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Stevens-Johnson Syndrome Induced by Polypharmacy (Suspected Sulfasalazine, Cefotaxime, and Levofloxacin): A Case Report

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ABSTRACT

Background: Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening conditions typically triggered by medications, characterized by widespread skin detachment and mucosal involvement. Prompt diagnosis and treatment are crucial for improving patient outcomes. The severity of these conditions can be assessed using the SCORTEN scale, which helps predict mortality risk. **Case Illustration:** We report the case of a 42-year-old female, Mrs. M, who developed erythematous lesions covering the body for less less than 10% of her body surface area (BSA) after being treated with sulfasalazine, cefotaxime, and levofloxacin. Her symptoms included mucosal involvement and a positive Nikolsky sign, indicative of SJS. The SCORTEN score calculated for this patient was 1/7, correlating with a 3,2% mortality risk. She was admitted to the emergency department and received supportive care at isolation room, including fluid management, wound dressing, and topical to systemic corticosteroids. **Discussion:** This case highlights the critical role of early identification and intervention in SJS/TEN, as timely discontinuation of the offending drug and the initiation of supportive therapy are vital for patient survival. The use of SCORTEN provided valuable prognostic information, guiding the intensity of the treatment approach. Despite the initial severity, the patient responded positively to the treatment regimen, with a gradual improvement in her condition and no significant long-term complications. **Conclusion:** This case underscores the importance of rapid diagnosis, immediate withdrawal of the causative agent, and comprehensive supportive care in managing SJS. The utilization of prognostic tools like SCORTEN can aid in tailoring the treatment approach and improving patient outcomes in such severe drug reactions.

Keywords: *stevens-johnson syndrome, toxic epidermal necrolysis, scorten, sulfasalazine, cefotaxime, levofloxacin, corticosteroids, drug-induced reactions, supportive care.*

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) most often triggered by medications, marked by extensive epidermal necrosis and detachment. SJS is characterized by a macular rash, painful blistering, bullous lesions, fever, purulent conjunctivitis, and stomatitis.[1] TEN, also known as Lyell's syndrome, is a more severe and potentially life-threatening condition[2], with a mortality rate of 5%–10% for SJS and up to 30%–40% for TEN.[3,4] SJS is defined as involving less than 10% of the total body surface area (TBSA), SJS/TEN

overlap involves 10%–30% TBSA, and TEN involves more than 30% TBSA.[5,6] The annual incidence rates for SJS range from 1 to 6 cases per million people, while TEN ranges from 0.4 to 1.45 cases per million people.[7]

The precise etiology and pathological mechanisms behind SJS/TEN remain unclear. Early research into the immunophenotype of lymphocytes found in blister fluid from SJS/TEN lesions suggested a cell-mediated cytotoxic reaction against keratinocytes, leading to extensive apoptosis.[8] Subsequent research indicated that cytotoxic T cells are drug-specific, restricted by human leukocyte antigen class I, and target the native drug rather than its metabolites.[9] Drugs can directly stimulate the immune system by binding to major histocompatibility complex class I and T-cell receptors, causing clonal expansion of drug-specific cytotoxic T cells that destroy keratinocytes directly and indirectly through the recruitment of other cells that release death mediators like granulysin.[10]

Numerous studies have identified various drugs, including anticonvulsants, sulfonamides, antibiotics, NSAIDs, antifungals, antimalarials, and allopurinol, as causative agents in hypersensitivity reactions leading to SJS/TEN.[4,11] The syndrome typically manifests 4–14 days after drug initiation but may not become apparent until 3–6 weeks after exposure.[6] However, there is limited information on how clinical symptoms of drug-induced SJS/TEN vary with different drugs. This case report aims to contribute to the understanding of the clinical presentation and management of drug-induced SJS/TEN, particularly highlighting the variability in symptoms based on the type of drug involved.

CASE ILLUSTRATION

Mrs. M, a 42-year-old female of Javanese ethnicity, residing in Kebayoran Baru, South Jakarta, was admitted to the hospital's emergency department on July 18, 2024. She practices Islam. Mrs. M presented to the emergency department with a history of red spots appearing on her body one day before admission. She reported that her skin felt blistered, and the bubbles that formed eventually burst, discharging clear fluid. Additionally, she experienced purulent conjunctivitis, swollen eyelids, and cracked lips.

The patient had been previously admitted to the same hospital on July 12, 2024, where she was diagnosed with typhoid fever and treated with cefotaxime. The day following her cefotaxime infusion, she developed swollen eyes, leading to a switch in her antibiotic regimen to oral levofloxacin. Mrs. M also had a history of osteoarthritis and had been taking oral sulfasalazine for nearly a month. The patient denied any known drug allergies. There was no reported family history of similar issues. Upon examination, Mrs. M appeared moderately ill. She was alert and oriented, with a body weight of 87.3 kg, height of 165 cm, and blood pressure of 111/64 mmHg. Her pulse was 94 beats per minute, respiratory rate of 20 per minute, temperature was 36.6°C, and SpO2 was 98% on room air.

Based on physical examination patient’s head showed normocephalic but with erythematous-purpuric lesions featuring exfoliation and erosion, presenting as lenticular to plaques, some of which were discrete while others were partially confluent, with indistinct borders. The eye examination

revealed erythema, positive discharge, and eyelid edema. Her mouth had erosive lesions on the lips. Similar erythematous-purpuric lesions with exfoliation and erosion were observed on her neck, thorax, abdomen, and extremities, with warm acral areas and a capillary refill time of less than 2 seconds.

