

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.

Stevens Johnson Syndrome

Authors

Amanda M. **Oakley**¹; Karthik Krishnamurthy².

Affiliations

¹ University of Auckland

² Orange Park Medical Center

Last Update: November 20, 2020.

Introduction

Previously known as Lyell syndrome, **Stevens-Johnson syndrome (SJS)** and toxic epidermal necrolysis (TEN) are variants of the same condition, and are distinct from erythema multiforme major, staphylococcal scalded skin syndrome, and other drug eruptions.[1][2][3]

Stevens-Johnson syndrome/toxic epidermal necrolysis is a rare, acute, serious, and potentially fatal skin reaction in which there are sheet-like skin and mucosal loss accompanied by systemic symptoms. Medications are causative in over 80% of cases.

Stevens-Johnson syndrome/toxic epidermal necrolysis is classified by the extent of the detached skin surface area.

- **Stevens-Johnson syndrome**: less than 10% body surface area
- Overlap **Stevens-Johnson syndrome/toxic epidermal necrolysis**: 10% to 30% body surface area
- Toxic epidermal necrolysis more than 30% body surface area

Etiology

Stevens-Johnson syndrome/toxic epidermal necrolysis is a rare and unpredictable reaction to medication that involves drug specific CD8+ cytotoxic lymphocytes, the Fas-Fas ligand (FasL) pathway of apoptosis, and granule-mediated exocytosis and tumor necrosis factor- α (TNF- α)/death receptor pathway. [4][5]

Current theories address the following mechanisms, among others.

- Granulysin, found in the cytotoxic granules, is the main cause of keratinocyte apoptosis.
- Fas-FasL, expressed on the activated cytotoxic T cells, can also destroy keratinocytes via the production of intracellular caspases.
- Cytotoxic T cells exocytose perforin and granzyme B, which create channels in the target cell membrane activating the caspases.
- TNF- α may cause apoptosis or protect from it.
- Nitrous oxide (NO) induced by TNF- α and interferon (IFN)- α may stimulate caspases.

Epidemiology

Stevens-Johnson syndrome/toxic epidermal necrolysis is estimated to affect two to seven million people each year, with **Stevens-Johnson syndrome** being three times more common than toxic epidermal necrolysis. **Stevens-Johnson syndrome/toxic epidermal necrolysis** can affect anyone with a genetic predisposition: any age, either sex and all races, although it is more common in older people and women. It is much more likely to occur in people infected with human immunodeficiency virus (HIV), with an estimated incidence of 1/1000.[6][7][8]

- Numerous medications have been reported to trigger **Stevens-Johnson syndrome/toxic epidermal necrolysis**.

- **Stevens-Johnson syndrome/toxic epidermal necrolysis** are rarely associated with vaccination and infections such as mycoplasma, cytomegalovirus, and dengue.

The drugs that most commonly cause **Stevens-Johnson syndrome/toxic epidermal necrolysis** are:

- Anticonvulsants: lamotrigine, carbamazepine, phenytoin, phenobarbitone
- Allopurinol, especially in doses of more than 100 mg per day
- Sulfonamides: cotrimoxazole, sulfasalazine
- Antibiotics: penicillins, cephalosporins, quinolones, minocycline
- Paracetamol/acetaminophen
- Nevirapine (non-nucleoside reverse-transcriptase inhibitor)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (oxicam type mainly)
- Contrast media.

Genetic factors include human leukocyte antigen (*HLA*) allotypes that lead to an increased risk of **Stevens-Johnson syndrome/toxic epidermal necrolysis** when exposed to aromatic anticonvulsants and allopurinol. Family members of a patient with **Stevens-Johnson syndrome/toxic epidermal necrolysis** should be advised that they are at risk of developing the disease and should be cautious about taking any medications associated with the disease.[9]

To date, findings have included the risk of **Stevens-Johnson syndrome/toxic epidermal necrolysis** in:

- Han Chinese, Thai, Malaysian and South Indian people if they carry *HLA-B*1502* and take aromatic anticonvulsants
- Han Chinese if they carry *HLA-B*5801* and take allopurinol
- Europeans if they carry *HLA-B*5701* and take abacavir, or if they carry *HLA-A*3101* and take carbamazepine.

