

## Toxic epidermal necrolysis and Stevens-Johnson syndrome

**Walayat Hussain** BSc MBChB MRCP,  
Specialist Registrar in Dermatology

**Nicholas M Craven** BM BCh MA FRCP,  
Consultant Dermatologist

Department of Dermatology, Burnley General  
Hospital, Burnley, Lancashire

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Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare, potentially life-threatening medical emergencies, characterised by widespread epidermal loss with mucous membrane involvement. Most cases are attributable to drugs (Table 1), so knowledge of these conditions is essential for all physicians. Rarely, infections (eg *Mycoplasma pneumoniae*) may be responsible.

The annual incidence of TEN and SJS is 0.4–1.2 and 1.2–6 cases per million per year, respectively.<sup>1</sup> Women are more fre-

quently affected (1.5:1) and the incidence increases with age.<sup>2</sup> Individuals at particular risk include 'slow acetylators', patients treated for brain neoplasms or head injury and immunocompromised patients. The risk of developing TEN is a thousand times higher in patients with HIV and AIDS than in the normal population.<sup>3</sup> Possible explanations include the HIV infection itself, the increased number of drugs these patients receive and the altered ratio between CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes.<sup>4</sup>

This article presents an overview of the aetiology, pathogenesis and clinical features of TEN and SJS and discusses the principles of management and the role of potential disease-modifying therapies.

### Pathogenesis

The precise molecular basis of TEN and SJS still remains to be fully elucidated. It appears that TEN patients, who have an

increased incidence of the haplotype HLA-B12,<sup>5</sup> demonstrate an inability to detoxify intermediate reactive drug metabolites. An immune response is then mounted against the antigenic complexes formed by the interaction of these metabolites and host tissues.<sup>6,7</sup> There is also compelling evidence that the end-point of TEN and SJS (ie epidermal necrolysis) is due to widespread apoptosis of keratinocytes.<sup>8</sup> Cytokines such as interleukin-6, tumour necrosis factor alpha and the CD95 system (Fas ligand and Fas receptor) appear to play a role in the induction of this apoptosis<sup>9–11</sup> and consequently have become targets for possible therapeutic interventions in TEN.

### Clinical features

It is not uncommon for patients to describe a prodrome, characterised by 48–72 hours of cough, sore throat, myalgia and anorexia, before the cutaneous manifestations become apparent in TEN and SJS. Once the skin is involved, it is possible to distinguish the two conditions clinically according to the extent of cutaneous involvement (Table 2).

Skin lesions usually begin as warm, dusky-red, morbilliform macules, initially discrete but subsequently becoming confluent. The epidermis sloughs in sheets, giving rise to flaccid blisters and leaving a characteristic moist, denuded dermis (Fig 1). This process may occur within several hours or take several days. Other notable features include:

- haemorrhagic crusting of the lips (Fig 2)
- conjunctivitis
- intense pain in affected areas of skin
- fever
- genital soreness and erosions
- arthralgia
- oesophageal/tracheal involvement (rare).

### Key Points

Toxic epidermal necrolysis and Stevens-Johnson syndrome are rare, life-threatening, mucocutaneous adverse reactions to drugs

Widespread epidermal loss occurs as a result of keratinocyte apoptosis

Complications develop similar to those seen after severe burns

Prompt drug withdrawal and supportive care in a burns/high dependency unit are the mainstay of treatment

The use of steroids and other disease-modifying interventions such as intravenous immunoglobulin lacks supportive evidence from randomised controlled trials

**KEY WORDS:** continuing medical education, Stevens-Johnson syndrome, toxic epidermal necrolysis

**Table 1. Drugs most frequently implicated in toxic epidermal necrolysis and Stevens-Johnson syndrome.**

Allopurinol	
Antibiotics	chloramphenicol macrolides penicillin quinolones sulfonamides*
Anticonvulsants	carbamazepine lamotrigine phenobarbitone phenytoin valproate
NSAIDs	
* most common. NSAID = non-steroidal anti-inflammatory drug.	

**Table 2. Cutaneous involvement in toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).**

Clinical entity	TEN	SJS	SJS-TEN overlap
Epidermal loss	>30%	<10%	10–30%



Fig 1. Acute changes of toxic epidermal necrolysis. Confluent erythematous macules over the chest and arm with areas of flaccid blistering and epidermal sloughing.