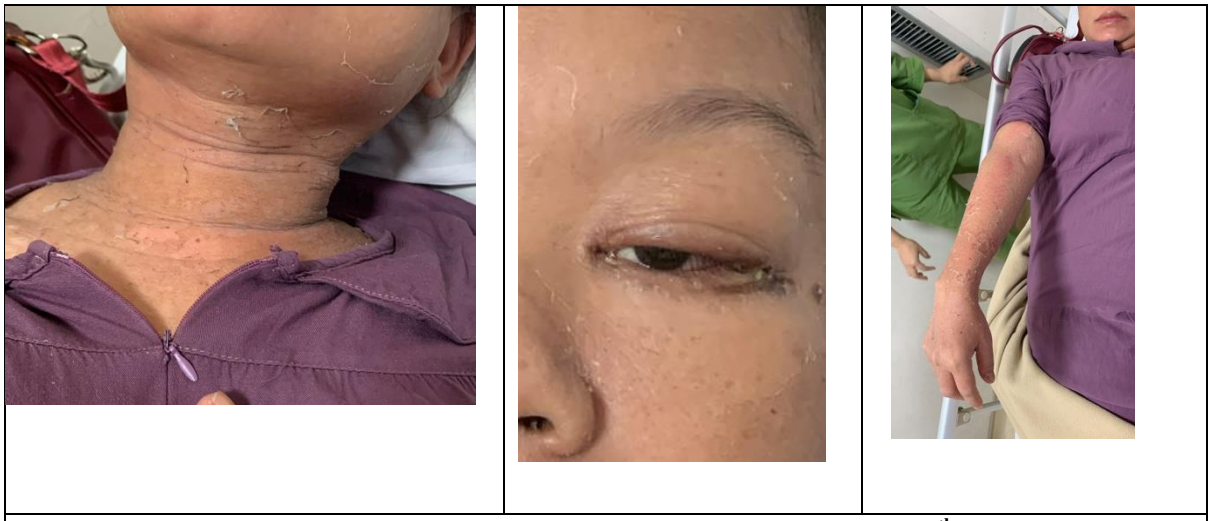

Figure 1. Patient's Clinical Effloresence Feature on July 18th 2024

Laboratory results showed a hemoglobin level of 11.5 g/dL, red blood cells at 4.9 million/µL, hematocrit at 37%, and a platelet count of 150,000/µL. The erythrocyte sedimentation rate (ESR) was elevated at 43 mm/h, with a white blood cell count of 5.5 million/µL. Differential leukocyte counts indicated 0% basophils, 2.0% eosinophils, 1.0% monocytes, 8.0% lymphocytes, 1.0% band neutrophils, and 88.0% segmented neutrophils. Blood glucose was measured at 83 mg/dL, and electrolyte levels were within normal limits. An X-ray of the right knee suggested osteoarthritis or rheumatoid arthritis.

Table 1. Laboratory Findings

Test	Result	Normal Range
Hemoglobin (Hb)	11.5 g/dL	12.0–16.0 g/dL
Erythrocytes (RBC)	4.9 million/µL	4.0–5.5 million/µL
Hematocrit (Hct)	37%	36%–46%
Platelets (Plt)	150,000/µL	150,000–450,000/µL
Erythrocyte Sedimentation Rate (ESR)	43 mm/h	0–20 mm/h
White Blood Cell Count (WBC)	5.5 million/µL	4.0–10.0 million/µL
Basophils	0%	0–1%
Eosinophils	2.0%	1–4%
Monocytes	1.0%	2–8%
Lymphocytes	8.0%	20–40%
Band Neutrophils	1.0%	0–5%
Segmented Neutrophils	88.0%	45–75%
Glucose (GDS)	83 mg/dL	70–100 mg/dL
Sodium	136 mmol/L	135–145 mmol/L
Potassium	4.0 mmol/L	3.5–5.0 mmol/L
Chloride	101 mmol/L	98–106 mmol/L

The patient was diagnosed with Stevens-Johnson Syndrome, with suspected causative agents including sulfasalazine, cefotaxime, and levofloxacin. Mrs. M was admitted to an isolation room, and suspected drugs were discontinued. She was started on intravenous fluids with Ringer's Lactate, 500 cc every 6 hours, and received dexamethasone injections (5 mg IV twice daily). Topical treatments included hydrocortisone ointment (2.5%) for erythematous and purpuric lesions twice daily and Kenalog ointment for erosive lesions on the lips twice daily. Open compresses with 0.9% NaCl were applied to erosive-exfoliative lesions on the lips and body. Eye care included Cendo Lyteers eye drops every 2 hours, Cendo Polydex eye drops every 4 hours, and Gentamicin eye ointment three times daily. Daily eyelid hygiene was performed. An internist was consulted and agreed with the fluid therapy and recommended a diet of strained porridge without seafood, providing 1700 kcal.

On July 19th 2024, Mrs. M reported no new lesions and a reduction in pain at the corners of her lips and eyes. On examination, she appeared moderately ill with stable vital signs. Dermatological status showed the same erythematous-purpuric lesions with exfoliation and erosion but with reduced eyelid edema and improved lip lesions. The treatment plan included continuing dexamethasone (5 mg IV twice daily, with tapering if improvement continued), intravenous fluids, hydrocortisone and Kenalog ointments, open compresses with NaCl, eye care as previously prescribed, and a diet of strained porridge.

