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OVERVIEW OF STEVENS-JOHNSONS SYNDROME- ITS ETIOLOGY AND TREATMENT

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ABSTRACT

Stevens–Johnson Syndrome (SJS) is a rare yet severe condition that primarily affects the skin and mucous membranes. It generally begins actually with flu-like symptoms and then progresses to certain painful skin rashes. The syndrome is usually triggered by adverse drug reactions or infections and is rooted in immune system dysfunction. A strong genetic correlation has been found with the HLA-B1502 allele, present in all affected patients in some populations, with Type IV hypersensitivity being the underlying immune mechanism. SJS and its more severe variant, Toxic Epidermal Necrolysis (TEN), result in extensive cell death that causes the outer layer of skin (epidermis) to separate from the underlying dermis. Sulfonamide antibiotics are a common cause. SJS is viewed generally as a milder form out of TEN. Risk factors include conditions like HIV/AIDS and systemic lupus erythematosus. It is commonly induced by medications such as corticosteroids, antibiotics, antihistamines, or intravenous immunoglobulin. Patients were observed to be typically required proper intensive medical care in the areas of burn or critical care units. Symptoms include inflammation, painful blisters in the mouth and eyes, and full-thickness damage to skin and mucosal tissues. Among drug-induced severe cutaneous adverse reactions (SCARs), SJS involves a distinct immune pathway, notably Type IVb hypersensitivity, which differs from other reactions like DRESS syndrome.

KEYWORDS: Rare disease, immune dysfunction, HLA-B1502, Type IV hypersensitivity.

INTRODUCTION

Stevens–Johnson Syndrome is considered to be an acute and seriously life-threatening dermatological condition. It exists on a spectrum with Toxic Epidermal Necrolysis (TEN), with SJS being the less severe form. Initial signs often include fever and flu-like symptoms, which are soon followed by painful blistering and skin peeling. The mucosal surfaces—such as those of the mouth and genitals—are frequently involved. Complications may include dehydration, systemic infections like sepsis, pneumonia, and even multi-organ failure. Medications such as lamotrigine, allopurinol, carbamazepine, nevirapine, and sulfonamide antibiotics are known to trigger the syndrome, although in some instances the cause remains unclear. The presence of systemic autoimmune disorders like lupus and immunodeficiency conditions such as HIV/AIDS increases susceptibility. SJS typically involves less than 10% of total body surface area. The syndrome represents a Type IV delayed hypersensitivity reaction. Related conditions like DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), TEN, and acute generalized exanthematous pustulosis are also considered in differential diagnosis. Treatment generally involves hospitalization in a burn or intensive care unit, focusing on symptom control using drugs like corticosteroids, antihistamines, antibiotics, and IV immunoglobulin. The incidence rate is about 1–2 cases per million people annually, with the skin usually healing within 2–3 weeks and full recovery taking months.[1] The associated mortality rate ranges from 5% to 10%.

History

Albert Stevens and Frank Johnson

Albert Stevens, a U.S.-born surgeon raised in India, was the son of a Baptist missionary. After moving to the United States at age ten, he completed a Bachelor of Arts from Yale University in 1905. In 1908, he became a Rhodes Scholar at Oxford and later earned his medical degree from Columbia University's College of Physicians and Surgeons in 1915. He demonstrated generosity early in his career by declining financial aid so that it could benefit another student in need. During World War I, he served as an assistant surgeon and was held as a prisoner of war by German forces. After the war, he worked at Bellevue Hospital in New York City. Following retirement, he relocated to Honolulu, Hawaii, where he taught and managed a small tropical fruit plantation. He passed away on August 6, 1945, at the end of World War II.

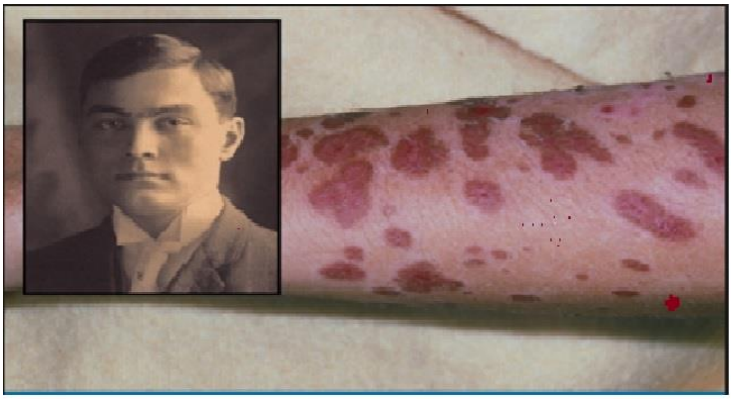

Figure 1.