Pathophysiology

The initial step for **Stevens-Johnson syndrome/toxic epidermal necrolysis** may be interaction/binding of a drug-associated antigen or metabolite with the major histocompatibility complex (MHC) type 1 or cellular peptide to form an immunogenic compound. The exact mechanism is speculative.[10]

Stevens-Johnson syndrome/toxic epidermal necrolysis is T-cell mediated.

- CD8+ cells are present in blister fluid and may induce keratinocyte apoptosis.
- Other cells of the innate immune system play a role.
- CD40 ligand cells are also present and may induce release of TNF-alpha, nitrous oxide, interleukin 8 (IL-8) and cell adhesion antibodies. TNF-alpha also induces apoptosis.
- Both Th1 and Th2 cytokines are present.

Other cells implicated in **Stevens-Johnson syndrome/toxic epidermal necrolysis** include macrophages, neutrophils, and natural killer (NK) cells.

The pharmacologic interaction of drugs with the immune system could result in binding of the responsible drug to MHC-1 and the T cell receptor. An alternative theory is a pro-hapten concept, in which drug metabolites become immunogenic and stimulate the immune system.

Histopathology

Histology of the skin reveals necrosis of keratinocytes, epidermal (or epithelial) necrosis and mild lymphocytic dermal infiltration. Direct immune fluorescence is negative.

Toxicokinetics

The drugs that precipitate **Stevens**-Johnson syndrome/toxic epidermal necrolysis tend to have long half-lives and are nearly always taken systemically. **Stevens**-Johnson syndrome/toxic epidermal necrolysis can develop within a few days to eight weeks after starting a new drug. A subsequent exposure can result in symptoms within a few hours.

History and Physical

The illness begins with nonspecific symptoms such as fever and malaise, upper respiratory tract symptoms such as a cough, rhinitis, sore eyes, and myalgia. Over the next three to four days, a blistering rash and erosions appear on the face, trunk, limbs, and mucosal surfaces.

- Erythematous, targetoid, annular, or purpuric macules
- Flaccid bullae
- Large painful erosions
- Nikolsky-positive (lateral pressure on the skin results in shedding of the epidermis)

Early on, toxic epidermal necrolysis displays widespread, tender erythroderma and erosions (with or without targetoid rash), whereas **Stevens**-Johnson syndrome is characterized more by targetoid rash, with fewer areas of denudation.

Mucosal ulceration and erosions can involve lips, mouth, pharynx, esophagus and gastrointestinal tract, eyes, genitals, upper respiratory tract. About half of patients have involvement of three mucosal sites.

The patient is very ill, anxious, and in pain. Liver, kidneys, lungs, bone marrow, and joints may be affected by **Stevens**-Johnson syndrome/toxic epidermal necrolysis. Typical symptoms include:

- Fever, malaise, headache, anorexia, pharyngitis
- Symptoms due to acute dysfunction of ocular, pulmonary, cardiovascular, gastrointestinal, renal, and hematological systems.

Features may overlap with other severe cutaneous adverse reactions (SCAR), such as acute generalized exanthematous pustulosis (causing subcorneal pustules) and drug hypersensitivity syndrome (causing a morbilliform eruption and involving other organs).

Evaluation

Investigations may include:

- Urgent frozen sections of skin biopsy: full-thickness skin necrosis
- Direct immune fluorescence: negative
- Complete blood count (CBC): anemia, lymphopenia, neutropenia, eosinophilia, atypical lymphocytosis
- Liver function tests (LFT): elevated transaminases, hypoalbuminemia
- Renal function: microalbuminuria, renal tubular enzymes in urine, reduced glomerular filtration, rising creatinine and urea, hyponatremia
- Pulmonary function: bronchial mucosal sloughing on bronchoscopy, interstitial infiltrates on chest x-ray
- Cardiac function: abnormal ECG and imaging.

The severity of **Stevens**-Johnson syndrome/toxic epidermal necrolysis is assessed using SCORTEN. One point is scored for each of the following seven criteria at admission.

