Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Pediatric Population
A Review

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Abstract: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe dermatologic reactions with mucocutaneous involvement that carry elevated mortality rates. They differ along a spectrum of severity based upon body surface area affected. These conditions, usually caused by a drug or infection, are believed to result from cell-mediated and often drug-specific cytotoxic reactions against keratinocytes, leading to widespread dermal-epidermal detachment. Studies attempting to identify potential curative therapies such as intravenous immune globulin (IVIG) and corticosteroids remain inconclusive. However, improved outcomes have been demonstrated by early withdrawal of offending medications, early transfer to an intensive care unit or burn unit, and aggressive supportive care. Due to the rare incidence of SJS and TEN, its recurrence among survivors hints at future vulnerability for these patients, and notorious offending medications should thus be avoided. This clinical review will highlight the diagnostic and therapeutic challenges posed by SJS and TEN, while emphasizing the need to maintain them high on the emergency medicine physician's differential. The review will also detail the supportive measures to take for preventing the rapid progression of mucocutaneous complications and subsequent sepsis-related mortality.

Key Words: Stevens-Johnson syndrome, toxic epidermal necrolysis, dermatologic reactions, mucocutaneous reactions, ALDEN, SCORTEN, RegiSCAR

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TARGET AUDIENCE

This article is intended for pediatric emergency medicine practitioners.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. Highlight the diagnostic and therapeutic challenges posed by Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
2. Elucidate the dermatologic and mucocutaneous complications of SJS and TEN.
3. Emphasize the importance of early intervention in preventing morbidity and mortality from SJS and TEN.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare yet severe cell-mediated reactions involving extensive epidermal necrosis and detachment, with mucocutaneous complications arising in ~90% of cases.[1] Stevens-Johnson syndrome and TEN differ only along a spectrum of severity based on percentage of body surface involvement (<10% in SJS, 10%c30% in SJS/TEN overlap, 30% in TEN). There are 1 to 7 and 0.4 to 1.5 cases per million people per year for SJS and TEN, respectively,[2–5] with an approximately equal incidence between male and female children.[6] The precise pathophysiology remains unclear, but skin damage is believed to result from cell-mediated and often drug-specific cytotoxic reactions against keratinocytes.

With their initial nonspecific manifestations and high mortality rates, SJS and TEN represent an early, significant diagnostic challenge for emergency medicine practitioners. Although current evidence remains inconclusive for potential curative measures, there are nevertheless critical steps that practitioners may take to decrease morbidity and mortality.

ETIOLOGY

Toxic epidermal necrolysis is triggered by medications or upper respiratory infection in 74% to 94% of cases.[7–9] In children, medications are the most common precipitant of SJS/TEN. Common culprit medications are sulfa antibiotics, phenobarbital, lamotrigine, carbamazepine, and NSAIDs.[10–13] Adverse effects usually present within the first 8 weeks after initiation, with greater risk at higher doses[14] and with rapid introduction.[10,15] In certain study populations, there is a genetic association with HLA-B alleles with lamotrigine-,[16,17] phenytoin-,[17] carbamazepine-,[18] and cold medicine-[19] induced SJS.

Potentially offending drugs can be scored upon 6 parameters by ALDEN (algorithm of drug causality for epidermal necrolysis): time delay from drug administration to reaction onset, probability of drug presence in the body, prior exposure to the same drug regardless of reaction at that time, presence of drug beyond the progression phase, drug notoriety as a cause of SJS/TEN, and the presence or absence of other etiologies. The SJS/TEN symptoms are not clearly attributed to a drug in 20% to 25% of cases (higher for children).[20]

Infection is the second most common precipitant. Main offenders include *Mycoplasma pneumoniae*, cytomegalovirus, herpes virus, and hepatitis A.[21–27] Other predisposing conditions include HIV (100-fold higher risk), malignancy, systemic lupus erythematosus, radiotherapy, collagen vascular disease, UV light, genetics, and underlying immunologic disease.[28–34]

Of note, some studies have shown recurrence of SJS/TEN in survivors. In a retrospective study of 55 cases, 10 children had recurrence between 2 months and 7 years after the first episode, 3 had multiple recurrences, and 1 died.[35] These findings may suggest a long-lasting vulnerability and genetic predisposition for SJS/TEN.

