# Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

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**ABSTRACT**
*Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are uncommon but serious cutaneous reactions with significant mortality and long-term morbidity. Multiple aspects of TEN and SJS are reviewed including classification and therapeutic options with emphasis on the importance of early diagnosis, burns unit care and the controversies in the use of systemic corticosteroids.*

**Keywords:** *Etiology, intravenous immunoglobulin, Stevens-Johnson syndrome, toxic epidermal necrolysis*

## INTRODUCTION

The term toxic epidermal necrolysis (TEN) was introduced in 1956 by Lyell to describe four patients with a syndrome featured by extensive epidermal detachment with mucous membrane involvement, leaving the skin surface looking scalded.[1] Necrolysis denotes necrosis and full thickness detachment of the epidermis. Toxic means severe constitutional symptoms and complications. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are two-related severe cutaneous blistering reactions often related to drug therapies, with a mortality rate between 16% and 30% for TEN and of less than 5% for SJS.[2] There are still controversies in classification, mechanism, and management of these conditions.

## EPIDEMIOLOGY

The incidence of TEN has ranged from 0.5 cases per million per year in the USA and 1.2 cases per million per year in France whereas the incidence of SJS and TEN is around 0.93 and 1.1 cases per million per year in Germany respectively.[2-4] Most cases of TEN are due to drugs. It is associated with altered immune states as in HIV infections, mycoplasma pneumonia, immunization and systemic lupus erythematosus.[5] Bastuji-Garin et al reported 2.7 times higher incidence of TEN in elderly older than 65 years attributed to an increased drug use.[6] A slight female preponderance was observed in most series with a female: male (F/M) ratio of 1.7:1. TEN and SJS have been described in all age groups and races.

## CLINICAL FEATURES

TEN is characterized by extensive full-thickness epidermal loss and mucous membrane involvement.[5] It presents with widespread epidermal sloughing on the background of painful purpuric macules and flaccid blisters at involved sites, resembling those of second-degree burns, resulting in denudation of large areas of oozing dermis. However, the prognosis of TEN appears to be worse than that of second-degree burns with the same extent because of involvement of the epithelium of other organs, especially the respiratory tract.[7] The entire body surface can be involved. Mucous membranes of oral cavity, conjunctivae and genitalia are usually severely eroded (85-95%) with significant pain and crust. Acute skin failure results in loss of fluid and electrolyte imbalance and protein depletion. Patients with TEN are typically preceded by a prodrome of fever, rash and sore throat. It is followed by progressive purpuric eruption with flaccid blisters and positive Nikolsky's sign predominantly over trunk and face. Involvement of other organs and mucous membranes accounts for increased mortality and long-term

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morbidity. Sepsis is the major complication that leads to death.[8] Most of the skin surface and mucous membranes are re-epithelialised in two to three weeks, consistent with the reported overall mean length of stay ranged from nine days to 21 days in some series.[3,7]

TEN and SJS are now considered to be variants within a continuous spectrum of different severity.[7] Those patients who initially present with a picture of SJS may progress to full-blown TEN in a few days by the confluence of individual lesions and the two conditions share similar aetiologies and histopathological findings. There is no consensus at the moment as to how best to classify this spectrum of diseases. It is difficult to study these serious skin reactions owing to the lack of unanimous definition, uncertainty in defining its onset, absence of reliable tests for assessment of risk factors and multitude of aetiological factors predisposing to the reaction.[4]

The two skin eruptions share many clinical features and are distinguished by the extent of body surface area involved. TEN is defined by full-thickness epidermal necrosis with epidermal detachment involving greater than 30% of total body surface, associated with morbilliform or confluent erythema and skin tenderness.[7] SJS is defined by less than 10% body surface involvement with the present of flat atypical target lesions distributed mainly over trunk and face. Overlap TEN-SJS is the entity that encompasses the skin condition with body surface involvement in the range of 10-30%.

The classification is further complicated by including erythema multiforme major (EMM) in the category of TEN. Nevertheless, there are distinguishing features between the two conditions by the pattern and distribution of skin lesions. EMM typically produces typical target lesions over extremities. The disease runs a benign clinical course and usually occurs after infection especially herpes simplex and mycoplasma in children. In contrast, patients suffering from TEN have widespread blisters predominantly over the trunk and face arising on erythematous or purpuric macules. They are usually drug-induced with high mortality rate.[9]

## DIFFERENTIAL DIAGNOSIS

Diseases with extensive desquamation or superficial subcorneal blisters include staphylococcal scalded skin syndrome and Kawasaki disease in children, and toxic shock syndrome in adults. Acute pustular psoriasis, drug-induced exanthematic pustulosis and linear IgA disease may resemble TEN when pustules are confluent, leading to positive Nikolsky's sign. Extensive fixed drug eruption and acute onset of paraneoplastic pemphigus may also mimic TEN.