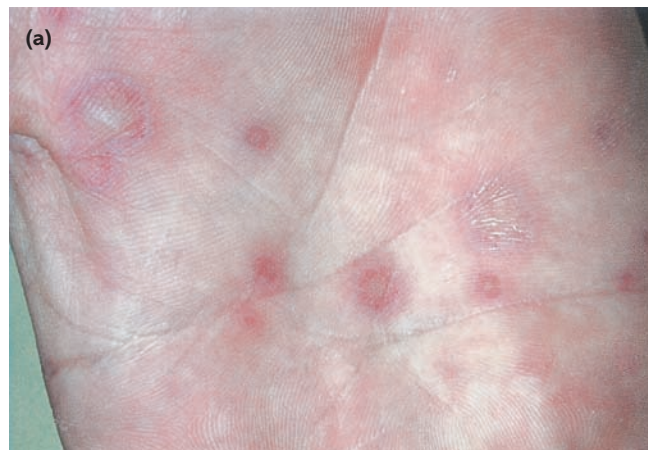


Fig 3. Target lesions: (a) typical three-zone target lesions on the hand in erythema multiforme; (b) atypical two-zone target lesions and haemorrhagic macules in toxic epidermal necrolysis.

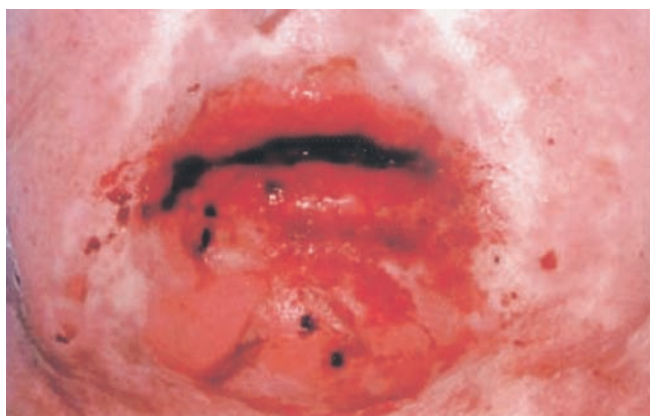


Fig 2. Mucosal involvement in toxic epidermal necrolysis. Haemorrhagic crusting and epidermal loss affecting the lips.

It is also possible on clinical grounds to differentiate erythema multiforme (EM) with mucosal involvement (EM major), from SJS or TEN based upon the appearances of the initial lesions seen in these conditions (Figs 3(a), 3(b); Table 3). This has prognostic implications because EM is a relatively common eruption, most frequently caused by infection with herpes simplex virus.

### Diagnosis

The diagnosis of established TEN and SJS can often be made clinically. The role of a skin biopsy and immunofluorescence is to exclude the main differential diagnoses, which include staphylococcal scalded skin syndrome, acute generalised exanthematous pustulosis, acute severe graft-versus-host disease and paraneoplastic pemphigus.

### Management

Once the diagnosis is suspected, all potential causative drugs should be discontinued without delay, as this is one therapeutic manoeuvre that has been shown to improve prognosis.<sup>12</sup> There is no definitive method of identifying the causative drug from a list of medications,

so it is recommended that all drugs be stopped if possible. In general, medications initiated in the 3–4 weeks prior to the onset of symptoms are usually responsible.<sup>1</sup>

Patients should be transferred to a burns or high dependency unit where staff will be familiar with the complexities of managing patients with wide-

Table 3. Features of 'target' lesions\* in erythema multiforme (EM), toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).

EM	3 zone iris or target lesion: <ul style="list-style-type: none"> <li>• centre = dusky erythema/purpura/blister</li> <li>• middle = oedema</li> <li>• periphery = erythema</li> </ul> Acral distribution
TEN & SJS	2 zone atypical, targetoid lesions* or purpuric macules Involve face/trunk/proximal limbs

\*A target lesion has the appearance of a dartboard bullseye, hence the name. It comprises three zones as indicated above. 'Targetoid' therefore refers to a lesion that may resemble the classical target lesion, however a targetoid lesion often comprises only two zones.

