



# Stevens Johnson Syndrome – “Steven Who? And Why I Should Care About His Johnson?”

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## Case

### Sick Patient with a Rash

#### Pertinent History

A 22-year-old female presents with a diffuse rash including desquamation of mucous membranes and lips. She was recently started on lamotrigine (Lamictal®) at an initial dose of 100 mg, Clonazepam 0.5 mg, and Doxycycline approximately 2 weeks ago. She reports that the rash began 3 days prior to presentation. She was seen at an outside hospital and was diagnosed with hand, foot, and mouth disease and treated with supportive care. Her rash continued to worsen, spreading to her trunk, groin, and mouth. She is unable to tolerate drinking liquids due to severe pain. She describes the rash on her body as pruritic. She has no past medical history of skin disorders.

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**PMH** Seizures, Anxiety Disorder

**Meds** Lamotrigine, Clonazepam, Doxycycline

### **Pertinent Physical Exam**

- Blood pressure 130/70, pulse 116, temperature 99.9 °F (37.7 °C), RR 16, SpO<sub>2</sub> 99%.

Except as noted below, the findings of a complete physical exam are within normal limits.

- Mouth: Multiple lesions in mouth, yellow crusting and desquamation of mucous membranes of lips, tongue, and buccal mucosa.
- Eyes: Conjunctival injection present bilaterally.
- Cardiovascular: Tachycardia present, regular rhythms, no murmurs.
- GU: Vaginal mucosal lesions noted.
- Skin: Skin is warm and dry. No erythema. Diffuse maculo papular rash with pink papules coalescing into plaques with superimposed vesicles and bullae.

### **ED Management**

The most likely diagnoses considered at the time of presentation were Erythema Multiforme Major and Stevens-Johnson Syndrome. Dermatology was consulted and evaluated the patient at the bedside. Based on the patient's clinical history and physical exam they felt the patient was more likely exhibiting Erythema Multiforme Major. The patient was admitted for further management and workup.

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### **Learning Points**

#### **Priming Questions**

1. What is the difference between Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis?
2. What are specific causes and risk factors of Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis that I can look for in a patient's history?
3. What is the treatment and disposition of Stevens-Johnson/Toxic Epidermal Necrolysis?

## Introduction/Background

1. Erythema Multiforme (EM) versus Stevens-Johnson Syndrome (SJS) versus Toxic Epidermal Necrolysis (TEN) is a confusing set of definitions. The definition has undergone revision over the years such that the final consensus definition divides the entities into two spectra [1].
  - Erythema Multiforme
    - Erythema Multiforme Minor: Typically presents with target lesions, however early on initial lesions may be raised erythematous papules. Typical target lesions contain three concentric zones. Lesions are most commonly on extensor surfaces of acral extremities (finger, hands, toes, feet) (Image 1) and spread centripetal [2, 3].
    - Erythema Multiforme Major: Combines the findings of EM minor with the involvement of one or more mucosal membranes. In one study, 63% of patients with EM had mucosal involvement [4]. Also by definition EM cannot have the detachment of skin greater than 10% of total body surface area (TBSA) [5].

### Erythema Multiforme Minor of the Hand



James Heilman, MD ([https://commons.wikimedia.org/wiki/File: Erythema\\_multiforme\\_minor\\_of\\_the\\_hand.jpg](https://commons.wikimedia.org/wiki/File:Erythema_multiforme_minor_of_the_hand.jpg)), “Erythema multiforme minor of the hand”, <https://creativecommons.org/licenses/by-sa/3.0/legalcode>

- SJS/TEN.
  - SJS/TEN are considered to be a single entity, just along different ends of the severity spectrum: When <10% of TBSA is involved, the disease is labeled as SJS. If >30% of TBSA is involved, it is called TEN. Between 10 and 30%, there is overlap between the two labels [6, 7].
  - Lesions predominate on the trunk and face and spread symmetrically to other areas of the body and the extremities (Image 2). This spectrum typically presents with diffuse erythema or purpuric macules and blistering. Ninety percent of the time one or more mucous membrane is affected with erosions (Image 3) [8, 9]. As the disease progresses, bullae form and coalesce, forming flaccid blisters with full thickness epidermal necrosis.

