Treatment of Severe Drug Reactions

1. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Definition

SJS and TEN are variants of the same process, presenting as severe mucosal erosions with widespread erythematous, cutaneous macules or atypical targets. The cutaneous lesions often become confluent and show a positive Nikolsky sign and epidermal detachment. In SJS, epidermal detachment involves less than 10% of the total body skin area; transitional SJS-TEN is defined by an epidermal detachment between 10 and 30%; TEN is defined by a detachment greater than 30%. Full-thickness epidermal necrosis is observed on pathological examination. This clinical definition separates SJS-TEN from erythema multiforme major.

Incidence

Based on case registries and observational studies, the incidence of TEN is estimated to be 1-1.4 cases per million inhabitants per year. The incidence of SJS is probably of the same order (1-3 cases per million inhabitants per year).

Etiology/Risk Factors

SJS-TEN is essentially drug-induced. Graft versus host disease is another well-established cause, independent of drugs. A few cases are related to infections (Mycoplasmapneumoniae), and a few other cases remain unexplained. The most extensive study of medication use and SJS-TEN mainly pointed to antibacterial sulfonamides, anticonvulsant agents, some nonsteroidal anti-inflammatory drugs and allopurinol. HIV infection dramatically increases the risk. A predisposing effect of autoimmune disorders, such as systemic lupus, and an HLA-linked, genetic susceptibility have been also suggested.

Prognosis

SJS-TEN is an acute, self-limited disease, with high morbidity, that is potentially life-threatening. Mortality rates are 5% with SJS, 30-35% with TEN and 10-15% with transitional forms. Epidermal detachment may be extensive, to the entire skin surface. As in severe burns, fluid losses are massive, producing electrolyte imbalance. Super-infection, thermoregulation impairment, excessive energy expenditure, alteration of immunologic functions and hematologic abnormalities are usual systemic complications. Mucous membrane involvement (oropharynx, eyes, genitalia and anus) require attentive nursing care. The tracheobronchial epithelium, and less often gastrointestinal epithelium can be involved and cause high morbidity. Age, percentage of denuded skin, neutropenia, serum urea nitrogen level, and visceral involvement are prognostic factors. There are different scoring systems for vital prognosis estimation, SAPS and SAPS 11 (Simplified Acute Physiology Score), which are not specific. A specific score (SCORTEN) has been recently elaborated and validated. After healing, altered pigmentation and corneal lesions are the main long-term complications.
Treatment

Early management
The management of patients must be prompt; early diagnosis with the early recognition and withdrawal of all potential causitive drugs is essential to a favorable outcome. Morbidity and mortality increase if the culprit drug is withdrawn late. We observed that death rates were lower when causative drugs with short elimination half-lives were withdrawn no later than the day when blisters or erosions first occurred. No difference was seen for drugs with long half-lives.

Second, intravenous fluid replacement must be initiated using macromolecules or saline solutions.

Third, the patient must be transferred to an intensive care unit or a burn center. Prompt referral reduces risk of infection, mortality rate and length of hospitalization.

Symptomatic treatment
General principles. The main types of symptomatic treatment are the same as for burns, and the experience of burn units is helpful for the treatment of TEN: environmental temperature control, careful and aseptic handling, sterile field creation, avoidance of any adhesive material, maintenance of venous peripheral access distant from affected areas (no central line when possible), initiation of oral nutrition by nasogastric tube, anticoagulation, prevention of stress ulcer, and medication administration for pain and anxiety control are all essential.

However, TEN and burned patients are not identical: burns happen in a very short time period (a few seconds) and do not spread thereafter; the TEN-SJS progress occurs during several days, including after hospital admittance. Cutaneous necrosis is more variable and often deeper in burns than in TEN.

These differences induce some important management specificities. Subcutaneous edema is a very uncommon feature of TEN, in contrast with burns, probably because of milder injury to blood vessels. Therefore the fluid requirements of TEN patients are habitually two-thirds to three-fourths of those of patients with burns covering the same area. Since the lesions are restricted to the epidermis and usually spare the hair follicles, the regrowth of epidermis is quick in patients with SJS-TEN. This supports a different approach of topical treatment.

