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Stevens Johnson Syndrome Review

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ABSTRACT

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are dermatologic emergencies that are distinguished by extensive epidermal necrolysis and sloughing. The incidence rates are location-dependent. Mortality rates vary from 4.8-9% to 14.8-48%, with females being more frequently affected than males.

Supportive care, infection control, wound care, and fluid and electrolyte management comprise nonpharmacologic treatment for SJS/TEN patients. The identification and cessation of the causative substance are the most critical components. The management of fluid, electrolytes, and nutrition is essential for SJS/TEN patients, as they have lower fluid requirements than burn patients.

Prophylactic antibiotics do not improve outcomes; however, infection prevention necessitates appropriate wound care and antiseptic handling. The decision to pursue surgical debridement is contingent upon the location of care, and the function of this treatment option has been a subject of controversy. Anti-shear therapy, which entails the preservation of denuded epidermis and the aspiration of blister fluid, has been demonstrated to be effective in decreasing mortality rates.

The disease's rarity has resulted in a scarcity of prospective studies on pharmacologic treatment for SJS/TEN. There have been reports of a variety of treatment regimens that involve corticosteroids, IVIg, cyclosporine, and TNF-alpha inhibitors. However, it is difficult to ascertain whether the disease's remission was caused by a specific treatment or the natural course of the disease.

Studies have demonstrated that supportive care and cyclosporine have the potential to serve as alternative treatments for SJS/TEN. A meta-analysis of 10 studies revealed that patients who received cyclosporine had a survival advantage, while a meta-analysis of 67 studies revealed that the combination of corticosteroids and IVIg resulted in statistically significant improvements in outcomes. The severity of illness scores in patients with SJS/TEN overlap or TEN was reduced by plasmapheresis, which entails plasmapheresis and corticosteroids. In 86.8% of patients, TNF-alpha inhibitors have also demonstrated positive outcomes, despite their immunosuppressive properties. Nevertheless, the most effective pharmacological treatment for SJS/TEN must be determined by taking into account practical factors, such as cost. There is a lack of consensus regarding the most effective treatment, and additional research is required to ascertain the most effective treatment.

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INTRODUCTION

Stevens-Johnson Syndrome (SJS) is a rare, life-threatening condition that is distinguished by severe mucocutaneous epidermal necrolysis and epidermal detachment.One The etiology of the condition is complex and is centered on a delayed-type hypersensitivity reaction that can be attributed to a variety of factors. The most prevalent cause is medication-related, with sulfonamides, antiepileptics, allopurinol, and nonsteroidal anti-inflammatory medications (NSAIDs) being among the most common.Two, three Infectious processes, including human immunodeficiency virus, herpesvirus, and Mycoplasma pneumoniae, as well as noninfectious processes, such as systemic lupus erythematosus, radiotherapy, and collagen disorders, are additional causes of SJS.Two Furthermore, SJS is categorized according to a spectrum. For body surface areas that are less

than 10% affected, SJS is administered. For those that are 10%–30% affected, SJS/toxic epidermal necrolysis (TEN) overlaps, and greater than 30% are affected by TEN.One Genetics also contribute to adverse drug reactions, as several human leukocyte antigen (HLA) genotypes within specific ethnic groups have been linked to these reactions.

The pathophysiology of SJS is not entirely comprehended; however, it is distinguished by the extensive apoptosis of keratinocytes. This cell-mediated, cytotoxic reaction is believed to involve a number of mediators, with T lymphocytes and natural killer cells (NK cells) being the most likely primary cause, resulting in the induction of apoptosis.One Additional mediators include cytotoxic proteins, including tumor necrosis factor alpha, perforin-granzyme B, and Fas-Fas ligand. However, recent research has suggested that granulysin may be the primary mediator of keratinocyte degradation in the reaction.Four Studies have demonstrated that granulysin is the most highly expressed cytotoxic molecule found in the blisters of patients with SJS, and the levels of granulysin within the blisters are correlated with the severity of the disease.Four The mechanism by which cytotoxic T lymphocytes and NK cells are activated to release molecules like granulysin is a topic of debate. It is hypothesized by certain theories that a drug or its metabolite is directly presented as an antigen to T lymphocyte receptors. Conversely, other theories propose that the drug or its metabolite binds noncovalently to the major histocompatibility complex and modifies the binding cleft, resulting in a self-peptide that can activate T cells.Four Extensive full-thickness keratinocyte necrosis and subepidermal bullae are the consequences of activated lymphocytes and NK cells in either scenario.

