**Abstract**
Severe cutaneous adverse reactions are associated with significant morbidity and mortality. They may be life-threatening for the affected patient and difficult to treat. Such conditions include toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). A clinical consensus definition of skin reactions in the spectrum of SJS/TEN have been established and well-defined diagnostic scores have been created for AGEP and DRESS, thus enabling definitive clinical recognition and epidemiologic investigation of these drug reactions. This review will focus on SJS and TEN, noting the clinical pattern, pathophysiology, and important diagnostic and therapeutic considerations in the management of SJS and TEN.

**Stevens Johnson syndrome and toxic epidermal necrolysis**
Based on a population-based registry in Germany, the incidence of SJS, SJS/TEN-overlap and TEN together between 1991 and 1995 (assuming that these reactions represent a single disease entity different from erythema multiforme with mucosal involvement (EM majus, EMM)) was estimated to be 1.53 -1.89 per one million inhabitants per year.\(^1,2\) Severe skin reactions may affect any age group. In the registry, the average age of patients with SJS, SJS/TEN-overlap, and TEN was 53.4 years (1-94 years) in a cohort of over 2200 patients. Approximately 75% of patients with SJS/TEN-overlap and TEN were greater than 40 years old, while only 40% of patients with SJS were over the age of 40. SJS and TEN affects men and women almost equally (with slight female predominance) while a female preponderance of around 65% can be observed in SJS/TEN-overlap. Since it is often difficult to define the actual reason for death in patients with SJS and TEN, death within 6 weeks after the onset of the reaction is considered to be related to the severe adverse reaction. Thus, mortality in SJS is 9%, in SJS/TEN-overlap 29% and in TEN 48%. Compared to previous years, the mortality rate seems even higher, probably reflecting the increased age of affected patients and associated medical comorbidities.\(^3\)

**Clinical pattern and diagnostic considerations**
SJS and TEN are characterized by erythematous skin and extensive detachment of epidermis and erosions of mucous membranes.\(^3\) SJS and TEN are thought to be a single disease entity of different severity with common causes and mechanisms.\(^4\) They are differentiated based on the extent of skin detachment limited to less than 10% of the body surface area (BSA) in SJS, 10%-30% BSA in SJS/TEN overlap, and greater than 30% of the BSA in TEN (Table 1; Figure 1).\(^5\) Hemorrhagic erosions of mucous membranes, including eyes, lips, mouth, pharynx, trachea, bronchi, vulva, glans penis, urethra and anus, are present in about 95% of cases (Figure 2a-2d). The histopathology shows scattered keratinocyte necrosis or full-thickness necrosis of the epidermis due to extensive apoptosis.\(^6\) Based on the almost identical histopathology of SJS/TEN and erythema multiforme (EM), SJS/TEN is often thought to be part of a broader EM-spectrum. For decades EM with mucosal involvement (EM majus, EMM) was considered to be the same as Stevens-Johnson syndrome; however, it is now understood that these are separate diseases and that EMM is predominantly due to infections rather than medications.\(^7\)

Further differential diagnoses of SJS vary with the clinical presentation and the extent of the skin detachment. Maculo-papular eruptions, which may also present with oral lesions and conjunctivitis, must be considered as a differential diagnosis in the early stage of the disease. In elderly patients a multiforme-like or target-like drug-induced eruption has to be taken into account as a differential diagnosis, whereas in children atypical forms of EMM exist with widely disseminated target lesions that are usually well demarcated and not confluent.\(^7\)
When blisters and skin detachment are already present, it is imperative to quickly exclude the possible diagnosis of staphylococcal scalded skin syndrome (SSSS) by performing a frozen section to evaluate the level of epidermal separation, which is intraepidermal in SSSS but subepidermal in TEN. The diagnosis should always be confirmed by conventional histopathologic examination as well. It is important to note that purpuric macules and target lesions are not seen in SSSS and mucosal involvement occurs rarely. SSSS is extremely rare, with 1 case per 10 million people per year, affecting 2 groups of high-risk patients, infants and children with acute staphylococcal infection and adults with renal failure or septicemia.

