Stevens-Johnson Syndrome-A life threatening skin disorder: A review

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Abstract

Stevens Johnson Syndrome (SJS), and TENS (Toxic Epidermal Necrolysis Syndrome) another form of SJS—are severe adverse reactions to medication. Adverse drug reactions (ADR’s) account for approximately 150,000 deaths per year in the U.S. alone, making drug reactions the fourth leading cause of death in the United States. SJS is one of the most debilitating ADR’s recognized. It was first discovered in 1922 by pediatricians A.M. Stevens and F.C. Johnson after diagnosing a child with severe ocular and oral involvement to a drug reaction. Almost any medication including over-the-counter drugs, such as Ibuprofen, can cause SJS. Most commonly implicated drugs are anti-convulsants, antibiotics (such as sulfa, penicillin and cephalosporin) and anti-inflammatory medications. SJS and TENS are life-threatening reactions. If left untreated, they can result in death. Complications can include permanent blindness, dry-eye syndrome, photophobia, lung damage, chronic obstructive pulmonary disease (COPD), asthma, permanent loss of nail beds, scarring of the esophagus and other mucous membranes, arthritis, and chronic fatigue syndrome. The aim of present article is to provide in depth knowledge about Stevens Johnson Syndrome which is no doubt, a rare genetic disorder. In this article the author has explained all the clinical aspects related to Stevens Johnson Syndrome.

Key words: SJS (Stevens Johnson Syndrome), TENS (Toxic Epidermal Necrolysis Syndrome), Adverse drug reactions (ADR’s), chronic obstructive pulmonary disease (COPD).

Introduction

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous disorders characterized by acute skin blisters and mucous membrane erosions. They are severity variants of drug reactions that result in necrosis of the epidermis and other epithelia. According to current definitions the main difference between the two is the extent of skin detachment.; 10%
for SJS and 30% for TEN. (Because SJS and TEN are very rare, the risk cannot be evaluated in cohorts of treated patients and case control studies are considered to be more accurate.

First described in 1922, Stevens-Johnson syndrome (SJS) is an immune-complex–mediated hypersensitivity complex that is a severe expression of erythema multiforme. It is known by some as erythema multiforme major, but disagreement exists in the literature. Most authors and experts consider Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) different manifestations of the same disease. For that reason, many refer to the entity as SJS/TEN. SJS typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of oral, nasal, eye, vaginal, urethral, GI, and lower respiratory tract mucous membranes may develop in the course of the illness. GI and respiratory involvement may progress to necrosis. SJS is a serious systemic disorder with the potential for severe morbidity and even death. Missed diagnosis is common.

Although several classification schemes have been reported, the simplest breaks the disease down as follows:
- Stevens-Johnson syndrome - A "minor form of TEN," with less than 10% body surface area (BSA) detachment
- Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) - Detachment of 10-30% BSA
- Toxic epidermal necrolysis - Detachment of more than 30% BSA

Sign and Symptoms of Stevens-Johnson syndrome

- Rash, blisters, or red splotches on skin
- Persistent fever
- Blisters in mouth, eyes, ears, nose, genital area
- Swelling of eyelids, red eyes
- Conjunctivitis
- Flu-like symptoms
- Recent history of having taken a prescription or over-the-counter medication
- Target lesions are not always seen in SJS

Pathophysiology

Stevens-Johnson syndrome is an immune-complex–mediated hypersensitivity disorder that may be caused by many drugs, viral infections, and malignancies. Cocaine recently has been added to the list of drugs capable of producing the syndrome. Additionally, the antidepressant mirtazapine and tumor necrosis factor (TNF) – alpha antagonists infliximab, etanercept, and adalimumab have been reported as causes. In up to half of cases, no specific etiology has been identified. Pathologically, cell death results causing separation of the epidermis from the dermis. The death receptor, Fas, and its ligand, FasL, have been linked to the process.

Mortality/Morbidity

- Mortality is determined primarily by the extent of skin sloughing. When BSA sloughing is less than 10%, the mortality rate is approximately 1-5%. However, when more than 30% BSA sloughing is present, the mortality rate is between 25% and 35%. Bacteremia/sepsis may also contribute to mortality.
- Lesions may continue to erupt in crops for as long as 2-3 weeks. Mucosal pseudomembrane formation may lead to mucosal scarring and loss of function of the involved organ system.
Esophageal strictures may occur when extensive involvement of the esophagus exists. Mucosal shedding in the tracheobronchial tree may lead to respiratory failure.