The condition now known as Stevens–Johnson Syndrome was first documented in two boys admitted to Bellevue Hospital, New York. Their skin showed dark red to purple bullseye-like lesions with normal skin in between. Symptoms included fever, conjunctivitis, and mucosal inflammation. One patient suffered complete loss of vision. Medical professionals had never encountered such a presentation before. This case was later acknowledged by *The Lancet* as the first description of what was eventually termed Stevens–Johnson Syndrome.

Clinical Features

Stevens–Johnson Syndrome is organized to come under the Type IV kind of hypersensitivity reaction which severely affects the body, skin and mucous membranes. SJS is considered the milder end of the spectrum, involving less than 10% of the body surface area. The overlap form involves 10–30%, while TEN exceeds 30% of skin detachment.[2] The syndrome typically begins with flu-like symptoms such as sore throat, fatigue, and fever. It is often misdiagnosed and mistakenly treated with antibiotics. Mucosal involvement is a hallmark, especially affecting the mouth, lips, and genitals. About 30% of affected children develop conjunctivitis. The damaged skin resembles like to be second-degree burns, with an over-all extensive epidermal sloughing.

Ocular Manifestations

1. **Eyelids:** Conditions like Meibomian gland dysfunction, trichiasis, and chronic blepharitis are common.
2. **Conjunctiva:** Patients may experience papillae, follicles, shrinkage, keratinization, symblepharon (adhesion between eyelid and eyeball), ankyloblepharon (fusion of eyelids), and shortening of fornices.

3. **Cornea:** Defects can occur in the epithelium, along with superficial punctate keratitis, stromal opacities, ulcers, and keratinization.

Causes

- SJS generally arises due to abnormal immune responses triggered by infections or medications.
- In about to 50% of cases, there is no specific cause to be identified.
- SJS and TEN are mutually considered as developed manifestations of a particular shared pathological process.
- Genetic predispositions—such as variations in HLA alleles and T-cell receptor function—can increase susceptibility by affecting how drugs are absorbed, metabolized, or excreted.

Etiology

Drug reactions account for roughly 50% of SJS and up to 95% of TEN cases. Frequently implicated medications include:

- Antibiotics: Cephalosporins, fluoroquinolones, and aminopenicillins (especially ampicillin and amoxicillin).
- Sulfonamides: Including cotrimoxazole and sulfasalazine.[3]

Drug and Non-Drug Causes

Common medication triggers include

- Antiepileptic drugs like as phenytoin, lamotrigine, carbamazepine, phenobarbital, and valproate.
- Other agents include drugs like piroxicam, allopurinol, and chlormezanone.

Non-drug-related causes are relatively uncommon and include:

- Infections, most notably caused by *Mycoplasma pneumoniae*.
- Graft-versus-host disease (GVHD).
- Vaccinations in rare instances.

In certain cases, no definitive cause can be identified despite thorough investigation.

Epidemiology

Early epidemiological data, collected prior to the widespread use of modern classification systems, indicate that the combined annual incidence of erythema multiforme major (EMM), Stevens–Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) in the U.S. is approximately four cases per million people.[4] Reports from countries such as France,

Germany, Italy, and Singapore suggest that TEN alone occurs in about one individual per million annually, including those cases now classified as TEN or SJS–TEN overlap syndromes.

Genetic Markers and Susceptibility

There is a well-established link between certain HLA alleles and susceptibility to SJS/TEN, often influenced by ethnic background. In 2004, a well known significant association was identified and discovered in the Han Chinese population, where 90% of all individuals with carbamazepine-induced SJS/TEN were carried the HLA-B*1502 allele. In contrast, only 3% of people who tolerated carbamazepine possessed this allele. This allele is notably absent among Caucasians and Japanese, which might explain the markedly higher incidence of SJS/TEN in Southeast Asians compared to those populations.