Systemic management. Pulmonary care includes aerosols, bronchial aspiration and physical therapy. If the trachea and bronchi are involved, intubation and mechanical ventilation are nearly always necessary. Early and continuous enteral nutrition decreases the risk of stress ulcer, reduces bacterial translocation and enterogenic infection, and allows earlier discontinuation of venous lines. Phosphorus levels must be measured and corrected, if necessary. Profound hypophosphoremaia is frequent and may contribute to altered regulation of glycemia and to muscular dysfunction. Most authors do not use prophylactic antibiotics. Catheters are changed and cultured regularly. Bacterial sampling of the skin lesions is performed the first day and every 48 hours. Indications for antibiotic treatment include an increased number of bacteria cultured from the skin with selection
of a single strain, a sudden drop in temperature, and deterioration in the patient's condition. *S. aureus* is the main bacteria present during the first days, and gram negative strains appear later.

Environmental temperature is raised to 30 to 32 degrees, C. This reduces caloric losses through the skin and the resultant shivering and stress. Heat loss can also be limited by raising the temperature of antiseptic baths to 35°C to 38°C and by using heat shields, infrared lamps, and air-fluidized beds.

Some drugs are needed. Thromboembolism is an important cause of morbidity and death; effective anticoagulation with heparin is recommended for the duration of hospitalization. Although this results in increased bleeding from the skin, it is usually limited in amount and does not require additional transfusion. Antacids reduce the incidence of gastric bleeding. Emotional and psychiatric support must not be forgotten. Tranquilizers such as diazepam and morphine analgesics can be used liberally if the respiratory status permits.

Insulin is administered when hyperglycemia leads to overt glycosuria or to increased osmolarity.

Many reviews have been published about intravenous and oral supplementation on burn care: oxandrolone and human growth factor are effective for decreasing hypercatabolism and net nitrogenous loss; ornithine alpha-ketoglutarate supplementation of enteral feeding is effective to reduce wound healing time; high dose ascorbic acid (66 mg/kg per hour) given during the first 24 hours reduces fluid volume requirements. The usefulness of these treatments is not established in TEN/SJS and is probably lower than for burns because of a shorter duration of skin detachment.

**Topical management.** No consensus exists about topical care. Possible approaches may be conservative or more aggressive (large operative debridement). In our opinion, conservative care is better than any surgical method. Even though we did not perform any study, it has been our experience that the areas with a positive Nikolski, potentially detached by any trauma healed much more rapidly where the epidermis stayed on site than on similar areas where the epidermis had been detached. We leave in place the involved "detachable" epidermis and use dressings only to protect it. Topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine) are used to paint, bathe, or dress the patients. Dressings may be gauzes with petrolatum, silver nitrate, polyvidoniodine, or hydrogels. Some authors use biologic skin covers after epidermal stripping (cadaveric allografts, cultured human allogeneic or autologous epidermal sheets). New dressings are being investigated: Apligraft(r), Biobrane(r), TransCyte(r) (human newborn fibroblasts cultured on the nylon mesh of Biobranee). In burns, topical recombinant bovine basic fibroblast growth factor allowed faster granulation tissue formation and epidermal regeneration than placebo.

Prevention of ocular sequelae requires daily examination by an ophthalmologist. Eye drops, physiologic saline, or antibiotics if needed, are instilled every 2 hours and developing synechiae are disrupted by a blunt instrument. It is suggested that wearing
gas-permeable scleral contact lenses reduces photophobia and discomfort; these lenses improve visual acuity and heal corneal epithelial defects in half of patients.\[17\]

Oral and nasal crusts are removed, and the mouth is sprayed with antiseptics several times a day.

**Specific treatment**

**Corticosteroids.** Corticosteroid use is highly debated. These drugs are a mainstay in some units, but other investigators consider systemic corticosteroids to provoke prolonged wound healing, increased risk of infection, masking of early signs of sepsis, severe gastrointestinal bleeding and increased mortality. A review of the literature shows only patients series and no randomized clinical trials. Several articles reported corticosteroids benefit: Tegelberg used 400 or 200 mg prednisone/day, gradually diminished over a 4 to 6 week period, and observed a single death among eight patients \[18\]. Others series claimed also excellent results but the diagnosis of SJS-TEN was debatable for most of the cases \[19,20,21,22,23\]. In two retrospective studies, no difference in mortality rates or infectious complications was noted in patients who received steroids before or after referral \[24,25\].