### Stevens-Johnson Syndrome



Dr. Thomas Habib ([https://commons.wikimedia.org/wiki/File:Stevens-johnson\\_syndrome.jpg](https://commons.wikimedia.org/wiki/File:Stevens-johnson_syndrome.jpg)), "Stevens-johnson-syndrome", <https://creativecommons.org/licenses/by-sa/3.0/legalcode>

## Stevens-Johnson Syndrome



James Heilman, MD ([https://commons.wikimedia.org/wiki/File: Mucosal\\_desquamation\\_in\\_a\\_person\\_with\\_Stevens-Johnson\\_syndrome.jpg](https://commons.wikimedia.org/wiki/File:Mucosal_desquamation_in_a_person_with_Stevens-Johnson_syndrome.jpg)), “Mucosal desquamation in a person with Stevens-Johnson syndrome”, <https://creativecommons.org/licenses/by-sa/3.0/legalcode>

2. Ninety percent of cases of EM are thought to be triggered by infection with Herpes Simplex Virus (HSV) being the most commonly identified pathogen [2, 10]. Certain classes of medication, particularly barbiturates, hydantoin, nonsteroidal anti-inflammatory drugs, penicillin's, phenothiazines, and sulfonamides, can also trigger EM [11].
3. The incidence of SJS/TEN is roughly 4–6 cases per million person/year [12, 13]. Mortality is approximately 5% for Stevens-Johnson syndrome, and anywhere from 30–50% for toxic epidermal necrolysis [7]. Approximately 50% of cases of SJS and 80–90% of cases of TEN are drug induced [14]. Mycoplasma pneumonia is likely the second most common cause, particularly in children, though this is somewhat controversial as it also can be the cause of EM [15].

## Physiology/Pathophysiology

1. The pathogenesis of SJS/TEN is not completely understood. It appears that through an unknown mechanism, cytotoxic T cells and natural killer cells begin to attack keratinocytes and cause massive apoptosis [16].
2. By and large, when suspecting possible SJS/TEN in patients and hunting for causes, it is all about the drug history. Certain drugs are more likely to cause SJS/TEN.

- Short-Term Drug Use vs Long-Term Drug Use.
  - The risk of SJS/TEN appears to be largely limited to the first 8 weeks of taking an at-risk medication. While it is possible to develop SJS/TEN after taking an at-risk drug for a longer period of time, it is unlikely [17, 18].
- Lamotrigine (Lamictal®) and SJS/TEN.
  - The patient in this case had been started on Lamotrigine around 2 weeks prior to her presentation to the ED. Seven to ten percent of patients started on Lamotrigine will develop a rash, but only 3 in 1000 will require hospitalization [19]. Rash and other skin conditions are more common in children, so this medication is often reserved for adults [20].
  - Appropriate dosing and dosing adjustment can prevent or decrease the risk of lamotrigine-associated rashes. In adults, the recommended initial dose of lamotrigine alone (in the absence of cytochrome P-450 inhibitors or enhancers) is 25 mg po daily for the first 2 weeks, 50 mg daily during weeks 3 and 4, and then weekly increases of 50–100 mg per day as clinically indicated. The patient in this case was started at 100 mg from day 1.

