Management of toxic epidermal necrolysis

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Toxic epidermal necrolysis and Stevens–Johnson syndrome are rare, life-threatening drug reactions. Widespread epidermal necrosis and mucosal erosions lead to complications similar to those developing after extensive burns. Treatment is supportive. The role of steroids and other potential disease-modifying agents remains to be established by controlled studies.

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are rare, life-threatening reactions, usually attributable to drugs. They form a spectrum of cutaneous reaction patterns characterized by the rapid development of widespread epidermal necrosis (*Figure 1*), involvement of mucosal surfaces (*Figure 2*), severe constitutional upset, and complications similar to those developing after extensive burns. In a classification based on the findings in over 200 patients, these conditions are distinguished on the basis of extent of cutaneous involvement: in TEN epidermal loss involves 30% or more of body surface area, SJS 10% or less, with cases in between being classified as TEN–SJS overlap (Bastuji-Garin et al, 1993). The incidence of TEN is between 0.4 and 1.2 cases per 10^6 population per annum; that of SJS is between 1 and 6 cases per 10^6 population per annum (Roujeau et al, 1995).

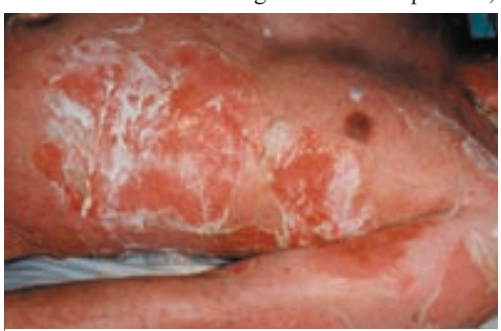

Figure 1. Toxic epidermal necrolysis with widespread epidermal necrosis. In areas damaged epidermis separates from underlying dermis in sheets with the appearance of wet tissue paper. Flaccid bullae can be seen laterally on the trunk. Silver sulphadiazine cream has been applied to areas of denuded dermis.

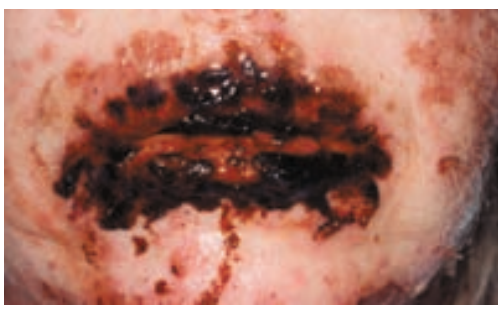

Figure 2. Haemorrhagic crusting of the lips in a patient with Stevens–Johnson syndrome.

RELATIONSHIP TO ERYTHEMA MULTIFORME

A degree of confusion persists regarding the association between SJS, TEN and erythema multiforme (EM). EM is a relatively common eruption with several recognized trigger factors, most commonly herpes simplex virus infection. It is characterized by the development of typical 'target' or 'iris' lesions comprising three concentric zones: a central area of dusky erythema or purpura, a middle zone of oedema and an outer erythematous ring (*Figure 3*). These lesions are usually found in an acral distribution, and mucous membrane involvement can occur in severe cases.

In contrast, the primary lesions in TEN and SJS are usually somewhat irregular, atypical target lesions of two zones (*Figure 4*) or flat purpuric macules, which tend to involve the trunk, face and proximal limbs preferentially. It is thus possible clinically to distinguish EM with mucosal involvement ('EM major') from TEN or SJS, reflecting their different aetiologies and prognosis (Assier et al, 1995).

AETIOLOGY OF TEN AND SJS

The great majority of cases of TEN or SJS are attributable to drugs. The commonest offenders are sulphonamides, with rates of up to 4.5 cases per million users per week. Other frequently

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implicated drugs include anticonvulsant agents, non-steroidal anti-inflammatory agents and allopurinol (Roujeau et al, 1995). The mechanisms of these reactions are not yet known, but may involve hypersensitivity reactions to the drug or reactive drug metabolites (Tagami et al, 1983; Friedmann et al, 1994). This hypothesis is supported by the observation that TEN can develop in the setting of graft *vs* host disease (Villada et al, 1990).

The incidence of TEN in human immunodeficiency virus (HIV) positive patients is increased, and in patients with full blown acquired immunodeficiency syndrome (AIDS) the incidence reaches about one case per 10^3 population per annum. This may reflect the associated immunological dysfunction (Saiag et al, 1992) in addition to the wider use of medications in this population. A higher than expected incidence of TEN is seen in systemic lupus erythematosus, and in patients treated for brain tumours or head injury. Occasionally SJS is attributed to infections such as *Mycoplasma pneumoniae*. In rare cases no cause can be found (Roujeau et al, 1990).

