Toxic epidermal necrolysis

Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis

Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP (Edin), Patrick H. McDonough, MD, and Brian W. Lee, MD, MS
Newark, New Jersey

CME INSTRUCTIONS

The following is a journal-based CME activity presented by the American Academy of Dermatology and is made up of four phases:

1. Reading of the CME Information (delineated below)
2. Reading of the Source Article
3. Achievement of a 70% or higher on the online Case-based Post Test
4. Completion of the Journal CME Evaluation

CME INFORMATION AND DISCLOSURES

Statement of Need:
The American Academy of Dermatology bases its CME activities on the Academy's core curriculum, identified professional practice gaps, the educational needs which underlie these gaps, and emerging clinical research findings. Learners should reflect upon clinical and scientific information presented in the article and determine the need for further study.

Target Audience:
Dermatologists and others involved in the delivery of dermatologic care.

Accreditation
The American Academy of Dermatology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AMA PRA Credit Designation
The American Academy of Dermatology designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AAD Recognized Credit
This journal-based CME activity is recognized by the American Academy of Dermatology for 1 AAD Credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

Disclaimer:
The American Academy of Dermatology is not responsible for statements made by the author(s). Statements or opinions expressed in this activity reflect the views of the author(s) and do not reflect the official policy of the American Academy of Dermatology. The information provided in this CME activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to the diagnostic, management and treatment options of a specific patient's medical condition.

Disclosures

Editors
The editors involved with this CME activity and all content validation/peer reviewers of this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors of this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Resolution of Conflicts of Interest
In accordance with the ACCME Standards for Commercial Support of CME, the American Academy of Dermatology has implemented mechanisms, prior to the planning and implementation of this Journal-based CME activity, to identify and mitigate conflicts of interest for all individuals in a position to control the content of this Journal-based CME activity.

Learning Objectives
After completing this learning activity, participants should be able to delineate the drugs that are a common cause of toxic epidermal necrolysis (TEN); list the human leukocyte antigen allotypes associated with TEN and that engender an increased risk of TEN caused by drugs including allopurinol and aromatic anticonvulsant agents; and differentiate TEN from milder drug eruptions.

Date of release: August 2013
Expiration date: August 2016

http://dx.doi.org/10.1016/j.jaad.2013.05.003

Technical requirements:

American Academy of Dermatology:
- Supported browsers: FireFox (3 and higher), Google Chrome (5 and higher), Internet Explorer (7 and higher), Safari (5 and higher), Opera (10 and higher).
- JavaScript needs to be enabled.

Elsevier:
Technical Requirements
This website can be viewed on a PC or Mac. We recommend a minimum of:
- PC: Windows NT, Windows 2000, Windows ME, or Windows XP
- Mac: OS X
- 128MB RAM
- Processor speed of 500MHz or higher
- 800x600 color monitor
- Video or graphics card
- Sound card and speakers

Provider Contact Information:
American Academy of Dermatology
Phone: Toll-free: (866) 503-SKIN (7546); International: (847) 240-1280
Fax: (847) 240-1859
Mail: P.O. Box 4014; Schaumburg, IL 60168

Confidentiality Statement:

American Academy of Dermatology: POLICY ON PRIVACY AND CONFIDENTIALITY

Privacy Policy - The American Academy of Dermatology (the Academy) is committed to maintaining the privacy of the personal information of visitors to its sites. Our policies are designed to disclose the information collected and how it will be used. This policy applies solely to the information provided while visiting this website. The terms of the privacy policy do not govern personal information furnished through any means other than this website (such as by telephone or mail).

E-mail Addresses and Other Personal Information - Personal information such as postal and e-mail address may be used internally for maintaining member records, marketing purposes, and alerting customers or members of additional services available. Phone numbers may also be used by the Academy when questions about products or services ordered arise. The Academy will not reveal any information about an individual user to third parties except to comply with applicable laws or valid legal processes.

Cookies - A cookie is a small file stored on the site user's computer or Web server and is used to aid Web navigation. Session cookies are temporary files created when a user signs in on the website or uses the personalized features (such as keeping track of items in the shopping cart). Session cookies are removed when a user logs off or when the browser is closed. Persistent cookies are permanent files and must be deleted manually. Tracking or other information collected from persistent cookies or any session cookie is used strictly for the user's efficient navigation of the site.

Links - This site may contain links to other sites. The Academy is not responsible for the privacy practices or the content of such websites.

Children - This website is not designed or intended to attract children under the age of 13. The Academy does not collect personal information from anyone it knows is under the age of 13.

Elsevier: http://www.elsevier.com/wps/find/privacypolicy.cws_home/privacypolicy

Toxic epidermal necrolysis is a life-threatening, typically drug-induced mucocutaneous disease. It is clinically characterized as a widespread sloughing of the skin and mucosa, including both external and internal surfaces. Histologically, the denuded areas show full thickness epidermal necrosis. The pathogenic mechanism involves antigenic moiety/metabolite, peptide-induced T cell activation, leading to keratinocyte apoptosis through soluble Fas ligand, perforin/granzyme B, tumor necrosis factor—alfa, and nitric oxide. Recent studies have implicated granulysin in toxic epidermal necrolysis apoptosis and have suggested that it may be the pivotal mediator of keratinocyte death. (J Am Acad Dermatol 2013;69:173.e1-13.)

Key words: apoptosis; drug eruption; erythema multiforme; granulysin; Stevens—Johnson syndrome; toxic epidermal necrolysis.

TOXIC EPIDERMAL NECROLYSIS

- **Toxic epidermal necrolysis is most commonly caused by drugs and begins with a prodrome of fever, anorexia, pharyngitis and morbilliform rash**
- **Toxic epidermal necrolysis is a systemic disease involving the ophthalmic, pulmonary, genitourinary, and gastrointestinal systems, in addition to the skin**

CAPSULE SUMMARY

- Toxic epidermal necrolysis is characterized by widespread sloughing of the skin and the mucosal surface of the oral cavity, gut, kidneys, eye, genitalia, and/or lungs.
- The mechanism of cell death is apoptosis via drug-induced $CD8^+$ cell exocytosis of granzyme B/perforin and granulysin and through the activation of the Fas—Fas ligand pathway and tumor necrosis factor—alfa/death receptor pathway.
- The pathogenesis of toxic epidermal necrolysis is initiated either by noncovalent, direct interaction of a drug antigenic moiety with a specific major histocompatibility complex I allotype or by covalent binding of a drug metabolite to a cellular peptide to form an immunogenic molecule.
- Certain human leukocyte antigen allotypes are associated with toxic epidermal necrolysis and engender an increased risk of toxic epidermal necrolysis caused by drugs including allopurinol and aromatic anticonvulsant agents.