Generalized bullous fixed-drug eruption (GBFDE) is characterized by well-defined round or oval plaques with dusky violaceous or brownish color. Bullae may develop within these plaques and histopathology shows similar features to SJS/TEN, but lesions usually do not affect more than 10% of the BSA. Fever, malaise and mucosal involvement are less frequent and severe as compared to SJS/TEN. However, recent evidence suggests that the mortality rate of GBFDE in elderly patients may be similar to that in SJS and SJS/TEN-overlap with a comparable amount of skin detachment. Previous fixed-drug eruptions are common in the history of patients with GBFDE. Autoimmune blistering diseases such as pemphigus vulgaris, bullous pemphigoid, IgA-linear dermatosis, and bullous phototoxic reactions should also be considered in the differential diagnosis. Occasionally, desquamation of large sheets of skin in exfoliative erythroderma may be clinically confused with epidermal detachment in SJS/TEN. That may sometimes also be the case for AGEP, where after confluence of dozens of non-follicular pustules a superficial Nikolsky-like phenomenon may mimic detachment in SJS/TEN.

Etiology and medication risk
Although drugs are the etiologic factors in the majority of an estimated 75% of SJS/TEN-cases, infections, such as upper respiratory and mycoplasma pneumoniae infections, as well as influenza-like illness, have been reported to be etiologic factors. Most patients with SJS and TEN report some drug intake; medications taken for years and others taken simultaneously to the time of onset of the reaction are unlikely to be the cause. Whether SJS or TEN can be attributed to a medication versus infection is sometimes confounded by the fact that many patients with acute infections immediately preceding their severe skin reaction also took anti-infective, antipyretic and/or analgesic medications. Often it is difficult to determine whether the symptoms (ie, oronasal soreness and conjunctival injection) are signs of an acute infection or the beginning of SJS/TEN itself. Therefore, it is crucial to determine the day of onset of the adverse reaction. To date, neither the possible interaction of infection and medication nor the role of drug-drug interactions in SJS/TEN has been clarified. Moreover, there is no reliable in vitro or in vivo test to determine the link between a specific drug and the severe cutaneous adverse reaction in an individual case. The detection of the culprit drug mainly relies on the history, specifically the time interval between beginning of drug use and onset of the adverse reaction. An algorithm for causality assessment in SJS/TEN called ALDEN (algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis) has been created in order to provide a structured approach to determine the inducing drug. It includes the findings of epidemiologic studies, including 2 multinational case-control studies, which provide risk estimates for drugs inducing SJS/TEN. Among medications believed to be linked with SJS/TEN, 2 were

**TABLE 1 Consensus definition of Stevens-Johnson syndrome and toxic epidermal necrolysis**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>EM majus</th>
<th>SJS/TEN overlap</th>
<th>TEN with maculae</th>
<th>TEN with widespread erythema (without spots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin detachment (%)</td>
<td>&lt;10%</td>
<td>10%-30%</td>
<td>&gt;30%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Typical target lesions</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atypical target lesions</td>
<td>raised</td>
<td>flat</td>
<td>flat</td>
<td>flat</td>
</tr>
<tr>
<td>Maculae</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Distribution</td>
<td>mainly limbs</td>
<td>widespread</td>
<td>widespread</td>
<td>widespread</td>
</tr>
</tbody>
</table>

Abbreviations: EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
highly associated with SJS/TEN in the most recent study: nevirapine and lamotrigine. Both shared the overall pattern of “highly suspected” drugs. Features that suggest high suspicion include recent start of drug use and infrequent co-administration with another “highly suspected” drug. 11 The manufacturer had proposed to avoid adverse reactions for both agents by slow titration of the dosage (lead-in periods or slow dose escalation). This recommendation however did not alter the rates of severe skin reactions such as SJS and TEN.11,14

