STEVENS-JOHNSON SYNDROME

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Introduction and Definition

Stevens-Johnson Syndrome (SJS) is recognized as a rare, acute, and potentially life-threatening mucocutaneous disorder characterized by extensive blistering and epidermal detachment. This severe adverse reaction is considered an immunological emergency, placing it on a continuum with Toxic Epidermal Necrolysis (TEN), differing primarily in the percentage of the total Body Surface Area (BSA) affected. SJS involves widespread apoptosis of **keratinocytes**, leading to the separation of the epidermis from the dermis, often resulting in large, painful erosions that mimic severe thermal burns. Historically, SJS has been referred to by various names, reflecting the evolving understanding of its pathology, including **erythema multiforme bullosum**, **erythema multiforme exudativum**, and in its more severe form, **erythema multiforme major**. However, modern classification recognizes SJS as distinct from true erythema multiforme, based largely on the severity of mucosal involvement and the typical triggers, which are overwhelmingly pharmacological in nature.

The syndrome typically begins with a non-specific prodromal phase, characterized by flu-like symptoms such as fever, malaise, myalgia, and arthralgia, which precede the onset of the characteristic skin lesions by several days. The hallmark of established SJS is the rapid development of macules, atypical targetoid lesions, and flaccid bullae, often concentrating on the trunk and face, before spreading to the extremities. Crucially, the disorder requires urgent medical intervention, usually necessitating admission to an intensive care unit or a specialized burn unit, due to the high risk of secondary infection, massive fluid loss, and systemic organ failure. The severity and poor prognosis associated with SJS necessitate immediate identification of the causative agent, as withdrawal of the offending drug is the single most critical factor influencing patient outcome and survival rates.

While the incidence of SJS is low, ranging from approximately two to seven cases per million people per year, the devastating impact on affected individuals is profound. The condition is fundamentally thought to be a hypersensitivity reaction to certain external agents, primarily pharmaceuticals, which induce a massive cytotoxic immune response directed against the patient's own skin cells. The immediate danger arises from the loss of the protective skin barrier, which exposes the underlying tissue to environmental pathogens, leading to sepsis, which is the leading cause of death in these patients. Furthermore, the mandatory involvement of at least two mucosal surfaces--the **eyes**, **oral cavity**, and **genitals**--is a defining feature that distinguishes SJS from less severe drug eruptions and contributes significantly to both acute morbidity and long-term sequelae.

Etiology and Causal Agents

The etiology of Stevens-Johnson Syndrome is overwhelmingly linked to exposure to certain

therapeutic agents, confirming the initial observation that SJS is a severe adverse drug reaction. A small number of infections, particularly those involving **Mycoplasma pneumoniae** or certain viruses, may also precipitate SJS, especially in pediatric populations, though drug exposure remains the dominant trigger in adult cases. The window of risk for drug-induced SJS is generally highest within the first few weeks to two months following the initiation of a new medication, although reactions can occur later. Identification of the specific pharmacological class responsible is vital for patient safety and for preventing recurrence, as re-exposure to the same drug or chemically related compounds often results in a rapid and even more severe reaction.

The most strongly implicated drug classes include the **anticonvulsive** agents and various **antibiotic** medications. Among anticonvulsants, aromatic compounds such as phenytoin, carbamazepine, lamotrigine, and phenobarbital carry a substantial risk. The mechanism often involves the formation of reactive metabolites that the body fails to adequately detoxify, leading to hapten formation and subsequent immune recognition. Similarly, widely used antibiotics, particularly the **sulfonamide** class (e.g., sulfamethoxazole), have long been recognized as high-risk agents. Other medications frequently implicated include non-steroidal anti-inflammatory drugs (NSAIDs), particularly the oxicam derivatives, and specific agents used for treating hyperuricemia, most notably **allopurinol**, which is responsible for a significant proportion of severe cases globally.