Drug	Relative risk
TMP/sulfa and other sulfonamide abx	172
Carbamazepine	90
Oxicam-NSAIDS	72
Corticosteroids	54
Phenytoin	53
Allopurinol	52
Phenobarbital	45
Valproic acid	25
Nevirapine	22
Cephalosporins	14
Pantoprazole	18
Tramadol	20
Lamotrigine	14
Sertraline	11
Quinolones	10
Aminopenicillins	6.7

3. There are certain patient risk factors that also make one more prone to develop SJS/TEN.
  - Patients with HIV are reported to have around 100-fold higher risk to develop SJS/TEN [21]. Active malignancy also increases the incidence, particularly hematologic cancers, at an estimate of at least two-fold [12]. High dose and rapid introduction of medications, systemic lupus, and radiation therapy also appear to increase the risk of SJS/TEN as well [22–24].

## Making the Diagnosis

### The Differential – Whoa! That Person Is Sick...and Look at that Rash!!

- Acute Generalized Exanthematous Pustolosis
- Drug Eruption
- Erythema Multiforme
- Erythroderma
- Kawasaki Disease (kids)
- Pemphigus Vulgaris
- Bullous Pemphigoid
- Staph Scalded Skin Syndrome (kids)
- Toxic Shock Syndrome

1. The diagnosis of SJS/TEN in the emergency department will always be a clinical diagnosis. There are no specific labs or imaging that will clinch the diagnosis. The patient’s history, particularly drug history, symptoms leading up to the start of a developing rash, and identifying the rash itself will make up your three components.
  - Typically a prodrome of an influenza-like illness (fever, malaise, headache, cough, and conjunctivitis) develops 1–3 weeks after initiation of drug [25].
  - Skin lesions appear 1–3 days after the prodrome [14]. As discussed above in the introduction, lesions start out as ill-defined coalescing macules with purpuric centers on the face and trunk and spread to extremities and mature into large confluent blisters that undergo epidermal detachment [26].
    - Blistering and epidermal detachment lead to a positive Nikolsky sign (light lateral pressure at what appears to be unaffected skin leads to sloughing) as well as a positive Asboe-Hansen sign (lateral extension of bullae with downward pressure).

### Nikolsky Sign



Source unknown—Public domain images



- Three to five days of sloughing lead to denuded or exposed underlying skin causing extreme pain, massive loss of fluid and protein, bleeding, evaporative heat loss with subsequent hypothermia, and infection.
  - There is also simultaneous mucosal involvement with cutaneous presentation.
    - Oral mucosa and the vermilion border are involved with painful hemorrhagic erosions.
    - Eighty percent of patients also have ocular involvement including pain, photophobia, severe conjunctivitis with discharge, corneal ulceration, and uveitis [27].
2. Particular lab findings are often present though nonspecific, and while seeing these abnormalities can bolster your confidence in your diagnosis of SJS/TEN, there are no labs to hang your hat on.
    - Anemia and lymphopenia are often seen, and neutropenia can be seen as well in a third of patients. Neutropenia in particular is indicative of a worse prognosis. Thrombocytopenia is seen as well but only in 10–20% of patients. Elevated erythrocyte sedimentation rate, mildly elevated serum transaminases, and elevated BUN are also often noted [7].
  3. As with many skin-related disorders, a biopsy can be very helpful and often definitively provide a diagnosis. Due to some skin diseases mimicking SJS/TEN, biopsy can be the only way to confirm the diagnosis. However, in the acute setting of the emergency department, skin biopsies are not going to happen, so the patient must be treated based on clinical judgment.

## Treating the Patient

1. Stop the offending drug! Review medications that are frequently associated with SJS and stop them. While not generally used in the acute phase of illness, there is an algorithm, ALDEN, that has been developed to help define drug causality [28]. However in the ED setting you can stop all medications that seem possible culprits, particularly looking at medications started in the last 8 weeks.
2. Employ anti-shear handling and try to avoid breaking large bullae if you can. Denuded skin leaks serum and becomes coated with necrotic debris. This combined with hemorrhagic crusting acts as an excellent substrate for bacteria leading to infection and possible sepsis, the leading cause of death in SJS/TEN [8].
  - Hold on antibiotics unless you actually think there is a wound infection. Most of these patients will have fevers due to the associated inflammatory response. Pull the trigger if other signs of possible infection including confusion, hypotension, reduced urine output or oxygen saturation, or if an obvious wound infection is present. Be sure to cover for *Staphylococcus* and *Pseudomonas* species with your antibiotic choice [8].
3. Remember that SJS/TEN can involve the mucosa and even the GI tract! Complications of pneumonias, ARDS, small bowel ulcers and colonic perforations have been reported [29–31].
4. The wounds from SJS/TEN can be thought of as similar to extensive burns. Treatment in a burn-unit setting is indicated and reduces mortality, particularly



