Management of Toxic Epidermal Necrolysis

Jan B. van der Meer, Professor and Chairman
Department of Dermatology, University Hospital Groningen, P.B. 30001, 9700 RB Groningen, The Netherlands

Introduction

Toxic epidermal necrolysis (TEN) is the most aggressive adverse skin-associated reaction to drugs, with a high mortality (up to 60%). The hallmark of the diagnosis is epidermal necrosis and detachment. The resulting loss of skin barrier function may lead to shock and sepsis. The major cause of death is sepsis. Important prognostic factors are age, percentage of body surface area affected, blood urea nitrogen, leukopenia (1). Pain and anxiety are extreme.

Provided the patient survives, the mean duration of TEN (after discontinuation of the offending drug) is about 3–6 weeks. Late ocular damage is a serious complication and occurs in 40–50% of cases (1).

From these data some major cornerstones of management can be deduced (Table I) which will be discussed below.

1. Early diagnosis

The diagnosis is based on clinical and histopathological characteristics.

Clinical characteristics

Early diagnosis is essential but can be obstructed by a variety of clinical pictures. Essentially, there are two different morphological types of lesions. The first is characterized by more or less extensive detachment of sheets of necrotic epidermis, which are shifted away easily, leaving denuded areas (erosions). This type might be called "prototypic TEN" (Fig. 1a). The second type is characterized by more or less extensive areas consisting of patchy purpuric macules and erosions "prototypic Stevens-Johnson Syndrome" (SJS) (Fig. 1b). Real purpura, however, does not occur, nor do typical target lesions as seen in erythema multiforme. Both types are merely variants of a single drug-induced process. In most cases some mucous membranes (eyes, nose, oropharynx, genitals, anus and, occasionally, esophagus and gut) may be involved as well.

Histopathological characteristics

The histopathology of the above-mentioned varieties is essentially identical: epidermal detachment (subepidermal bulla) with widespread epidermal necrosis (apoptosis) and only scant epidermal and dermal inflammation (Fig. 1c). Contrary to the general belief the necrosis in second-degree burn patients involves the dermis as well (Fig. 1d).

Table I. *Cornerstones of management*

Early diagnosis
Immediate elimination of the culprit drug
Intensive care
Careful daily monitoring of the disease process
Pulse therapy with corticosteroids

Based on historical as well as nosological grounds, the term "SJS" as such should be reserved for conditions caused by micro-organisms, as probably applied in the case of the two patients in the original report by Stevens and Johnson (2).

2. Immediate elimination of the culprit drug

Although a large amount of different drugs have been incriminated as possible causes of TEN, those summarized in Table II are the most frequently encountered. Unfortunately, there is no reliable test to confirm a relationship between a suspected culprit drug and TEN. However, clinical experience indicates that drugs recently introduced during the few months before any sign of TEN are probable candidates.

Table II. *Drugs most frequently associated with TEN*

Allopurinol
Oxicam Non Steroid Anti-inflammatory Drugs (NSAID)
Phenytoin and other anticonvulsants
Sulphonamide antibiotics
Pyrazolone derivatives
Chlormezazone