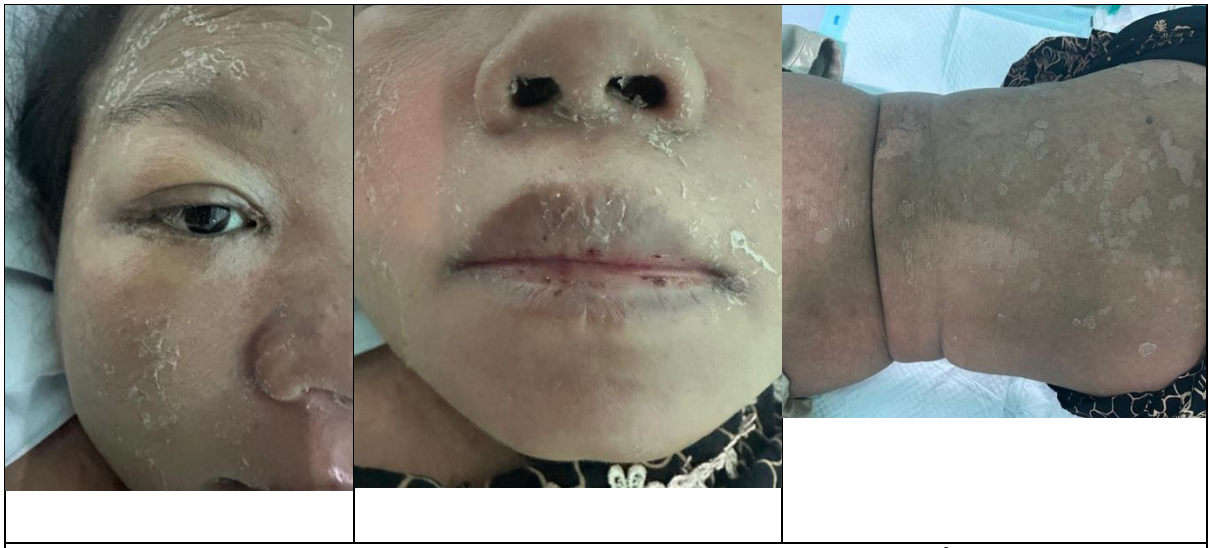

Figure 2. Patient's Clinical Effloresence Feature on July 19th 2024

On July 20th 2024 follow up, Mrs. M reported no new lesions and no pain in the corners of her lips and eyes. Examination revealed her condition had improved, with mild symptoms remaining. Dermatological status showed reduced erythema and edema in the eye region, with persistent erosive lesions at the corners of the lips. The treatment plan included reducing dexamethasone to 5 mg IV once daily, continuing intravenous fluids, hydrocortisone and Kenalog ointments, open compresses with NaCl, eye care, and a diet of rice providing 2500 kcal. She was advised that discharge would be considered after further evaluation.

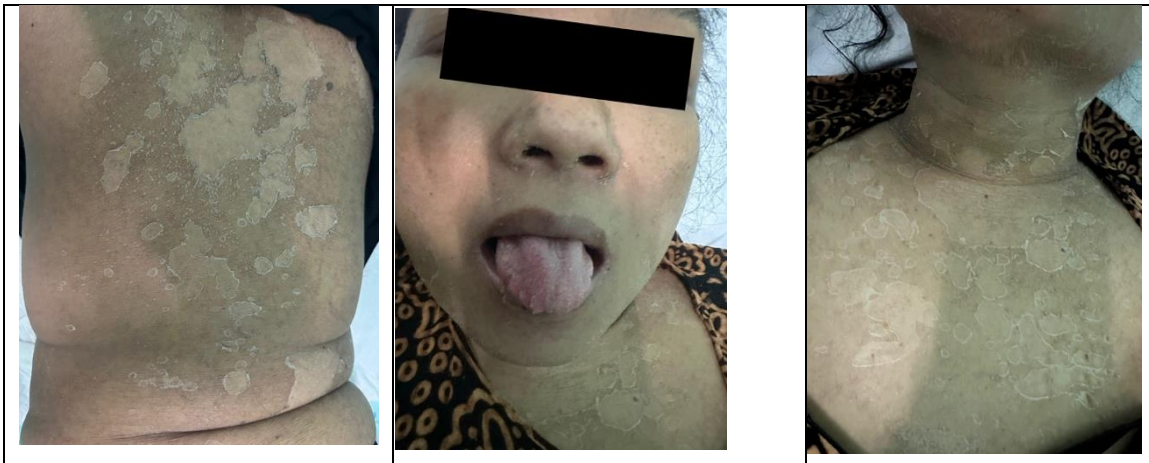

Figure 3. Patient's Clinical Effloresence Feature on July 20th 2024

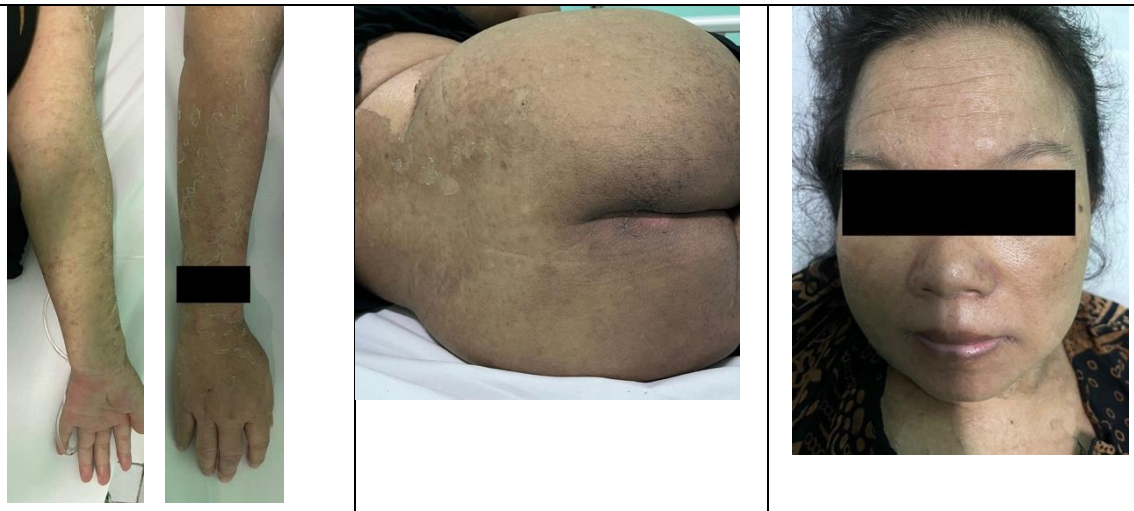

Figure 4. Patient's Clinical Effloresence Feature on July 21st 2024

Table 2. Patient's SCORTEN

Criterion	Mrs. M's Status	Points
Age (> 40 years)	42 years	1
Cancer	No active cancer	0
Early mortality (BSA >30%)	Assumed <10 % BSA involvement	0
Heart rate ≥120 bpm	94 bpm	0
Initial serum urea ≥10 mmol/L	Not provided	0

Initial serum bicarbonate ≤20 mmol/L	Not provided	0
Glucose ≥14 mmol/L	83 mg/dL (<252 mg/dL)	0
Total SCORTEN Score: 1/7		