Toxic epidermal necrolysis (TEN) is an acute life-threatening mucocutaneous disorder that has an estimated incidence of 0.4 to 1.9 per million people annually worldwide.[1-3] The overall combined incidence of Stevens—Johnson syndrome (SJS), SJS/TEN overlap, and TEN is estimated to be 2 to 7 per million cases per year.[4-8] SJS has an annual incidence of 1.2 to 6 per million people,[9] approximately outnumbering TEN threefold. Studies have shown a thousand-fold increase in the incidence of SJS and TEN among those with an HIV infection, which is estimated at 1 in 1000.[10] A multicenter study from sub-Saharan Africa, where there is a high prevalence of HIV, confirmed the association between SJS/TEN and HIV and revealed an association with a high frequency of antiretroviral drug use.[11]

TEN occurs in all age groups, with 1 case described in a fetus, and is more frequently found in women and the elderly.[7,12-14]

HISTORY

- **Toxic epidermal necrolysis is most commonly caused by drugs and begins with a prodrome. It is also known as Lyell syndrome, which was first delineated by Alan Lyell in 1956**

In 1939, Debre et al[15] first described a case that appeared to be TEN. The name TEN was proposed by Lyell[16] in 1956 after he recognized "a toxic eruption, which closely resembles scalding" in 4 patients, 1 of whom was later reclassified as having staphylococcal scalded skin syndrome.[17] SJS was first reported in 2 pediatric patients as a "new eruptive fever associated with stomatitis and ophthalmia" in 1922 by 2 American physicians, Albert Mason Stevens and Frank Chambliss Johnson.[18] Erythema multiforme (EM) was first described by von Hebra in 1862 as mild, self-limited eruption caused by a herpes simplex virus (HSV) infection.[9,19]

From Dermatology, Preventive Medicine, and Pathology, Rutgers University New Jersey Medical School, Newark.
Dr McDonough is currently affiliated with Dermatology, University of Texas Southwestern Medical School, Dallas, Texas.
Funding sources: None.
Conflicts of interest: None declared.

Reprint requests: Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP (Edin), Professor & Head, Dermatology, Rutgers University New Jersey Medical School, Medical Sciences Building H-576, 185 S Orange Ave, Newark, NJ 07103-2714. E-mail: roschwar@cal.berkeley.edu.
0190-9622/$36.00

Abbreviations used:

ALDEN:	algorithm for drug causality for epidermal necrolysis
APC:	antigen presenting cell
BSA:	body surface area
CD40L:	CD40 ligand
EM:	erythema multiforme
FasL:	Fas ligand
HLA:	human leukocyte antigen
MHC:	major histocompatibility complex
NF-κB:	nuclear factor kappaB
NK:	natural killer
NO:	nitric oxide
PBMC:	peripheral blood mononuclear cell
sFasL:	serum Fas ligand
SJS:	Stevens–Johnson syndrome
TEN:	toxic epidermal necrolysis

CLASSIFICATION

- **While Stevens–Johnson syndrome and toxic epidermal necrolysis may well be variants of the same spectrum of disease, differing by the severity of body surface area affected, some experts believe that they are etiologically and pathologically distinct diseases**
- **Stevens–Johnson syndrome may be defined by the involvement of ≥2 mucous membranes or by the relatively smaller percentage of body surface area affected when compared to toxic epidermal necrolysis**

The categorization of EM, SJS, and TEN remains a topic of ongoing controversy because of the incomplete elucidation of pathogenic mechanisms. There are differing opinions on the classification of EM major and SJS as well as SJS and TEN. Based on similar histologic findings, SJS has been synonymously associated with EM major since 1983[20]—both feature the involvement of ≥2 mucous membranes in addition to skin lesions. Bastuji-Garin et al[21] in 1993 and Roujeau et al[22] in 1994 proposed differentiation of the two based on clinical and etiologic information[23]: EM major is characterized by acrally distributed typical targets related to mycoplasma infection. SJS consists of widespread blisters caused by a drug reaction, arising on erythematous or purpuric macules predominantly located on face and trunk. In contrast, TEN and SJS, initially described as separate entities, gradually have been unified as aspects of a spectrum within the same entity based on similar clinical and histopathologic features with variable severity in epidermal detachment.[21]

EM minor, EM major, SJS, and TEN share many features and were once considered to be in the same spectrum of reactive skin disorders.[24] EM is now regarded to be a separate condition with clinical, epidemiologic, and etiologic characteristics distinct from those of SJS and TEN.[25] Bastuji-Garin et al[21] proposed SJS, SJS/TEN overlap, and TEN as classifications based on severity of epidermal detachment. This classification system divides the spectrum of these reactive skin disorders into 5 categories: (1) EM major—detachment of <10% of BSA plus localized target lesions; (2) SJS—detachment of <10% of BSA plus widespread erythematous or purpuric macules or flat atypical target lesions; (3) overlapping SJS/TEN—detachment between 10% and 30% of BSA plus widespread erythematous or purpuric macules or atypical target-like annular patches; (4) TEN with spots—detachment of >30% of BSA plus widespread erythematous or purpuric macules or atypical target lesions; and (5) TEN without spots—detachment in large epidermal sheets >10% BSA without purpuric macules or target lesions.[21] We believe that SJS, SJS/TEN overlap, and TEN are variants of the same entity, but this classification scheme is imperfect because it does not take into account the differences in etiologies of these diseases.

CLINICAL FEATURES

- **Drug reactions are responsible for 80% to 95% of cases of toxic epidermal necrolysis, which involves epidermal sloughing of >30% of the body surface area**
- **Toxic epidermal necrolysis may be morbilliform, defined as a fine, discrete maculopapular exanthem, or consist of atypical targetoid macules**
- **Nearly all patients with toxic epidermal necrolysis have flaccid bullae, skin erosions, and painful inflammation and ulceration in the oral cavity over the span of 1 day to 2 weeks**

Clinically, EM should be differentiated from SJS/TEN. EM is a self-limited condition associated with mild or no systemic involvement. It is characterized by the pathognomonic "target" lesions with 3 concentric zones: a central dusky/dark red area, a paler pink/edematous zone, and a peripheral red ring. "Atypical papular lesions" have round, edematous, palpable lesions with only 2 zones and/or poorly defined borders.[24,26] EM is symmetrically distributed on the distal extremities with minimal epidermal detachment, often to 1% or 2% of BSA (<10% of BSA).[27,28] Various mucosal site involvement is observed in EM, SJS, and TEN (25-60% for EM, with minimal mucosal involvement for EM minor; 92-100% of patients for SJS; and nearly all patients for TEN).[26,29-31]

TEN displays denudation of the epidermis in sheets during the acute phase (Figs 1-3). SJS is characterized by confluent purpuric macules or

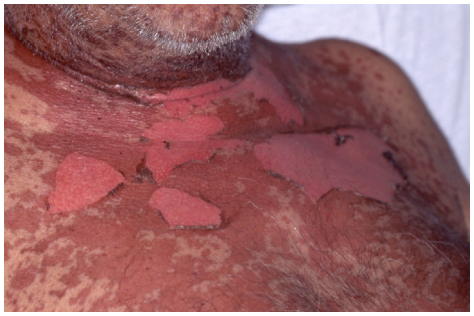

Fig 1. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the trunk.

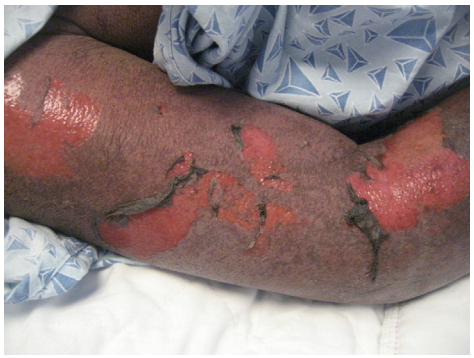

Fig 2. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the right upper extremity.