CLINICAL COURSE

Initial manifestations are commonly fever and flu-like symptoms (malaise, myalgias, arthralgias, dysphagia, photophobia, conjunctival itching/burning). Involvement of skin and mucosa arises 1 to 3 days later. Macules with purpuric centers give way to large blisters, vesicles, and bullae. Epidermal detachment with Nikolsky's sign of the bullae (sloughing of the superficial skin layer with slight rubbing pressure) then presents 3 to 5 days later and leaves behind large denuded areas of skin. These signs manifest first on the face and thorax, and then spread outward symmetrically. Distal portions of the arms and legs are relatively spared but palms and soles can be an early site for lesions.[36] Affected areas are tender to touch. Re-epithelization begins 1 week after onset and may take up to 3 weeks, though faster in children.[37]

The large wound areas may cause severe pain, massive fluid and protein loss, electrolyte imbalances, bleeding, evaporative heat loss with subsequent hypothermia, insulin resistance, hypercatabolic state, infection and bacteremia, hypovolemic shock with renal failure, and multiple organ dysfunction.

Of note, the denuded skin predisposes the patient to bacterial superinfection, most commonly by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Sepsis thereby serves as the main cause of death in SJS/TEN cases.

Ophthalmic complications also present in up to 30% of surviving children and adults, occurring within 2 to 6 weeks of drug initiation.[38] These include severe conjunctivitis with purulent discharge, swollen and erythematous eyelids, suppurative keratitis, endophthalmitis, pain, and photophobia. Most concerning is the long-term vision loss that may occur from chronic corneal inflammation.

Other physiologic systems potentially affected include pulmonary (pneumonia, interstitial pneumonitis, acute respiratory distress syndrome, mechanical ventilation in 25%[39] with its associated higher mortality[40]), gastrointestinal (diarrhea, melena, small bowel ulcerations, colonic perforation, small bowel intussusception, stenosis, strictures, stomatitis), vulvovaginitis, and urologic (urethritis).

DIAGNOSIS

The dermatologic manifestations of SJS and TEN may initially appear similar to erythema multiforme (EM), staphylococcal scalded skin syndrome (SSSS), Kawasaki disease (KD), or morbilliform drug reaction. Stevens-Johnson syndrome and TEN carry a higher morbidity and mortality rate in comparison to most other etiologies; therefore, they must remain high on the emergency physician's differential diagnosis. Nevertheless, there exist subtle clinical signs that may help distinguish these dermatologic conditions.

Erythema multiforme is a localized eruption of the skin and mucous membranes compared with the systemic involvement of SJS and TEN. The lesions of EM are peripherally located target lesions with limited epidermal detachment. Notably, despite numerous lesions, EM typically has less than 10% body surface area (BSA) involvement. Mucous membrane involvement is absent or limited to 1 surface, most often the mouth.[41,42]

Staphylococcal scalded skin syndrome is caused by a specific strain of staphylococcus with exfoliative exotoxins. A prodrome of sore throat or purulent conjunctivitis may be present for 48 hours followed by fever, malaise, and skin findings. In young children, SSSS may progress from widespread erythema to blister formation and desquamation, not altogether different from SJS and TEN. However, SSSS lesions are never dusky or purpuric in appearance due to the exotoxin cleavage of intracellular desmoglein 1–mediated connections compared with the epidermal necrosis of SJS and TEN. Staphylococcal scalded skin syndrome blisters commonly affect flexures. Notably, there is no mucous membrane involvement. Both syndromes bullae are Nikolsky sign positive, yet SSSS demonstrates Nikolsky sign on unaffected skin.[43]