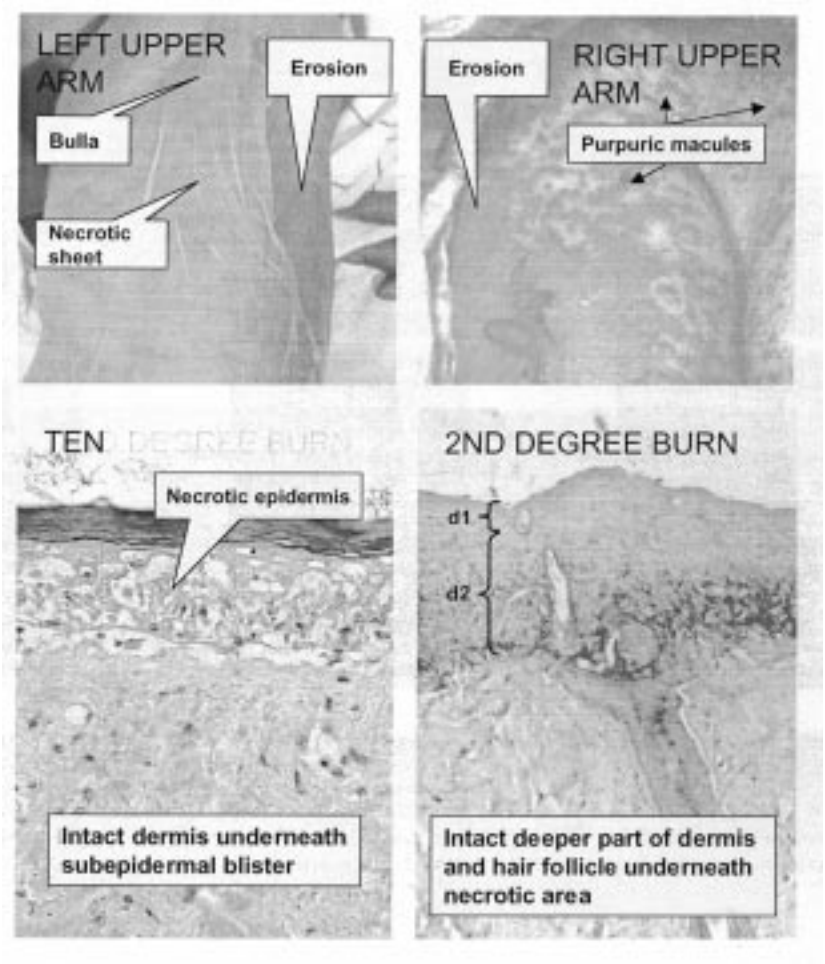

Fig. 1. (a) Extensive detachment of the epidermis: "prototypic TEN". (*b)* More or less extensive areas consisting of patchy purpuric macules and erosions: Aprototypic Stevens-Johnson Syndrome. (*c)* Extensive epidermal necrosis and detachment confirming the diagnosis Toxic Epidermal Necrolysis. (*d)* In second-degree burn necrosis comprises upper dermis as well (magnification 1/3 of Fig 1c). 1. necrotic epidermis; 2. necrotic part of the dermis and of a hair follicle.

Since there is no reliable report mentioning any case of TEN caused by two or more chemically different drugs at the same time, TEN is considered to be caused by one drug at a time.

3. Intensive care

The intensive care procedures usually applied within a burn centre are followed under strict sterile conditions. These procedures do not necessarily have take place in a burn unit, as often propagated. Specifically, all TEN patients were subjected to standard barrier nursing procedures in a laminar flow unit using an "air-fluidized" bed (Hill-Rom, Vianen, The Netherlands). The unit temperature was adjusted to 35°C, room temperature to 28°C and room humidity to 90%. These measures prevent hypothermia (3). Since there is an increased need of nutrients, as in other patients with severe illnesses, the administration of nutrients should meet the increased daily caloric requirements.

No prophylactic antibiotic therapy is given. Pain alleviation is preferably accomplished by the administration of a combination of oxazepam and paracetamol. Opiates may cause decreased gastrointestinal motility, with resulting constipation as a side-effect.

Biochemical and hematological determinations for monitoring purposes (anemia, neutropenia, kidney and liver dysfunctions) are performed as usual, as are chest X-ray tests.

4. Careful daily monitoring of the disease process

In our clinic we apply clinical as well as microscopical methods for the monitoring of the patient's condition.

Clinical monitoring generally is performed by daily measurements of the body surface area (BSA) with detached skin (1). At our clinic we use the same procedure as that used in burn centres (4) (a modified rule of nine).

Since this clinical method does not unequivocally distinguish between recent re-epithelialization and erosions, we recently introduced microscopy as an additional method for answering the question of whether re-epithelialization actually has occurred or not. The biopsies are taken from the central area of the most active sites. In serious cases (extensive detachment) this is done every day,

in less serious cases every other day during the first week after the start of the dexamethasone pulse therapy (see below).

