# life threatening cutaneous drug reactions [created by Paul Young; 03/10/07]

## general

- Adverse cutaneous reactions to drugs are frequent, affecting 2% to 3% of all hospitalized patients. Fortunately, only about 2% of adverse cutaneous reactions are severe and very few are fatal

## causative drugs

- More than 100 drugs have been associated with the development of SJS/TEN
- Sulfonamides are the most strongly associated with TEN followed by antibiotic drugs (in descending order of frequency: cephalosporins, quinolones, aminopenicillins, tetracyclines, macrolides), imidazole antifungals, anticonvulsants (phenobarbital, phenytoin, valproic acid, carbamazepine, and lamotrigine), then nonsteriodal anti-inflammatory drugs (especially oxicam), allopurinol, and others.
- the risk for developing TEN is largely confined to the start of antiepileptic therapy, that is, within the first 8 weeks, after which it was not associated with an increased risk. The incubation time for all other drugs varies from a few days to 2 to 3 weeks, but may be up to 1 month.

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## classification

- The clinical pattern of the individual skin lesion is classified into 4 types:
1. Typical targets:
- individual lesions less than 3 cm in diameter with a regular round shape, well-defined border, and at least 3 different zones, that is, 2 concentric rings around a central disk. One ring consists of palpable edema, paler than the center disk.
2. Raised atypical targets:
- round, edematous, palpable lesions, similar to EM but with only 2 zones and/or a poorly defined border.
3. Flat atypical targets:
- round lesions characteristic of EM but with only 2 zones and/or a poorly defined border and nonpalpable with the exception of a potential central blister.
4. Macules with or without blisters:
- nonpalpable, erythematous, or purpuric macules with an irregular shape and size and often confluent. Blisters often occur on all or part of the macule.

1. Bullous erythema multiforme:
- detachment less than 10% of BSA, localized typical targets or raised atypical targets.
2. Stevens Johnson Syndrome:
- detachment less than 10% of BSA, widespread erythematous or purpuric macules of flat atypical targets
3. Overlap Stevens Johnson Syndrome / toxic epidermal necrolysis:
- detachment between 10% and 30% of BSA, widespread purpuric macules or flat atypical targets.
4. toxic epidermal necrolysis with spots:
- detachment greater than 30% of BSA, widespread purpuric macules or flat atypical targets.
5. toxic epidermal necrolysis without spots:
- detachment greater than 10% of BSA, large epidermal sheets and no purpuric macules.

- The involved BSA should measure the extent of detached and detachable epidermis (which is often much less than the area of erythema) at the worst stage of the disease

## clinical manifestations

- The initial symptoms of TEN, that is, before the appearance of frank mucocutaneous sloughing, include:
(i) fever (all cases)
(ii) conjunctivitis (32% of cases),
(iii) pharyngitis (25% of cases), and
(iv) pruritus (28% of cases).

- The cutaneous lesions begin with a burning and painful eruption.
- This eruption extends symmetrically from the face and upper part of the body to the entire body, predominantly on the trunk and proximal limbs.
- The initial lesions are poorly defined macules with darker centers.
- Maximal extension of lesions usually occurs in 2 or 3 days, but can be manifested in a few hours. There is a sheet like loss of epidermis and the appearance of flaccid blisters that spread with pressure in TEN.
- Nikolsky's sign is positive over large areas involved by confluent erythema.

- Mucous membranes (in increasing order of frequency: oropharynx, eyes, genitalia, anus) are commonly affected 1 to 3 days before the skin lesions appear.
- Widespread painful mucosal erosions result in impaired alimentation, photophobia, and painful micturition.

- Gastrointestinal or tracheobronchial epithelium can be involved via a process of necrosis resulting in profuse diarrhea or respiratory distress, respectively, and causing high morbidity.

- Blood abnormalities are also almost always present. Anemia and lymphopenia are found in virtually all patients, neutropenia in 30% of patients (indicating a poor prognosis), and thrombopenia in 15% of patients.

- Fluid losses are massive and accompanied by with electrolyte imbalance.

- During the first days, skin lesions are usually colonized by Staphylococcus aureus; they are later invaded by gram negative rods.

- Thermoregulation is impaired and energy expenditure is increased.

- Re-epidermization begins after a few days, and most of the skin surface is re-epithelialized in 3 weeks.

## treatment

- Both SJS and TEN are life-threatening diseases, and so the management of patients must be prompt.
- Early diagnosis with the early recognition and withdrawal of all potential causative drugs is essential to a favorable outcome.
- Morbidity and mortality decrease if the culprit drug is withdrawn no later than the day when blisters of erosions first occurred.

- 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.
- 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, and maintenance of venous peripheral access distant from affected areas.

- The early fluid requirement of TEN patients are two thirds to three fourths of those of patients with burns covering the same area.

- Intubation and mechanical ventilation are nearly always necessary if the trachea and bronchi are involved.
- Patients require ophthalmology review early and frequently
- There is no consensus about topical care. Topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine) are usually used to paint, bathe, or dress the patients. Silver sulfadiazine, which is very popular in burn units, should be avoided because sulfonamides are frequently implicated in the etiology of TEN
- Dressings may be gauzes with petrolatum, silver nitrate, polyvidone iodine, hydrogels, Hydrone, Vigilon (semipermeable dressings), SoftSorb, and others that can also be impregnated with silver nitrate.

- Corticosteroids have for years been the mainstay therapy for TEN and SJS There are no randomized clinical trials on the use of corticosteroids in the treatment of these life-threatening diseases.
- IVIG has been used