- Age older than 40 years
- Presence of a malignancy

- Heart rate of more than 120
- Initial percentage of epidermal detachment greater than 10%
- Serum urea level greater than 10 mmol/L
- Serum glucose level greater than 14 mmol/L
- Serum bicarbonate level less than 20 mmol/L

The risk of dying from **Stevens**-Johnson syndrome/toxic epidermal necrolysis depends on the score. The mortality rate is more than 40 times higher in those with bicarbonate levels less than 20 mmol/L compared with those with higher levels. A SCORTEN ranges with their associated mortality (in %) are as follows: score 0-1 (3.2%), score 2 (12.1%), score 3 (35.3%), score 4 (58.3%), and score 5 (>90%).^{[11][12]}

In patients on multiple drugs known to cause **Stevens**-Johnson syndrome/toxic epidermal necrolysis, the algorithm ALDEN has been developed to determine likely cause.

- Period between drug intake and onset of reaction (index day): 5 to 28 days (score of 3), 29 to 56 days (2), 1 to 4 days (1), more than 56 days (–1), index day (–3) for first episode; 1 to 4 days (score of 3), 5 to 56 days (1) for subsequent episode
- Presence of drug on index day or within five times elimination half-life: stopped (1), unknown (0), stopped earlier (–1), continued beyond index day (–2)
- Previous history of adverse reaction to the same drug: **Stevens**-Johnson syndrome/toxic epidermal necrolysis (4), **Stevens**-Johnson syndrome/toxic epidermal necrolysis to a similar drug (2), other reaction to same or similar drug (1), none (0), previous use without reaction (–2)
- The notoriety of the drug, according to SCAR study: high risk (3), lower risk (2), possible risk (1), under surveillance or new drug (0), no evidence of association (–1)
- Other possible cause: infection (–1), another drug that high risk (–1 for each other drug)

Treatment / Management

Patients should undergo multidisciplinary assessment in a specialized hospital environment. ^{[13][14][15]}

- Intensivist
- Dermatologist
- Plastics/burns specialist
- Ophthalmologist
- Gynecologist/urologist
- Respiratory physician
- Physical therapist
- Nutritionist

Care of a patient with **Stevens**-Johnson syndrome/toxic epidermal necrolysis requires supportive care ^[16], including:

- Cessation of the suspected causative drug(s)
- Hospital admission: preferably to an intensive care and/or burn unit
- Fluid replacement (crystalloid)
- Nutritional assessment: may require nasogastric tube feeding
- Temperature control: warm environment, emergency blanket

- Pain relief
- Supplemental oxygen and in some cases, intubation with mechanical ventilation
- Sterile/aseptic handling

Skincare requires daily examination of skin and mucosal surfaces for infection, non-adherent dressings, and avoidance of trauma to the skin. Mucosal surfaces require careful cleansing and topical anesthetics.

- Gentle removal of necrotic skin/mucosal tissue
- Culture of skin lesions, axillae, and groins every two days

Antibiotics may be required for secondary infection but are best avoided prophylactically.

It is unknown whether systemic corticosteroids are beneficial, but they are often prescribed in high dose for the first three to five days of admission. Granulocyte colony-stimulating factor (G-CSF) may be of benefit in patients with severe neutropenia.

Other drugs reported effective include systemic corticosteroids, ciclosporin, TNF-alpha inhibitors [17], N-acetylcysteine, and intravenous immunoglobulins. Their role remains controversial.

Differential Diagnosis

Other acute exfoliative conditions that may need consideration include:

- Other severe cutaneous adverse reactions (SCAR) to drugs, such as drug hypersensitivity syndrome (DHS), acute generalised exanthematous pustulosis (AGEP)
- Other forms of drug eruption
- Erythema multiforme (EM) major
- Staphylococcal scalded skin syndrome
- Pemphigus vulgaris and pemphigus foliaceus
- Acute graft versus host disease.[18]

Prognosis

Stevens-Johnson syndrome/toxic epidermal necrolysis is potentially very serious with high mortality, predicted by the extent and severity at presentation (see SCORTEN and ALDEN above).