Subsequent studies across Southeast Asia (e.g., in Hong Kong, Malaysia, India, Singapore, Thailand, Vietnam, Indonesia, and the Philippines) confirmed a 2.3% to 8.4% prevalence of HLA-B*1502 in the general population. In Malaysia and China, the frequency of this allele among individuals with carbamazepine-induced reactions was as high as 75%.

Another allele, HLA-B*5801, has been linked to severe cutaneous reactions from allopurinol, a drug used to treat hyperuricemia. Among Taiwanese patients with allopurinol-induced hypersensitivity, 100% carried this allele, while only 15% of those who tolerated the drug did. Similar findings have also been revised and documented in Thai populations.[5] However, Japanese studies have shown only a moderate correlation, and an alternate association with HLA-B*4801 has been proposed for drug-induced reactions like DRESS.

Furthermore, HLA-B*5701 has been strongly linked to abacavir hypersensitivity, particularly in Caucasians. Screening for this allele before abacavir administration has proven effective in reducing hypersensitivity reactions. Interestingly, this allele appears to be rare among East Asian populations such as Koreans.

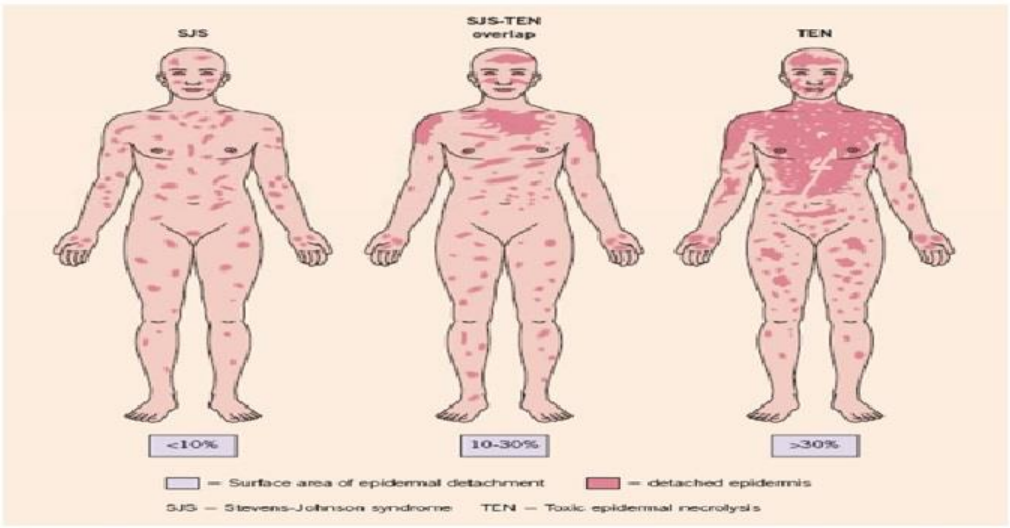

Figure 2: Role of Natural Killer Cells.

Besides cytotoxic T lymphocytes (CTLs), natural killer (NK) cells play a vital role in the pathogenesis of SJS/TEN. Blisters in affected skin are infiltrated by both CTLs and NK cells. These immune cells interact with HLA class I molecules, which either stimulate or inhibit their cytolytic activity through specific receptors known as killer activating receptors (KARs) and killer inhibitory receptors (KIRs).

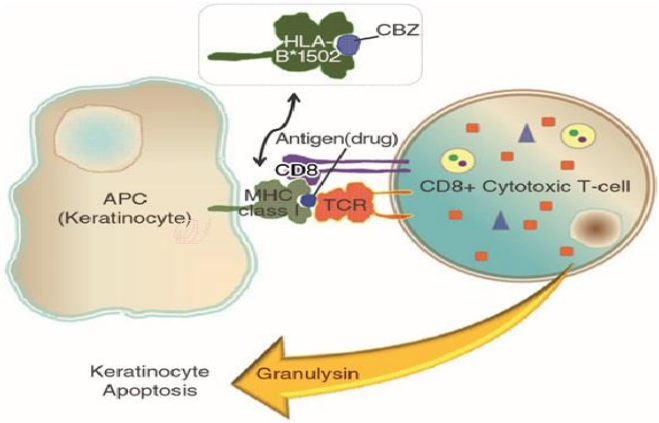

Figure: 3.