The most recent case-control study confirmed a high risk for all drugs previously suspected of causing SJS and TEN such as anti-infective sulfonamides (especially co-trimoxazole), allopurinol, carbamazepine, phenytoin, phenobarbital, and oxicam-NSAIDs, with the exception of valproic acid. Most of these “highly suspected” drugs were taken on a long-term basis, and among cases exposed to them, 85% to 100% had started the treatment less than 8 weeks before onset of the reaction (Table 2). The median time latency between the beginning of drug use and index day was less than 4 weeks (15 days for carbamazepine, 24 days for phenytoin, 17 days for phenobarbital, 20 days for allopurinol), whereas it was much longer for drugs with no associated risk (above 30 weeks for valproic acid, ACE-inhibitors and calcium channel blockers). For allopurinol, 56 of 66 exposed patients were recent users in contrast to only one of 27 controls, leading to a substantially increased risk for recent users. In general, no significant risk persisted after 8 weeks of use.

Many drugs of common use, such as beta-blockers, ACE-inhibitors, calcium channel blockers, sulfonamide-related diuretics and sulfonylurea anti-diabetics, insulin, and propionic acid NSAIDs like ibuprofen were not associated with an increased risk to induce SJS/TEN (Table 2).11

Genetics and pathophysiology

Two decades ago, genetic susceptibility was suspected for TEN and different HLA-loci were found in patients with TEN caused by anti-infective sulfonamides or oxicam-NSAIDs.15 In recent years, a very strong association between carbamazepine-induced SJS in Han-Chinese patients and the major histocompatibility complex haplotype HLA-B*1502 was observed.16 These findings could not be confirmed in European patients. Furthermore, study of one cohort of European carbamazepine-induced cases of SJS showed an association with a variety of HLA-B alleles, and no association was found between SJS and the specific allele or haplotypes described by the Taiwanese group.17

A very strong association between allopurinol-induced severe cutaneous adverse reactions, both SJS/TEN and DRESS, and HLA-B*5801 was also found in Chinese patients.18 A weaker association between this particular haplotype was confirmed for European patients with SJS/TEN due to allopurinol, where only 55% of affected patients were positive for HLA-B*5801.19 These important findings suggest that the genetic predisposition to develop SCAR is highly associated with specific drugs, and ethnicity matters much more than previously thought.

Although drugs are the etiologic factor in the majority of SJS/TEN cases, the link between a certain drug and epidermal necrosis still remains to be determined. T-cells, especially CD8+ lymphocytes, as well as cytokines have been demonstrated to play an important role in this process.20 The cytotoxic mitochondrial protein,
granulysin, was identified to be the most important factor mediating epidermal destruction. Its concentration was very high in the blister fluid of SJS/TEN patients, and increased with the severity of the disease and was higher in TEN than in SJS. It is important to note that granulysin levels are not reduced by intravenous immunoglobulins, which are sometimes used as a treatment option for TEN.21

**Therapeutic management**

Since the pathophysiologic mechanism of SJS/TEN remains unknown, the approach to treatment is primarily supportive and symptom-targeted. Symptomatic management, however, is of major importance for patients, especially those with severe disease whose extensive skin detachment requires intensive care in specialized units. Furthermore, treatment should also be aimed at prevention of long-term sequelae such as strictures of mucosal membranes and symblepharon, which are significant causes of morbidity in patients with SJS and TEN.7

In the immediate management of SJS/TEN, it is widely accepted that all potential medication triggers must be withdrawn in order to reduce morbidity and mortality. Impaired renal or hepatic function, long medication half-lives, and persistent reactive metabolites may continue to cause further progression of the disease long after the culprit medication has been discontinued.22 Drugs which have been started in the 4 weeks before the onset of the skin reaction without any previous use are most likely to cause SJS/TEN.11