Technique

Anaesthesia for skin biopsy is achieved by freezing the skin through a small hole (approximately 1 cm^2) in a sterile piece of sheet, covering the skin area of choice using ethylchloride spray. This allows a minimal area to be totally frozen. This biopsy procedure limits damage to the fragile bullous skin. Since repeated freezing proved to be damaging to the recovering epidermis, this method also prevents adjacent skin from becoming frozen, so that it remains suitable for future biopsies. Except for the first biopsy for diagnosis, at which time a 4-mm punch biopsy is taken, all other punch biopsies were 3 mm in diameter. Care is taken to obtain all follow-up biopsies around the first diagnostic biopsy, which is obtained from the centre of the most severely affected site. Since these biopsies are taken for emergency monitoring purposes, they were snap-frozen in liquid nitrogen and stored at -80°C until use. Cryostat sections of 4µ were cut and stained with Haematoxylin-Eosin (HE).

The relevance of this additional monitoring method is illustrated in Fig. 2, where biopsies are shown from a patient featuring reoccurrence of TEN (re-TEN). In this patient, initially, phenytoin was considered the culprit drug (compare Table II) and was stopped immediately. This conclusion was supported by finding beginning re-epithelialization (Fig. 2a) five days after the first dexamethasone injection. However, upon decrease of the dexamethasone serum concentration (which occurs within a few days), re-TEN was diagnosed 10 days after elimination of phenytoin and eight days after the first dexamethasone injection (Fig. 2b). After the subsequent elimination of oxazepam and a second dexamethasone pulse regimen at the same time, re-epithelialization now started within 24 hours (Fig. 2c). Six days after the first injection of the second dexamethasone pulse regimen re-epithelialization was complete (Fig. 2d). Thus histopathology offers rapid and reliable information as to the question of whether re-epithelialization actually occurs and to what extent.

5. Pulse therapy with corticosteroids

Spontaneous recovery (without dexamethasone pulse therapy) takes 3–6 weeks and, despite optimal intensive care, "background" mortality is still 30%. Also ocular damage is high, ranging from 40–50%. Several authors have reported trials to reduce the occurrence of these complications by the administration of corticosteroids. Guibal et al. (5) consider corticosteroids detrimental. In their study the mean dose of corticosteroids was 30 mg of prednisolone equivalents given daily for at least 3 weeks. Evidently, even this low dose therapy, given for a prolonged period of time, is life threatening.

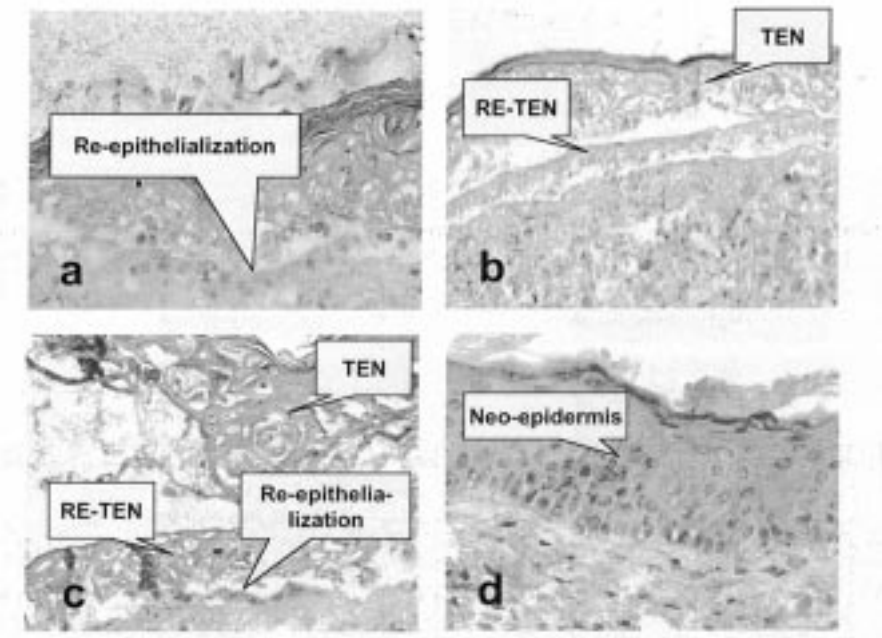

Fig. 2. (a) Beginning re-epithelialization underneath the necrotic epidermis. *(b)* Reoccurrence of TEN 5 days after the last dexamethasone injection. (*c*) Re-epithelialization after subsequent elimination of oxazepam and a second dexamethasone pulse regimen at the same time. (*d*) Almost complete recovery of the epidermis within a week after the start of the second dexamethasone pulse regimen.