The skin and mucous membrane manifestations of KD can be confused for SJS and TEN. Both entities may present with fever; one of the classic criteria for KD is fever for at least 5 days. Rash typically appears within 5 days of fever onset and is often accompanied by desquamation in the perianal or periungal regions. The KD polymorphous exanthema differs in that it is atypical to have bullous or vesicular lesions, more commonly morbilliform rashes, EMs, or erythrodermas are described. Kawasaki disease bilateral conjunctivitis is nonexudative, compared with heavily exudative SJS, and may have pathognomonic limbic sparing. Changes in the lips and oral cavity include a diffusely erythematous oropharynx, strawberry tone, or red fissured lips. Lastly, the remaining typical criteria help differentiate KD including cervical lymphadenopathy and changes in the extremities such as Raynaud phenomena.[44]

Classic morbilliform drug eruptions, also referred to as maculopapular or exanthematous, may be confused with early SJS and TEN. Drug eruptions are pruritic or asymptomatic and importantly lack the characteristic mucosal involvement and skin pain.[45,46] The time course from drug exposure to skin findings differ; morbilliform drug eruptions occur within the 5 to 14 days of exposure[13] compared with SJS and TEN onset within 8 weeks of drug initiation.[15]

Although not often performed and results not available in the emergency department, biopsy can distinguish SJS and TEN from other entities.[47,48] Biopsy shows apoptosis, necrosis, and vacuolization of keratinocytes; dermal-epidermal separation; and lymphocytic infiltration of perivascular regions.

MANAGEMENT

The impact of the emergency physician in the treatment of SJS-TENS is reflected in early detection, withdrawal of offending agents, initiating supportive care, early consultation with specialists (ophthalmology, gynecology), and early intensive care unit (ICU) admission or burn center referral.

Early intervention has a significant effect on morbidity and mortality. Withdrawal of the offending drug has been shown to decrease mortality and improve prognosis. In a 10-year observational study of 113 patients, there was better prognosis (outcome measure: no death before hospital discharge) by approximately 30% (odds ratio, 0.69) for each day before blister development that the drug was withdrawn.[49] In a retrospective study of 19 patients, there was a 21% mortality with early withdrawal versus the predicted mortalities by APACHE II (22%) and SCORTEN (score of toxic epidermal necrosis) (30%).[50] Drugs with long half-lives had increased risk of death (odds ratio, 4.9), independent of drug withdrawal.[49]

Aggressive supportive care is a mainstay of treatment: wound care[51] (wound debridement with biologic dressing,[52–55] moisture-retentive ointments, nonadherent monocrystalline gauze materials, fluidized air beds, silver nitrate or chlorhexidine dressing on infected wounds[53,54]), fluid and electrolyte management[56] (increased water loss from denuded dermis; volume loss approximately one third less than that for burn victims[57]), nutritional support (early oral feeding,[7] high-calorie requirements similar to those in burn injury[58,59]), temperature management (up to 30°C–32°C to prevent excessive caloric expenditures from epidermal loss[1]), ocular care (daily lubrication, daily erythromycin drops to prevent infection, corticosteroid drops to reduce inflammation[60]), pain control, and pulmonary toilet. Although many of these

treatments are managed and more prominent in the inpatient setting, sterile handling, pain control, and fluid management are simple but effective interventions.

Of utmost importance is the monitoring and treatment of superinfections that may cause death by sepsis. This entails sterile handling and antiseptic solutions. Signs for which to monitor include skin lesion changes, increased quantity of cultured bacteria, sudden temperature decreases, or general deterioration. Prophylactic antibiotics are not indicated, as these can cause emergence of resistant bacteria and negatively impact survival.[61]

The SCORTEN scale for SJS/TEN triage and prognosis[62] has been validated for adults and children combined on days 1 and 3 of hospitalization, though not yet so for children alone.[63,64] Independent prognostic factors are age older than 40 years, malignancy, BSA detached greater than 10%, heart rate of more than 120 beats per minute, urea level greater than 10 mmol/L, glucose level greater than 14 mmol/L, and bicarbonate level less than 20 mmol/L. Transfer to nonspecialized wards is advocated with limited skin involvement, SCORTEN score 0 to 1, and non–rapidly progressive disease.[65] Some advocate that the transfer from burn care centers to ICU or burn unit (due to similar management strategies) is recommended with more severe disease with SCORTEN score of 2 or higher.[65]

