# STEVENS JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS

**By: GREG JONES**

# Contents

# ~About the Author~

Having practiced for over 35 years, Greg Jones is the founder of Greg Jones Law and is licensed to practice law in North Carolina, South Carolina, Georgia, and Texas. He has offices in both North Carolina and Puerto Rico, often associating with other top trial lawyers across the nation to get his clients the best representation possible. He focuses his practice on plaintiff personal injury litigation involving product liability claims against pharmaceuticals and medical device manufacturers. He is an active member of many local, state, and national trial lawyers associations. He frequently travels to conferences and lectures, where he consults with other attorneys regarding personal injury representation.

One of Greg's main areas of practice is helping victims of Stevens-Johnson Syndrome. For over 15 years, Greg has seen thousands and thousands of SJS claims being caused by

common over the counter and prescription drugs. He, along with other partner firms, has successfully collected millions for this devasting condition.

Greg has received various honors and recognition's over the years, including his listings in Super Lawyers, Top 100 Trial Lawyers, Who's Who in American Law, Who's Who in America, Best Attorneys of America, Top Lawyers in North Carolina, and Nation's Top One Percent by the National Association of Distinguished Counsel.

He has also been listed as a Top-Rated Lawyer and received the Client Distinction Award by Martindale Hubbell, 10 Best in Client Satisfaction for 2015 by the American Institute of Personal Injury Attorneys. Recently his firm was featured as North Carolina's Most Influential Law Firm of 2016 by Corporate Vision. Greg has been seen in many publications and on television, including the Wall Street Journal, USA Today, *Inc.*, ABC, NBC, CBS, Fox, and many more.

- Super Lawyers, 2009
- "2007-20202 Top 100 Trial Lawyers", The American Trial Lawyers Association
- Who's Who in American Law
- Best Attorneys of America
- Top Lawyers in North Carolina
- North Carolina's Most Influential Law Firm of 2016

This book about SJS speaks volumes about his field expertise and how he has helped people with SJS. He is one of the most renowned personal injury attorneys who know every detail and legal aspect of SJS and is always determined to get the best solution possible for his clients.

# Stevens-Johnson Syndrome

## Chapter 1- What is Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) is a rare and serious disorder affecting the skin and mucous membrane. It is caused by a reaction to certain medicines and often appears as flu-like symptoms followed by rash and blistering of the skin across large areas of the body. SJS is a serious adverse drug reaction that can be fatal. If you suspect you are suffering from SJS, immediately contact a medical professional for help.

The first case of the stevens-Johnson syndrome was first recorded in 1922, described by two American pediatricians named Albert Mason Stevens and Frank Chambliss Johnson. They reported the cases of 2 boys of age 7 and 8 years old with a history of an extraordinary, generalized eruption with continued fever, having inflamed oral cavity, and severe pus

discharging conjunctivitis. Primary care physicians misdiagnosed both cases under the assumption of hemorrhagic measles.

Initially, Stevens-Johnson syndrome was considered synonymous with erythema multiform (EM) as both have similar initial symptoms. Erythema Multiform has two forms: minor and major. The minor (EM) is mild and often goes away in a few weeks. The EM major is rare, but it is potentially severe, and it can be life-threatening.

## ~Signs of SJS? ~

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**Acute phase (unspecific)**

It starts in the three weeks of the administration of the drug, and the frequent symptoms are as follows:

- Fever of 100.4 F and above

- A sore mouth and throat
- Malaise
- Fatigue
- Burning eyes
- Headache
- Joint pain
- Cough

These are early symptoms. When the rash appears, it may look like an arrow target, i.e., darker in the center with lighter edges.

As the intensity of the disorder increase, the symptoms get severe; the cutaneous phase begins with signs like:

- Widespread unexplained pain in the skin
- A spreading red or purplish rash. It isn't itchy, but it spreads in an hour or days.

- Eruptions on the skin, the mucous membrane of the mouth, nose, eyes, and genitals. These blisters are painful.
- Shedding of the skin within days after the blisters form.
- Facial swelling, crusty lips are the features of SJS.
- Purulent conjunctivitis
- There is marked erythema of the skin that leads to papules, vesicles, and necrosis.
- The severity of symptoms at the mouth, Gastrointestinal tract, genitals are associated with heavy bleeding, scarring, and other long-term complications.