MANAGEMENT OF TEN AND SJS

Diagnosis of established TEN and SJS can usually be made clinically. Biopsy of an affected area of skin can help to exclude conditions such as staphylococcal scalded skin syndrome and paraneoplastic pemphigus.

Identification of the causative drug can be difficult, as patients will often be taking multiple medications. There are as yet no reliable tests that will identify the culprit drug from a list of possible candidates. In general, drugs that have been commenced in the 3 or 4 weeks before the onset of symptoms are usually responsible (Roujeau et al, 1995). In practice, if any doubt persists, then all drugs should be stopped if possible. Prompt discontinuation of causative drugs has been shown to improve the prognosis (Garcia-Doval et al, 2000).

Supportive therapy

The patient should be managed in a unit familiar with managing widespread skin loss and the associated medical complications, such as a burns unit or appropriate high dependency unit. Supportive therapy is directed at replacement of lost fluids, maintaining a warm environment to reduce heat loss, topical antiseptic preparations to reduce colonization of the skin with potentially pathogenic organisms, and regular monitoring for sepsis (Revuz et al, 1987). Fluid replacement requirements often exceed those required for burns of similar extent in view of the mucous membrane involvement with consequent impaired intake for several days before presentation. Requirements depend upon extent of involvement of skin and mucous membranes, and may be 5–7 litres in the first 24 hours. Peripheral lines are preferable to central lines, which increase risk of sepsis.

Nutritional support is important, and fine-bore nasogastric tube feeding is usually required until the oral mucosa has healed (Roujeau et al, 1990). Any lines should be checked daily for signs of infection, should be changed at least every 3 days, and the tips of all discarded lines and catheters should be sent for culture. Antibiotics should not be given routinely as a prophylactic measure as this risks promoting resistance. If signs of sepsis develop, initial antibiotic therapy can be guided by results of swabs taken from the skin and mucous membranes. Indicators of infection include rising or falling temperature, rigors, hypotension, fall in urine output, deterioration of respiratory status, diabetic control or level of consciousness (Revuz et al, 1987).

Ophthalmological review should be obtained as soon as possible after diagnosis to minimize the risk of conjunctival scarring and blindness. Regular instillation of antiseptic eye drops and separation of newly forming synechiae are required (Roujeau et al, 1990). Oral and nasal debris should be cleaned regularly and an antiseptic mouthwash used several times a day. Topical preparations to the skin may have a soothing effect, but additional analgesia with opiates is often required, and care should be taken to monitor for respiratory depression. Respiratory failure can develop as a result of

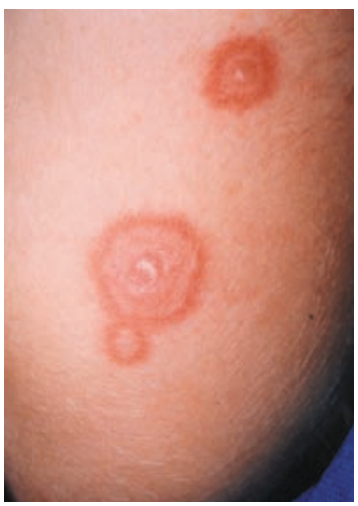

Figure 3. Typical 'target' or 'iris' lesion of erythema multiforme minor showing a central area of dusky erythema, a middle zone of oedema and an outer erythematous ring.

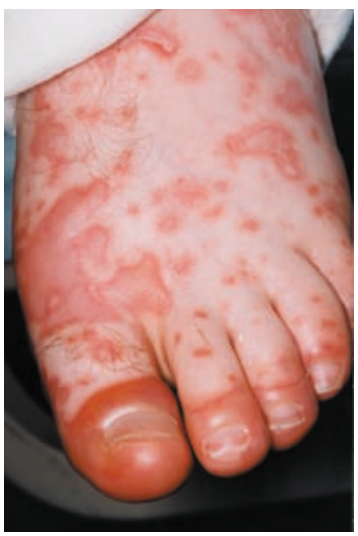

Figure 4. Atypical target lesions showing irregular erythematous papules with central blistering.

bronchial obstruction from epithelial necrosis, pulmonary infection or oedema resulting from increased alveolocapillary permeability. Such patients will require intubation and ventilation in intensive care (Lebargy et al, 1997).

Disease-modifying agents

The use of systemic steroids in the management of TEN and SJS remains controversial. A number of reports suggest that the use of steroids increases morbidity and mortality, usually through increasing risk of sepsis. In a retrospective study Rasmussen (1976) compared the progress of 17 children with SJS treated with prednisolone 40–80 mg/m^2 to 15 treated with supportive care only. Both groups were similar in terms of age, sex and extent of cutaneous and mucosal involvement. The steroid group had more complications (mostly infections) and longer mean duration of hospitalization (21 *vs* 13 days) than the non-steroid group. It is likely that a number of these cases, recorded as having iris lesions, would now be classified as bullous EM rather than SJS.