By contrast, other studies claimed that corticosteroid use was detrimental. Thirty patients with SJS or TEN were included in an uncontrolled prospective study. The first 15 patients received corticosteroids and the mortality rate was 66%. Therefore, the next 15 patients were treated without corticoids and the mortality rate was 33% \[26\]. Both groups were similar in other described aspects. However, 11 of the 15 patients "without corticosteroids" had received corticosteroids prior to referral. Thus no conclusion may be made about exclusive early administration of corticosteroids. In a retrospective study, a multivariate analysis of prognostic factors showed that corticosteroid therapy was an independent factor for increased mortality \[17\]. Other series provided the same conclusion \[27\].

Moreover, many TEN cases have occurred during treatment with high doses of corticosteroids for preexistent disease \[4,28,29\].

In conclusion, today, according to most authors, systemic corticosteroids are of unproven benefit in early forms and are clearly deleterious in advanced forms of TEN/SJS.

**Intravenous immunoglobulin (IVIG)**

One uncontrolled clinical trial pointed out the possible usefulness of IVIG. It was based on in vitro demonstration that intravenous immunoglobulins can inhibit Fas-Fas ligand mediated apoptosis. Ten consecutive patients with TEN of moderate severity were treated with different doses of IVIG (0.2 to 0.75 g/kg of body weight per day for four consecutive days); all survived \[30\]. However, no randomized clinical trial is published on this, and other authors have not obtained the same results. Rational evaluation of the benefit of this treatment cannot currently be done.

**Immunomodulating agents**
Some case reports claimed a benefit of plasmapheresis for treatment of TEN/SJS. However, according to an open trial (8 consecutive patients with historical controls), plasma exchange produces no significant difference in mortality, length of hospital stay, or time to re-epithelialization. Cyclophosphamide was also proposed. Eight patients with TEN were treated by only cyclophosphamide (initial dose: 300 mg per day); all survived. Other series are not interpretable, on account of concomitant therapy by cyclophosphamide and corticosteroids. Anecdotally, some cases of cyclophosphamide-induced TEN were reported; one included a positive rechallenge test.

In a retrospective comparative study, cyclosporin was safe and was associated with a more rapid re-epithelialization rate and a lower mortality rate (0/11 vs. 3/6) than treatment with cyclophosphamide and corticosteroids. Cyclosporin has also received attention as a useful drug for treatment of TEN, however, further investigations are needed to evaluate the real value of cyclosporin.

**N-acetylcysteine.** NAC increases the clearance of several drugs and their metabolites and in vitro inhibits production of TNF-oc and IL-1P. We found no evidence of clinical effectiveness in TEN. A randomized trial has shown lack of effectiveness of NAC in prevention of hypersensitivity reactions to trimethoprim-sulfamethoxazole in patients with HIV infection. Moreover, high doses of NAC may inactivate not only the culprit drug but also other drugs, potentially useful for the patient.

**Other medications.** We found only case reports but no good evidence on the use of granulocyte colony stimulating factor, heparin, monoclonal antibodies against cytokines and pentoxifylline.

**Thalidomide.** Thalidomide has been proposed as a treatment of TEN because it is a potent inhibitor of TNF-a action. This drug was tested in the only randomized clinical trial ever published in TEN. It was a double-blind, randomized, placebo-controlled study; the regimen was a 5-day course of thalidomide 400 mg daily. The study was stopped after the inclusion of only 22 patients because there was an unexplained significant excess of mortality in the thalidomide group (10 of 12 patients died, compared with 3 of 10 in the placebo group). Based on this unique trial, thalidomide seems to be detrimental in TEN.

In conclusion, we believe that no specific treatment has been proven to be beneficial for TEN/SJS, which is a self-limited disease. For us, to date, the best management is supportive care alone.

**Follow-up**

**Sequelae.** Sun exposure must be avoided for several months because UV can worsen hyperpigmentation sequelae. Sunblocks are recommended.

Ophthalmologic follow-up is mandatory looking for sicca syndrome, keratitis and corneal lesions. If needed, artificial tears and lubricants are prescribed. The most severe inflammatory corneal lesions may progress for months or years and result in severe impairment of vision. Corticosteroid eye drops are not effective in preventing the activity
of corneal lesions. Many ophthalmologists use topical cyclosporin, but there is no firm evidence for the efficacy of this treatment. The grafting of autologous cells from the limbus, supposed to contain stem cells is a promising approach.\[36\]

Synechiae in the mouth or genitalia may necessitate surgery. Glycemia must be followed-up because diabetes may develop after SJS-TEN.