*Nikolsky sign* is always present in SJS. The Nikolsky sign is a skin finding in which the top layer of the skin comes off when the lower layer is rubbed. The skin appears as a burn or patch resulting from a thermal injury.

# ~Toxic Epidermal Necrolysis~

TEN (Toxic epidermal necrolysis) is the SJS spectrum's extreme side.

**What is toxic epidermal necrolysis (TEN)?**

This is the severe form of Stevens Johnsons Syndrome resulting due to an adverse reaction to a drug. The skin cells in the epidermis die off and result in the skin shedding, exposing the mesoderm. It occurs in 0.5-1.4 per million in a year, and the death rate is 25-50%. The mean age for TEN is 42.5, but the incidence increases with age.

It is considered the extreme side of the spectrum as it leaves the skin exposed to infections and may drain out the body fluids. The only difference between SJS and TEN is the amount of epidermal detachment. In 74% to 90% of cases of TEN, it is triggered by a medicine or upper respiratory tract infection. The epidermal detachment in SJS is 10% of the body surface area, but it goes up to 30% in TEN.

The targeted areas of the symptoms are the mouth. They first appear on the face and thorax and spreads outward symmetrically. The ophthalmic symptoms initiate within 2 to six weeks of drug administration, and they are common in 30% of the cases. People affected with SJS/TEN also develop a pulmonary infection, pneumonia, acute respiratory distress syndrome, and 25% of the cases appear to be of mechanical ventilation associated with death.

The SJS syndrome and TEN are differentiated based on skin involvement. The necrotic skin that is already detached (blisters and eruptions) or the detachable skin in the case of the Nikolsky sign are some of the deciding factors if a person has the SJS or TEN.

# Chapter 2: Reasons behind SJS/TEN

**SJS and TEN are primarily, if not solely, caused by drugs.**

It has been reported in burn surgery and dermatology textbooks, and other textbooks on the subject of SJS and TEN, that up to 80-95% of TEN cases are caused by drugs, with only 5% or less described as having idiopathic etiology. Drugs are responsible for the vast majority of cases of both SJS and TEN[1, 2]

Certain medications react and lead to the development of this syndrome. In the beginning, it might not be that hazardous, but as the symptoms worsen, the pain and agony are hard to

[1] Roujeau, JC, Toxicology, "Clinical Heterogeneity of drug hypersensitivity," Vol. 209; pp. 123-129, (2005)
[2] Roujeau, JC, et al., Am J Clin Dermatol., "Differential Diagnosis of Severe Cutaneous Drug Eruptions," Vol. 4(8); pp. 561-572, (2003**)**

see. Medications are the most common cause of SJS/TEN, and the common medicines that can trigger SJS include sulfa antibiotics, phenobarbital (used to treat insomnia anxiety and some seizures), carbamazepine (it controls epileptic seizer, reduces pain in diabetic patients resulting due to peripheral nephropathy), and NSAIDs.

NSAIDs are common over the counter pain and inflammation drugs.

There are six parameters ALDEN (algorithm for drug causality for epidermal necrolysis) to categorize the potential drugs. The six parameters are:

1. The time delay from drug administration to reaction onset
2. Probability of drug presence in the body or you can also call it the bioavailability of the drug
3. Prior exposure to the same drug regardless of the reaction

4. Availability of drugs beyond the progression phase of diseases.
5. Drug notoriety as a cause of SJS/TEN
6. Presence or absence of other etiologies

The medications that commonly cause SJS are anticonvulsants, NSAIDs, corticosteroids, antidepressants, Nevirapine, and allopurinol.

