Ellerbe S, Lowe NJ. Burn unit management of toxic epidermal necrolysis. *Arch Surg*. 1978;113:758–759.
143. Tompkins RG, Burke JF. Burn therapy 1985: acute management. *Intensive Care Med*. 1986;12:289–295.
144. Goldstein SM, Wintroub BW, Elias PM, et al. Toxic epidermal necrolysis: unmuttiding the waters. *Arch Dermatol*. 1987;123:1153–1156.
145. Halebian PH, Corder VJ, Herndon D, et al. A burn center experience with toxic epidermal necrolysis. *J Burn Care Rehabil*. 1983;4:176–183.
146. Pasulka PS, Wachtel TL. Nutritional considerations for the burned patient. *Surg Clin North Am*. 1987;67:109–131.
147. Gamelli RL. Nutritional problems of the acute and chronic burn patient: relevance to epidermolysis bullosa. *Arch Dermatol*. 1988;124:756–759.
148. Demling RH. Burns. *N Engl J Med*. 1985;313:1389–1398.
149. Loirat P, Rohan J, Baillet A, et al. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. *N Engl J Med*. 1978;299:915–919.
150. MacFarlane AW, Curley R. Management of toxic epidermal necrolysis with a hydrogel dressing and fluidized-bead bed: report of three cases. *Clin Exp Dermatol*. 1987;12:354–356.
151. Prasad JK, Feller I, Thomson PD. Use of amnion for the treatment of Stevens-Johnson syndrome. *J Trauma*. 1986;26:945–946.
152. Ruocco V, Vimonte D, Luongo C, et al. Hyperbaric oxygen treatment of toxic epidermal necrolysis. *Cutis*. 1986;38:267–271.
153. Arstikaitis MJ. Ocular aftermath of Stevens-Johnson syndrome. *Arch Ophthalmol*. 1973;90:376–379.
154. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol*. 2000;130:25–32.
155. Dohlman CH, Terada H. Keratoprosthesis in pemphigoid and Stevens-Johnson syndrome. *Adv Exp Med Biol*. 1998;438:1021–1025.
156. Kamanabroo D, Schmitz-Landgraf W, Czarnetzki BM. Plas-