Beyond direct drug exposure, patient-specific factors play a critical role in determining susceptibility to SJS. Genetic predisposition is increasingly recognized, with specific human leukocyte antigen (HLA) alleles strongly associated with increased risk when certain drugs are administered. For example, the HLA-B*1502 allele is strongly correlated with carbamazepine-induced SJS in populations of Southeast Asian descent, while HLA-B*5801 is highly associated with allopurinol-induced SJS, regardless of ethnicity. These genetic markers suggest that the individual's immune system presentation of drug metabolites dictates whether a cytotoxic reaction will be launched. Other risk factors include pre-existing systemic diseases such as systemic lupus erythematosus, HIV infection, and concurrent radiation therapy, all of which may impair immune regulation or increase general inflammatory burden, thereby lowering the threshold for developing this devastating reaction.

Pathophysiology and Mechanism of Action

The underlying pathophysiology of Stevens-Johnson Syndrome involves a complex interplay of drug metabolism abnormalities and subsequent cell-mediated cytotoxicity, classifying it broadly as a Type IV delayed hypersensitivity reaction. The central event is massive, widespread **keratinocyte apoptosis**--the programmed death of the epidermal cells. This process is initiated when the immune system, specifically cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells, recognizes drug-derived antigens or altered self-proteins displayed on the surface of epidermal

cells. The reaction is not antibody-mediated but rather driven by the direct killing action of immune cells, facilitated by potent pro-inflammatory mediators.

A key mechanism involves the **Fas-Fas ligand (FasL)** signaling pathway. Fas is a death receptor expressed on the surface of various cells, including keratinocytes, while FasL is expressed by activated CTLs. When a T-cell recognizes a keratinocyte presenting a drug antigen, it upregulates FasL expression. The binding of FasL to Fas triggers a cascade within the keratinocyte, activating caspase enzymes that ultimately lead to cellular self-destruction. In SJS and TEN, this mechanism is highly amplified, leading to the rapid destruction of large sheets of the epidermis. Furthermore, other cytotoxic molecules released by T-cells, such as **granzyme B** and **perforin**, contribute significantly to cell membrane damage and rupture, accelerating the process of epidermal necrosis and detachment.

Recent research has also highlighted the role of granulysin, a cytotoxic molecule released by CTLs, which appears to be highly concentrated in the blister fluid of SJS and TEN patients and may be a major effector molecule in promoting keratinocyte death. The initial trigger, whether a drug or a pathogen, causes the release of inflammatory cytokines (e.g., TNF-alpha and IL-18) which recruit and activate the T-cells. This inflammatory environment creates a positive feedback loop, exacerbating the cytotoxic attack. The massive destruction of the epidermis results in the formation of subepidermal bullae, where the necrotic epidermis lifts off the viable dermis, creating the characteristic large, fluid-filled lesions observed clinically. This loss of the protective barrier and the exposure of the raw dermis is what accounts for the severe systemic consequences, including massive insensible water loss, electrolyte imbalances, and thermoregulatory dysfunction, requiring critical care support.

Clinical Presentation and Symptoms

The clinical course of Stevens-Johnson Syndrome typically follows a predictable progression, beginning with a prodromal phase that mimics a common viral illness. This phase lasts between one and three weeks and includes symptoms such as high-grade **fever**, profound **malaise**, headache, cough, and generalized body aches. This non-specific presentation often leads to misdiagnosis or delay in recognizing the impending severe cutaneous reaction. The transition from the prodrome to the eruptive phase is often abrupt and alarming, marked by the rapid onset of painful cutaneous and mucosal lesions.

The characteristic skin lesions initially manifest as poorly defined, often coalescing erythematous macules and patches, frequently accompanied by atypical target lesions, which have two zones rather than the three zones seen in classic erythema multiforme. Within hours to days, these lesions evolve into **flaccid blisters** (bullae) as the epidermis begins to detach from the underlying dermis. A key diagnostic sign is the Nikolsky sign, where gentle lateral pressure on

seemingly unaffected skin causes the epidermis to shear off, indicating widespread subclinical epidermal detachment. The distribution of lesions often starts on the face and trunk before spreading centrifugally, but by definition, SJS involves epidermal detachment covering less than 10% of the total BSA.