Other than immunologic and pharmaceutical triggers, genetic predisposition can play a significant role in the development of SJS. Various studies prove that genetic changes are found in the increased risk of the SJS/TEN. The genetic changes that alter the gene makeup are associated with the HLA-B gene. As mentioned, that SJS is mostly caused by immunologic triggers where the T cells are involved in the production of granulysin; the HLA-B genes belong to the human leukocyte antigen family. People with active HLA-B gene are prone to SJS/TEN. This activation is most commonly found in Asian descendants. The FDA suggests a genetic test before the administration of carbamazepine in the Asian population.

Many studies report that infectious diseases are the second triggers for the SJS manifestation. Infections like mycoplasma pneumonia are prevalent in the pediatric population.

The M. pneumonia is a common respiratory pathogen known for causing various respiratory issues ranging from a mild respiratory tract infection to severe atypical pneumonia. It is believed that over 200 medications are associated with SJS development; some of them are strongly linked to others. The medicines responsible for causing falls under a very broad range, but studies report that epileptic drugs and NSAIDs are the most common ones leading to its development.

The other suspected drugs like allopurinol, NSAIDs, and anticonvulsants are still at a higher risk for SJS development. Allopurinol is reported to have a higher tendency to cause SJS than others, reported in various studies.

The onset of reaction or the symptoms is recorded in the latency period when a medicine starts reacting. It is usually less than four weeks for many medicines found to cause SJS, but for carbamazepine, it is 15 days, 24 days for phenytoin, 17 for phenobarbital, and 20 for allopurinol. The latency

period is extended in medicines not identified or associated with SJS/TEN, such as valproic acid.

Other than these identified medicines to induce SJS/TEN, many others can also cause the onset of SJS if there is some underlying immunologic disorder or gene predisposition.

# Chapter 3: Treatment of SJS/TEN

From different studies, it has been researched that certain medicines contribute to the onset of SJS/TEN. There are genetic causes to this disease, but the major role lies on the part of medicine. Knowing that some specific medicines cause SJS/TEN, our first line of action will stop the causative medicine. The severity of symptoms of SJS or toxic epidermal necrolysis determines the length of the treatment and its effectiveness.

Many studies have researched different treatments for SJS/Ten. Based on the severity of the symptoms and the body surface area's coverage, the chances of morbidity and mortality are high in many cases. This chapter will cover the different researches and proven treatments for this disease in detail.

## Early management

With SJS and TEN symptoms being identified, the early management requires a prompt action of initiating the causative drug withdrawal. There is a high risk of increased morbidity and mortality among the SJS patients or toxic epidermal necrolysis in a late withdrawal. Researches report that medicines with short-eliminated half-lives when withdrawn upon diseases' inset resulted in lower death rates. The withdrawal effects were found successful upon the immediate withdrawal of the drug upon the appearance of blisters or erosion. However, it is found that during with longer eliminated half-lives had no results.

Another effective early management measure is to go for fluid replacement initiated by using macromolecules and saline solutions.

Transferring the patients to an intensive care unit or burn unit can reduce the risk of infection, mortality rate, and length of hospitalization.

## General principles of symptomatic management

The major treatments for SJS/TEN are the same as those for burns. The experience of the burn unit proves essential in treating severe symptoms. The following measures can help in managing the symptomatic symptoms.

- Providing environmental temperature control
- Creating a sterile field
- Avoiding the use of adhesive materials
- Careful and aseptic handling
- Maintain peripheral venous access distant from the affected areas (ensuring no central line when possible)
- Initiating oral nutrition through a nasogastric tube
- Prevention of stress ulcers
- Administration of pain medication
- Controlling anxiety

All these measures are essential in managing the symptoms based on their severity.

While treating the symptoms, it is essential to bear in mind that SJS symptoms and burn symptoms are not similar. They appear to be the same, but they are the opposite. The major difference between the symptoms is the time duration. For instance, burn happens for a short time, and it does not spread but SJS symptoms of epidermal detachment stay over a long time with a tendency to spread.

The differences between the symptoms of SJS and urn require specified management. Subcutaneous edema is very uncommon to develop in SJS, and therefore it requires two-third or three-fourth of the fluids compared to the burns.

## Systematic management

The studies and research have been reported that SJS and TEN confines to the body surface area or the epidermis and attack the internal organs and systems. The treatment measures vary as following.