**Prevention of recurrence.** Survivors of TEN/SJS should not be re-exposed to the suspected offending agent(s) or to related compounds. For example, cross-reactions have been reported between different anticonvulsant agents or non-steroidal anti-inflammatory drugs, such as the oxicams. Drugs of the same pharmacologic class can be used provided they are structurally different from the culprit drug. Because genetic factors are suspected in drug-induced blistering disorders, the suspected drug should not be used in the blood relatives of the patient.

There are no specific statistics on the risk of re-use of culprit drugs or on the possibility of desensitization in patients with TEN. Some data are available for prevention or for desensitization in benign cutaneous adverse drug reactions, especially in AIDS.\[37,38,39\]

. **Hypersensitivity Syndrome (DRESS)**

**Definition**

A variety of hypersensitivity responses are responsible for most cutaneous reactions to drugs. The term 'hypersensitivity syndrome' usually refers to a specific, severe, idiosyncratic reaction, defined by a widespread and long-lasting papulopustular or erythematous skin eruption often progressing to exfoliative dermatitis, with fever, lymphadenopathy, and visceral involvement (hepatitis, pneumonitis, myocarditis, periarditis, nephritis).\[40\] Blood alterations are also rather characteristic with eosinophilia in about 90% and mononucleosis in about 40% of cases.\[41\] In order to clarify the nosology, we have proposed the acronym 'DRESS' (Drug Rash with Eosinophilia and Systemic Symptoms) to name the hypersensitivity syndrome.

**Incidence/Prevalence**

For phenytoin, carbamazepine, and phenobarbital, the incidence of DRESS has been estimated to 1 reaction per 5,000 to 10,000 exposures.\[42\]

**Etiology/Risk Factors**

By definition, drugs are the causal agent. Anticonvulsants, sulfonamides, dapsone, allopurinol, minocycline and gold salts are among the most frequent culprit drugs. Detoxification defects have been implicated in the pathophysiology of this syndrome, with an inherited component. Slow acetylation is probably one of the risk factors. A role of viral co-infection is also suspected (specifically, a reactivation of the herpes virus HHV6).\[43,44,45\]
Prognosis

DRESS is potentially life-threatening. The mortality rate is estimated at near 10%. In other cases, recovery is usually total. Rash and hepatitis may persist for weeks; some cases persist for months.

Treatment

Acute period
DRESS syndrome must be promptly recognized and all potential culprit drugs withdrawn. The typical delay between beginning the administration of a drug and the onset of the reaction is two to six weeks.

Systemic corticosteroids are often used (0.5 to 1 mg/kg). This therapy rapidly improves symptoms and laboratory measurements, but its impact on the long term disease course is not known. Controlled clinical trials are lacking. Relapses of rash and hepatitis may occur as corticosteroids are tapered. A chronic HHV6 activation promoted by systemic steroids could explain these relapses.

While waiting for better evidence, we recommend using systemic steroids only for patients with life-threatening visceral manifestations such as interstitial pneumonitis or nephritis. In milder cases, topical steroids improve the skin manifestations. Interferon cc has been used in a few cases of long-lasting DRESS. This is not enough to allow appropriate evaluation.

When the skin rash results in exfoliative dermatitis supportive care consists of warming the environmental temperature and using local antiseptics and topical corticosteroids. If the erythroderma is severe, the cutaneous blood flow is significantly increased; cardiac failure may occur in elderly patients or those with prior cardiac disease and should be carefully monitored and treated. Oral antipyretics and topical corticosteroids are helpful to decrease this risk.

Prevention of recurrence
To distinguish the culprit drug among several suspected drugs, drug administration timing and its temporal relationship to the onset of the syndrome must be evaluated in detail. The use of flow sheets documenting symptoms, drugs and dates may be helpful. Consideration must be given to the likelihood of a particular drug to cause the syndrome when multiple drugs are involved. Patch tests and in-vitro lymphocyte tests have been used, but the sensitivity and specificity of these tests are variable, depending on the drug.

Cross-reactions are frequent between the three main aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), and all three must be avoided by the patient if one has been causative. It may be difficult to find a safe alternative anticonvulsant therapy.

As for TEN/SJS, first-degree relatives should be alerted to their elevated risk of such reactions to the same drug(s).