Mean adjusted mortality reported for the Nationwide Inpatient Sample 2009-2012 (US) was 4.8% for SJS, 19.4% for SJS/TEN overlap, and 14.8% for TEN.[19]

In Créteil, France, 66 of 361 patients diagnosed with **Stevens-Johnson syndrome/toxic epidermal necrolysis** died (18%): 2% with SJS, 12% with SJS/TEN overlap, and 26% with TEN.[20] There has been a trend towards improved mortality in recent years, attributed mainly to better supportive care than in earlier decades.

Complications

In the acute phase, sepsis is the most common serious risk of **Stevens-Johnson syndrome/toxic epidermal necrolysis**. Organ failure may occur, including pulmonary, hepatic and renal systems.

The most common long-term complications of **Stevens-Johnson syndrome/toxic epidermal necrolysis** are ocular (including blindness), cutaneous (pigmentary changes and scarring), and renal. Mucosal involvement with blisters and erosions can lead to strictures and scarring.[21]

Consultations

The care of patients with **Stevens-Johnson syndrome/toxic epidermal necrolysis** is multidisciplinary. Patients with blistering involving > 10% of the skin surface are usually admitted to intensive care units or burns units for supportive

care.

Pearls and Other Issues

Death is mainly due to sepsis and multiorgan failure. Contributing causes are:

- Gastrointestinal bleeding
- Pulmonary embolism
- Myocardial infarction and pulmonary edema

People who have survived **Stevens**-Johnson syndrome/toxic epidermal necrolysis must avoid the causative drug or structurally related medicines as **Stevens** Johnson syndrome/toxic epidermal necrolysis may recur. Cross-reactions can occur between:

- Anticonvulsants carbamazepine, phenytoin, lamotrigine and phenobarbital
- Beta-lactam antibiotics penicillin, cephalosporin, and carbapenem
- Nonsteroidal anti-inflammatory drugs
- Sulfonamides sulfamethoxazole, sulfadiazine, sulfapyridine

Stevens-Johnson syndrome/toxic epidermal necrolysis survivors may have scarring. Severe consequences can include:

- Ocular sequelae: dry eye, photophobia, pain, symblepharon, corneal scarring or neovascularization, trichiasis, reduced visual acuity, and blindness
- Cutaneous scarring, depigmentation, development of new melanocytic nevi, and pruritus
- Nail dystrophy, onycholysis, and loss of nails (this may recover over time)
- Diffuse scalp hair thinning
- Oral complications: discomfort, dry mouth, periodontal disease, gingival inflammation, synechiae
- Esophageal strictures
- Vulvovaginal stenosis or occlusion in females, and phimosis in males
- Persistent pulmonary disease: bronchitis, bronchiectasis, bronchiolitis obliterans, organizing pneumonia, respiratory tract obstruction

Enhancing Healthcare Team Outcomes

The management of SJS is interprofessional. A number of specialists are usually involved in the care of these patients including a dermatologist, intensivist, ophthalmologist, pulmonologist, nephrologist, plastic surgeon and gastroenterologist, functioning as an interprofessional team. The acute care of these patients is provided by the wound care. In addition, the pharmacist must closely assess the medications that the patient is receiving to prevent exacerbation of the disorder, or determine if any of the patient's medications could be the trigger for the condition. Even after treatment, these patients may have severe cosmetic deficits and may require mental health counseling. If the lesions occur across joints, the patient may benefit from physical therapy to restore function and muscle strength. The patient has to be educated on the use of ocular lubricants because of the sicca-like syndrome. Many patients do lose weight after suffering a severe reaction and should be referred to a dietitian. Following discharge, the patients need long-term follow-up to ensure that there are no functional deficits including visual loss. Once a patient has suffered an SJS, it is highly recommended that the patient wear a warning bracelet indicating the toxic agent or allergen.[22][16] (Level V)