Pulmonary complications are severe in patients with SJS and TEN. Pulmonary care includes aerosols, bronchial aspirations, and physiotherapy. If trachea and bronchi are involved, then it is advised to use intubation and mechanical ventilation as a necessity.

Initiating early and continuous enteral nutrition is essential to reduce the risk of stress ulcer developments, bacterial translocation, and enterogenic infections. It also allows the early discontinuation of venous lines.

Profound hypophosphatemia is common in patients with severe complications of SJS/TEN that can result in muscular dysfunction and regulation of glycemia. Muscular

dysfunction can be prevented by monitoring and correcting the phosphate levels in the body whenever necessary. The bacterial sampling of the skin lesions is performed on the first day and every 48 hours. The epidermal detachment exposes the skins to multiple microorganisms with a high risk of infection. Antibiotic treatment is determined based on the number of bacteria cultured from the skin and the sudden drop in body temperature.

It is vital to increase the environmental temperature from 30- to 32 degrees centigrade. Doing so prevents the caloric losses from the skin, and it also reduces the shivering and stress resulting from the caloric loss. Antiseptic baths with an increased temperature of 38C can limit the body's heat loss that may fluctuate the homeostasis.

Thromboembolism is another major cause of morbidity and death in SJS/TEN. It happens due to an obstruction in the blood vessels and can be resolved by giving the patient anticoagulation treatment.

The anticoagulation treatment involves the effective use of Heparin during hospitalization. It also requires to monitor the amount of bleeding as Heparin is a blood thinner that can result in excessive bleeding from the skin. It rarely gets to the need for blood transfusion in case of an open wound. Another common form of bleeding in SJS is gastric bleeding that can be treated by using antacids. Patients with SJS are not only suffering physically but emotionally. Seeing their skin being detached and inner layer exposed, bearing excruciating pain can take a toll on their emotional and mental health. Providing emotional and psychiatric support to SJS victims is vital to help them cope with their situation.

## Medical Management of SJS/TEN

### Steroids

The role of steroids in SJS/TEN treatment is still debated to date, but many cases have revealed the postive effect of steroids as a treatment model for SJS/TEN in some cases.

The majority of cases are ascribed to the antibody-mediated cell-dependent cytotoxicity type of hypersensitivity to the steroids. As the syndrome itself results from certain drugs and medication, in patients with hypersensitivity to steroids, this treatment mode is not preferred.

The corticosteroids have been found essential in treating the SJS/TEN, and the doses can be increased depending on the severity and speed of recovery.

**Immunoglobulins**

Immunoglobulins are a class of proteins found in the serum and cells of the immune system and serve as antibodies. Many studies have found some beneficial effects of administering intravenous immunoglobulins to patients with SJS/TEN. A survey reveals that cyclosporine is the second most commonly used immunomodulator in SJS/TEN treatment.

Cyclosporine specifically targets granulysin, responsible for the mediation of the keratinocyte apoptosis leading to disease progression. A treatment trial was conducted on 29 patients with the initial administration of 3mg/kg/day of cyclosporine for ten days and later tapered down to a month's use. The trial study reported the stabilization of epidermal detachment with the use of cyclosporine.

Using cyclosporine as an immunomodulator to treat SJS/TEN have proven to be one of the effective treatments so far. It is associated with stabilizing the epidermal detachment, reduced mortality rate, and reduced hospital stay.

Many studies claim cyclosporine to be a safer and preferred treatment for SJS/TEN compared to intravenous immunoglobulin. Patients receiving treatment through intravenous immunoglobulins are prone to higher mortality than those receiving cyclosporine.

# Chapter 4: Legal remedies for SJS

Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis is a potentially life-threatening drug caused by various drugs. As discussed earlier in this book about the medicines that have been found causative in this disorder. The class fo drugs that are responsible for causing the SJS/TEN are as follows:

- Antibiotics like penicillin, amoxicillin, ampicillin
- Sulfa drugs and other drugs that include sulfa like Bactrim
- Acne medications like tetracycline and Accutane
- Cold medications and pain-relieving drugs acetaminophen (Tylenol), NSAIDs like ibuprofen (Advil/Motrin), and Tamiflu and Lamictal.
- Medications used for treating seizures like Tegretol, Dilantin, and Depakote
- Gout medications like Allopurinol.