Halebian et al (1986) reported a 33% mortality in fifteen consecutive patients with TEN treated in a burns unit with supportive measures only, compared with 66% mortality in the historical control group treated with steroids. Eleven of the 'non-steroid' group had nevertheless initially been commenced on steroids by the referring institutions before arrival at the burns unit. Guibal et al (1995) reported a number of cases of TEN occurring in patients already taking high-dose steroids. In these patients the onset of TEN appeared to be delayed following exposure to the culprit drug, but the progression of TEN was not halted.

Conversely, a number of case reports and short studies advocate the use of high dose steroids in the early part of the evolution of these conditions. Stables and Lever (1993) reported a patient whose condition appeared to stabilize 12 hours after commencing on prednisolone 60 mg daily. Martinez and Atherton (2000) described two children, one with SJS and one with bullous EM (with typical target lesions). Both were subject to recurrent attacks which appeared to be abated by intravenous methylprednisolone (20 mg/kg/day for 3 days), commenced within 24–48 hours of the onset of skin signs. Tripathi et al (2000) reported 13 patients with SJS, all treated with intravenous methylprednisolone 160–240 mg/day on admission to the unit (1–14 days after onset of symptoms). One patient died from unrelated causes. This extends to 67 their series of patients diagnosed as SJS and treated with steroids. However, few patients are recorded as having bullous lesions, and it is possible that a number of these patients would be classified by dermatologists as having hypersensitivity syndrome rather than SJS. Nevertheless, it is possible that the use of high dose steroids may prove beneficial in aborting further epithelial loss in patients with evolving TEN or SJS; this needs to be tested in a randomized controlled trial. It is generally accepted, however, that continued administration of steroids is counterproductive once extensive skin loss has occurred.

There are several reports of small numbers of patients with TEN treated with other potential disease-modifying treatments. Heng and Allen (1991) reported five patients with TEN; four survived following treatment with cyclophosphamide 100–300 mg daily, and steroids (prednisolone 60–120 mg or methylprednisolone 1 g daily). The fifth died having had supportive treatment only. Arévalo et al (2000) reported improved outcome in 11 consecutive patients with TEN treated with cyclosporin 3 mg/kg/day compared to six historical controls treated with cyclophosphamide and steroids. Both groups were of comparable age, with similar extent of skin loss and delay between onset of TEN and admission. Patients treated with cyclosporin had more rapid re-epithelialization, were less likely to suffer multiorgan failure, and had a lower mortality (0 of 11 *vs* 3 of 6).

Viard et al (1998) demonstrated that pooled human intravenous immunoglobulin (IVIG) contains antibodies that, in vitro, block the Fas-mediated keratinocyte apoptosis occurring in TEN. In a subsequent pilot study, 10 consecutive patients with TEN were treated with IVIG at 0.2–0.75 g/kg/day for 4 days. Progression of skin disease stopped within 24–48 hours, and all patients survived. Egan et al (1999) report a retrospective study of 16 patients, six of whom were selected to have plasmapheresis (one to four treatments) based on rapid progression of disease in the 24 hours after admission. Overall mortality was 4/16 (25%); none of the patients treated with plasmapheresis died.

Interpretation of such studies is limited by a number of factors. In particular, a lack of uniformity in defining the conditions makes it difficult to compare studies, and the variable rate and extent of progression of both TEN and SJS cause difficulty in assessing the efficacy of a given intervention in an uncontrolled study. Thus, although these treatments may appear promising, formal assessment is required in randomized controlled trials before their use can be recommended. The only such trial undertaken so far is of thalidomide, selected as a potent inhibitor of tumour necrosis factor alpha (a cytokine impli-

cated in the pathogenesis of TEN). The trial was stopped early with mortality in the treatment arm significantly higher than that in the placebo arm (Wolkenstein et al, 1998).

PROGNOSIS

The mortality of TEN is approximately 30% and of SJS is below 5% (Roujeau and Stern, 1994). Infection is the main cause of death; less common causes include gastrointestinal haemorrhage, pulmonary embolism, respiratory failure and renal failure. Survivors are at risk of scarring from mucosal involvement: 40–50% of survivors develop ocular sequelae including keratoconjunctivitis sicca, squamous metaplasia of conjunctivae, corneal pannus and blindness. Strictures can form following involvement of tracheal, oesophageal, anal and genital mucosae (Roujeau et al, 1990).