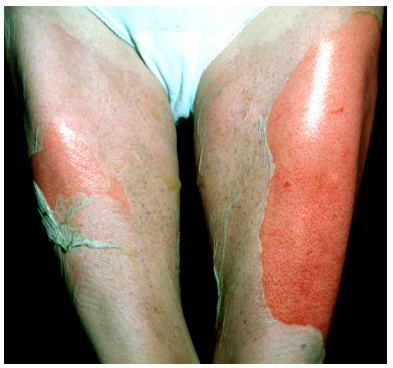

Fig 3. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the bilateral lower extremities.

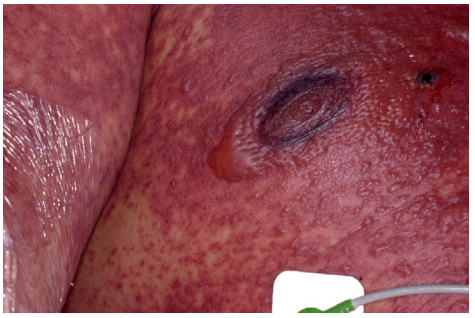

Fig 4. Toxic epidermal necrosis. Extensive blisters and erosions involving >30% of the body surface area.

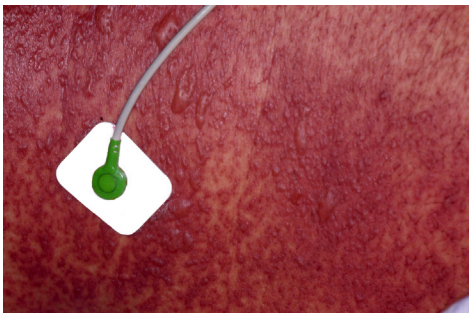

Fig 5. Toxic epidermal necrosis. Extensive blisters and erosions.

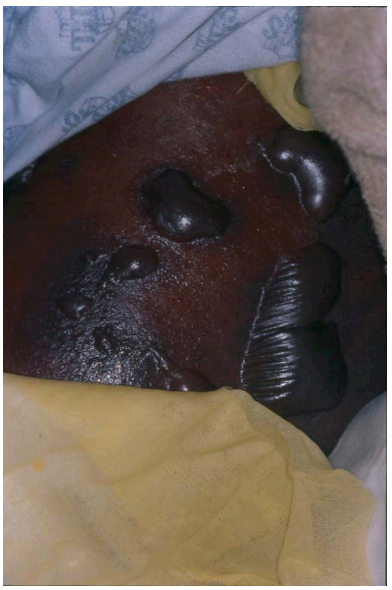

Fig 6. Toxic epidermal necrosis. Intense bullae formation that is positive for the Nikolsky and Asboe–Hansen signs.

atypical flat targetoid lesions, with blisters and erosions covering <10% of BSA, 10% to 30% of BSA for SJS/TEN overlap, and >30% of BSA for TEN by definition[27] (Figs 4 and 5). As previously mentioned, there are a few exceptions in which "TEN without spots" exhibit >10% epidermal detachment on a large patch of erythema without preceding confluent purpuric macules or atypical flat target lesions. They most often begin with a prodrome of fever, malaise, anorexia, pharyngitis, headache, and rash, which may be morbilliform, defined as a fine, discrete maculopapular exanthem, or consist of atypical targetoid macules.[16,32-35] Flaccid bullae, skin erosions, and painful inflammation and ulceration in the oral cavity

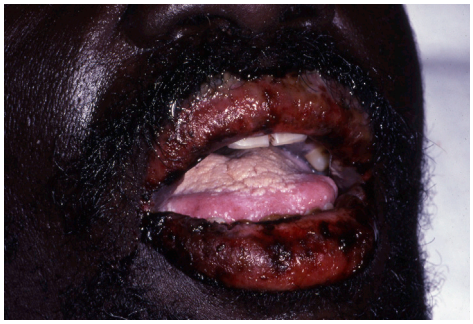

Fig 7. Toxic epidermal necrosis. Severe oral mucositis that may result in dysphagia and dysphasia.

comprise the major signs, which develop over a period of 1 day to 2 weeks[33] (Fig 6). The skin is often tender to the touch, with lateral pressure producing shedding of the epidermis from the dermis, known as the Nikolsky sign,[36,37] which is also seen in patients with autoimmune bullous skin disease.[29] Painful inflammation and ulceration of the mucosal surfaces occurs in 87% to 100% of cases of TEN, with oral involvement in 71% to 100% (Fig 7), ocular involvement in 50% to 78%, genital involvement in 40% to 63%, and lesions at all 3 sites occurring in 34% to 50% of patients.[10,12,33,38,39] Reepithelialization in TEN begins within several days, with slower healing occurring at mucosal sites and in areas of pressure, maceration, or infection.[12,33,38]

SYSTEMIC MANIFESTATIONS

- **Toxic epidermal necrolysis is associated with erosion, necrosis, and severe dysfunction of the ocular, pulmonary, cardiovascular, gastrointestinal, and renal systems, as well as aberrations in the hematopoietic system**

TEN has been described as acute skin failure,[40] but multiple organ systems are also involved, with erosion and necrosis occurring in the conjunctivae, trachea, bronchi, gut, and kidney.[35,41-45] We therefore view TEN as an extensive sloughing of both the internal and external mucocutaneous membranes. Acute renal failure with increased microalbuminuria and renal tubular enzymes in the urine, which is suggestive of glomerular structure alteration and proximal tubular damage, has been identified.[41,46] However, no direct correlation has been found between the extent of TEN and microalbuminuria or enzymuria. The nephrotoxic properties of the cytokines implicated in the pathogenesis of TEN have been linked to the destruction of the tubular cells, glomerular filtration barrier, and mesangial cells.[41] In the absence of histologic data, other etiologies of renal dysfunction cannot be excluded, such as stress, hypovolemia, and low cardiac output. Pulmonary involvement causing adult respiratory distress syndrome, bronchiolitis obliterans, and subcutaneous emphysema has been documented.[44,47] A prospective clinical study of pulmonary complications in patients with TEN found that 25% of them developed early pulmonary dysfunction, as evidenced by hypoxemia (mean PO_2 of 59 ± 8 mm Hg), dyspnea, and bronchial mucosal sloughing on fiberoptic bronchoscopy. Although pulmonary dysfunction is often not detectable on a chest radiograph at the time of admission, subsequent series have revealed interstitial infiltrates.[48] Anemia, leukopenia, and hepatitis are commonly seen. Severe abdominal pain, diarrhea, transiently elevated liver enzymes, hypoalbuminemia, hyponatremia, encephalopathy, and myocarditis may also be present.[12,35,38,47,49]

ETIOLOGY

- **The majority of cases of toxic epidermal necrosis are the result of a hypersensitivity reaction to a drug**
- **Other causative agents include *Mycoplasma pneumonia*, dengue virus, cytomegalovirus, and contrast medium**

Although TEN has occurred after measles-mumps-rubella vaccination,[50,51] infection with *Mycoplasma pneumonia*[7,52,53] and dengue virus,[54] reactivation of cytomegalovirus,[55] and after the administration of contrast agents,[56,57] the overwhelming number of cases are related to drug hypersensitivity. In the European Severe Cutaneous Adverse Reaction (EuroSCAR) study surveillance of medications, a number of them were classified as being high risk: nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, cotrimoxazole and other antiinfective sulfonamides, sulfasalazine, allopurinol, and oxicam nonsteroidal antiinflammatory agents (Table I).[58] Roujeau et al[28] previously implicated many of these drugs in TEN and also noted an increased risk with aminopenicillins, cephalosporins, and quinolones. TEN usually occurs between 7 days and 8 weeks after drug ingestion, with a mean time of onset ranging from 6 days to 2 weeks.[7,12,28,37,59] Upon readministration of the implicated drug, TEN may develop within hours.[59]