Pathophysiology

SJS is classified as a Type IV delayed hypersensitivity reaction. In this immune response, drug metabolites activate T helper cells and cytotoxic T cells, which then mount an autoimmune attack against the body's own tissues.[6] The subtype responsible for tissue damage is primarily Type IVc, characterized by the activity of cytotoxic T cells and NK cells. Other SCAR-related reactions like DRESS are mediated by Type IVb, while Type IVd

(involving eosinophils) underlies conditions like acute generalized exanthematous pustulosis (AGEP).

Drugs or their metabolites stimulate CD4+ and CD8+ T cells by interfering with antigen presentation pathways. They may bind covalently to host proteins, forming new drug-peptide complexes (neoantigens) that are presented on HLA molecules by antigen-presenting cells. These complexes are then recognized by T-cell receptors, triggering cytotoxic responses. Alternatively, some drugs can bind directly to HLA grooves or modify HLA conformation to mimic a non-self antigen.

Since there are over 13,000 known HLA serotypes, and each individual carries only a subset, only certain people are genetically predisposed to develop SJS in response to specific medications. Thus, the risk of SCARs is highly HLA-dependent, and only those who express certain high-risk HLA types will be affected by specific drugs.[7]

Despite these insights, the exact mechanism behind SJS/TEN is not fully elucidated. One prominent theory suggests that impaired drug metabolism leads to persistent T-cell activation, which targets keratinocytes—the primary cells in the epidermis. CD8+ T cells are especially critical in the formation of skin blisters.

Granulysin, a cytotoxic molecule secreted by CTLs and NK cells, has been identified as a major factor contributing to keratinocyte apoptosis. Its concentration in the blister fluid actually correlates with severity of disease.

Another proposed mechanism involves the Fas–Fas ligand pathway, where soluble Fas ligands released by mononuclear cells bind to the Fas receptor on keratinocytes, inducing programmed cell death and subsequent blistering.

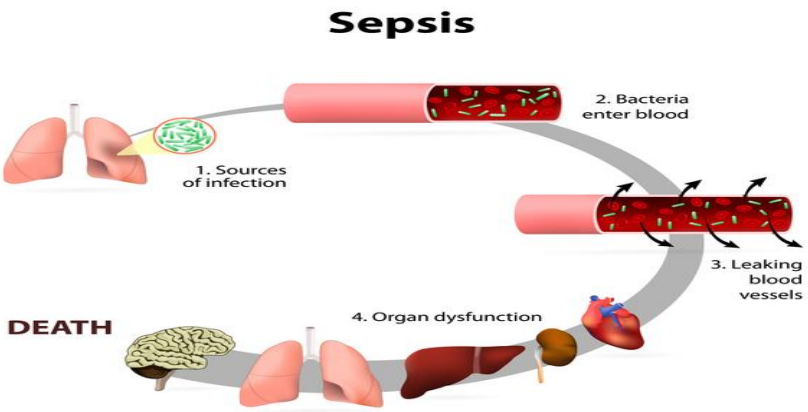

Figure: 4.

Signs and Symptoms

Typically, within fraction of 1 to 3 weeks after intiating starting the original causative medication, patients tend to begin to exhibit various non-specific symptoms such as malaise, fever, headache, cough, cold and eye irritation (keratoconjunctivitis). Soon after, the characteristic target-shaped macules appear, often with starting on the face, neck, below and upper torso. These lesions tend to erupt suddenly and may emerge across various body regions at the same time. The individual macules may merge to form large, fragile blisters that rupture and peel within 1 to 3 days, leaving behind exposed, painful areas. Loss of nails, epidermis, and eyebrows is common. The soles and palms may also be affected. Pain in the skin, mucosal surfaces, and eyes is a frequent complaint. In some cases, generalized redness (erythema) may be the earliest skin manifestation of toxic epidermal necrolysis (TEN).