**Table 4. Signs of sepsis in toxic epidermal necrolysis and Stevens-Johnson syndrome patients.**

- Temperature fluctuations (high or low)
- Rigors
- Hypotension
- Oliguria
- Reduced respiratory rate
- Labile glucose readings
- Reduced consciousness

spread epidermal loss. Supportive therapy is paramount and involves:

- *Fluid and electrolyte balance*, preferably via peripheral rather than central lines to reduce the risk of infection.
- *Temperature regulation* to minimise heat loss.
- *Topical antiseptics* to reduce skin colonisation with potential pathogenic organisms.
- *Oral and nasal toilet*: debris should be cleaned regularly and an antiseptic mouthwash used several times a day.
- *Nutritional support*: nasogastric feeding is often needed until the oral mucosa heals.
- *Monitoring for signs of sepsis* (Table 4): antibiotics should not be administered prophylactically as this encourages resistance.
- *Pain relief*: opiates are commonly required so patients need monitoring for signs of respiratory depression.
- *Intubation and ventilation*: if there is extensive epithelial necrosis of the airways, which may precipitate bronchial obstruction, or if signs of adult respiratory distress syndrome develop.
- *Ophthalmological review* should be sought urgently to minimise the risk of serious ocular sequelae, including conjunctival scarring and possible blindness. Antiseptic eye drops should be used frequently and any synechiae which have formed separated.

**Table 5. (a) The SCORTEN scoring system.**

SCORTEN variables
• Extent of epidermal detachment >10%
• Age >40 years
• History of malignancy
• Heart rate >120/min
• Urea >10 mmol/l
• Glucose >14 mmol/l
• Bicarbonate <20 mmol/l

**(b) Predicting mortality in toxic epidermal necrolysis and Stevens-Johnson syndrome using the SCORTEN system. One point is scored for each variable present in the first 24 hours after admission.**

SCORTEN total	Predicted mortality rate (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
≥5	90

**Therapeutic interventions**

As a consequence of the low incidence of TEN, data on the use of potential ‘disease-modifying’ therapies consist of case reports and small, uncontrolled series.

**Steroids**

To date, the use of systemic steroids remains controversial. Some suggest that high-dose steroids used early in the evolution of TEN and SJS can stabilise the condition by halting further epithelial loss.<sup>14,15</sup> Others argue that steroids increase both morbidity and mortality as a consequence of the increased risk of sepsis.<sup>16,17</sup> It is now generally accepted that steroids provide no benefit once extensive epidermal loss has taken place, but the controversy will persist until a randomised, controlled trial is undertaken specifically to answer this question.

**Other therapies**

Other treatments, including cyclosporin (3-4 mg/kg/day),<sup>18,19</sup> cyclophosphamide (100-300 mg/day),<sup>20</sup> N-acetylcysteine

(2 g/6 hr)<sup>21</sup> and plasmapheresis,<sup>22,23</sup> have also been used with reported benefit. Antibodies present in pooled human intravenous immunoglobulin (IVIG) preparations block Fas-mediated keratinocyte apoptosis *in vitro*. There is some evidence that IVIG at 0.2-1 g/kg/day may halt the progression of skin disease in TEN and improve prognosis<sup>24,25</sup> although this is disputed.<sup>26</sup>

**Prognosis**

The mortality of TEN (30%) is at least sixfold higher than SJS (<5%).<sup>27</sup> The primary cause of death is infection (*Staphylococcus aureus* and *Pseudomonas aeruginosa*), and multi-organ failure is not uncommon. Recently, the SCORTEN grading system<sup>28</sup> (severity-of-illness score for TEN) has been developed to predict outcome in TEN (Table 5(a) and 5(b)).

Mucosal scarring is a significant risk for survivors. Almost 50% may develop serious ocular complications which, in addition to those mentioned earlier, include:

- corneal pannus



- conjunctival squamous metaplasia
- keratoconjunctivitis sicca
- symblepharon (adhesion of one or both eyelids to the eyeball)
- entropion
- trichiasis.

If the trachea, oesophagus or anal and genital mucosae are involved, strictures may develop.<sup>13</sup> Shedding of the nails may result in permanent anonychia.

Patients should not be discharged from hospital without clear instructions to avoid the culprit drug and ideally all structurally related drugs. A 'Medic-Alert' bracelet is advisable, stating the drug(s) to which the patient has reacted. Familial cases of TEN have been recorded; therefore it is worthwhile informing first-degree relatives of their increased risk of an adverse reaction to the same drug(s).<sup>29</sup>

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