Sassolas et al[60] developed an algorithm of drug causality for epidermal necrolysis (ALDEN) and reassessed the risk–benefit profiles of all cases enrolled in the EuroSCAR study (Table II). ALDEN assigned each drug a score from −1 to 10 based on 6 parameters: (1) the time delay from initial drug intake to onset of reaction; (2) the probability of drug presence in the body on the index day; (3) a previous history of adverse reaction to the same

Table I. Drugs at risk for causing toxic epidermal necrolysis*

Nevirapine
Lamotrigine
Carbamazepine
Phenytoin
Phenobarbital
Cotrimoxazole and other antiinfective sulfonamides
Sulfasalazine
Allopurinol
Oxicam nonsteroidal antiinflammatory drugs
Aminopenicillins
Cephalosporins
Quinolones

*Data from Roujeau et al[28] and Mockenhaupt et al.[58]

Table II. Drugs that are commonly associated with a risk of Stevens–Johnson syndrome/toxic epidermal necrolysis based on the algorithm for drug causality for epidermal necrolysis*

Allopurinol	Minocycline	Phenytoin
Carbamazepine†	Nevirapine	Sulfasalazine
Fluoroquinolones	Nonsteroidal antiinflammatory drugs	Trimethoprim-sulfamethoxazole
Lamotrigine	Phenobarbital	

*Data from Dobrosavlijevic et al,[50] Mockenhaupt et al,[58] Guillaume et al,[59] and Sassolas et al.[60]
†Human leukocyte antigen-B*1502 pharmacogenetic screening recommended for patients of Han Chinese/Southeast Asian ancestry.

drug; (4) the presence of the drug beyond the progression phase of the disease; (5) the drug notoriety based on previous results of the SCAR study; and (6) the presence or absence of other etiologic causes. The score is categorized as very probable (≥ 6), probable (4-5), possible (2-3), unlikely (0-1), and very unlikely (<0; Table III).

There was an overall accordance between the results of ALDEN and the case control analysis of the EuroSCAR study.[58,60] ALDEN may be a practical, objective tool that allows immediate causality assessment of drugs in SJS and TEN without the need for expensive case control analysis in the future. ALDEN has practical implications not only for the clinicians, but also for pharmaceutical companies, regulatory agencies, and research institutes.

IMMUNOPATHOGENESIS

- **Toxic epidermal necrolysis is a T cell–mediated disease with $CD8^+$ cells acting as the major mediator of keratinocyte death**

Table III. Algorithm for drug causality for epidermal necrolysis*

Category and description	Score
Period between the drug intake and onset of reaction (index day)	
5-28 days	3
29-56 days	2
1-4 days	1
>56 days	−1
Drug started on index day	−3
With previous history of adverse reaction, 1-4 days	3
With previous history of adverse reaction, 5-56 days	1
Presence of drug in the body on index day	
Stopped on the index day or within 5 times the elimination half-life before the index day	0
Stopped at a time point before the index day by >5 times the elimination half-life†	−1
Stopped at a time point before the index day by >5 times the elimination half-life	−3
Previous history of adverse reaction	
SJS/TEN from same drug	4
SJS/TEN from similar drug	2
Other reaction from similar drug	1
No history of exposure to the drug	0
Previous use without any reaction	−2
Continued drug use beyond index day	
Stopped or unknown	0
Continued	−2
Drug notoriety derived from previous results of the SCAR study‡	
"High risk"	3
"Lower risk"	2
"Under surveillance"	1
All other drugs, including newly released drugs	0
"No evidence of association"	−1
Other possible etiologic alternatives	
Infectious agent	−1
If the patient is taking multiple drugs and at least 1 drug has a score >3, subtract 1 point from each of the other drugs	−1

SCAR, Severe cutaneous adverse reaction; *SJS*, Stevens–Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Data from Dobrosavlijevic et al.[50]
†Presence of liver or kidney dysfunction classification: very probable (≥ 6), probable (4-5), possible (2-3), unlikely (0-1), and very unlikely (<0).
‡Data from Hung et al[46] and Yamane et al.[47]

- **Two theories have emerged to explain the activation of $CD8^+$ cells: the pharmacologic interaction of drugs with the immune system and the pro-hapten theory**
- **Particular human leukocyte antigen allotypes are involved in the pathogenesis of toxic epidermal necrolysis and increase the risk of experiencing this drug reaction**

TEN is a T cell—mediated disease with a preponderance of $CD8^+$ lymphocytes found in blister fluid[61-63] and in perivascular superficial dermis with evidence of epidermal exocytosis.[64,65] $CD8^+$ cytotoxic T cells, along with natural killer (NK) cells, are theorized to be the major inducers of keratinocyte apoptosis.[61-63] Despite the central role of $CD8^+$ cells, $CD4^+$ cells and cells of the innate immune system ($CD3^-CD56^+$ NK cells, dendritic cells, mast cells, $CD14^+CD16^+$ monocytes, granulocytes, and NK/T cells) also play a role in TEN.[66] However, the mere presence of a cell type in lesional skin does not by itself imply causality. The complex interplay between many of these cells makes it difficult to distinguish the primary culprit. Caproni et al[65] studied the cellular infiltrate in skin samples from patients with TEN and found a strong representation of CD40 ligand (CD40L) staining cells in the dermis with some of the CD40L cells infiltrating the epidermis. CD40L is a molecule expressed on the surface of activated $CD4^+$ cells and is an important costimulator of macrophages, dendritic cells, B cells, and epithelial cells, leading to the release of tumor necrosis factor—alfa (TNF-α), nitric oxide (NO), interleukin 8 (IL-8), and cell adhesion molecules. Caproni et al[67] also found soluble CD40L (sCD40L) elevated in the sera of patients with TEN, raising the possibility that sCD40L could be used as a marker of TEN/SJS. The $CD4^+$ cells in the dermis and epidermis of patients with TEN were documented to have no Th1 or Th2 polarization, with equal concentrations of Th1-related cytokines and Th2-related cytokines found in the skin samples. Th1 helper T cells secrete IL-2 and interferon-gamma (INFγ) and are responsible for the activation of macrophages and cytotoxic T cells. Th2 helper T cells secrete IL-4, IL-5, IL-10, and IL-13 and are responsible for eosinophil activation and B cell class switching to immunoglobulin E antibodies.[68] Although little is known about the Th2 response in TEN, it could be an attempt to downregulate the Th1 response and limit the damage caused by cytolytic T cells.[69]