DISCUSSION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute, and potentially life-threatening conditions characterized by hypersensitivity reactions mediated by immune complexes, often linked to drug use.[11] These syndromes result in extensive epidermal detachment, separation of the dermal-epidermal junction, and involvement of mucous membranes. The general condition of patients can range from mild to severe. SJS was first described by Albert Stevens and Frank Johnson in 1922, following the identification of two cases involving widespread epidermal eruption accompanied by fever, stomatitis, and severe purulent conjunctivitis.[12]

Both SJS and TEN can affect children and adults of all races. The incidence rate ranges from 1 to 10 cases per million people per year, with pediatric cases constituting about 20% of the total. The mortality rate for SJS varies between 1% and 4%, whereas TEN has a significantly higher mortality rate, ranging from 25% to 35%. TEN is more frequently observed in women, while SJS is more common in men. The incidence of these conditions increases with age and is influenced by various predisposing factors, including comorbidities, polypharmacy, genetic predispositions, and immunosuppression (notably in HIV patients, where the incidence is 1000 times higher than in the general population, with a rate of 1 per 1000 cases per year). Other contributing factors include malignancies and concurrent use of radiotherapy and anticonvulsants.[13]

Lu et al (2016)'s study, which uses data representative of the ethnically and racially diverse US population, reveals that race is a strong predictor of the risk for SJS/TEN as a type of ULDAE. We found that Asians and Blacks face a risk of SJS/TEN that is 12 and 5 times higher than that of Whites, respectively. These significant associations persisted across various reference groups. In contrast, despite being the largest minority group in the US during the study period, Hispanics exhibited a low frequency of these serious events, suggesting their risk is not higher than that of Whites or other racial groups. This variance in risk aligns with the frequencies of HLA-B5801 in the US population (i.e., 7.4% in Asians, 4% in Blacks, 1% in Whites, and 1% in Hispanics). Given that allopurinol is the only ULD with an established link to SJS/TEN, and considering its prevalent use in the US, our findings advocate for extra caution when prescribing allopurinol to Asians and Blacks and support the ACR's recommendation to screen for HLA-B5801 in high-risk Asians.[10]

Study analysis indicates that Asians in the US are approximately 12 times more likely than Whites to experience SJS/TEN as a ULDAE. This is consistent with a recent Taiwanese population-based study, which reported a higher incidence of hospitalized AHS compared to a US Medicaid study from five states (2 vs. 0.69 cases per 1000 allopurinol users, respectively). The latter study also found that Whites were underrepresented among AHS cases (24%), which aligns with our results, although it

did not include data on minority races. Additionally, a New Zealand study reported an increased risk of AHS among Chinese descendants compared to European descendants (OR = 24.2 [95% CI, 3.0 to 199.0]).[16] These findings collectively suggest a substantially higher risk of allopurinol-induced SJS/TEN among Asians compared to Whites, reflecting their higher allele frequencies of HLA-B5801.[26] Consequently, the Taiwanese Food and Drug Administration has adopted a new policy recommending febuxostat as an alternative first-line ULD for CKD patients to reduce allopurinol-associated SJS/TEN risk due to the high background risk in their population.[3]

The NIS database aggregates various Asian populations (e.g., Chinese, Asian Indians, Filipinos, Vietnamese, Koreans, and Japanese) into one category. Therefore, our results reflect the average risk across these diverse Asian groups, similar to the overall HLA-B5801 allele frequency among US Asians (7.4%) [26]. It is worth noting that the allele frequency of HLA-B5801 is low among US Japanese (0.8%), comparable to Whites and the Japanese population in Japan (0.6%) [26]. Thus, while we could not estimate risk specifically for US Japanese individuals, we anticipate a risk level similar to that of Whites. This is consistent with anecdotal evidence from Japan, where ULD is used for treating asymptomatic hyperuricemia, particularly when accompanied by cardiovascular-renal-metabolic comorbidities.[33] In contrast, recent Taiwanese studies advise against this practice due to the increased risk of AHS associated with asymptomatic hyperuricemia and renal or cardiovascular conditions.[14,15]

The causes of SJS and TEN can be categorized into several groups:[16]

- **Drug-induced:** Medications are the primary cause of SJS (50% - 80% of cases) and TEN (up to 80% of cases). Infections, combinations of infections and drugs, and malignancies can also be involved. More than 100 drugs have been identified as potential causes of SJS or TEN. Drug reactions usually appear after the first 8 weeks of medication use, depending on the dose.
- Antibiotics are the most common triggers, followed by analgesics, cough and cold medications, NSAIDs, antiepileptics, and antigout drugs. Among antibiotics, penicillins and sulfonamides are the most frequently implicated, accounting for 26% of cases. In the antiepileptic category, drugs such as phenytoin, lamotrigine, carbamazepine, valproic acid, oxcarbazepine, and barbiturates are known to trigger SJS within the first 60 days of use. Nevirapine is an antiretroviral drug associated with SJS. Other drugs reported to cause SJS include modafinil, high-dose allopurinol (≥200 mg per day), mirtazapine, TNF-alpha antagonists, cocaine, and sertraline.
- **Infections:** Infections are the second most common cause after drugs. Viruses frequently reported as triggers include group A beta-hemolytic streptococcus, diphtheria, brucellosis, lymphogranuloma venereum, mycobacteria, Mycoplasma pneumoniae, rickettsia, tularemia, and typhoid fever. Fungal infections such as paracoccidioidomycosis, dermatophytosis, and histoplasmosis have also been associated with SJS. Most patients diagnosed with SJS have a history of upper respiratory tract infections.

- **Genetic factors:** Certain human leukocyte antigens (HLAs) are suspected to contribute to the risk of SJS. For example, HLA-B1502 is associated with an increased risk for reactions to carbamazepine, phenytoin, and lamotrigine. HLA-B5802 and HLA-A3101 are linked to increased risk for carbamazepine, while HLA-B5801 is associated with allopurinol. Other HLAs, such as HLA-B44, HLA-A29, HLA-B12, HLA-DR7, HLA-A2, HLA-A0206, and HLA-DQB1-0601, are also associated with higher risks of SJS, particularly in relation to specific drugs and ocular complications.