A retrospective review of 199 patients showed mortality of 32% with early ICU/burn unit transfer versus 51% with transfer after 1 week.[66] Longer hospital stays may occur if transfer to the burn unit takes place after 1 week.[67] Emphasizing the need for aggressive emergency department supportive care, other negative prognostic factors include hypernatremia,[68] increased serum urea nitrogen, neutropenia, thrombocytopenia, visceral involvement, and delayed presentation.[8,61,69]

Definitive evidence is currently lacking for potential curative therapies, the most promising being IVIG[56,70–73] and corticosteroids.[74–80] There exist very few randomized prospective trials due to rarity of the condition and ethical considerations. One such study in children showed a shorter fever duration with the use of methylprednisolone versus supportive care alone.[77] Overall, studies for IVIG and corticosteroids have shown minimal standardization for medication dosing, treatment duration, and outcome measures, among others. Results have also varied for time to skin healing, mortality rates, and hospitalization duration, among others. Data in children are particularly conflicting.[81,82] There is therefore no curative therapeutic intervention that can be definitively recommended at this time.

Reflecting the severity of disease and need for prompt and appropriate intervention, the large RegiSCAR study demonstrated 10% and more than 30% mortality for SJS and TEN, respectively. It showed 23% mortality at 6 weeks and 34% at 1 year (lower for children). Mortality was slightly lower when a drug was identified as the precipitating cause. Within 90 days, the major prognostic factor for death was disease severity. Beyond 90 days, the prognostic factors were serious comorbidities and age. Major causes of death were sepsis, acute respiratory distress syndrome, and multisystem organ failure.[83]

CONCLUSIONS

Stevens-Johnson syndrome and TEN present initially with nonspecific dermatologic and mucocutaneous manifestations. As the precise pathogenesis by which drugs and infections cause these symptoms remains unclear, strong conclusive evidence is correspondingly lacking for potentially curative measures such as IVIG and corticosteroids. Especially without proper aggressive supportive interventions, SJS and TEN progress rapidly and produce high mortality rates. Therefore, these conditions represent a significant diagnostic and therapeutic challenge to the emergency physician.

Emergency department physicians must be on guard for new, seemingly nontriggered alerting signs such as skin tenderness, blistering, mucositis, and fever. If such early signs are present, physicians should at least inquire whether "notorious" drugs (sulfonamide antibiotics, phenobarbital, lamotrigine, carbamazepine, NSAIDs, allopurinol) were initiated within the past 2 months. All nonessential drugs must be withdrawn immediately due to evidence supporting improved outcomes.

Aggressive supportive management has also been shown to improve outcomes, so physicians should strongly consider transfer to an ICU or burn unit. An ophthalmology consult must also be initiated early to prevent common and long-lasting sequelae.

With sepsis being the main contributor to mortality, physicians must also monitor for superinfection by such signs as visible changes in skin lesions, increased quantity of cultured bacteria, sudden temperature decrease, and general deterioration. Lastly, SJS/TEN is quite rare and thus, its recurrence suggests there may be future vulnerability for such at-risk individuals. Surviving patients and their families should be educated to avoid offending medications and their analogs.

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CME EXAM
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CME EXAMINATION
July 2016

Please mark your answers on the ANSWER SHEET.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Pediatric Population: A Review, *Alerhand et al.*

1. A parent brings her 8-year-old son to the emergency department, describing a 2-day onset of seemingly nontriggered skin rash. She points to several target-shaped erythematous lesions on the dorsum of his hands, as well as mild irritation of his gums. The patient is in no distress and has no other complaints. Which is the most likely diagnosis?
   A. Staphylococcal scalded skin syndrome
   B. Erythema multiforme
   C. Stevens-Johnson syndrome
   D. Drug phototoxicity