Macrophages, neutrophils, and NK cells have been implicated in TEN, with some studies reporting macrophages as the most abundant cell type found in cutaneous samples.[65,70] Tohyama et al[71] noted the presence of numerous $CD14^+CD16^+$ monocyte lineage cells infiltrating the epidermis and the dermoepidermal junction of SJS/TEN skin lesions, which may enhance the proliferation and cytotoxicity of $CD8^+$ T cells via the CD137/CD137L system. The monocyte/macrophages may contribute to the apoptotic process via production of TNF-α, TNF-related apoptosis-inducing ligand, and TNF-related weak apoptosis inducer.[72] Neutrophils and factor $XIIIa^+$ dendritic cells have also been found in these skin samples,[65,70,73] but their role in TEN has not been clarified. NK cells have been found in the blister fluid along with highly toxic cytolytic T cells that express the NK receptor CD56. These 2 cell types are understood to be the main inducers of keratinocyte apoptosis.[62,63] The importance of $CD8^+$ T lymphocytes in TEN pathogenesis has been reinforced recently with the advent of a novel, human-oriented TEN mouse model. This new mouse model unlocks vast potential in diagnostic and therapeutic research.[74]

The mechanism of T cell activation in TEN remains under investigation. There are 2 predominant theories: the pharmacologic interaction of drugs with the immune system (p-i concept) and the pro-hapten concept. In the pro-hapten concept, drugs are digested into metabolites that bind covalently to cellular peptides, creating an immunogenic molecule capable of stimulating the breadth of the immune system. The p-i concept asserts that a drug can stimulate the immune system by noncovalently binding directly to the major histocompatibility complex (MHC) I and the T-cell receptor (TCR), much like the drug would bind to its pharmacologic target. In this model, the drug's affinity for the MHC I molecule and TCR would induce only a T cell response, which would account for the lack of B cell proliferation seen in TEN.[75] Sulfamethoxazole (SMX) and abacavir have been studied in an effort to determine which theory is responsible for T cell activation; however, no clear answer has emerged. Castrejon et al[76] took lymphocytes from patients with known hypersensitivity reactions to SMX, including 1 patient who experienced SJS, and found that SMX-induced clonal expansion of T cells could occur independent of antigen presenting cells (APCs), confirming studies showing that SMX can directly bind to the MHC I molecule and TCR to activate T cells.[77,78] This study also found that SMX metabolites were unable to induce T cell proliferation when the APCs were incubated with glutathione and glutaraldehyde, known inhibitors of antigen presentation, supporting the idea that SMX can stimulate T cells by acting as a pro-hapten.[76]

Recent work on abacavir-induced hypersensitivity reactions revealed that $CD8^+$ cell proliferation was prevented by inhibition of antigen processing by APCs and by the use of APCs with deficiencies in the MHC antigen presentation pathway, favoring the role of the pro-hapten concept in abacavir-induced T cell activation.[79] Additional research on drug-induced T cell activation is necessary to determine whether the p-i concept, the pro-hapten concept, or both are responsible for T cell activation in TEN.

Many studies have revealed the genetic relationship between MHC I allotype and drug hypersensitivity reactions. In Han Chinese patients with TEN/SJS, a strong association exists between aromatic antiepileptic agents, including carbamazepine, phenytoin, oxcarbazapine, and lamotrigine, and the MHC I allotype human leukocyte antigen (HLA)-B*1502[80-82] as well as between allopurinol and HLA-B*5801.[83] The association between HLA-B*1502 and carbamazepine-induced TEN/SJS also exists in Thai,[84,85] Malaysian,[86] and South Indian[87] populations, but not in Japanese, Korean,[88-90] or European[91] populations, while the association between allopurinol and HLA-B*5801 is also found in patients of European descent.[92] In addition, a correlation was also shown between HLA-B*5701 and abacavir-induced hypersensitivity reactions[93,94] and between carbamazepine-induced hypersensitivity reactions and HLA-A*3101 in Europeans.[95]

The strong association between TEN and certain MHC allotypes has led to the speculation that these allotypes are not simply genetic markers, but are involved in the pathogenesis of TEN.[96] This idea was explored by investigating the role of HLA-B*5701 in the pathogenesis of abacavir drug hypersensitivity reaction. In this study, peripheral blood mononuclear cells (PBMCs) from abacavir-naïve patients with the HLA-B*5701 allotype were found to activate $CD8^+$ but not $CD4^+$ cells when incubated with abacavir. In contrast, none of the PBMCs from abacavir-naïve patients without the HLA-B*5701 allotype elicited T cell activation. In addition, alteration of a single serine residue at position 116 in the F pocket of the HLA-B*5701 allotype prevented the abacavir-induced $CD8^+$ cell activation. These results show the $CD8^+$ cell–specific activation by abacavir, the importance of the MHC I allotype in the pathogenesis of drug hypersensitivity reactions, and the specificity between abacavir and a particular HLA allotype. It is unclear whether the antigen that binds to the F pocket of HLA-B*5701 is abacavir itself, a metabolite of abacavir, or a hapten–peptide adduct.[79]

ETIOLOGY OF APOPTOSIS

- **Apoptosis is the cause of keratinocyte death, with $CD8^+$ cell exocytosis of granzyme B/perforin and granulysin implicated as the primary mediators of apoptosis**
- **Soluble Fas ligand, nitric oxide (NO), and tumor necrosis factor–alfa also contribute to keratinocyte apoptosis**

While a complete understanding of the pathophysiology of TEN remains elusive, recent studies have expanded our knowledge of the mechanisms underlying epidermal death. Apoptosis was found to be the cause of cell death in TEN,[97] with granulysin most recently implicated as the pivotal trigger of the apoptosis. Other pathogenic factors include Fas ligand (FasL), TNF-α, perforin/granzyme B, and NO.

A strong case has been evinced for granulysin as the predominant cause of keratinocyte apoptosis in TEN.[98] Granulysin is a molecule found in the cytotoxic granules, along with granzyme B and perforin, of $CD8^+$, NK, and NK/T cells and is important as a tumoricidal and bactericidal agent. Upon activation of the cytolytic or NK cell, granulysin is exocytosed and appears to "scissor through" the membranes of target cells, causing ionic instability, which leads to mitochondrial damage and cell apoptosis.[99] In a study on granulysin and TEN, Chung et al[98] compared the gene expression of blister fluid cells with PBMCs and found a 10- to 20-fold increase in blister cell expression of granulysin, an eightfold increase in granzyme B, a threefold increase in perforin, and a twofold increase in serum FasL (sFasL). Measurement of granulysin levels in the blister fluid followed the same pattern, revealing a 2- to 4-orders of magnitude increase in granulysin compared with perforin, granzyme B, and sFasL, with granulysin levels correlating with the disease severity. Immunohistochemistry of skin biopsy specimens found intense granulysin staining of the edges of the necrotic epidermis in patients with TEN, with only weak granulysin staining in patients with a drug-induced maculopapular eruption. When the cytotoxicity of the purified recombinant forms of the above proteins was assessed using the concentrations found in the blister fluid, only granulysin elicited significant apoptosis of keratinocytes, and was able to do so at concentrations much lower than sFasL, perforin, or granzyme B found in the blister fluid.[100] In the final portion of this study, Chung et al[98] intradermally injected purified recombinant granulysin and granzyme B into separate rats and found that skin necrosis and blistering, reminiscent of TEN, occurred only in the rats injected with granulysin. Granulysin was also found to exhibit cytotoxicity in a dose-dependent fashion. Abe et al[101] then showed that serum levels of granulysin were increased in 4 of 5 patients with TEN/SJS before skin detachment or the development of mucosal lesions, and that granulysin levels were increased in only 1 of 24 patients with ordinary drug-induced skin reactions. Together, these studies strongly argue for granulysin as an important inducer of apoptosis in TEN and as a promising marker for early diagnosis.[98,101]