Drugs are the most frequent triggers of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see Table 3). In up to 15–30% of cases, no specific offending agent can be identified.[12] Although the triggers of SJS/TEN are well-documented, their pathophysiology remains incompletely understood. These conditions are thought to be T-cell-mediated type IV hypersensitivity reactions. Several hypotheses explain how drugs might provoke an immunological response leading to SJS/TEN.[19,20]

The first hypothesis, known as the hapten/pro-hapten concept, suggests that small-molecule drugs covalently bind to serum proteins, forming complexes that are recognized by certain HLA molecules and presented to T-cells, triggering an immune response. The pharmacological interaction (p-i) concept proposes that chemically inert drugs, which do not covalently bind with serum proteins, directly bind to HLA molecules, thereby activating T-cells. The altered peptide concept posits that drugs bind within HLA binding pockets, altering the presentation of self-proteins to T-cells, leading to the immune system recognizing these proteins as non-self and initiating a response. Despite the uncertainty about the exact mechanism, these processes result in T-cell activation in response to a drug or infection, leading to epidermal necrosis.[17]

Early theories suggested that keratinocyte death was mediated by interactions between soluble Fas ligand (sFasL) and the Fas receptor on keratinocytes. Later studies identified granulysin as a more critical mediator of apoptosis. Chung et al. found that granulysin levels in the blister fluid of SJS/TEN patients were 2–4 times higher than those of perforin, granzyme B, and sFasL. Reducing granulysin levels decreased cytotoxicity, and injecting granulysin into mice skin induced an SJS/TEN-like reaction.[6,21] Further research confirmed granulysin's significant role in the disease and showed that its levels in blister fluid correlated with disease severity. Although granulysin appears to be the primary driver of epidermal necrosis, it does not act in isolation. Su et al. examined serum levels of 28 cytokines and chemokines, identifying several that were upregulated in SJS/TEN patients, with granulysin and IL-15 correlating with disease severity. Additionally, necroptosis, or programmed necrosis, has been explored and found to contribute to keratinocyte death, potentially offering important diagnostic insights.[22]

Table 3. List of Medications at Risk for SJS/TEN[6,11]

High Risk	Moderate Risk	Low Risk

Allopurinol	Cephalosporins	Beta blockers
Carbamazepine	Macrolides	ACE inhibitors
Cotrimoxazole and other sulfonamides	Quinolones	Calcium Channel Blockers
Sulfasalazine	Tetracyclines	Thiazide diuretics
Lamotrigine	Acetic acid NSAIDs (e.g., diclofenac)	Sulfonylureas
Nevirapine	Insulin	Propionic acid NSAIDs (e.g., ibuprofen)
Oxicam NSAIDs (e.g., meloxicam)		
Phenobarbital		
Phenytoin		

Ny. M's history reveals she received sulfasalazine for osteoarthritis, a high risk drug known to potentially trigger SJS/TEN. The onset of her symptoms after receiving sulfasalazine strongly suggests that this medication could have played a significant role. Additionally, she was also received intravenous cefotaxime and oral levofloxacin after intravenous cefotaxime being replaced, another moderate risk drug linked to SJS/TEN.

The development of Toxic Epidermal Necrolysis (TEN) primarily results from a severe T-lymphocyte-mediated immune reaction, which leads to the destruction of keratinocytes expressing foreign antigens. Elevated levels of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are detected in blister fluid, contributing to the recruitment of cytotoxic T-cells to the epidermis. This interaction induces cell death through apoptosis, mediated by a cascade of intracellular enzymes known as caspases.[18]

TEN often begins with a prodromal phase that may include symptoms like fever, malaise, cough, stinging eyes, and a sore throat. The disease progresses to present with erythematous rashes, bullae, and extensive detachment of the epidermis from the dermis. Cutaneous lesions are characterized by diffuse erythema with target-like lesions, which are round, less than 3 cm in diameter, and feature three concentric zones: a central area of dusky erythema, a middle zone of edema, and an outer ring of erythema with a defined edge. The diagnosis of SJS is made when these target lesions are accompanied by involvement of at least two mucous membranes. TEN can be associated with severe complications such as multi-organ failure, sepsis, gastrointestinal hemorrhage, and pulmonary embolism.

Ocular complications occur in 50% to 88% of TEN cases and may include purulent conjunctivitis, corneal ulceration, anterior uveitis, entropion, dry eye syndrome, and significant visual loss. Pulmonary involvement is common but generally mild, with only 10 to 20% of cases requiring ventilatory support. In the first case, pulmonary involvement was noted, leading to hospital-acquired pneumonia. Pulmonary complications reported in TEN range from tracheobronchial mucosal necrosis to pulmonary edema, acute respiratory distress syndrome, and pneumonia, affecting 20–50% of patients. Additionally, genital involvement in TEN may present with erosive and ulcerative vaginitis, as well as vulvar bullae.

In evaluating patient's symptoms, the rapid onset and progression of her condition align with what is typically seen in drug-induced SJS/TEN. The extensive erythematous and purpuric lesions, along with exfoliation and mucosal involvement, are characteristic features of these syndromes. The involvement of her eyes and cracked lips further supports the diagnosis, as mucosal involvement is a hallmark of SJS.[6]

Laboratory findings from Ny. M's tests show normal ranges for hematological parameters and electrolytes, which helps rule out other potential causes but does not specifically identify SJS/TEN. A more detailed analysis, such as assessing granulocyte levels or testing for cytokines and chemokines, could provide further insights. Granulysin levels, for instance, are known to be elevated in SJS/TEN and could be indicative of the disease's severity.

Certain populations are more susceptible to SJS, including slow acetylators (individuals with liver organs unable to detoxify drug metabolites), immunocompromised individuals (especially those with HIV), and brain tumor patients undergoing radiotherapy alongside antiepileptic drugs. Drug metabolites may have a direct toxic effect or act as haptens that interact with body tissues, making them antigenic. The presentation of these antigens triggers the production of tumor necrosis factor-alpha (TNF-α) by dendritic cells and macrophages in the epidermis, leading to the recruitment and proliferation of T lymphocytes. Subsequently, activated cytotoxic T lymphocytes (CD8) induce apoptosis in epidermal cells through three main pathways:[18]

1. **Fas-FasL Interaction**: Fas is a membrane protein that, upon interacting with Fas ligand, induces apoptosis via the activation of intracellular caspases. The source of FasL production is not fully known but is suspected to come from T lymphocytes, NK cells, keratinocytes themselves, or peripheral blood mononuclear cells.
2. **Perforin/Granzyme B Pathway**: Perforin and granzyme B are involved in the apoptosis of keratinocytes. Inhibition of these molecules can reduce the cytotoxic effects of lymphocytes on keratinocytes.
3. **Granulysin**: Granulysin, a cytolytic protein produced by cytotoxic T lymphocytes, NK cells, and NKT cells, binds to cell membranes, disrupting them and causing cell death. High levels of granulysin are found in blister fluid of SJS/TEN patients.