## PATHOLOGY

The histological examination of advanced skin lesions shows necrosis of entire epidermis in TEN starting from the basal and the Malpighian layers. The necrotic epithelium detached from minimally altered dermis. The upper dermis shows moderate infiltration by mononuclear cells and epidermal changes begin as intercellular oedema with a sparse exocytosis of mononuclear cells, mainly CD8 T-lymphocytes and macrophages and occasional satellite cell necrosis. Direct immunofluorescence is usually negative. The histological pattern shows a predominantly necrotic pattern in which major epidermal necrosis and minimally inflammatory infiltration are found. This is in contrast to the more pronounced dermal inflammation and exocytosis in EMM.[9] EMM differs from SJS and TEN by having a denser and deeper lymphocytic infiltrate, and increased amount of extravasated erythrocytes.[10]

## PATHOGENESIS

The pathogenesis of TEN and SJS is still unclear. TEN is generally considered as a hypersensitivity reaction to drugs such as antibiotics, analgesics and anticonvulsants and to events such as viral infections.[2] One theory suggests that patients with TEN have an abnormal metabolism of the culprit drug. Instead of being metabolized, the offending drug is deposited in the epidermis leading to a series of immune reactions and rejection.[11] The epidermis is infiltrated by activated lymphocytes, mainly CD8 cells and macrophages. The dermal infiltrate consists of mainly activated T-lymphocytes, predominantly T helper cells. The number of Langerhans' cells are marked reduced in the epidermis.[12] Severe cases of cutaneous acute graft-vs-host disease can lead to a clinical and histologic syndrome similar to TEN, thus supporting TEN to be a cellular immune reaction. This cell-mediated immune

response leads to keratinocyte apoptosis by cytotoxic T-lymphocytes and cytokines, especially α-TNF.[13] Acute keratinocyte death in TEN occurs as a result of apoptosis through cytotoxic cell-mediated process involving CD95 (Fas) cell surface receptor-ligand system. Keratinocytes in TEN express lytically active Fas ligand (FasL).[14]

## AETIOLOGY

TEN is essentially an idiosyncratic, drug-induced reaction. Roujeau et al showed that only a small number of patients (4.5%) with TEN had not taken any drugs.[4] The most thorough multi-center study in Europe revealed that antibiotics particularly sulfonamides, NSAIDs, anti-convulsants and allopurinal increased the risk of TEN and SJS in decreasing order.[15] Among non-sulfonamide antibiotics, aminopenicillins, quinolones, cephalosporins, tetracyclines and imidazoles were significantly associated with TEN. This study confirmed the responsibility of the previously reported drugs. Allopurinal is considered to be relatively low risk as compared with other chronically used drugs. Roujeau et al reported a ratio of 1.3 TEN cases per $10^8$ sales (seven cases out of 253 TEN patients) for allopurinal compared with 230 cases per $10^8$ sales for sulphadiazine.[2] In contrast, Chan reported five cases of TEN related to allopurinal out of twenty patients in a five-year series in Singapore.[16] The apparent higher incidence of TEN and SJS related to allopurinal in Asians can be due to differences in genetic background, especially HLA types. Lack of an accurate drug history and multiple medications make identification of culprit drug difficult. The condition often begins within 3 weeks of initiation of therapy or much shorter upon re-exposure.

The occurrence of SJS and TEN in the setting of brain metastasis and phenytoin use was well reported.[17] Reduction of the dose of steroids may increase the risk of a hypersensitivity reaction. The authors had suggested avoiding routine anticonvulsant prophylaxis in all cerebral metastasis because of this potential serious complication. Cautions should be taken if patients receiving cranial radiotherapy develop scalp erythema after introduction of anticonvulsants and tapering of steroids. This may represent the first sign of SJS and the drugs should be withheld immediately.

Recent viral infections may play a role in TEN and SJS patients. Cutaneous drug reactions are more common in patients with human immunodeficiency virus (HIV) infection and the acquired immuno-deficiency syndrome (AIDS).[18] The incidence of TEN and SJS increased to a thousand-fold in patients with AIDS.[19] Sulfonamides are the most frequently implicated agents. Near all patients with acute Epstein-Barr virus (EBV) mononucleosis syndrome treated with ampicillin developed skin eruptions. Previous study noted 6% of TEN patients had clinical and/or serological evidence of a recent viral infection.[2] Mycoplasma pneumoniae infections have been related to TEN.[20] Specific viral infections had been shown to increase Fas and/or FasL expression and increased sensitivity to Fas/FasL-dependent apoptosis.[21] All these findings support the hypothesis that underlying viral infections may trigger and activate the severe cutaneous reactions in susceptible individuals receiving drugs.

Recently human herpesvirus type 6 (HHV-6) and cytomegalovirus (CMV) reactivation had been reported in patients with drug hypersensitivity syndrome characterized by skin rash, fever, liver dysfunction and lymphadenopathy. One patient developed TEN as part of the hypersensitivity syndrome.[22] The authors proposed an aetiological role of the viral infection in the pathogenesis of hypersensitivity syndrome. They also hypothesized that reactivation of HHV-6 may seriously interact with some of the enzymes that detoxify the drugs, such as cytochrome P450, as viruses may induce antibodies to cytochrome P450 components.