FasL is a transmembrane protein from the TNF family that is expressed on the surface of cytotoxic

T cells, NK cells, immune privileged cells of the testes and eye, and keratinocytes. When cytotoxic T cells are activated, FasL is expressed on their surface and binds to its receptor on target cells, which activates intracellular caspases, leading to the controlled destruction of the target cell. In addition, FasL can be cleaved from its cell membrane by metalloproteinases, producing a soluble from of FasL, which retains the capacity to bind to the Fas receptor and trigger apoptosis.[102,103] Multiple studies have established the importance of the Fas—FasL pathway in the pathogenesis of TEN.[104-107]

Granzyme B and perforin have been shown to play a role in TEN keratinocyte and endothelial apoptosis. Cytolytic T cells, when activated by a target cell, exocytose perforin and granzyme B molecules, which create channels in the target cell membrane and activate caspases, respectively, causing cell apoptosis.[108] In a study of patients with TEN, mononuclear cells from the blister fluid were shown to induce apoptosis in the presence of anti-Fas antibodies, but not in the presence of inhibitors of perforin/granzyme B, implicating perforin/granzyme B as the cause of the apoptosis.[61,62] The level of these molecules was also found to be correlated with severity of the drug reaction, suggesting that perforin/granzyme B testing could be used to differentiate TEN from more mild drug eruptions.[109] Recent studies on biopsy specimens from patients with drug-induced eruptions, including TEN, reported endothelial apoptosis, with immunohistochemical staining revealing granzyme B and TNF-α around the dermal vessels. Although FasL was not found in the biopsy specimens, sFasL could not be excluded as a cause of the endothelial apoptosis, because the biopsy specimens were drawn 2 to 4 days after the drug eruption, when sFasL levels have been shown to precipitously decline.[110,111]

Other cytokines and molecules, such as TNF-α and NO, have been implicated in the apoptosis of TEN. TNF-α has been shown to activate the "death receptor" TNF-R1, causing caspase activation and cell death, and TNF-α is elevated in the blister fluid,[100] skin,[112] and sera[92] of patients with TEN. Although increased TNF-α is found in TEN, its role remains unclear. In addition to causing apoptosis, TNF-α is also known to activate the antiapoptotic nuclear factor-kappaB (NF-κB) pathway,[113] leading to speculation that it functions mainly in a protective role in TEN.[100,113] This idea may explain the increased mortality found in TEN patients treated with the anti—TNF-α agent thalidomide. Although the increased mortality may have been caused by a paradoxical increase in TNF-α, the specter that TNF-α mainly acts in an antiapoptotic capacity in TEN could not be excluded.[114] NO has been implicated in apoptosis, and is believed to stimulate the activity of caspases through the action of p53.[115] Prebullous skin samples of patients with TEN/SJS have shown increased levels of inducible NO synthase (iNOS).[116] IFN-α and TNF-α secreted by activated T cells have been shown to induce iNOS expression, NO-dependent FasL upregulation, and ultimately apoptosis in keratinocytes; this implicates IFN-α, TNF-α, and iNOS as the potential molecular bridge between the drug-specific immune response on one side and the expression of proapoptotic molecules on the other.[117] The combination of TNF-α, NO, and the ensuing elevation of reactive oxygen species may also contribute to resultant oxidative stress and the disruption of the intracellular machinery and membrane, which leads to apoptosis.[118]

In summary, TEN is initiated either by noncovalent, direct interaction of a drug with a specific MHC I allotype or by covalent binding of a drug metabolite to a cellular peptide, forming an immunogenic molecule. $CD8^+$ cells, activated by keratinocytes and APCs expressing specific MHC I and antigen, release INF-γ, causing the activation of macrophages and keratinocytes and perforin/granzyme B and granulysin. The activated macrophages and keratinocytes upregulate MHC I and release TNF-α and chemoattractants, while granulysin and perforin/granzyme B diffuse through the epidermis, acting as the major inducers of apoptosis. Activated $CD8^+$ cells and keratinocytes also upregulate FasL, which, along with TNF-α, induces additional apoptosis. Neutrophils, drawn to the skin by chemoattractants, and NO, released from activated keratinocytes, would seem to play a minor role in apoptosis. The presence of Th2 cytokines most likely indicates an attempt to dampen the inflammatory response and to curtail the activation and proliferation of cytotoxic T cells.

CONCLUSION

TEN is a life-threatening, usually drug-induced mucocutaneous reaction that is characterized by flaccid bullae and cutaneous and mucosal epithelial denudation. Drug-induced $CD8^+$ cell activation is highly specific for particular HLA allotypes, placing certain populations at a greater risk for developing TEN. While sFasL, TNF-α, and granzyme B/perforin are important in the pathogenesis of TEN, granulysin appears to be the main mediator of the apoptosis. The importance of this molecule in TEN should continue to be elucidated with the hope of spurring new treatment options to

lower the morbidity and mortality associated with this deadly condition.

REFERENCES

1. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet 1999;353: 2190-4.
2. La Grenade L, Lee L, Weaver J, Bonnel R, Karwoski C, Governale L, et al. Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. Drug Saf 2005; 28:917-24.
3. Lissia M, Mulas P, Bulla A, Rubino C. Toxic epidermal necrolysis (Lyell's disease). Burns 2010;36:152-63.
4. Rzany B, Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J, et al. Epidemiology of erythema exsudativum 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; 49:769-73.
5. Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Stolley PD, et al. Using a claims database to investigate drug-induced Stevens-Johnson syndrome. Stat Med 1991;10: 565-76.
6. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, 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;126:43-7.
7. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Fléchet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. Arch Dermatol 1990;23:1039-58.
8. Schöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol 1991;127:839-42.
9. French LE, Prins C. Toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. Edinburgh: Mosby; 2003. pp. 323-31.
10. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson Syndrome in an HIV cohort: an observational, retrospective case series study. Am J Clin Dermatol 2012;12:49-54.
11. Saka B, Barro-Traoré F, Atadokpédé FA, Kobangue L, Niamba PA, Adégbidi H, et al. Stevens—Johnson syndrome and toxic epidermal necrolysis in sub-Saharan Africa: a multicentric study in four countries. Int J Dermatol 2013; 52:575-9.
12. Rodriguez G, Trent JT, Mirzabeigi M, Zaulyanov L, Bruce J, Vincek V. Toxic epidermal necrolysis in a mother and fetus. J Am Acad Dermatol 2006;55(5 suppl):S96-8.
13. Sanmarkan AD, Sori T, Thappa DM, Jaisankar TJ. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis over a period of 10 years. Indian J Dermatol 2011;56:25-9.
14. Bastuji-Garin S, Zahedi M, Guillaume JC, Roujeau JC. Toxic epidermal necrolysis (Lyell syndrome) in 77 elderly patients. Age Ageing 1993;22:450-6.
15. Debre R, Lamy M, Lamotte M. L'erythrodermie bulleuses avec epidermolyse. Bull Soc Pediatr 1939;37:231-8.
16. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol 1956;68:355-61.
17. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. Br J Dermatol 1979;100:69-86.
18. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia: report of two cases in children. Am J Dis Child 1922;24:526-33.
19. Alexander MK, Cope S. Erythema multiforme exudativum major (Stevens-Johnson syndrome). J Path Bact 1954;68: 373-80.
20. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. J Am Acad Dermatol 1983;8:763-75.
21. 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;129:92-6.
22. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. J Invest Dermatol 1994;102:28S-30S.
23. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. J Dermatol 1997;24:726-9.
24. Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. Am Fam Phys 2006;74:1883-8.
25. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens—Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol 1995;131:539-43.
26. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol 2012;51:889-902.
27. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. Exp Rev Clin Immunol 2001;7:803-15.
28. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333:1600-7.
29. Harr T, French L. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
30. Letko E, Papaliodis DN, Papaliodis GN, Daoud YJ, Ahmed AR, Foster CS. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. Ann Allergy Asthma Immunol 2005;94:419-36.
31. Rasmussen JE. Toxic epidermal necrolysis. A review of 75 cases in children. Arch Dermatol 1975;111:1135-9.
32. Schwartz RA. Toxic epidermal necrolysis. Cutis 1997;59:123-8.
33. Revuz J, Penso D, Roujeau JC, Guillaume JC, Payne CR, Wechsler J, et al. Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients. Arch Dermatol 1987; 123:1160-5.
34. Ruiz-Maldonado R. Acute disseminated epidermal necrolysis types 1, 2 and 3: study of 60 cases. J Am Acad Dermatol 1985; 13:623-35.
35. Avakian R, Flowers FP, Araujo OE, Ramos-Caro FA. Toxic epidermal necrolysis: a review. J Am Acad Dermatol 1991;25: 69-79.
36. Grando SA, Grando AA, Glukhenky BT, Doguzov V, Nguyen VT, Holubar K. History and clinical significance of mechanical symptoms in blistering dermatoses: a reappraisal. J Am Acad Dermatol 2003;48:86-92.
37. Goodman H. Nikolsky sign; page from "notable contributors to the knowledge of dermatology". AMA Arch Derm Syphilol 1953;68:334-5.