A defining and often debilitating feature of SJS is the severe involvement of **mucous membranes**. At least two mucosal sites are typically affected, including the oral cavity, the ocular surface, and the anogenital regions. Oral lesions are extremely painful, appearing as hemorrhagic erosions and crusting that severely impede eating, swallowing, and even speaking, contributing to malnutrition and dehydration. Ocular involvement is particularly dangerous, ranging from severe purulent conjunctivitis to pseudomembrane formation, corneal erosions, and ulceration. If not promptly and aggressively managed, this ocular damage can lead to permanent vision impairment, chronic dry eye syndrome, and even blindness. Genital and urethral involvement can cause painful urination and later lead to strictures and scarring, highlighting the systemic and destructive nature of the disease.

Diagnosis and Differential Diagnosis

The diagnosis of Stevens-Johnson Syndrome is primarily a clinical one, based on the characteristic morphology of the skin lesions, the mandatory involvement of mucosal surfaces, and the calculation of the percentage of epidermal detachment. A detailed and rapid history focusing on drug exposure in the preceding two to six weeks is paramount, aiming to identify and immediately withdraw the causative agent. However, due to the high mortality associated with delayed or incorrect treatment, confirmatory tests are often performed rapidly upon admission to ensure appropriate classification and management.

A **skin biopsy** remains the gold standard for histological confirmation. Histopathology reveals full-thickness epidermal necrosis, characterized by widespread, apoptotic keratinocytes, often with a sparse lymphocytic infiltrate at the dermal-epidermal junction. This finding is critical for distinguishing SJS from other blistering disorders, such as severe bullous impetigo or pemphigus. Direct immunofluorescence studies are usually negative, which helps rule out autoimmune bullous diseases. Laboratory tests usually reveal non-specific findings such as leukocytosis, anemia, and elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate). Liver enzyme elevation may also be noted, particularly if the causative drug, like certain anticonvulsants, causes systemic organ damage.

The most critical aspect of the differential diagnosis is the distinction between SJS, SJS/TEN Overlap, and full-blown Toxic Epidermal Necrolysis (TEN). These three conditions represent a spectrum of the same disease mechanism, differentiated solely by the extent of epidermal detachment:

Stevens-Johnson Syndrome (SJS): Epidermal detachment involving less than **10%** of the BSA.

SJS/TEN Overlap: Epidermal detachment involving between **10% and 30%** of the BSA.

Toxic Epidermal Necrolysis (TEN): Epidermal detachment involving more than **30%** of the BSA.

Other conditions that must be excluded include staphylococcal scalded skin syndrome (SSSS), which primarily affects children and involves a superficial cleavage plane; generalized fixed drug eruptions; and severe cases of paraneoplastic pemphigus, although the latter lacks the strong correlation with recent drug intake seen in SJS.

Treatment and Management Strategies

Management of Stevens-Johnson Syndrome requires immediate, aggressive, and specialized care, ideally within a medical intensive care unit (ICU) or a dedicated burn unit, as the clinical care mimics the management of severe thermal burns. The single most important therapeutic intervention is the immediate and definitive **withdrawal of the suspected offending drug**. If multiple drugs are potential culprits, all non-essential medications must be discontinued until the primary cause is identified, which can significantly halt the progression of the disease.

The cornerstone of acute SJS treatment is comprehensive supportive care aimed at maintaining homeostasis. This involves rigorous fluid and electrolyte management to compensate for the massive evaporative losses from the denuded skin surfaces, careful attention to wound care using non-adherent dressings and sterile techniques to prevent secondary infection (sepsis), and meticulous nutritional support, often requiring nasogastric tube feeding due to severe oral pain. Pain management is paramount and typically requires high-dose intravenous opioids. Furthermore, temperature regulation is critical, as the loss of skin leads to hypothermia and increased metabolic demand.

Specific treatments aimed at modulating the immune response remain controversial and highly debated among specialists.

Systemic Corticosteroids: Early, high-dose use was previously common but is now largely discouraged due to evidence suggesting they may increase the risk of sepsis without improving mortality, though some specialists advocate for extremely high-dose pulse therapy very early in the disease course.

Intravenous Immunoglobulin (IVIG): IVIG is hypothesized to block the Fas-FasL interaction, thereby inhibiting keratinocyte apoptosis. While widely used, clinical trial evidence supporting its efficacy remains mixed, and it is usually reserved for rapidly progressing cases or those transitioning toward TEN.