**Supportive care**

Cutaneous thermoregulation is impaired by the compromised skin barrier, thus increasing the room temperature to 30-32°C is important, especially for patients with large amounts of epidermal detachment. Patients with skin loss of more than 30% have a high risk for a variety of systemic complications and should be treated in highly specialized skin centers. If these are not available, burn units or intensive care facilities with daily dermatologic consultation may be the best alternative. Patients with SJS/TEN require fluid replacement with electrolyte solution (0.7 ml/kg/% affected area) and albumin solution (5% human albumin, 1 ml/kg/% affected area). Importantly, SJS/TEN patients need only about 70% of the fluids of burn patients. Nutritional needs should be considered; nutrition through a gastric tube (1500 calories in 1500 ml over the first 24 hours, increasing by 500 calories daily to 3500-4000 calories daily) is often needed. Monitoring for infection is mandatory and, if clinical suspicion arises, empiric treatment with anti-infective medications should be started until culture and sensitivity results are available. Sedation and pain management depending on the disease severity should be ensured.7,23 Placement of the patient on an alternating pressure air mattress may also help to reduce pain. Professional psychological support for the patient and family members has been shown to be beneficial.

### TABLE 2

**At-risk medications and recommendations for identifying causal medications in Stevens-Johnson syndrome and toxic epidermal necrolysis**

<table>
<thead>
<tr>
<th>A. Drugs with a high risk to induce SJS/TEN11</th>
</tr>
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<tbody>
<tr>
<td>Their use should be carefully determined and they should be suspected promptly.</td>
</tr>
</tbody>
</table>

- Allopurinol
- Carbamazepine
- Co-trimoxazole (and other anti-infective sulfonamides and sulfasalazine)
- Lamotrigine
- Nevirapine
- NSAIDs (oxicamtype; ie, meloxicam)
- Phenobarbital
- Phenytoin

- An interval of 4-28 days between beginning of drug use and onset of the adverse reaction is most suggestive of an association between the medication and SJS/TEN.
- When patients are exposed to several medications with important clinical benefit for the patient, the timing of administration is important to determine which one(s) must be stopped and if some may be continued or re-introduced.
- The risks of various antibiotics to induce SJS/TEN are within the same order of magnitude, but substantially lower than the risk of anti-infective sulfonamides.
- Valproic acid does not seem to have an increased risk for SJS/TEN in contrast to other anti-epileptics.
- Diuretics and oral anti-diabetics with sulfonamide structure do not appear to be risk factors for SJS/TEN.

<table>
<thead>
<tr>
<th>B. Drugs with a moderate (significant but substantially lower) risk for SJS/TEN</th>
</tr>
</thead>
</table>
| Cephalosporines
| Macrolides
| Quinolones
| Tetracyclines
| NSAIDs (acetic acid type; ie, diclofenac) |

<table>
<thead>
<tr>
<th>C. Drugs with no increased risk for SJS/TEN</th>
</tr>
</thead>
</table>
| Beta-blockers
| ACE-inhibitors
| Calcium channel blockers
| Thiazide diuretics (with sulfonamide structure)
| Sulfonylurea anti-diabetics (with sulfonamide structure)
| Insulin
| NSAIDs (propionic acid type; ie, ibuprofen) |

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Skin-directed therapy
Although blisters in SJS/TEN are fragile, they should ideally be left in place and only punctured if necessary, allowing the blister roof to serve as a biologic dressing. Erosions may be treated with chlorhexidine, octenisept or polyhexanide solutions and covered with nonadherent mesh gauze. The latter is even more important when TEN-specific conditions (including warm room temperature, alternating pressure mattress, etc.) lead to increased dryness of the skin. Silver sulfadiazine should be avoided at least until antibacterial sulfonamides are ruled out as the potential cause of the reaction. Some burn care physicians are in favor of debridement of the skin under general anesthesia with application of allografts or other forms of coverage. However, this rather aggressive approach is often not practical for patients and may increase the risk for scarring.7,23

