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Review article

# A review of toxic epidermal necrolysis management in Japan

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*Abbreviations:*
BSA, body surface area; DFPP, double filtration plasmapheresis; DIHS, drug-induced hypersensitivity syndrome; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; mPSL, methylprednisolone; NSAID, non steroidal anti-inflammatory drugs; PE, plasma exchange; SCORTEN, score of toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor

ABSTRACT

Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction characterized by necrosis of the epidermis. Its incidence is approximately 1 per million a year and average mortality rate is high at 25–50%. TEN has a flu-like prodrome, followed by atypical, targetoid erythematous or purpuric macules on the skin. These macules coalesce to form flaccid blisters that slough off as areas of epidermal necrosis. Drugs such as allopurinol, sulfonamides, and carbamazepine are the most common causes. The human leukocyte antigen (HLA)-B*15:02 in Asians being administered carbamazepine and the HLA-B*58:01 antigen in patients of all ethnicities being administered allopurinol are known to be high-risk factors. Rapid diagnosis, discontinuation of the causative drug, and supportive treatment are essential for better prognosis and improvement of sequelae. Till now, systemic corticosteroids and intravenous immunoglobulins have been used as the most common active interventions; however, no gold standard has been established. In Japan, physicians follow a unique diagnostic criteria and treatment guideline to improve the diagnosis rate and streamline treatments. This may be a contributing factor for the lower mortality rate (14.3%). The efficacy of systemic corticosteroids, immunoglobulins, and plasmapheresis may have been beneficial as well. In Japan, TEN is defined as an epidermal detachment of over 10% of the body surface area (BSA), while the globally accepted definition established by Bastuji-Garin describes it as an epidermal detachment of over 30% of the BSA. In Japanese individuals, HLA-A*02:06, HLA-A*02:07, HLA-A*31:01 and HLA-B*51:01 may be linked to higher risks of TEN.


## Introduction

Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction characterized by necrosis of the epidermis. Keratinocyte cell death causes detachment of the skin and mucous membrane from the dermal-epidermal junction.[1] The incidence rate is 0.5–1.4 per million per year and the average mortality rate is 25–50%.[2–7] The mean patient age is 42.6 years and the incidence increases with age.[2,3] SJS and TEN have become to be classified under a single category, and the difference between them is the amount of epidermal detachment.[8] However, in this review, TEN specifically will be discussed because of its exceptional high mortality, rarity and intense symptoms compared to SJS. In a typical course of TEN, the first symptom is a flu-like prodrome.[9] Fever, malaise, and pharyngitis may occur before the onset of mucocutaneous symptoms. Clinically, atypical targetoid macules appear on the skin. These macules coalesce to form flaccid blisters that slough off as areas of epidermal necrosis (Fig. 1).[1] Drugs, especially antibacterial and antiepileptic drugs, are the most common cause. Specific human leukocyte antigen (HLA) alleles are high-risk factors as well. HLA-B*15:02 in Asians being administered carbamazepine and HLA-B*58:01 in people of all ethnicities being administered allopurinol have been reported to be high-risk factors for TEN.[1] Rapid diagnosis, discontinuation of the causative drug, and initiation of supportive treatment are essential for better prognosis and improvement of sequelae. Till now, systemic corticosteroids and intravenous immunoglobulins (IVIg) have been used as the most common active interventions; however, no gold standard has been established.[10] In Japan, as in the rest of the world, TEN is an important disease. In this review, the situation of TEN in Japan at the present will be discussed.

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**Fig. 1.** Patient of toxic epidermal necrolysis with epidermal sloughing showing bare dermis. Coalescing violaceous macules can also be seen. There is widespread involvement of trunk and extremities. Erosions with hemorrahagic crusts on lips can also be seen.