Cyclosporine: This immunosuppressant drug is gaining favor, particularly in Europe, as it inhibits T-cell activation and proliferation, thereby suppressing the cytotoxic cascade. Early initiation of cyclosporine has shown promising results in reducing the duration of skin re-epithelialization and possibly lowering mortality rates.

Crucially, all patients require immediate ophthalmologic consultation to manage the severe ocular complications. Treatment involves intensive lubrication, topical steroids, and sometimes surgical interventions to prevent corneal damage and subsequent vision loss.

Prognosis and Long-Term Sequelae

The prognosis for Stevens-Johnson Syndrome is guarded, reflecting its status as a life-threatening emergency. The acute mortality rate for SJS alone typically ranges from 5% to 15%, increasing dramatically in elderly patients, those with underlying comorbidities, and especially those whose disease progresses to SJS/TEN overlap or full TEN. The primary cause of death in the acute phase is overwhelming **sepsis**, usually originating from the exposed cutaneous or mucosal surfaces, followed by multi-organ failure and severe pulmonary complications, such as pneumonia or acute respiratory distress syndrome (ARDS).

For survivors, the long-term morbidity and impact on quality of life can be substantial, as the immune-mediated damage often leads to permanent tissue scarring. The most frequent and often severe long-term sequelae involve the **ocular system**. Chronic complications include severe dry eye syndrome, photophobia, trichiasis (in-turned eyelashes), symblepharon (adhesion of the conjunctiva to the eyelid), and corneal opacity, often necessitating complex reconstructive surgery or lifelong specialized care to prevent total blindness. These ocular issues can severely limit a patient's daily activities and employment opportunities.

Other significant long-term complications include chronic dermatological issues, such as permanent hyperpigmentation or hypopigmentation, skin scarring, and impaired sweating capacity. Furthermore, mucosal scarring can lead to functional impairment, including esophageal strictures, chronic vulvovaginal erosions, and urethral strictures, particularly in males, which require urological intervention. Pulmonary sequelae, such as bronchiolitis obliterans, are also reported, causing restrictive lung disease. Due to the traumatic nature of the illness, many survivors also require ongoing psychological support to manage post-traumatic stress disorder (PTSD), depression, and anxiety related to the acute hospitalization and permanent disfigurement.

Distinction from Toxic Epidermal Necrolysis (TEN)

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are widely accepted as being part of the same disease spectrum, representing varying degrees of severity of the same underlying T-cell mediated cytotoxic reaction. The distinction between the two is quantitative, based strictly on the

percentage of **Body Surface Area (BSA)** exhibiting epidermal detachment. Understanding this distinction is critical because the extent of skin loss directly correlates with the severity of systemic involvement, the risk of complications, and the overall mortality rate.

While SJS is defined by less than 10% BSA detachment, TEN is defined by detachment greater than 30%. SJS/TEN Overlap occupies the intermediate range (10-30%). The clinical presentation is otherwise identical, involving the same prodromal symptoms, blistering morphology, and mandatory mucosal involvement. However, the prognosis differs markedly; the mortality rate for full TEN can exceed 30%, making it significantly more lethal than SJS. Patients diagnosed with TEN typically require more immediate and intensive resource allocation, including transfer to specialized burn centers, due to the extreme physiological stress imposed by the massive loss of skin barrier function.

The severity assessment and prognosis estimation in both SJS and TEN are often aided by the use of scoring systems, such as the **SCORTEN** scale (Score of Toxic Epidermal Necrolysis). This prognostic tool utilizes seven independent risk factors present at the time of admission, including age, heart rate, presence of malignancy, initial percentage of BSA detachment, and specific laboratory values (e.g., blood urea nitrogen, glucose, bicarbonate levels). The SCORTEN score calculates the probability of death, guiding clinicians in their decision-making regarding the urgency of transfer and the level of supportive care required. Although named for TEN, the SCORTEN scale is routinely applied to SJS patients as well, providing a standardized measure of disease severity and anticipated outcome.