Common symptoms include

- High fever
- Painful blisters on occurred facially like on mucosal surfaces such as the eyes, mouth, nose, and genitals
- Unexplained widespread skin tenderness
- Red or purplish skin rashes that spread quickly
- Shedding of skin following blister formation

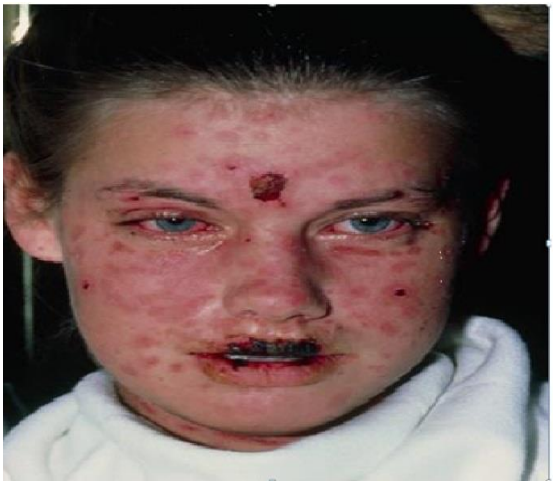

Figure: 5.

Prior to rash development in Stevens–Johnson Syndrome, individuals may experience

- Fever
- Burning or irritated eyes
- Sore throat or mouth
- Cough
- Fatigue or lethargy

Diagnosis

- Based primarily on clinical evaluation
- Confirmed through skin biopsy, when necessary

Diagnosis involves assessing the appearance and rapid evolution of skin and mucosal lesions. Histological analysis of affected tissue typically reveals necrotic epithelium, a hallmark feature.[8]

The differential diagnosis includes

- Viral exanthems
- Erythema multiforme
- Other drug-induced skin rashes

For TEN, distinguishing diagnoses may include

- Toxic shock syndrome
- Exfoliative erythroderma
- Paraneoplastic pemphigus

In pediatric cases, SJS/TEN must be differentiated from staphylococcal scalded skin syndrome (SSSS), which is usually marked by lack of mucosal involvement and may be linked to recent staphylococcal infections or drug use.

Treatment

- Intravenous immunoglobulin (IVIG)
- Plasma exchange (plasmapheresis)
- Cyclosporine therapy
- Comprehensive supportive care

Early recognition and immediate management in a critical care setting—preferably in an ICU or specialized burn unit—significantly improves prognosis. Patients with ocular involvement require urgent ophthalmologic evaluation and intervention.

Immediate discontinuation of the suspected drug is crucial. Patients are isolated to minimize infection risk and provided with fluid resuscitation, electrolytes, blood products, and nutritional support as needed. Skin care is managed similarly to burn cases, with daily wound care and prevention/treatment of secondary bacterial infections. The use of generally prophylactic antibiotics is completely controversial and typically avoided.

Cyclosporine (administered at 3–5 mg/kg/day) suppresses CD8+ T cells and has been associated with a shorter disease duration and reduced mortality rates. While systemic corticosteroids have been linked to increased risks of infection and masked sepsis—potentially raising mortality—recent findings suggest early pulse corticosteroids may benefit ocular outcomes.

Plasmapheresis may help remove circulating drug metabolites or harmful antibodies. A high-dose regimen of IVIG (e.g., 2.7 g/kg over 3 days) aims to block Fas ligand-mediated apoptosis. However, results have been mixed; some small-scale studies report no survival benefit or even higher mortality rates compared to conventional treatment.

Prevention

- Survivors of SJS or TEN should strictly avoid re-exposure to the causative drug.
- Any sign of mucosal ulceration, skin rash, or lesion recurrence warrants immediate medical attention.[9]

- Patients with a history of these conditions should not self-medicate, especially with antibiotics or over-the-counter medications, without physician supervision.
- When consulting a new doctor, it is crucial for patients to inform them of any history of SJS/TEN.
- Individuals known to carry HLA alleles associated with drug hypersensitivity should not be prescribed those drugs.

CONCLUSION

Stevens–Johnson Syndrome presents with partial-thickness skin damage, resembling second-degree burns, and involves complete loss of the epidermis, requiring burn-like supportive treatment. SJS is originally a rare, modified immune-mediated hypersensitivity disorder with identification of an incidence of approximately 7.1 cases per million individuals were found annually. It may progress into erythema multi-forme in up to 49 cases per million. The condition disproportionately affects females, with a reported male-to-female ratio of 1:2, though this may vary.

SJS exists in three clinical forms

- Mild: Erythema multiforme (<10% of total body surface area)
- Moderate: Classic Stevens–Johnson Syndrome (10–30% TBSA)
- Severe: Toxic Epidermal Necrolysis (TEN), involving >30% TBSA

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