Advice on avoidance of the culprit drug and structurally related drugs must be given to survivors of TEN and SJS. As familial cases have been reported first degree relatives of all patients should be advised of their increased risk of developing adverse reactions to the same drugs (Fischer and Shigeoka, 1983).

CONCLUSION

Management of TEN and SJS should be undertaken in liaison with the local dermatologist. Effective treatment requires prompt recognition of the conditions, withdrawal of the causative drug, initiation of supportive therapy and transfer to an appropriate environment for continued care. Improvements in supportive therapy have improved the prognosis of these conditions, but mortality for TEN remains around 30% overall. There is a pressing need for randomized controlled trials to assess the efficacy of potential disease-modifying treatments such as steroids, cyclosporin and IVIGs. Continued epidemiological surveillance is required to provide early warning of the risk of TEN and SJS in newly marketed drugs. Finally, the development of reliable in vitro testing for drug sensitivity would facilitate determination of 'culprit' drugs in cases of TEN and SJS, and could provide evidence of degree of risk to close relatives. HM

Conflict of interest: Dr Craven is currently working with the EuroSCAR group to establish a multinational multicentre trial of intravenous immunoglobulins in toxic epidermal necrolysis.

Arévalo JM, Lorente JA, González-Herrada C, Jiménez-Reyes J (2000) Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* **48:** 473–8

Assier H, Bastuji-Garin S, Revuz J, Roujeau JC (1995) Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* **131**: 539–43

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. *Arch Dermatol* **129**: 92–6

Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ (1999) Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol* **40:** 458–61

Fischer PR, Shigeoka AO (1983) Familial occurrence of Stevens-Johnson syndrome. *Am J Dis Child* **137**: 914–6

Friedmann PS, Strickland I, Pirmohamed M, Park BK (1994) Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. *Arch Dermatol* **130**: 598–604

Garcia-Doval I, LeCleach L, Bocquet H, Otero X-L, Roujeau J-C (2000) Toxic epidermal necrolysis and Stevens-Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* **136**: 323–7

Guibal F, Bastuji-Garin S, Chosidow O, Saiag P, Revuz J, Roujeau J-C (1995) Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol* **131:** 669–72

Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT (1986) Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg* **205**: 503–12

Heng MCY, Allen SG (1991) Efficacy of cyclophosphamide in toxic epidermal necrolysis. *J Am Acad Dermatol* **25**: 778–86

Lebargy F, Wolkenstein P, Gisselbrecht M et al (1997) Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* **23:** 1237–44

Martinez AE, Atherton DJ (2000) High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. *Pediatr Dermatol* **17:** 87–90

Rasmussen JE (1976) Erythema multiforme in children. Response to treatment with systemic corticosteroids. *Br J Dermatol* **95**: 181–6

Revuz R, Roujeau J-C, Guillaume J-C, Penso D, Touraine R (1987) Treatment of toxic epidermal necrolysis. *Arch Dermatol* **123:** 1156–8

Roujeau J-C, Chosidow O, Saiag P, Guillaume J-C (1990) Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol* **23:** 1039–58

Roujeau JC, Kelly JP, Naldi L et al (1995) Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* **333:** 1600–7

Roujeau J-C, Stern RS (1994) Severe adverse cutaneous reactions to drugs. *N Engl J Med* **331:** 1272–85

Saiag P, Caumes E, Chosidow O, Revuz J, Roujeau J-C (1992) Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol* **26:** 567–74

Stables GI, Lever RS (1993) Toxic epidermal necrolysis and systemic corticosteroids. *Br J Dermatol* **128**: 357

Tagami H, Tatsuta K, Iwatski K, Yamada M (1983) Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. *Arch Dermatol* **119:** 910–3

Tripathi A, Ditto AM, Grammer LC et al (2000) Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy and Asthma Proc* **21:** 101–5

Viard I, Wehrli P, Bullani R et al (1998) Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* **282:** 490–3

Villada G, Roujeau J-C, Cordonnier C et al (1990) Toxic epidermal necrolysis after bone marrow transplantation: study of nine cases. *J Am Acad Dermatol* **23:** 870–5

Wolkenstein P, Latarjet J, Roujeau J-C et al (1998) Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* **352**: 1586–9

KEY POINTS

- Toxic epidermal necrolysis and Stevens–Johnson syndrome are rare but potentially devastating adverse reactions to drugs.
- Certain groups, such as those infected with human immunodeficiency virus, are at particular risk.
- Supportive treatment is aimed at replacing lost fluids, treating infections, monitoring cardiorespiratory function, and preventing scarring of mucosal surfaces.
- Randomized controlled trials are required to assess the efficacy of steroids and other potential disease-modifying interventions.