Outcomes

The outcomes of patients with SJS depends on the extent and severity of skin involvement. For those with a mild eruption, the lesions usually heal in 12-16 weeks. Mild scarring may occur, but there is usually no functional loss

unless the eyes and other mucous membranes are involved. When the involved skin area is more than 20%, mortality rates of 1-27% have been reported. The presence of concomitant bacterial infection can increase the mortality rates. Factors that adversely affect the outcome include advanced age, leucopenia, presence of a malignancy, renal dysfunction, hyperglycemia, and more than 10% BSA involvement. Survivors of SJS may develop inverted eyelids, sicca-like syndrome, visual loss, and corneal neovascularization, but an interdisciplinary approach will lead to better outcomes.[23][24] [Level 5]

Continuing Education / Review Questions

- [Access free multiple choice questions on this topic.](#)
- [Earn continuing education credits \(CME/CE\) on this topic.](#)
- [Comment on this article.](#)

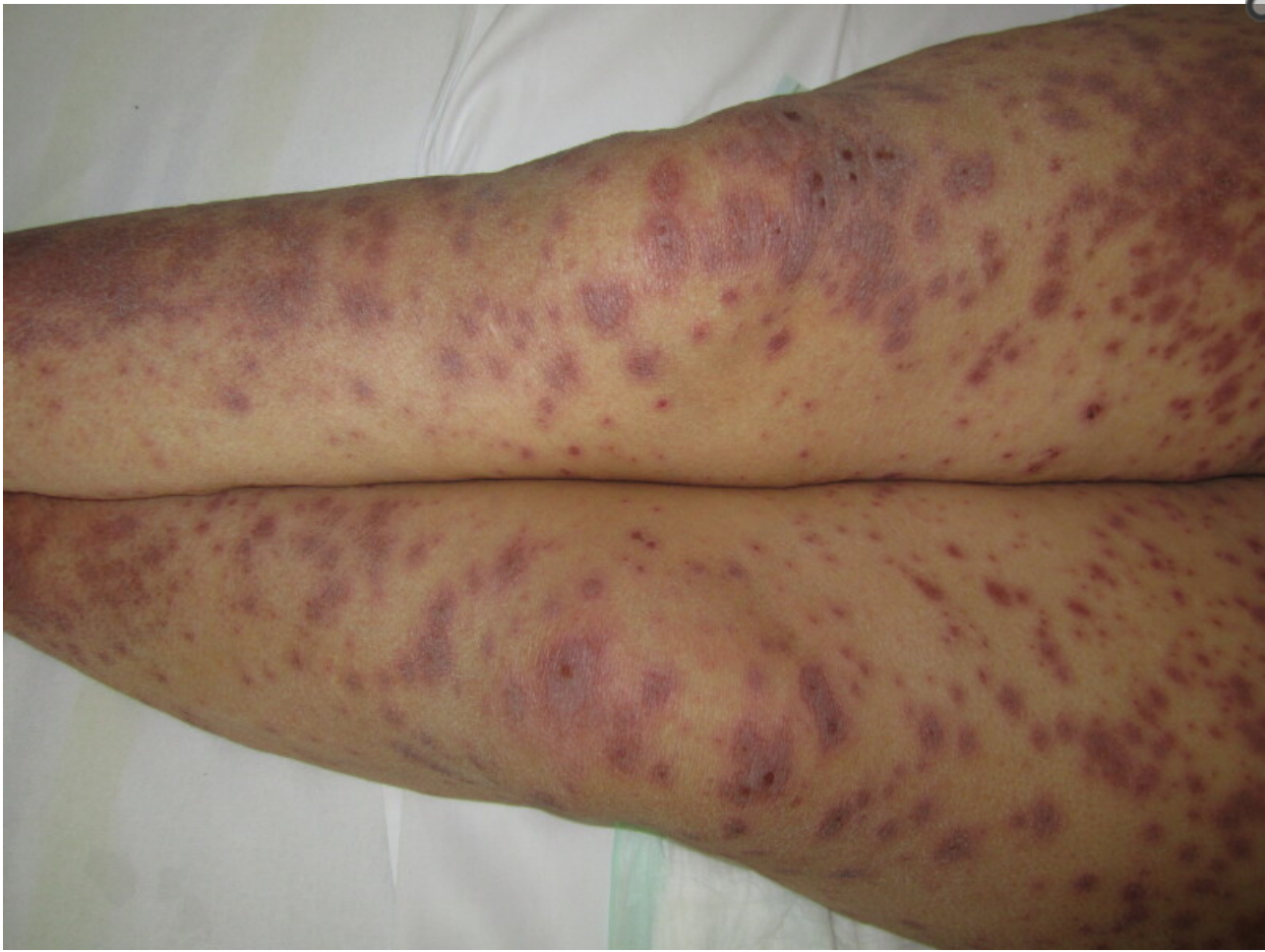
References

1. Jha N, Alexander E, Kanish B, Badyal DK. A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Center in Punjab. *Indian Dermatol Online J.* 2018 Sep-Oct;9(5):299-303. [PMC free article: [PMC6137653](#)] [PubMed: [30258795](#)]
2. Auyeung J, Lee M. Successful Treatment of **Stevens**-Johnson Syndrome with Cyclosporine and Corticosteroid. *Can J Hosp Pharm.* 2018 Jul-Aug;71(4):272-275. [PMC free article: [PMC6118827](#)] [PubMed: [30186001](#)]
3. Iyer G, Srinivasan B, Agarwal S, Ravindran R, Rishi E, Rishi P, Krishnamoorthy S. Boston Type 2 keratoprosthesis- mid term outcomes from a tertiary eye care centre in India. *Ocul Surf.* 2019 Jan;17(1):50-54. [PubMed: [30157458](#)]
4. Frey N, Bodmer M, Bircher A, Jick SS, Meier CR, Spoendlin J. **Stevens**-Johnson Syndrome and Toxic Epidermal Necrolysis in Association with Commonly Prescribed Drugs in Outpatient Care Other than Anti-Epileptic Drugs and Antibiotics: A Population-Based Case-Control Study. *Drug Saf.* 2019 Jan;42(1):55-66. [PubMed: [30112729](#)]
5. Sato S, Kanbe T, Tamaki Z, Furuichi M, Uejima Y, Suganuma E, Takano T, Kawano Y. Clinical features of **Stevens**-Johnson syndrome and toxic epidermal necrolysis. *Pediatr Int.* 2018 Aug;60(8):697-702. [PubMed: [29888432](#)]
