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