38. Kim KJ, Lee DP, Suh HS, Lee MW, Choi JH, Moon KC, et al. Toxic epidermal necrolysis: analysis of clinical course and SCORTEN-based comparison of mortality rate and treatment modalities in Korean patients. Acta Derm Venereol 2005;85: 497-502.
39. Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR, Taibjee SM, Shah F, et al. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. Clin Exp Dermatol 2010;35:853-62.
40. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. J Am Acad Dermatol 2007;56:181-200.
41. Blum L, Chosidow O, Rostoker G, Philippon C, Revuz J, Roujeau JC. Renal involvement in toxic epidermal necrolysis. J Am Acad Dermatol 1996;34:1088-90.
42. Michel P, Joly P, Ducrotte P, Hemet J, Leblanc I, Lauret P, et al. Ileal involvement in toxic epidermal necrolysis (Lyell syndrome). Digest Dis Sci 1993;38:1938-41.
43. Dasgupta A, O'Malley J, Mallya R, Willaims JG. Bronchial obstruction due to respiratory mucosal sloughing in toxic epidermal necrolysis. Thorax 1994;49:935-6.
44. Wallis C, McClymont W. Toxic epidermal necrolysis with adult respiratory distress syndrome. Anaesthesia 1995;50:801-3.
45. Dolan PA, Flowers FP, Araujo OE, Sheretz EF. Toxic epidermal necrolysis. J Emerg Med 1989;7:65-9.
46. Hung CC, Liu WC, Kuo MC, Lee CH, Hwang SJ, Chen HC. Acute renal failure and its risk factors in Stevens-Johnson syndrome and toxic epidermal necrolysis. Am J Nephrol 2009;29:633-8.
47. Yamane Y, Aihara M, Ikezawa Z. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. Allergol Int 2007;56:419-25.
48. Lebargy F, Wolkenstein P, Gisselbrecht M, Lange F, Fleury-Feith J, Delclaux C, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. Intensive Care Med 1997;23:1237-44.
49. Goens J, Song M, Fondu P, Blum D, Achten G. Haemtological disturbances and immune mechanisms in toxic epidermal necrolysis. Br J Dermatol 1986;114:255-9.
50. Dobrosavlijevic D, Milinkoic MV, Nikolic MM. Toxic epidermal necrolysis following morbilli-parotitis-rubella vaccination. J Eur Acad Dermatol Venereol 1999;13:59-61.
51. Ball R, Ball LK, Wise RP, Braun MM, Beeler JA, Salive ME. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. Pediatr Infect Dis J 2001;20:219-23.
52. Stevens D, Swift PG, Johnston PG, Kearney PJ, Corner BD, Burman D. Mycoplasma pneumoniae infections in children. Arch Dis Child 1978;53:38-42.
53. Fournier S, Bastuji-Garin S, Mentec H, Revuz J, Roujeau JC. Toxic epidermal necrolysis associated with *Mycoplasma pneumoniae* infection. Eur J Clin Microbiol Infect Dis 1995; 14:558-9.
54. Grieb G, Alazemi M, Das R, Dunda SE, Fuchs PC, Pallua N. A rare case of toxic epidermal necrolysis with unexpected fever resulting from dengue virus. Case Rep Dermatol 2010;2: 189-94.
55. Khalaf D, Toema B, Dabbour N, Jehani F. Toxic epidermal necrolysis associated with severe cytomegalovirus infection in a patient on regular hemodialysis. Mediterr J Hematol Infect Dis 2011;3:e2011004.
56. Baldwin BT, Lien MH, Khan H, Siddique M. Case of fatal toxic epidermal necrolysis due to cardiac catheterization dye. J Drugs Dermatol 2010;9:837-40.
57. Garza A, Waldman AJ, Mamel J. A case of toxic epidermal necrolysis with involvement of the GI tract after systemic contrast agent application at cardiac catheterization. Gastrointest Endosc 2005;62:638-42.
58. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35-44.
59. Guillaume JC, Roujeau JC, Revuz J, Penso D, Touranine R. The culprit drugs in 87 cases toxic epidermal necrolysis (Lyell's syndrome). Arch Dermatol 1987;123: 1166-70.
60. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharm Ther 2010; 88:60-8.
61. Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol 2004;114:1209-15.
62. Nassif A, Bensussan A, Dorothee G, Mami-Chouaib F, Bachot N, Bagot M, et al. Drug Specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. J Invest Dermatol 2002;118:728-33.
63. Paquet P, Pierard GE, Quatresooz P. Novel treatment for drug-induced toxic epidermal necrolysis (Lyell's syndrome). Int Arch Allerg Immunol 2005;136:205-16.
64. Miyauchi H, Hosokawa H, Akaeda T, Iba H, Asada Y. T-cell subsets in drug-induced toxic epidermal necrolysis. Possible pathogenic mechanism induced by CD8-positive T cells. Arch Dermatol 1991;127:851-5.
65. Caproni M, Torhia D, Schincaglia E, Volpi W, Frezzolini A, Schena D, et al. The CD40/CD40L system is expressed in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Br J Dermatol 2006;154:319-24.
66. Powell LP, Baum LG. Overview and compartmentalization of the immune system. In: Hoffman R, Furie B, Benz E, McGlave P, Silverstein L, Shattil SJ, editors. Hematology: basic principles and practice. Orlando (FL): Churchill Livingstone; 2008. pp. 95-104.
67. Caproni M, Antiga E, Parodi A, Schena D, Marzano A, Quaglino P, et al. Elevated circulating CD40 ligand in patients with erythema multiforme and Stevens-Johnson syndrome/-toxic epidermal necrolysis spectrum. Br J Dermatol 2006;154: 1006-7.
68. Goldsby RA, Osborne BA, Kindt TJ, editors. Kuby immunology. New York: W. H. Freeman and Company; 2007.
69. Caproni M, Torchia D, Schincaglia E, Volpi W, Frezzolini A, Schena D, et al. Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis. Br J Dermatol 2006;155:722-8.
70. Paquet P, Paquet F, Al Saleh W, Reper P, Vanderkelen A, Pierard GE. Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis. Am J Dermatopathol 2000;22: 413-7.
71. Tohyama M, Watanabe H, Murakami S, Shirakata Y, Sayama K, Lijima M, et al. Possible involvement of $CD14^+$ $CD16^+$ monocyte lineage cells in the epidermal damage of Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2012;166:322-30.
72. Tohyama M, Hashimoto K. Immunological mechanisms of epidermal damage in toxic epidermal necrolysis. Drug Allergy 2012;12:376-82.