6. Yang SC, Hu S, Zhang SZ, Huang JW, Zhang J, Ji C, Cheng B. Corrigendum to "The Epidemiology of **Stevens**-Johnson Syndrome and Toxic Epidermal Necrolysis in China". *J Immunol Res.* 2018;2018:4154507. [PMC free article: [PMC6046113](#)] [PubMed: [30050956](#)]
7. Velasco-Tirado V, Alonso-Sardón M, Cosano-Quero A, Romero-Alegría Á, Sánchez-Los Arcos L, López-Bernus A, Pardo-Lledías J, Belhassen-García M. Life-threatening dermatoses: **Stevens**-Johnson Syndrome and Toxic Epidermal Necrolysis. Impact on the Spanish public health system (2010-2015). *PLoS One.* 2018;13(6):e0198582. [PMC free article: [PMC6005565](#)] [PubMed: [29912947](#)]
8. Safiri S, Ashrafi-Asgarabad A. The risk of **Stevens**-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs: Comment on data sparsity. *Epilepsia.* 2018 May;59(5):1083-1084. [PubMed: [29723404](#)]
9. Wolf R, Marinović B. Drug eruptions in the mature patient. *Clin Dermatol.* 2018 Mar - Apr;36(2):249-254. [PubMed: [29566929](#)]
10. Tangamornsuksan W, Lohitnavy M. Association Between HLA-B*1301 and Dapsone-Induced Cutaneous Adverse Drug Reactions: A Systematic Review and Meta-analysis. *JAMA Dermatol.* 2018 Apr 01;154(4):441-446. [PMC free article: [PMC5876888](#)] [PubMed: [29541744](#)]
11. Richard EB, Hamer D, Musso MW, Short T, O'Neal HR. Variability in Management of Patients With SJS/TEN: A Survey of Burn Unit Directors. *J Burn Care Res.* 2018 Jun 13;39(4):585-592. [PubMed: [29901804](#)]
12. Ortonne N. [Histopathology of cutaneous drug reactions]. *Ann Pathol.* 2018 Feb;38(1):7-19. [PubMed: [29279184](#)]
13. Plachouri KM, Vryzaki E, Georgiou S. Cutaneous Adverse Events of Immune Checkpoint Inhibitors: A Summarized Overview. *Curr Drug Saf.* 2019;14(1):14-20. [PubMed: [30058498](#)]
14. Lerma V, Macías M, Toro R, Moscoso A, Alonso Y, Hernández O, de Abajo FJ. Care in patients with epidermal necrolysis in burn units. A nursing perspective. *Burns.* 2018 Dec;44(8):1962-1972. [PubMed: [30005991](#)]
15. Kumar R, Das A, Das S. Management of **Stevens**-Johnson Syndrome-Toxic Epidermal Necrolysis: Looking Beyond Guidelines! *Indian J Dermatol.* 2018 Mar-Apr;63(2):117-124. [PMC free article: [PMC5903040](#)]