When we consult a doctor for an ailment, we intend to get the treatment to recover from the disease instead of getting another due to a medication reaction. Seeing your loved one or yourself suffering from the painful and severe symptoms of the SJS. The treatments of SJS can slow down the progression, but the syndrome cannot completely vanish.

Hundreds of lawsuits have been filed against pharmaceutical manufacturers as they were aware of the risk of developing SJS as a result of medication. Still, they inadequately warned the users. Many people are unaware of SJS/TEN as the occurrence ratio is way too low; also, the common over the counter drugs do not have any warning or intimation telling the user about the development of SJS/TEN.

If you are sure that you have developed SJS as an allergic reaction to a medicine. In that case, you are entitled to compensation by filing a lawsuit against the medicine manufacturer. SJS attorneys or personal injury attorneys are actively investigating the cases of SJS/TEN for failing to

warn the medication users about the disorder. Many drugs associated with SJS/TEN are with an inadequate warning on the product label, and the manufacturers can be held liable for that through a lawsuit.

From 1969 to 2012, there have been reported 107 cases of the SJS/TEN resulting from acetaminophen. Out of those 107 cases, 12 people died and 67 were hospitalized and got successfully treated. After these reported reactions, the FDA started to add warning labels to the product label of medicines associated with the SJS/TEN.

A report from the FDA states that the appearance of SJS/TEN symptoms usually occurs within 28 days, but it can also appear later. The report also highlighted that anyone who develops these disorders after taking acetaminophen should immediately stop the medicine and visit a doctor or emergency room.

The FDA ensures that such warning shall be visible on the product labels, but if they are not there, the manufacturer can be held accountable through a lawsuit. In 2012 or 2013, the US Court of Appeal held a $ 21.06 million verdict against a pharmaceutical company as NSAID manufactured by them for causing SJS/TEN. It caused permanent near blindness and skin burns over about 60% of the body. The woman filed the lawsuit.

The mortality rate in SJS/TEN is high besides its rare occurrence; hence plaintiffs can file the lawsuit against the pharmaceutical companies. Personal injury lawyers can claim compensation from the patients suffering from the SJS/TEN.

The Greg Jones law firm has been assisting the patient suffering from SJS/TEN for the past thirty years. They offer services catering to different medicines for children and adults alike. Their firm has been dealing with the compensation cases for the following medicine.

- Bextra
- Children's Advil
- Children's Tylenol
- Children's Motrin
- Daypro
- Diclofenac
- Dilantin
- Diflucan
- Dolobid
- Feldene
- Flagyl
- Lamictal
- Naprosyn
- Neurontin
- Relafen
- Remicade

The medicine as mentioned above has been associated with the development of SJS/TEN, and Greg Jones law firm has

been assisting people in filing lawsuits against the manufactures for not warning their users regarding SJS/TEN.

## Definitions

***Macules**: It is a flat, discolored, and distinct area of skin, usually less than 1 cm in length, does not change its texture or thickness.*

***Epidermal detachment:** the epidermis is the outermost layer of our skin that tends to shed due to any reason. The epidermal detachment refers to the shedding of the skin due to SJS symptoms.*

***Oral lesions**: The oral lesions are ulcers that appear in the mucous membrane of the oral cavity.*

***Necrolysis:** It is a severe blistering rash that exposes the inner red layer by shedding the epidermis.*

***Conjunctivitis:** It is also known as "Pink Eye." It is the inflammation of the transparent membrane of the eye covering the eyelid and eyeball.*

***Hypophosphatemia:*** *It is an electrolyte disorder where the body experiences extremely low phosphate levels in the blood leading to difficulty in breathing, weakness, and loss of appetite.*

***Thromboembolism*** *refers to a blood vessel's obstruction due to a blood clot dislodged from another site during circulation.*

***Immunoglobulin:*** *It is a class of proteins found in the serum and cells of the immune system and serves as antibodies.*