Clinically, SJS/TEN are categorized into three groups based on the extent of body surface area (BSA) involvement. The clinical symptoms are divided into two phases: the acute phase and the residual symptoms phase.

Acute Phase

SJS/TEN typically begins within eight weeks of drug exposure. Initial symptoms, or prodromal symptoms, can be nonspecific, such as fever and flu-like symptoms (itching and burning eyes, sore throat, cough with productive sputum, runny nose, headache, malaise, and arthralgia). These symptoms

can last up to a week. Following this period, red lesions with a burning sensation appear symmetrically on the face, upper torso, and upper extremities, with distal limbs typically unaffected.[6-10]

Early skin lesions present as erythematous macules that may evolve into purpuric macules, with irregular shapes that progressively coalesce. Lesions then develop into papules, vesicles, blisters, and urticarial plaques that are usually not itchy. Typical lesions have a "target" appearance with two color zones: a central area of vesicles, purpura, or necrosis surrounded by erythematous macules. This appearance is pathognomonic. Atypical lesions may resemble erythema multiforme, consisting of concentric ring-shaped zones. [6-10]

Lesions usually begin on the face and chest and then spread symmetrically outward. They can appear anywhere but are most commonly found on the palms, soles, dorsal hands, and extensor surfaces of the lower extremities. These areas are painful to touch. Within three to five days, epidermal detachment and the formation of fragile blisters occur, leading to the exposure of large areas of necrotic skin. Nikolsky's sign is positive in the area surrounding the lesions but is not specific to SJS/TEN as it can also appear in autoimmune skin diseases. [6-10]

Dead skin layers increase the risk of secondary infections, with *Staphylococcus aureus* and *Pseudomonas aeruginosa* being the most common. Sepsis is a leading cause of death in SJS/TEN. Secondary infections can lead to scarring and increased morbidity. Extensive lesions result in severe pain, massive fluid and protein loss, electrolyte imbalance, insulin resistance, hypercatabolic state, infections and bacteremia, hypovolemic shock with renal failure, and multi-organ failure. Reepithelialization begins one week after onset and continues for three weeks, with faster recovery in children. [6-10]

Mucosal involvement can affect two or more mucosal surfaces. The most common mucosal abnormalities are in the mouth (100%), followed by the genital area (50%). Mucosal lesions may appear concurrently with skin lesions or earlier. Mucosal signs include erythema, edema, blisters, ulceration, and necrosis. Mucosal lesions start with enanthem and edema, leading to erosions and pseudomembranes in the eyes, mouth, genitalia, throat, and upper respiratory tract in up to 90% of cases. Gastrointestinal and respiratory lesions occur in 10% to 30% of cases. [6-10]

Ocular involvement occurs in 39% to 61% of cases, typically 2 to 6 weeks after drug exposure. Ocular symptoms include conjunctival lesions with hyperemia, purulent secretions, erosions, chemosis, photophobia, and tearing. Other findings include eyelid edema, membrane or pseudomembrane formation on the eye, and corneal erosion. Severe cases may present with scarring lesions, symblepharon, corneal ulcers, and anterior uveitis. [6-10]

Other systems that can be affected include the pulmonary system (pneumonia, interstitial pneumonitis, acute respiratory distress syndrome, mechanical ventilation), gastrointestinal system (diarrhea, melena, small bowel ulcers, colon perforation, intussusception, stenosis, stricture, stomatitis), renal system (proteinuria, microalbuminuria, hematuria, and azotemia), vulvovaginitis, and urethritis.[6-10]

Residual Symptoms

Residual symptoms are common during the final phase of TEN. The most frequent residual symptoms are hyper- and hypopigmentation of the skin (62.5%), eye complications (50%), and nail dystrophy (37.5%). Long-term ocular complications include dry eye (46%), trichiasis (16%), symblepharon (14%), distichiasis (14%), vision loss (5%), entropion (5%), ankyloblepharon (2%), lagophthalmos (2%), and corneal ulcers (2%). Long-term mucosal complications occur in 73% of patients with mucosal involvement during the acute phase.[15]

In Yoo et al. study, clinical characteristics of 92 patients with drug-induced Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) were examined. The average age at diagnosis was 58.7 years, with a significant number of patients being between 60 and 80 years old. There was a slightly higher proportion of men (56.5%) compared to women (43.5%). Among the cases, SJS was the most prevalent, accounting for 68.5%, followed by SJS/TEN overlap at 14.1%, and TEN at 17.4%. The average body surface area (BSA) affected at diagnosis was 19.9%, and none of the patients had a history of severe cutaneous adverse reactions (SCARs) prior to this diagnosis.[23]

The latent period between drug intake and the onset of symptoms averaged 16.3 days. The majority of patients (80.4%) were exposed to a single drug, while 19.6% received multiple medications. Most cases involved oral administration of drugs (75%), with fewer cases receiving intravenous (IV) or subcutaneous (SC) administration (23.9%), and a minimal number using eyedrops (1.1%). Treatment primarily involved systemic corticosteroids or intravenous immunoglobulin (IVIG), administered to 76.1% of patients, while 16.3% received both treatments, and 7.6% received only supportive care. The duration of treatment averaged 17.9 days. Most patients (91.3%) recovered, while 8.7% did not survive. Analysis of causative drugs revealed that antibiotics were the most frequent trigger, responsible for 30.4% of cases, with amoxicillin/clavulanate being the most common. Allopurinol was identified as the second most common single drug causing SJS/TEN (21.7%). Antiepileptics, predominantly carbamazepine, were implicated in 18.5% of cases, and NSAIDs accounted for 16.3% of cases, with piroxicam, ibuprofen, loxoprofen, and meloxicam being the specific drugs identified. [23]