The identification of early indicators of SJS can be exceedingly challenging, frequently resulting in misdiagnoses and a delay in treatment. Numerous patients will exhibit nonspecific prodromal symptoms that manifest within one to three weeks of the drug's introduction. Mucosal lesions frequently manifest initially and may encompass the oral, respiratory, conjunctival, and genitourinary regions. These lesions typically commence as diffuse, ill-defined erythematous macules with purpuric centers. They advance to vesicles and bullae before sloughing off after a few days. Skin biopsy is performed to confirm the diagnosis, which reveals full-thickness dermal necrosis.One This acute phase of SJS typically lasts between 8 and 12 days and may lead to extensive, painful areas of denuded skin. Re-epithelialization will commence approximately one week after the commencement of symptoms and may continue for up to three weeks. Various treatment modalities, such as intravenous immunoglobulin, corticosteroids, cyclosporine, and plasmapheresis, have been employed with varying degrees of success. Nevertheless, the primary focus of SJS treatment is the early recognition, immediate cessation of the causative drug, supportive care, and early transport to the burn unit if necessary. The aggregate mortality rate for SJS is less than 10%, while TEN has a mortality rate ranging from 30 to 50%. Co-infection and respiratory failure are the most prevalent causes of mortality in patients with SJS. The development of adhesions and strictures throughout the gastrointestinal and urogenital tracts can occur, and long-term complications, particularly ocular complications, can be disabling. If feasible, the patient should be admitted to an intensive care unit or burn unit in the event that the skin involvement is extensive.

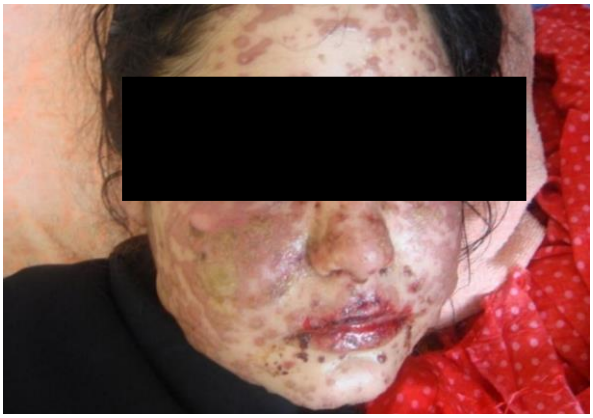

Figure 1. SJS

SJS Epidemiology/Pathophysiology/Risk Factors/ Presentation Presentation

Within the initial weeks, SJS patients experience a prodromal phase that includes fever, malaise, rhinorrhea, photophobia, and erythema. Following the prodromal period, patients transition into a phase that is primarily characterized by cutaneous manifestations, including the development of mucosal and cutaneous lesions that can be readily removed by applying pressure to the skin. This condition is recognized as the Nikolsky sign and is a distinguishing characteristic of SJS. Less than 10% of the body is affected by epidermal detachment in SJS.Nine The oropharynx, conjunctiva, genitals, and gastrointestinal tract are the primary sites of mucosal lesions. Lesions are atypical and flat, initially forming on the trunk and subsequently disseminating to the extremities.eleven A poor predictor of prognosis, blood investigations of SJS manifest with anemia and leukopenia. Long-term complications may include gastrointestinal complications, periodontal disease, visual impairment, skin lesions, and vaginal and urethral stenosis. Additionally, changes in pigmentation.

Pathophysiology

The pathogenesis of SJS is not entirely comprehended; however, there are numerous mechanisms that can account for the syndrome's pathological process. One mechanism was predicated on HLA phenotypes. The immune response that initiates SJS can be triggered by the binding of specific molecules to HLA peptides. Various pharmacological agents have the capacity to bind to specific HLA molecules or T-cell receptors, thereby eliciting an immune response, by bypassing processing from an antigen presenting cell. Additionally, it has been demonstrated that specific

pharmaceuticals, including carbamazepine and abacavir, can alter specific HLA peptides, leading to an enhanced presentation of self-peptides and an autoimmune reaction. Keratinocyte destruction is primarily mediated by cytotoxic CD8+ T-cells and natural killer-like cytotoxic T-cells during the initial stages of SJS. Monocytes are the predominant cell type in the latter phases of the disease. Nevertheless, certain studies have demonstrated that the presence of CD14+ monocytes in the early phases of the syndrome may result in increased CD8+ T-cell toxicity and proliferation. Keratinocyte destruction can be induced by a variety of components of the apoptotic pathway, in addition to T-cell-mediated cytotoxicity. Keratinocyte apoptosis has been associated with the upregulation of FasL by cytotoxic mediators, such as TNF-alpha.20 TRAIL and TNF-like weak inducer of apoptosis (TWEAK) are additional components of the apoptotic pathway that have been identified as contributing to keratinocyte apoptosis in SJS.