- Ocular sequelae may include corneal ulceration and anterior uveitis. Blindness may develop secondary to severe keratitis or panophthalmitis in 3-10% of patients. Vaginal stenosis and penile scarring have been reported. Renal complications are rare.

**Clinical History**

- Typically, the disease process begins with a nonspecific upper respiratory tract infection.
- This usually is part of a 1- to 14-day prodrome during which fever, sore throat, chills, headache, and malaise may be present.
- Vomiting and diarrhea are occasionally noted as part of the prodrome.
- Mucocutaneous lesions develop abruptly. Clusters of outbreaks last from 2-4 weeks. The lesions are typically nonpruritic.
- A history of fever or localized worsening should suggest a superimposed infection; however, fever has been reported to occur in up to 85% of cases.
- Involvement of oral and/or mucous membranes may be severe enough that patients may not be able to eat or drink.
- Patients with genitourinary involvement may complain of dysuria or an inability to void.
- A history of a previous outbreak of Stevens-Johnson syndrome (SJS) or of erythema multiforme may be elicited. Recurrences may occur if the responsible agent is not eliminated or if the patient is reexposed.
- Typical symptoms are as follows:
  - Cough productive of a thick purulent sputum
  - Headache
  - Malaise
  - Arthralgia

**Physical**

- The rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema.
- The center of these lesions may be vesicular, purpuric, or necrotic.
- The typical lesion has the appearance of a target. The target is considered pathognomonic. However, in contrast to the typical erythema multiforme lesions, these lesions have only two zones of color. The core may be vesicular, purpuric, or necrotic; that zone is surrounded by macular erythema. Some have called these targetoid lesions.
- Lesions may become bullous and later rupture, leaving denuded skin. The skin becomes susceptible to secondary infection.
- Urticarial lesions typically are not pruritic.
- Infection may be responsible for the scarring associated with morbidity.
- Although lesions may occur anywhere, the palms, soles, dorsum of the hands, and extensor surfaces are most commonly affected.
- The rash may be confined to any one area of the body, most often the trunk.
- Mucosal involvement may include erythema, edema, sloughing, blistering, ulceration, and necrosis. An example of this type of involvement.
- Although some have suggested the possibility of Stevens-Johnson syndrome (SJS) without skin lesions, most believe that mucosal lesions alone are not enough to establish the diagnosis. Some are now calling cases without skin lesions "atypical" or "incomplete." This group of authors suggested that the combination of urethritis, conjunctivitis, and stomatitis made the diagnosis of SJS in a patient with *Mycoplasma pneumoniae*-induced signs and symptoms.
- The following signs may be noted on examination:
Fever, Orthostasis, Tachycardia, Hypotension, Altered level of consciousness, Epistaxis, Conjunctivitis, Corneal ulcerations, Erosive vulvovaginitis or balanitis, Seizures, coma

Causes

- Drugs and malignancies are most often implicated as the etiology in adults and elderly persons.
- Pediatric cases are related more often to infections than to malignancy or a reaction to a drug.
- A medication such as sulfon, phenytoin, or penicillin had previously been prescribed to more than two thirds of all patients with Stevens-Johnson syndrome (SJS). The anticonvulsant oxcarbazepine (Trileptal) has also been implicated. Hallgren et al reported ciprofloxacin-induced Stevens-Johnson syndrome in young patients in Sweden and commented on several others. Metry et al reported Stevens-Johnson syndrome in 2 HIV patients treated with nevirapine and mentioned one other in the literature. The authors speculated that the problem may extend to other non-nucleoside reverse transcriptase inhibitors. Indinavir has been mentioned.
- More than half of the patients with Stevens-Johnson syndrome report a recent upper respiratory tract infection.
- The 4 etiologic categories are (1) infectious, (2) drug-induced, (3) malignancy-related, and (4) idiopathic.
- Viral diseases that have been reported include herpes simplex virus (HSV), AIDS, coxsackie viral infections, influenza, hepatitis, mumps, lymphogranuloma venereum (LGV), rickettsial infections, and variola.
- Bacterial etiologies include group A beta streptococci, diphtheria, Brucellosis, mycobacteria, Mycoplasma pneumoniae, tularemia, and typhoid. An "incomplete" case was recently reported after Mycoplasma pneumoniae infection.
- Coccidioidomycosis, dermatophytosis, and histoplasmosis are the fungal possibilities.
- Malaria and trichomoniasis have been reported as protozoal causes.
- In children, Epstein-Barr virus and enteroviruses have been identified.
- Antibiotic etiologies include penicillins and sulfa antibiotics. Anticonvulsants including phenytoin, carbamazepine, valproic acid, lamotrigine, and barbiturates have been implicated.