2. When using ALDEN to assess a drug's role in triggering SJS or TEN, which of the following does not make the drug a more likely culprit?
   A. Minimal time delay from drug administration to reaction onset
   B. Absence of other etiologies
   C. Drug notoriety as a cause of SJS or TEN
   D. Elevated measured serum level of drug

3. A 5-year-old girl with early skin desquamation and fever is admitted to the pediatric ICU. Her medical team suspects SJS and seeks to examine a skin biopsy for confirmation. Which biopsy finding would not support their leading diagnosis?
   A. Nuclear hyperproliferation within keratinocytes
   B. Lymphocytic infiltration of perivascular regions
   C. Dermal-epidermal separation
   D. Keratinocyte apoptosis

4. A pediatric ICU resident arrives for her shift and receives sign-out on a child with TEN confirmed by skin biopsy. Over the 6-day hospital course, the patient has been receiving intravenous fluids, attentive skin care, ophthalmologic consultation, and intensive nutritional support. Given the patient's poor condition and continued deterioration, the medical team recently decided to attempt a trial of corticosteroids. What potential cause of death would be most likely in this patient?
   A. Renal failure
   B. Decreased immune response
   C. Respiratory arrest
   D. Sepsis

5. A well-appearing 4-year-old child is being prepared for hospital discharge after surviving a 7-day hospital stay for SJS. His mother expresses her concern that her child's symptoms may "suddenly return again for no reason." What are the most appropriate discharge instructions for the physician to provide?
   A. Administer oral Benadryl immediately if symptoms recur.
   B. Continually maintain overhydration to prevent vulnerability to SJS and TEN.
   C. Avoid notorious medications known to cause SJS and TEN.
   D. Having already developed SJS, the patient now carries immunity against it.

ANSWER SHEET FOR THE *PEDIATRIC EMERGENCY CARE* CME PROGRAM EXAM July 2016

Please answer the questions on page 477 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____

Street Address _____

City/State/Zip _____

Daytime Phone _____

Specialty _____

1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

Your completion of this activity includes evaluating them. Please respond to the following questions below.

Please rate this activity (1 - minimally, 5 - completely)	1	2	3	4	5
Was effective in meeting the educational objectives	○	○	○	○	○
Was appropriately evidence-based	○	○	○	○	○
Was relevant to my practice	○	○	○	○	○

Please rate your ability to achieve the following objectives, both before this activity and after it:
1 (minimally) to 5 (completely)

	Pre					Post				
	1	2	3	4	5	1	2	3	4	5
1. Highlight the diagnostic and therapeutic challenges posed by Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).	○	○	○	○	○	○	○	○	○	○
2. Elucidate the dermatologic and mucocutaneous complications of SJS and TEN.	○	○	○	○	○	○	○	○	○	○
3. Emphasize the importance of early intervention in preventing morbidity and mortality from SJS and TEN.	○	○	○	○	○	○	○	○	○	○

How many of your patients are likely to be impacted by what you learned from these activities?
within the next 6 months? (1 - definitely will not change, 5 - definitely will change)

○ <20% ○ 20%–40% ○ 40%–60% ○ 60%–80% ○ >80%

Do you expect that these activities will help you improve your skill or judgment	1	2	3	4	5
	○	○	○	○	○

How will you apply what you learned from these activities (mark all that apply):

- In diagnosing patients ○
- In monitoring patients ○
- In educating students and colleagues ○
- As part of a quality or peformance improvement project ○
- For maintenance of board certification ○
- To consider enrolling patients in clinical trials ○
- In making treatment decisions ○
- As a foundation to learn more ○
- In educating patients and their caregivers ○
- To confirm current practice ○
- For maintenance of licensure ○

Other _____

Please list at least one strategy you learned from this activity that you will apply in practice:

How committed are you to applying these activities to your practice in the ways you indicated above? (1 - minimally, 5 - completely)	1	2	3	4	5
	○	○	○	○	○

Did you perceive any bias for or against any commercial products or devices?	Yes	No
	○	○

If yes, please explain:

How long did it take you to complete these activities? _____ hours _____ minutes

What are your biggest clinical challenges related to pediatric emergency care?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

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