Risk Factors

Infection, malignancy, autoimmune disorders, substance use, and specific HLA phenotypes all increase the likelihood of developing SJS. The primary cause is hypersensitivity reactions to specific pharmaceuticals. Lamotrigine, nevirapine, phenytoin, and NSAIDs (particularly celecoxib and ibuprofen) are among the numerous medications that are used. Carbamazepine is the second drug associated with SJS, while lamotrigine is the first. The risk of SJS is increased when allopurinol is prescribed at a dosage of 200 mg or higher. Additionally, the presence of specific HLA phenotypes may serve as a trigger when combined with specific medications. The HLA-B 15:02 allele has been associated with carbamazepine-induced SJS in the Asian population. There were 23 associations observed between the HLA-B 57:01 allele and abacavir, as well as between the HLA-B 58:01 allele and allopurinol. The presence of chronic comorbid conditions, including HIV, mycoplasma infections, and tuberculosis, is another significant risk factor. The likelihood of developing adverse cutaneous reactions and progressing to SJS is 1000 times higher in individuals with HIV. Ocular manifestations and a more severe illness presentation may also result from the presence of underlying conditions. Female sex and non-white ethnicity are additional risk factors.

Management of Stevens-Johnson Syndrome (SJS)

Category	Details
Diagnostic Criteria	- **Clinical Presentation**: Sudden onset of flu-like symptoms (fever, sore throat, cough), followed by painful red or purplish rash that spreads and blisters. - **Skin Involvement**: Less than 10% of body surface area (BSA). - **Mucosal Involvement**: Affects at least two mucous membranes (e.g., oral, ocular, genital). - **Histopathology**: Biopsy shows necrotic keratinocytes and epidermal detachment.
Initial Management	- **Discontinuation of Offending Agents**: Immediate cessation of the suspected drug(s) responsible for triggering SJS. - **Hospitalization**: Admission to a hospital, preferably to an ICU or burn unit for severe cases.
Supportive Care	- **Fluid and Electrolyte Management**: IV fluids to maintain hydration and electrolyte balance. - **Nutritional Support**: Enteral nutrition if possible to maintain caloric intake. - **Wound Care**: Use non-adherent dressings, and manage blisters to prevent secondary infections. - **Pain Management**: Analgesics to control pain from skin lesions and mucosal involvement. - **Temperature Regulation**: Keep the patient in a warm environment to prevent hypothermia.
Pharmacologic Treatments	- **Systemic Corticosteroids**: Use is controversial; may be considered in the early stages for anti-inflammatory effects. - **IV Immunoglobulin (IVIG)**: Mixed evidence; some studies suggest benefit, typically administered within the first few days of symptom onset. - **Cyclosporine**: Increasingly supported by evidence for its efficacy in reducing mortality and promoting faster skin healing. - **Antibiotics**: Only if there is a confirmed secondary bacterial infection.
Emerging Therapies	- **TNF-α Inhibitors**: Agents like etanercept are being researched for their potential to modulate the immune response in SJS. - **Mesenchymal Stem Cell Therapy**: Investigated for their potential to promote healing and reduce inflammation. - **Amniotic Membrane Grafts**: Used especially in cases of severe ocular involvement to prevent scarring and vision loss. - **Biologics**: Newer biologic agents are under investigation for their immunomodulatory effects.
Monitoring and Follow-up	- **Regular Ophthalmologic Exams**: To monitor and manage ocular involvement, preventing complications such as blindness. - **Long-term Follow-up**: Necessary to detect late

	complications such as skin scarring, mucosal strictures, and psychological impact. - **Multidisciplinary Care**: Involvement of dermatologists, ophthalmologists, intensivists, and other specialists as needed for comprehensive management.

CONCLUSION

SJS is a delayed-type hypersensitivity disease that is life-threatening and is distinguished by the detachment of the epidermis and mucocutaneous epidermal necrolysis. A prodromal phase typically precedes the onset of symptoms, which include flu-like symptoms such as malaise, fever, and rhinorrhea. Subsequently, patients develop a mucocutaneous dermatitis that is indicative of SJS and exhibits a positive Nikolsky sign. Despite its rarity, SJS has a mortality rate of approximately 10% and necessitates prompt treatment with supportive therapies. An elevated prevalence of SJS is associated with specific risk factors. These include malignancy, infection, autoimmune disorders, drug use, and specific HLA phenotypes. NSAIDS, allopurinol, certain antibiotic classes, and antiepileptics are the most prevalent catalysts for SJS. One of the antiepileptics that is most frequently linked to SJS is lamotrigine, a pre-synaptic voltage-gated sodium channel inhibitor.

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