## COMPLICATIONS

Concerning the complications of TEN and SJS, conjunctivitis was a constant feature in most patients. Chronic xerostomia and dry eyes were observed in some TEN patients after the incidents. Most of the patients had marked and prolonged post-inflammatory hyperpigmentation that can be disfiguring. The ocular sequelae (30-40%) is potentially disabling in survivors.[7] Synechiae between eyelids and conjunctivae often occur, necessitating frequent use of eye lubricants to prevent this complication. Nail dystrophy, hypertrophic scars and phimosis can occur. Pulmonary complications comprise pneumonia and sloughing of tracheobronchial mucosa that worsen the prognosis in particular. Less

frequent findings include leukopenia and thrombocytopenia.

Appropriate care of extensive epidermal loss and careful fluid and electrolyte management in a burns unit contribute substantially to the reduced complication and improved survival rate in TEN.[23] The overall reported mortality of TEN is up to 36%, sepsis being the most important complication and cause of death.[8] Common sources of sepsis include skin, lungs, urinary catheter and intravenous lines. The increased body surface involvement may predispose the patient to greater risk of disseminated sepsis. Bastuji-Garin et al identified seven independent risk factors for death, namely age above 40 years, malignancy, tachycardia above 120/min, initial percentage of epidermal detachment above 10%, serum urea above 10 mmol/L, serum glucose above 14 mmol/L and bicarbonate below 20 mmol/L.[24]

## MANAGEMENT

The main principles of symptomatic therapy are the same as for major burns. The timely treatment of TEN patients offered by specialized burns centers may contribute to the lowered mortality in recent series. There is a trend of improving survival and reducing complications over the last decades with the prompt identification and treatment of patients with TEN in burns unit.[23]

All potential aetiological drugs are to be discontinued immediately when any early suggestive features of TEN or SJS arise, as prompt withdrawal of suspected drugs might decrease mortality, especially for drugs with short half-life.[25] All patients should receive meticulous wound care with antibiotic cream, paraffin and emulsifying ointment, but topical silver sulphadiazine is avoided owing to the strongest association with the conditions.[15] Adequate supportive care is needed for wound dressings and isolation techniques. Intravenous fluid for volume, electrolytes and nutritional support are often required especially when the patients are unable to swallow. Surveillance of sepsis and careful fluid and electrolyte balance are achieved through regular monitoring. Systemic antibiotics are given only in patients with evidence of sepsis. Patients should receive regular eye and mouth care and are followed up regularly by ophthalmologists. Pain management includes use of paracetamol and morphine, and regular chest physiotherapy is also necessary. A skin biopsy for light microscopy and immunofluorescence is warranted to confirm the diagnosis and rule out other blistering diseases not related to drugs.

Any effective specific treatment for TEN or SJS should be able to halt the progression of necrolysis and promote early re-epithelialisation. The use of systemic corticosteroids to abate the inflammatory reaction for the treatment of TEN remains the most controversial issue.[8] Small case numbers and lack of well-designed controlled studies produced contrasting results. Since the most important cause of death in TEN is overwhelming sepsis, many authorities believe that systemic corticosteroids are contraindicated based on a number of recent studies reporting a higher morbidity and mortality with their usage.[26] Corticosteroids can also delay healing, masking early signs of sepsis and induce gastrointestinal bleeding. TEN can develop in patients who are receiving high-dose corticosteroids.[5] On the other hand, some authors suggest use of a short course of systemic corticosteroids at earlier stages for few days to no more than a week, but their benefits have never been proven in controlled clinical trials as the diseases are self-limiting upon discontinuation of the offending drugs.[27] Others have tried plasmaphoresis and cyclosporin. Thalidomide appears deleterious and increased mortality rate.[28]

Intravenous immunoglobulin has the sound theoretical basis as a promising therapeutic agent of TEN. Fas-blocking antibodies contained in IVIG inhibit the interaction between Fas receptors expressed on keratinocytes and FasL and prevent the apoptotic process that plays a pivotal role in TEN.[29] Previous open study and isolated case reports had demonstrated decreased keratinocyte apoptosis, prompt interruption of progression of skin disease and shortening of duration of complete healing after IVIG were given to TEN patients. Although IVIG therapy is generally safe, the treatment costs are immense. One course of IVIG therapy to administer 1 g/kg/day for 3 days costs about $30,000 for an average-size adult.

## CONCLUSION

Early diagnosis, prompt withdrawal of all potentially responsible drugs and initiation of supportive

care in a burns unit remain the most important measures in managing this uncommon but potentially fatal drug-related disease.

***Learning points:***
***Early diagnosis, prompt withdrawal of all potentially responsible drugs and initiation of supportive care in a burns unit remain the most important measures in managing toxic epidermal necrolysis.***

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