with TEN [32–34]. There are some important differences between SJS/TEN and burns!

- In SJS/TEN, the extent of skin damage is limited to the superficial dermal layers of the skin.
  - SJS/TEN has less fluid, electrolyte and energy requirements. 2 ml/kg × % affected TBSA of fluid is usually adequate to maintain urine output and blood pressure in the normal range [35]. Burns usually require more fluid resuscitation [36].
  - TEN often involves the GI tract, respiratory system, and the ocular system in addition to the skin. Significant sequelae in these organ systems are possible.
5. As there is frequent involvement of ocular surfaces and genital areas, often multiple specialties are involved in the inpatient management including ophthalmology and gynecology.
  6. IVIG, steroids, and cyclosporin have all been used in the treatment of SJS/TEN with mixed results [37]. These may be started in consultation with other services or the admitting team. In the ED, initial treatment is mostly supportive care.
  7. Prognosis.
    - SCORTEN scoring system (SCORE of Toxic Epidermal Necrosis) has been developed that predicts the probability of hospital mortality [38]. There are seven parameters including age, malignancy, heart rate, TBSA, serum urea, glucose, and bicarbonate. Each positive is 1 point for a total of 7 points. The higher the score the greater mortality.

Scorten		
Risk factor	0 Points	1 Point
Age	<40 years	>40 years
Associated malignancy	No	Yes
Heart rate	<120	>120
Serum BUN (mg/dL)	<28	>28
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<252	>252

*Risk factors and mortality rate: 0–1 (3.2%), 2 (12.1%), 3 (35.3%), 4 (58.3%), 5 or more (>90%)*

## Case Conclusion

A punch biopsy was performed that was inconclusive: Erythema Multiforme Major versus Stevens-Johnson Syndrome. The patient was treated with one dose of IVIG which was not continued due to poor patient tolerance. The patient gradually improved with supportive care.

## Discussion

These observations are made based on this writer’s experience with SJS/TEN.

As with all emergency department presentations, these patients can be sick or not sick. There are so many skin conditions and diseases out there, you are not going to

diagnosis everyone. But look at the whole picture to determine whether you need a more thorough workup or need to get consultants involved. What are the vitals? How does the patient look? Are they septic? The fundamentals of emergency medicine will help guide your management.

For any patient with a rash that gives you a concern for SJS/TEN, get that good drug history. Luckily, the data show that there are certain drugs to look out for, and they were likely started in the last few weeks to a month. If they have one of the “likely suspects,” then start becoming more concerned.

When in doubt, ask for help and ask for it early. If you see a rash on a patient that makes your skin hurt, lots of scattered bullae/open wounds, get those burn and/or dermatology consults in early. These patients experience a great deal of insensible water loss; they need early fluids, wound care, and admission.

And one more thing, when starting a new medication on a patient, follow the directions!

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## Pattern Recognition

### Steven-Johnson Syndrome/Toxic Epidermal Necrolysis

- Prodrome of flu-like illness
- Painful rapidly progressing targetoid rash
- Nikolsky Sign
- Mucosal involvement
- Drug of notoriety recently started

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Colin Kaide: Callibra, Inc.-Discharge 123 medical software company. Medical Advisory Board Portola Pharmaceuticals. I have no relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product.

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