When comparing the different types of SJS/TEN, patients with TEN had a significantly higher proportion of NSAID-induced cases and a larger BSA affected. The mean age of diagnosis and the latent period did not vary significantly across the different SJS/TEN types. However, patients with SJS/TEN overlap and TEN were more likely to have been treated with multiple drugs. Mortality rates increased from SJS to TEN, though the difference was not statistically significant. Drug-specific analysis showed that NSAIDs were associated with a higher BSA and a greater likelihood of TEN. In contrast, AEDs were linked to a lower BSA at diagnosis. The allopurinol group had the longest latent period, while acetaminophen, despite having only two cases, showed the shortest latent period. The treatment outcomes were generally positive across all drug groups, with the highest mortality rates observed among patients exposed to antibiotics and allopurinol. [23]

Before diagnosing SJS/TEN, it is essential to consider a broad differential diagnosis, which includes various desquamating and vesiculobullous dermatoses such as pemphigus vulgaris, linear IgA bullous dermatosis, staphylococcal scalded skin syndrome (SSSS), and erythema multiforme major (EMM). Historically, EMM and SJS/TEN were considered to be part of the same disease spectrum due to similarities in clinical and histopathologic presentations (see Figure 5). However, it has since been established that they are distinct conditions. Accurate diagnosis relies heavily on clinical evaluation, as outlined in Table 5.[21]

TEN resembles a superficial dermal burn, characterized by fluid shifts, hypermetabolism, and high nutritional needs. The primary goal is to prevent secondary infections through effective wound care, as these infections are the most common cause of death. Early diagnosis, prompt withdrawal of the suspected drug, and immediate transfer to a specialized unit such as an intensive care or burn unit are crucial for improving survival rates.[5,7]

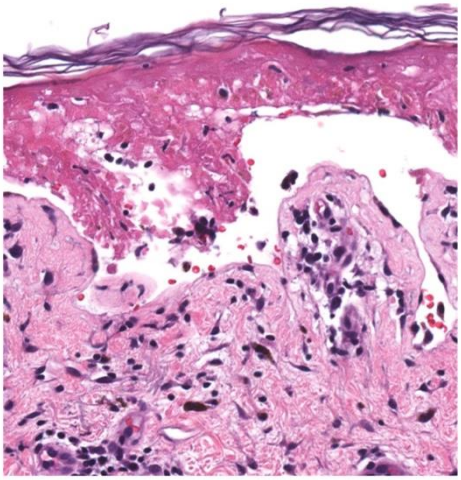

Figure 5. Illustrates the histopathology of Stevens-Johnson Syndrome, showing full-thickness epidermal necrosis, an orthokeratotic stratum corneum, and sparse dermal inflammation—features that are supportive but not specific. [21]

Table 4. Lists the differential diagnoses for suspected SJS/TEN

- Erythema multiforme major
- Pemphigus vulgaris
- Staphylococcal scalded skin syndrome
- Bullous pemphigoid
- Generalized fixed drug eruption (BFDE)
- Linear IgA bullous dermatosis
- Acute generalized exanthematous pustulosis
- Paraneoplastic pemphigus
- Phototoxic eruptions
- Acute or subacute cutaneous lupus with epidermal necrosis (Rowell syndrome)

Table 5. Outlines Distinguishing Characteristics Between SJS/TEN And Erythema Multiforme (EM)[21]

Characteristic	SJS/TEN	EM
Lesions	Atypical target lesions: macules with central clearing and poorly demarcated components; large sheets of painful desquamation in later stages	Typical target lesions: papules with a dark center and well-demarcated, concentric components
Distribution	Typically starts on the face and trunk with centrifugal spread	Typically on the face and acral skin, rarely involving the trunk
Triggers	Drugs (see Table 3)	Infection (most commonly HSV and M. pneumonia)
Mucosal Involvement	Very common; often involves ≥2 mucosal surfaces	Rare; typically involves only one mucosal surface if present
Recurrence	Rarely observed with the removal and avoidance of the causative drug	Frequently seen
Histopathology	Early Stage: Basal layer liquefaction with vacuolar interface changes, scattered necrotic keratinocytes, and interface lymphocytes Late Stage: Subepidermal split with full-thickness epidermal necrosis	Biopsy in the late stages of SJS/TEN may show comparatively less inflammation than in EM

Wound management with nonadhesive wet silver nitrate dressings helps maintain a moist environment, accelerates re-epithelialization, reduces pain, and lowers infection rates. Blistered skin should be treated conservatively as it naturally promotes re-epithelialization. Modern skincare options include biological or biosynthetic temporary skin replacements (e.g., porcine xenografts), Biobrane (a skin substitute), and Aquacel Ag (a moisture-retentive hydrofiber dressing with silver). Umbilical cord mesenchymal stem cell transplantation is an emerging and promising method for skin regeneration due to its self-renewal capacity, multilineage differentiation potential, paracrine effects, and immunosuppressive properties.[6]

Pain management is critical, as patients often experience background pain. Long-acting opioids and paracetamol should be used for pain relief. Encouraging oral feeding is important to prevent gastrointestinal tract adhesions, but parenteral feeding may be necessary if nutritional needs are not met orally. SJS/TEN patients often have impaired temperature regulation due to skin loss and should be cared for in controlled temperature and humidity environments. Monitoring fluid balance closely is essential due to significant insensible fluid losses, which can lead to dehydration and renal impairment. Eye care involves frequent lubrication (every 1-2 hours) and early consultation with an ophthalmologist. Nonhealing corneal ulcers may require bandage contact lenses and amniotic membrane transplantation for severe cases.[21]

The use of corticosteroids is debated. They have antiapoptotic effects, inhibit initiating pathways, and down-regulate Fas ligand (FasL) in apoptotic tissues. Some studies support early high-dose corticosteroid therapy (1–2 mg/kg/day of prednisolone for 3–5 days), with dexamethasone 8 to 16 mg/day being recommended, though the dose may be adjusted based on recovery. However, opponents argue that corticosteroids may increase the risk of sepsis, prolong hospital stays, and increase mortality.[21]