Mockenhapupt et al stressed that most anticonvulsant-induced SJS occurs in the first 60 days of use. In late 2002, the US Food and Drug Administration (FDA) and the manufacturer Pharmacia noted that Stevens-Johnson syndrome (SJS) had been reported in patients taking the cyclooxygenase-2 (COX-2) inhibitor valdecoxib. In 2007, the US FDA reported SJS/TEN in patients taking modafinil (Provigil). Allopurinol has recently been implicated as the most common cause in Europe and Israel.

- The most recent additions to possible drug-induced cases include the antidepressant mirtazapine and the TNF-alpha antagonists infliximab, etanercept, and adalimumab.
- Various carcinomas and lymphomas have been associated.
- Stevens-Johnson syndrome (SJS) is idiopathic in 25-50% of cases.
Diagnosis and Management

- Burns, Chemical  Erythema Multiforme
- Burns, Ocular  Staphylococcal Scalded Skin Syndrome
- Burns, Thermal  Toxic Epidermal Necrolysis
- Dermatitis, Exfoliative  Toxic Shock Syndrome

Laboratory Studies
- No specific laboratory studies (other than biopsy) exist that can definitively establish the diagnosis of Stevens-Johnson syndrome.
- A complete blood count (CBC) may reveal a normal white blood cell (WBC) count or a nonspecific leukocytosis. A severely elevated WBC count indicates the possibility of a superimposed bacterial infection.
- Skin and blood cultures have been advocated because the incidence of serious bacterial bloodstream infections and sepsis contribute to morbidity and mortality.
- Determine renal function and evaluate urine for blood.
- Electrolytes and other chemistries may be needed to help manage related problems.
- Cultures of blood, urine, and wounds are indicated when an infection is clinically suspected.
- Bronchoscopy, esophagogastroduodenoscopy (EGD), and colonoscopy may be indicated.

Prognosis
- Individual lesions typically should heal within 1-2 weeks, unless secondary infection occurs. Most patients recover without sequelae.
- Development of serious sequelae, such as respiratory failure, renal failure, and blindness, determines prognosis in those affected.
- Up to 15% of all patients with Stevens-Johnson syndrome (SJS) die as a result of the condition. Bacteremia and sepsis appear to play a major role in increased mortality.
- The SCORTEN score looks at a number of variables and uses them to prognosticate risk factors for death in both SJS and TEN. The variables include the following:
  - Age >40 years
  - Malignancy
  - Heart rate >120
  - Initial percentage of epidermal detachment >10%
  - BUN level >10 mmol/L
  - Serum glucose level >14 mmol/L
  - Bicarbonate level <20 mmol/L
- Mortality rates are as follows:
  - SCORTEN 0-1 >3.2%
  - SCORTEN 2 >12.1%
  - SCORTEN 3 >35.3%
  - SCORTEN 4 >58.3%
  - SCORTEN 5 or more >90%

Treatment

Prehospital Care
Paramedics should recognize the presence of severe fluid loss and should treat patients with Stevens-Johnson syndrome (SJS) as they would patients with thermal burns.
Emergency Department Care

Most patients present early and prior to obvious signs of hemodynamic compromise. The single most important role for the ED physician is to detect Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) early and initiate the appropriate ED and inpatient management. Withdrawal of the suspected offending agent is critically important. Timing of withdrawal has been linked to outcome.