## Diagnosis

In Japan, TEN is characterized by an epidermal necrolysis greater than 10% of the BSA. Although it is recognized that TEN can occur following SJS, unlike in the rest of the world, there is no SJS/TEN overlap, where epidermal necrolysis occurs in 10–30% of the BSA.[11] Because it is a fatal disease, the Japanese Research Committee on severe adverse reaction has created a diagnostic criteria and treatment guideline to provide a speedy and accurate diagnosis and effective treatment. A scoring system different from SCORTEN, which is typically used worldwide has also been created to determine the severity of the condition. Besides total epidermal necrosis, area and severity of mucosal lesions, percentage of blisters or erosions, systemic symptoms (fever, respiratory failure, and liver impairment) are included.[12]

## Support to TEN patients

Japan has a unique relief system for patients suffering from severe adverse drug reactions, and it was put in place in 1980. When a Japanese patient who was administered a medication for a reasonable licensed cause suffers from a severe drug reaction that requires treatment by admission or results in severe sequelae or death, the government financially supports the patient or his/her family for the treatment. This relief system also serves as a useful means of accumulating data on TEN in Japan for further analysis.[13]

## Incidence rate, causes, and common symptoms

For 2005–2007, the incidence rate of TEN in Japan was 0.28–0.52 per million per year.[14] A retrospective study of 65 TEN cases in Japan between 2000 and 2006 through published medical journals, and another retrospective study of 35 TEN cases in 2 university hospitals in Japan between 2000 and 2013 provides the following insights (Table 1).[15,16] As per the Japanese guideline, patients with over 10% skin detachment, mucous membrane erosions, and skin lesions were diagnosed with TEN. SJS/TEN overlap cases were also considered to have TEN. The skin lesions were macules, atypical target-like lesions, bullae, or erosions. In the former study, 31 patients were men and 34 women, and the mean patient age was 45.7 years. All cases were caused by drugs, such as NSAIDs, antibiotics, and anticonvulsants. Cephalosporin was found to be the most common causative antibiotic with 10 cases, and carbamazepine the most common anticonvulsant with 8 cases. Patients developed symptoms within 2 weeks. The range of skin detachment was 10–70%, while the mean was 49.6%. Additional symptoms involving other organs, especially the liver and kidney, and the respiratory system were common in many patients. Hepatitis was the most common form of organ involvement, noted in 41 cases. Elevation of serum alanine aminotransferase level was the most common blood test abnormality, observed in 33 cases (100 IU/l–1000 IU/l). 7 cases of sepsis were also reported; in patients with SJS, only 1 case of sepsis occurred. Ocular complications were seen in 6 cases.[15] In the latter study, 17 patients were men and 18 women, and the mean patient age was 56.6 years. All cases were caused by drugs, such as NSAIDs, cold medicines, antibiotics, and anticonvulsants. Out of the cases where the causative drug was determined, antibiotics were the most common with 7 cases. The average interval until patients developed symptoms was 11.7 days. The range of skin detachment was 10–100% of BSA, while the mean was 44.7%. Additional symptoms involving other organs, especially the liver and kidney, and the gastrointestinal system were common in many patients. Hepatitis was the most common form of organ involvement, noted in 15 cases. 6 cases of sepsis were also reported; in patients with SJS, only 1 case of sepsis occurred. Keratoconjunctivitis including conjunctival injection and erosions, and pseudomembranes were seen in 17 cases. Labial and oral erosions were observed in 19 cases. Genital problems, found mainly by pain during urination, were observed in 17 cases of TEN.[16]

## Mortality rate

Ranging from 6.2% to 32%, the most recent reported mortality rate for TEN was 14.3% (2000–2013).[13,15–17] The most recent

**Table 1**
Summary of the 2 studies of TEN patients in Japan by Yamane *et al.*[15,16]

| | | |
|---|---|---|
| Number of patients | 65 | 35 |
| Year | 2000–2006 | 2000–2013 |
| Background of patients | From articles of medical journals, review | 2 university hospitals, case series |
| Male/female | 31/34 | 17/18 |
| Mean age | 45.7 | 56.6 |
| Most common causative drug | Cephalosporin | Antibiotics |
| Time until symptoms | 2 weeks | Average of 11.7 days |
| Range of skin detachment | 10–70% (Average 49.6%) | 10–100% (Average 44.7%) |
| Most common organ involvement | Hepatitis | Hepatitis |
| Sepsis patients | 7 | 6 |
| Ocular complications | 6 | 17 |
| Mortality rate | 6.20% | 14.30% |

TEN, toxic epidermal necrolysis.