Other experimental treatments include chimeric anti-TNF-α antibodies (e.g., infliximab) and thalidomide, as elevated cytokine levels (e.g., IL-6 and TNF-α) have been found in TEN patients' skin. Recombinant granulocyte colony-stimulating factor has shown potential for accelerating re-epithelialization in some case reports, but more robust data are needed before these treatments can be considered standard care. Further multicenter studies are necessary to deepen our understanding of SJS/TEN's pathophysiology and to explore and validate treatment options. [21]

The acute phase of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) involves several critical steps: discontinuing the suspected causative drug, supportive care, and active interventions. Firstly, it is essential to stop the use of the drug suspected to be causing the condition as soon as possible. The prognosis improves significantly with early discontinuation of the offending drug, while delays in stopping the medication can worsen outcomes and increase mortality. The timeline of drug administration should be reviewed meticulously, covering 1 to 4 weeks prior to the onset of symptoms. Supportive care is crucial in this phase, focusing on fluid and electrolyte replacement. It is important to maintain urine output between 50-80 mL per hour using intravenous fluids, such as 0.5% NaCl with 20 mEq of KCl. Aggressive therapy is required due to the frequent occurrence of hyponatremia, hypokalemia, and hypophosphatemia. Skin lesions should be managed conservatively without debridement, and topical sulfa treatments should be avoided. [21]

Active interventions may include systemic corticosteroids, which remain a subject of debate. Corticosteroids can reduce the synthesis of pro-inflammatory molecules, inhibit the production of leukotrienes and prostaglandins, and exert antiproliferative effects. Theoretically, these actions could help control the immune response in SJS/TEN. Studies suggest that systemic corticosteroids, especially high-dose short-term regimens, may improve prognosis. For patients in good general condition with non-extensive lesions, prednisone 30-40 mg per day may suffice. In more severe cases, intravenous steroids such as dexamethasone, administered 4-6 times daily at 5 mg each, may be used. After 2-3 days, the dosage can be reduced to 5 mg per day, then switched to oral corticosteroids like prednisone 20 mg daily, tapering down to 10 mg as needed. Treatment duration is generally about 10 days. [21]

Intravenous immunoglobulin (IVIG) is used due to its ability to inhibit Fas-mediated cell death, thanks to its anti-Fas content. Various studies and case reports have demonstrated the benefits of IVIG in managing SJS/TEN. Cyclosporine A is a potent immunosuppressant that inhibits Th2 cytokine activation, cytotoxic mechanisms by CD8 cells, and has anti-apoptotic effects by blocking Fas-L, nuclear factor kB, and TNF alpha. When used early in the disease, cyclosporine can halt disease progression without increasing sepsis risk. It has been associated with a shorter duration of re-epithelialization and hospital stay compared to supportive care alone, without increasing mortality. Plasmapheresis or hemodialysis aim to remove the offending drug and its metabolites, as well as inflammatory mediators like cytokines, but their use remains controversial and is not generally recommended. Anti-Tumor Necrosis Factor (TNF) therapies, such as monoclonal antibodies against TNF, have been successfully used in some patients. [21]

Table 6. Dosage Comparison for SJS/TEN Therapy		
Therapy	**Dose**	**Dose for Child (30 kg)**
Methylprednisolone	2 mg/kg/dose	60 mg
IVIG	0.5-2 g/kg/dose	15-60 g
Cyclosporine	3-6 mg/kg/dose	90-180 mg
Etanercept	0.8 mg/kg/dose	24 mg
Infliximab	5 mg/kg/dose	150 mg

The SCORTEN score helps assess severity and prognosis. Key parameters include age over 40 years, presence of malignancy, tachycardia over 120 beats per minute, skin involvement greater than 10%, and elevated serum urea or glucose levels. Each factor contributes to the overall SCORTEN score, which predicts the likelihood of mortality. The SCORTEN score provides a framework for evaluating the severity and prognosis of SJS/TEN, guiding treatment and management decisions.[24,25]

Table 7. SCORTEN			
Parameter	**Score**	**Total Score**	**Mortality Risk (%)**
Age > 40 years	Yes = 1	0-1	3.2
	No = 0		
Presence of malignancy	Yes = 1	2	12.1
	No = 0		
Tachycardia > 120 beats/min	Yes = 1	3	35.8
	No = 0		
Skin area affected > 10%	Yes = 1	4	58.3
	No = 0		
Serum urea > 180 mg/dL	Yes = 1	>5	90.0
	No = 0		
Serum glucose > 252 mg/dL	Yes = 1		
	No = 0		

In this case, with a total SCORTEN score of 1, Mrs. M has a relatively low estimated mortality risk of about 3.2%. This suggests that her prognosis is more favorable compared to higher SCORTEN scores, and her overall risk of death from SJS/TEN is lower. However, continued close monitoring and management are essential due to the serious nature of the condition.

CONCLUSION

In conclusion, Mrs. M's SCORTEN score of 1 suggests a relatively favorable prognosis for her Stevens-Johnson Syndrome (SJS), with an estimated mortality risk of around 3.2%. Her age and lack of active cancer are positive factors that contribute to this prognosis. The key challenges include the incomplete data on other critical parameters such as serum urea and bicarbonate, which could impact her condition and treatment. To improve her outcome, it is crucial to promptly discontinue the offending medication, provide supportive care with careful fluid management, and monitor her closely for complications. Addressing potential issues such as eye care and infection prevention will be important

in managing her condition effectively. Overall, while the prognosis is optimistic, continuous and tailored management will be essential for ensuring the best possible recovery.

Effective management of SJS/TEN should focus on early discontinuation of the offending drug, supportive care including fluid and electrolyte replacement, and careful monitoring. Given the complexities involved, ongoing vigilance, and tailored interventions are essential for optimizing outcomes. Furthermore, ensuring thorough follow-up and addressing potential complications, particularly regarding eye care and infection control, will be vital in improving her overall prognosis.

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