- Care in the ED must be directed to fluid replacement and electrolyte correction.
- Skin lesions are treated as burns.
- Patients with SJS/TEN should be treated with special attention to airway and hemodynamic stability, fluid status, wound/burn care, and pain control.
- Treatment is primarily supportive and symptomatic. Some have advocated cyclophosphamide, plasmapheresis, hemodialysis, and immunoglobulin. Most authorities believe that corticosteroids are contraindicated.
- Manage oral lesions with mouthwashes.
- Topical anesthetics are useful in reducing pain and allowing the patient to take in fluids.
- Areas of denuded skin must be covered with compresses of saline or Burow solution.
- Underlying diseases and secondary infections must be identified and treated. Offending drugs must be stopped.
- The use of systemic steroids is controversial. Some authors believe that they are contraindicated. Treatment with systemic steroids has been associated with an increased prevalence of complications. The ophthalmology literature contains several papers that advocate systemic and topical steroids to minimize ocular morbidity.
- In a large European study designed to evaluate the efficacy of various treatments, the EuroSCAR Study "found no sufficient evidence of a benefit for any specific treatment." The group looked at mortality in patients treated with IV immunoglobulins and corticosteroids.
- Address tetanus prophylaxis.

Early management

The management of patients must be prompt; early diagnosis with the early recognition and withdrawal of all potential causitive drugs is essential to a favorable outcome. Morbidity and mortality increase if the culprit drug is withdrawn late. We observed that death rates were lower when causative drugs with short elimination half-lives were withdrawn no later than the day when blisters or erosions first occurred. No difference was seen for drugs with long half-lives.

Second, intravenous fluid replacement must be initiated using macromolecules or saline solutions. Third, the patient must be transferred to an intensive care unit or a burn center. Prompt referral reduces risk of infection, mortality rate and length of hospitalization.

Symptomatic treatment

General principles

The main types of symptomatic treatment are the same as for burns, and the experience of burn units is helpful for the treatment of TEN: environmental temperature control, careful and aseptic handling, sterile field creation, avoidance of any adhesive material, maintenance of venous peripheral access distant from affected areas (no central line when possible), initiation of oral nutrition by nasogastric tube, anticoagulation, prevention of stress ulcer, and medication administration for pain and anxiety control are all essential. However, TEN and burned patients are not identical: burns happen in a very short time period (a few seconds) and do not spread thereafter; the TEN-SJS progress occurs during several days, including after hospital admittance. Cutaneous necrosis is more variable and often deeper in burns than in TEN.
These differences induce some important management specificities. Subcutaneous edema is a very uncommon feature of TEN, in contrast with burns, probably because of milder injury to blood vessels. Therefore, the fluid requirements of TEN patients are habitually two-thirds to three-fourths of those of patients with burns covering the same area. Since the lesions are restricted to the epidermis and usually spare the hair follicles, the regrowth of epidermis is quick in patients with SJS-TEN. This supports a different approach of topical treatment.

**Systemic management**

Pulmonary care includes aerosols, bronchial aspiration and physical therapy. If the trachea and bronchi are involved, intubation and mechanical ventilation are nearly always necessary. Early and continuous enteral nutrition decreases the risk of stress ulcer, reduces bacterial translocation and enterogenic infection, and allows earlier discontinuation of venous lines. Phosphorus levels must be measured and corrected, if necessary. Profound hypophosphoremia is frequent and may contribute to altered regulation of glycemia and to muscular dysfunction. Most authors do not use prophylactic antibiotics. Catheters are changed and cultured regularly. Bacterial sampling of the skin lesions is performed the first day and every 48 hours. Indications for antibiotic treatment include an increased number of bacteria cultured from the skin with selection of a single strain, a sudden drop in temperature, and deterioration in the patient's condition. *S. aureus* is the main bacteria present during the first days, and gram negative strains appear later. Environmental temperature is raised to 30 to 32 degrees,C. This reduces caloric losses through the skin and the resultant shivering and stress. Heat loss can also be limited by raising the temperature of antiseptic baths to 35v’ to 38(C and by using heat shields, infrared lamps, and air-fluidized beds. Some drugs are needed. Thromboembolism is an important cause of morbidity and death; effective anticoagulation with heparin is recommended for the duration of hospitalization.