73. Quinn AM, Brown K, Bonish BK, Curry J, Gordon KB, Sinacore J, et al. Uncovering histologic criteria with prognostic significance in toxic epidermal necrolysis. Arch Dermatol 2005;141:683-7.
74. Saito N, Yoshioka N, Abe R, Qiao H, Fujita Y, Hoshina D, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis mouse model generated by using PBMCs and the skin of patients. J Allergy Clin Immunol 2013;131:434-41.
75. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol 2011;127(3 suppl):S74-81.
76. Castrejon JL, Berry N, El-Ghalesh S, Gerber B, Pichler WJ, Park BK, et al. Stimulation of human T cells with sulfonamides and sulfonamide metabolites. J Allergy Clin Immunol 2010;125:411-8.
77. Schnyder B, Burkhart C, Schnyder-Frutig K, von Greyerz S, Naisbitt DJ, Pirmohamed M, et al. Recognition of sulfamethoxazole and its reactive metabolites by drug-specific $CD4^+$ T cells from allergic individuals. J Immunol 2000;164:6647-54.
78. Engler OB, Strasser I, Naisbitt DJ, Cerny A, Pichler WJ. A chemically inert drug can stimulate T cells in vitro by their T cell receptor in non-sensitized individuals. Toxicology 2004;197:47-56.
79. Chessman D, Kostenko L, Lethborg T, Purcell AW, Williamson NA, Chen Z, et al. Human leukocyte antigen class I-restricted activation of $CD8^+$ T cells provides the immunogenetic basis of systemic drug hypersensitivity. Immunity 2008;28:822-32.
80. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
81. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007;48:1015-8.
82. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RC, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349-56.
83. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134-9.
84. Locharernkul C, Loplumiert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia 2008;49:2087-91.
85. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 2010;51:926-30.
86. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian populations. Int J Dermatol 2011;50:221-4.
87. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol 2009;75:579-82.
88. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics 2008;9:1617-22.
89. Kashiwagi M, Aihara M, Takahashi Y, Yamazaki E, Yamane Y, Song Y, et al. Human leukocyte antigen genotypes in carbamazepine-induced severe cutaneous adverse drug response in Japanese patients. J Dermatol 2008;35:683-5.
90. Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Korea. Epilepsy Res 2011;97:190-7.
91. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, et al. A marker for Stevens-Johnson syndrome…: ethnicity matters. Pharmacogenomics J 2006;6:265-8.
92. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18:99-107.
93. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002;359:727-32.
94. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-2.
95. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med 2011;364:1134-43.
96. Yang CW, Hung SI, Juo CG, Lin YP, Fang WH, Lu IH, et al. HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol 2007;120:870-7.
97. Paul C, Wolkenstein P, Adle H, Wechsler J, Garchon HJ, Revuz J, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol 1996;134:710-4.
98. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14:1343-50.
99. Krensky AM, Clayberger C. Biology and clinical relevance of granulysin. Tissue Antigens 2009;73:193-8.
100. Nassif A, Moslehi H, Le Gouvello S, Bagot M, Lyonnet L, Michel L, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. J Invest Dermatol 2004;123:850-5.
101. Abe R, Yoshioka N, Murata J, Fujita Y, Shimizu H. Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome. Ann Intern Med 2009;151:514-5.
102. Abe R. Toxic epidermal necrolysis and Stevens-Johnson syndrome: soluble Fas ligand involvement in the pathomechanisms of these diseases. J Dermatol Sci 2008;52:151-9.
103. Nagata S. Apoptosis by death factor. Cell 1997;88:355-65.
104. Viard I, Wehril P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490-3.
105. Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. Am J Pathol 2003;162:1515-20.
106. Murata J, Abe R, Shimizu H. Increased soluble Fas ligand levels in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis preceding skin detachment. J Allergy Clin Immunol 2008;122:992-1000.
107. Stur K, Karlhofer FM, Stingl G. Soluble FAS ligand: a discriminating feature between drug-induced skin eruptions and viral exanthems. J Invest Dermatol 2007;127:802-7.

108. Darmon AJ, Nicholson DW, Bleackley RC. Activation of the apoptotic protease CPP32 by cytotoxic T-cell-derived granzyme B. Nature 1995;377:446-8.
109. Posadas SJ, Padial A, Torres MJ, Mayorga C, Leyva L, Sanchez E, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. J Allergy Clin Immunol 2002;109:155-61.
110. Verneuil L, Leboeuf C, Vidal JS, Ratajczak P, Comoz F, Ameisen JC, et al. Endothelial damage in all types of T-lymphocyte-mediated drug-induced eruptions. Arch Dermatol 2011;147:579-84.
111. Verneuil L, Ratajczak P, Allabert C, Leboeuf C, Comoz F, Janin A, et al. Endothelial cell apoptosis in severe drug-induced bullous eruptions. Br J Dermatol 2009;161:1371-5.
112. Paquet P, Nikkels A, Arrese JE, Vanderkelen A, Pierard GE. Macrophages and tumor necrosis factor alpha in toxic epidermal necrolysis. Arch Dermatol 1994;130:605-8.
113. Chave TA, Mortimer NJ, Sladden MJ, Hall AP, Hutchinson PE. Toxic epidermal necrolysis: current evidence, practical management and future directions. Br J Dermatol 2005;153:241-53.
114. Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L, et al. Randomized comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet 1998;352:1586-9.
115. Brune B, von Knethen A, Sandau KB. Nitric oxide and its role in apoptosis. Eur J Pharmacol 1998;351:261-72.
116. Lerner LH, Qureshi AA, Reddy BV, Lerner EA. Nitric oxide synthase in toxic epidermal necrolysis and Stevens-Johnson syndrome. J Invest Dermatol 2000;114:196-9.
117. Viard-Leveugle I, Gaide O, Jankovic D, Feldmeyer L, Kerl K, Pickard C, et al. TNF-α and IFN-γ are potential inducers of Fas-mediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis. J Invest Dermatol 2013;133:489-98.
118. Paquet P, Piérard GE. New insights in toxic epidermal necrolysis (Lyell's syndrome): clinical considerations, pathobiology and targeted treatments revisited. Drug Saf 2010;33:189-212.