In contrast, we introduced dexamethasone pulse (DP) therapy into the management of TEN (6). Specifically, dexamethasone is administered via intravenous infusion at a dose of 1.5 mg/kg body weight for 3 consecutive days. Each infusion is allowed to enter the body within 30–60 minutes. (For comparison: 100 mg dexamethasone equals approximately 660 mg prednisolone.) Only this single regimen of three injections is given.

Table III summarizes our data. DP therapy was given to 7 patients with TEN. In our first 4 cases this regimen was combined with one dose of 500 mg cyclophosphamide in addition to the last gift of dexamethasone, analogous to the procedure Pasricha et al. (7) applied in pemphigus vulgaris. Starting with our 5th patient – who was a child of 14 years – the pulse therapy consisted only of dexamethasone (as mentioned above). In this child, microscopical investigation showed that re-epithelialization was already substantial at day three and at that moment it was decided to eliminate cyclophosphamide from the pulse regimen, because high doses of cyclophosphamide might interfere with fertility. Afterwards, further mono-therapy with DP showed that cyclophosphamide did not add substantially to the process of healing, and it was decided to eliminate cyclophosphamide from our protocol.

From the data in Table III it can be concluded that recovery was rapid. This was irrespective of the percentage of detached skin area. The BSA of detachment at the moment of re-TEN of the patient, shown in Fig. 2, was 90%! Even in this patient the skin recovered within a week.

We currently have a broad experience with DP therapy in a variety of serious dermatological conditions (Pemphigus vulgaris, systemic lupus erythematosus, pyoderma gangraenosum, serious vasculitis, necrotising fasciitis). Over 30 patients received more than 100 DP regimens. Very few side effects were seen. Only facial flushing and sleeping problems were observed in the first few days of this therapy. Dexamethasone pulse therapy, therefore, seems safe and effective.

Table III. *Dexamethasone pulse therapy in 7 patients with TEN*

Therapy	Dose (mg/day)	Days	No. of patients	Recovery time
Dexamethasone	100	3	all 7 cases	6 days
Cyclophosphamide	500	1	4 out of 7	6 days

Summary and conclusions

1. TEN can be defined as the most serious drug eruption, with high mortality.
2. The different clinical pictures are variants of a single drug-induced process.
3. The hallmark of the diagnosis is the microscopical demonstration of extensive epidermal necrosis and detachment.
4. Damage of the barrier function may lead to shock and sepsis. Sepsis is the main cause of death.
5. The cornerstones of management are:
   a. Early diagnosis
   b. Immediate elimination of the (suspected) culprit drug
   c. Intensive care under sterile conditions
   d. Careful daily monitoring of the disease process by daily clinical determinations of the body surface area of detachment according a modification of the rule of nine, together with regular microscopy to verify whether re-epithelialization actually occurs.
   e. Pulse therapy with dexamethasone (1.5 mg/kg for 3 consecutive days). This will lead to rapid clearance of the skin lesions and to subsequent substantial reduction of mortality and blindness; DP therapy appears safe.

References

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331: 1272–1285.
2. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia. Am J Clin Nutr 1922; 24: 526–533.
3. Timsit JF, Mion G, Le Gulluche Y, Carsin H, et al. Severe hypothermia occurring during the course of toxic epidermal necrolysis in patients treated with air-fluidized beds [letter]. Arch Dermatol 1991; 127: 739–740.
4. Lund CC, Browder NC. The estimate of areas of burns. Surg Gynecol Obstet 1944; 79: 352–356.
5. Guibal F, Bastuji-Garin S, Chosidow O, Saiag PH, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. Arch Dermatol 1995; 131: 669–672.
6. van der Meer JB, Baart de la Faille H, Beerthuizen GIJM, Kardaun SH, et al. Stevens Johnson syndroom en toxische epidermale necrolyse: Therapiebeleid voor een levensbedreigend duo. Ned Tijdschr Geneeskd 1996; 140: 1538–1543.
7. Pasricha JS, Thanzama J, Khan UK. Intermittent high-dose dexamethasone-cyclophosphamide therapy for pemphigus. Br J Dermatol 1988; 119: 73–77.