Although this results in increased bleeding from the skin, it is usually limited in amount and does not require additional transfusion. Antacids reduce the incidence of gastric bleeding. Emotional and psychiatric support must not be forgotten. Tranquilizers such as diazepam and morphinic analgesics can be used liberally if the respiratory status permits. Insulin is administered when hyperglycemia leads to overt glycosuria or to increased osmolarity. Many reviews have been published about intravenous and oral supplementation on burn care: oxandrolone and human growth factor are effective for decreasing hypercatabolism and net nitrogenous loss; ornithine alpha-ketoglutarate supplementation of enteral feeding is effective to reduce wound healing time; high dose ascorbic acid (66 mg/kg per hour) given during the first 24 hours reduces fluid volume requirements.

**Topical management**

No consensus exists about topical care. Possible approaches may be conservative or more aggressive (large operative debridement). In our opinion, conservative care is better than any surgical method. Even though we did not perform any study, it has been our experience that the areas with a positive Nikolski, potentially detached by any trauma healed much more rapidly where the epidermis stayed on site than on similar areas where the epidermis had been detached. We leave in place the involved "detachable" epidermis and use dressings only to protect it. Topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine) are used to paint, bathe, or dress the patients. Dressings may be gauzes with petrolatum, silver nitrate, polyvidoneiodine, or hydrogels. Some authors use biologic skin covers after epidermal stripping (cadaveric allografts, cultured human allogeneic or autologous epidermal sheets). New dressings are being investigated: Apligraft(r), Biobrane(r), TransCyte(r) (human newborn fibroblasts cultured on the
nylon mesh of Biobranee). In burns, topical recombinant bovine basic fibroblast growth factor allowed faster granulation tissue formation and epidermal regeneration than placebo.

Prevention of ocular sequelae requires daily examination by an ophtalmologist. Eye drops, physiologic saline, or antibiotics if needed, are instilled every 2 hours and developing synechiae are disrupted by a blunt instrument. It is suggested that wearing gas-permeable scleral contact lenses reduces photophobia and discomfort; these lenses improve visual acuity and heal corneal epithelial defects in half of patients.

Oral and nasal crusts are removed, and the mouth is sprayed with antiseptics several times a day.

**Specific treatment**

**Corticosteroids**
Corticosteroid use is highly debated. These drugs are a mainstay in some units, but other investigators consider systemic corticosteroids to provoke prolonged wound healing, increased risk of infection, masking of early signs of sepsis, severe gastrointestinal bleeding and increased mortality. A review of the literature shows only patients series and no randomized clinical trials. Several articles reported Corticosteroids benefit: Tegelberg used 400 or 200 mg prednisone/day, gradually diminished over a 4 to 6 week period, and observed a single death among eight patients.

**Medication**
No specific drug treatment has been consistently shown to be beneficial in the treatment of Stevens-Johnson syndrome. The choice of antibiotic depends on the associated infection. The use of systemic corticosteroids is controversial. They are useful in high doses early in the reaction, but morbidity and mortality actually may increase in association with corticosteroid use. Clinical and laboratory evidence suggesting bloodstream infection mandates the use of antibiotics. The most common organisms include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and Enterobacteriaceae species.

**Complications**
- Ophthalmologic - Corneal ulceration, anterior uveitis, panophthalmitis, blindness
- Gastroenterologic - Esophageal strictures
- Genitourinary - Renal tubular necrosis, renal failure, penile scarring, vaginal stenosis
- Pulmonary - Tracheobronchial shedding with resultant respiratory failure
- Cutaneous - Scarring and cosmetic deformity, recurrences of infection through slow-healing ulcerations

**Discussion and Conclusion**
- Above discussion shows that Stevens Johnson syndrome (SJS) is a severe cutaneous disorder characterized by acute skin blisters and mucous membrane erosions. They are severity variants of drug reactions that result in necrosis of the epidermis and other epithelia. No treatment is available for Stevens Johnson syndrome. Care is supportive. Genetic counselling is indicated, further consultations of Clinical geneticist, Developmental paediatrician, Neurologist, Cardiologist, Ophthalmologist, Dentist, Orthopaedist, Psychologist, Physical and occupational therapist, Speech language pathologist and Audiologist may be required time to time. Family members of people with Stevens Johnson syndrome will also need help in coping with the stresses of the disease. Social and psychiatric support can help with family relationships and antisocial behaviour. Family therapy and genetic counselling are often useful for alleviating family conflict and stressors related to relationship losses.
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