[PubMed: 29692452]

16. Schneider JA, Cohen PR. **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures.** *Adv Ther.* 2017 Jun;34(6):1235-1244. [PMC free article: PMC5487863] [PubMed: 28439852]
17. Zhang S, Tang S, Li S, Pan Y, Ding Y. Biologic TNF-alpha inhibitors in the treatment of **Stevens-Johnson syndrome and toxic epidermal necrolysis: a systemic review.** *J Dermatolog Treat.* 2020 Feb;31(1):66-73. [PubMed: 30702955]
18. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol.* 2013 Aug;69(2):187.e1-16; quiz 203-4. [PubMed: 23866879]
19. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and Mortality of **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults.** *J Invest Dermatol.* 2016 Jul;136(7):1387-1397. [PubMed: 27039263]
20. Bettuzzi T, Penso L, de Prost N, Hemery F, Hua C, Colin A, Mekontso-Dessap A, Fardet L, Chosidow O, Wolkenstein P, Sbidian E, Ingen-Housz-Oro S. Trends in mortality rates for **Stevens-Johnson syndrome and toxic epidermal necrolysis: experience of a single centre in France between 1997 and 2017.** *Br J Dermatol.* 2020 Jan;182(1):247-248. [PubMed: 31323695]
21. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.** *Clin Rev Allergy Immunol.* 2018 Feb;54(1):147-176. [PubMed: 29188475]
22. Papp A, Sikora S, Evans M, Song D, Kirchhof M, Miliszewski M, Dutz J. Treatment of toxic epidermal necrolysis by a multidisciplinary team. A review of literature and treatment results. *Burns.* 2018 Jun;44(4):807-815. [PubMed: 29627131]
23. Antoon JW, Goldman JL, Shah SS, Lee B. A Retrospective Cohort Study of the Management and Outcomes of Children Hospitalized with **Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.** *J Allergy Clin Immunol Pract.* 2019 Jan;7(1):244-250.e1. [PMC free article: PMC7014963] [PubMed: 29859332]
24. Antoon JW, Goldman JL, Lee B, Schwartz A. Incidence, outcomes, and resource use in children with **Stevens-Johnson syndrome and toxic epidermal necrolysis.** *Pediatr Dermatol.* 2018 Mar;35(2):182-187. [PubMed: 29315761]

Figures



Erythematous, Purpuric, Macules, targetoid lesions, **Stevens** Johnson Syndrome. Contributed by DermNetNZ



Widespread early morbilliform eruption with flaccid bullae in patient with toxic epidermal necrolysis. Contributed by DermNetNZ



Healing Toxic epidermal necrolysis. Contributed by Dr. Shyam Verma, MBBS, DVD, FRCP, FAAD, Vadodara, India

Copyright © 2020, StatPearls Publishing LLC.

This book is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, duplication, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, a link is provided to the Creative Commons license, and any changes made are indicated.

Bookshelf ID: NBK459323 PMID: 29083827