- mapheresis in severe drug-induced toxic epidermal necrolysis. *Arch Dermatol*. 1985;121:1548–1549.
157. Arevalo JM, Lorente JA, Gonzalez-Herrada C, et al. Treatment of toxic epidermal necrolysis with cyclosporine A. *J Trauma*. 2000;48:473–478.
 158. Furubacke A, Berlin G, Anderson C, et al. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis. *Intensive Care Med*. 1999;25:1307–1310.
 159. Simons HM. Acute life-threatening dermatologic disorders. *Med Clin North Am*. 1981;65:227–243.
 160. Moncada B, Quevedo ME, Lorincz AL. Abnormal T-cell response in toxic epidermal necrolysis. *Arch Dermatol*. 1994;130:116–117.
 161. Parsons JM. Management of toxic epidermal necrolysis. *Cutis*. 1985;36:305–307, 310–311.
 162. Sheretz EF, Jegasothy BV, Lazarus GS. Phenytoin hypersensitivity reaction presenting with toxic epidermal necrolysis and severe hepatitis. *J Am Acad Dermatol*. 1985;12:178–181.
 163. Rzany B, Schmitt H, Schopf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. *Acta Derm Venereol (Stockh)*. 1991;71:171–172.
 164. Okano M, Kitano Y, Igarashi T. Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol*. 1987;17:303–304.
 165. Gerard A, Schooneman F, Roche G, et al. Lyell's syndrome treatment by plasma exchange. *Plasma Ther Transfus Technol*. 1984;5:259–260.
 166. Chaidemenos GC, Chrysomallis F, Sombolos K, et al. Plasmapheresis in toxic epidermal necrolysis. *Int J Dermatol*. 1997;36:218–221.
 167. Klausner JD, Freedman VH, Kaplan G. Thalidomide as an anti-TNF- α inhibitor: implications for clinical use. *Clin Immunol Immunopathol*. 1996;81:219–223.
 168. Moreira AL, Sampaio EP, Zmuidzinis A, et al. Thalidomide exerts its inhibitory action on tumor necrosis factor α by enhancing mRNA degradation. *J Exp Med*. 1993;177:1675–1680.
 169. Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. *Acta Dermatol Venereol*. 2003;83:430–432.
 170. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. *Arch Dermatol*. 2003;139:39–43.
 171. Prins C, Kerdel FA, Padilla RS, et al; TEN-IVIG Study Group. Toxic epidermal necrolysis-intravenous immunoglobulin. *Arch Dermatol*. 2003;139:26–32.
 172. Tristani-Firouzi P, Petersen MJ, Saffle JR, Morris SE, Zane JJ. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children. *J Am Acad Dermatol*. 2002;47:548–552.
 173. Stella M, Cassano P, Bollero D, Clemente A, Giorgio G. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology*. 2001;203:45–49.
 174. Renfro L, Grant-Kreis JM, Daman LA. Drug-induced toxic epidermal necrolysis treated with cyclosporine. *Int J Dermatol*. 1989;28:441–444.
 175. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol*. 1984;10:973–978.
 176. Ellman MH, Freitzin DF, Olson W. Toxic epidermal necrolysis associated with allopurinol administration. *Arch Dermatol*. 1975;111:986–990.
 177. Roupe G, Ahlmen M, Fagerberg B, et al. Toxic epidermal necrolysis with extensive mucosal erosions of the gastrointestinal and respiratory tracts. *Int Arch Allergy Appl Immunol*. 1986;80:145–151.
 178. Tagami H, Iwatsuki K. Elevated serum amylase in toxic epidermal necrolysis. *Br J Dermatol*. 1986;115:250–251.
 179. Coetzer M, van der Merwe AE, Warren BL. Toxic epidermal necrolysis in a burn patient complicated by acute pancreatitis. *Burns*. 1998;24:181–183.
 180. Moutsopoulos HM, Webber BL, Vlagopoulos TP, et al. Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. *Am J Med*. 1979;66:733–736.

Requests for reprints should be addressed to:
 C. Stephen Foster, MD
 Immunology and Uveitis Service
 Massachusetts Eye and Ear Infirmary
 243 Charles St
 Boston, MA 02114
 E-mail: fosters@uveitis.org

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Letko et al. 2005;94:419–436.

CME Test Questions

1. All of the following are considered to be part of the diagnostic criteria of Stevens-Johnson syndrome (SJS) except
 - a. “targetlike” lesions each less than 3 cm
 - b. involvement of at least 2 mucosal sites
 - c. biopsy specimen demonstrating epithelial cell necrosis
 - d. duration of entire episode of fewer than 6 weeks
 - e. severe arthralgias and multiple joint arthritis
2. Which of the following is not part of the diagnostic criteria of toxic epidermal necrolysis (TEN)?
 - a. sudden onset of epidermal detachment
 - b. positive Nikolsky sign
 - c. diagnosis of the staphylococcal scalded skin syndrome
 - d. skin biopsy specimen showing full-thickness epidermal necrosis and detachment
 - e. sudden onset and generalization within 24 to 48 hours
3. All of the following have been implicated in causing SJS-TEN except
 - a. infection
 - b. immunosuppressive agents
 - c. air pollution
 - d. vaccination
 - e. systemic diseases
4. The only universally accepted, definitively effective treatment for SJS-TEN is
 - a. immunosuppressive agents
 - b. systemic corticosteroids
 - c. nonsteroidal anti-inflammatory drugs
 - d. supportive care
 - e. intravenous immunoglobulin therapy
5. The least frequent cause of TEN in adults is
 - a. antibiotics
 - b. analgesics
 - c. nonsteroidal anti-inflammatory drugs
 - d. antigout drugs
 - e. chemotherapy

Answers found on page 456.