Severity of mucosal involvement is often independent of the degree of skin detachment. For all affected mucosal surfaces, specialized care is crucial and requires a multidisciplinary approach. Genital erosions in females may lead to adhesions or strictures, which can generally be avoided by appropriately placed wet dressings or sitz baths. Oral erosions should be treated with desinfectant mouthwash. Lip erosions can be treated with bland ointments, like dexpanthenol ointment. In cases with eye involvement, ophthalmologic care is critical and specialized lid care should be provided daily in addition to anti-inflammatory eye drops. Extensive blepharitis can lead to entropion with trichiasis (ingrowing eye lashes) that may cause corneal damage, especially if a sicca syndrome evolves because of lacrimal duct injury. Different specialized approaches to ocular problems (stem cell generation of replacement cells) exist, but are not yet generally accepted nor widely available.7,23

Immunomodulatory therapy for SJS/TEN
Various immunomodulatory treatments for SJS/TEN have been proposed, such as glucocorticosteroids, intravenous immunoglobulins (IVIG), and cyclosporine. Most publications on steroid use are case reports or case series, the results of which are difficult to compare. Documented complications of systemic therapy with glucocorticosteroids include increased rate of infections, the risk of masking septicemia, delay of re-epithelialization, prolonged duration of hospitalization, and higher mortality.7,23

Intravenous immunoglobulins (IVIG) are also controversial. They have been reported as an effective treatment of TEN based on the hypothesis that antibodies in pooled human IVIG block the Fas-mediated necrosis of keratinocytes in vitro. Several case compilations on SJS/TEN patients treated successfully with IVIG have been published, but cautious interpretation is warranted as numerous cases appear repeatedly in these papers.24 More recently, a meta-analysis revealed no benefit of IVIG concerning death as the outcome.25 In a highly specialized intensive care unit in a department of dermatology in France, a controlled observational therapeutic study of 34 patients with SJS/TEN using IVIG for treatment was performed.26 Based on the specific severity of illness score for TEN called SCORTEN, prognostic factors were evaluated.27 Mortality was higher than predicted and patients died due to renal failure. Two further studies performed in North American burn units also suggested no improvement of the outcome of patients with TEN following treatment with IVIG.26,29

Another controlled trial using cyclosporine in the treatment of SJS/TEN was performed in France showing a lower death rate than expected based on SCORTEN estimations.30 The beneficial results may be explained by the potential effect of cyclosporine on granulysin. However, further immunologic investigations are necessary to validate this hypothesis. Controlled studies of cyclosporine should be strongly encouraged, since it is currently the most promising approach for treatment of SJS/TEN.

Plasmapheresis, hyperbaric oxygen, and cyclophosphamide have also been reported as a successful treatment of TEN in case reports and case series. However, they are only of limited value, as these observations were not controlled studies. Because thalidomide, an effective TNF-alpha-inhibitor in vitro, caused a higher death rate in the only randomized controlled trial in TEN, use of this class of medications in TEN is not currently recommended.3,7,23

The aim of any immune modulating treatment should be to reduce the substantial mortality in patients with a high risk to die.31 Low mortality in patients with minimal risk to die (ie, young patients with limited skin detachment) should not be the appropriate criterion for evaluation of the efficacy of a treatment; it is important to note that low-risk patients have been included in a number of published reports, further complicating their interpretation.

Therapeutic modalities outside of a certain study protocol have been compared based on patients included in the EuroSCAR-study, which primarily aimed at risk estimation of drugs inducing SJS/TEN. In this observational study, mortality data were examined in conjunction with treatment with corticosteroids, IVIG, steroids and IVIG in combination, and supportive care only in 281 patients with SJS/TEN from France and Germany. The results revealed that treatment with corticosteroids was associated with a clinical benefit for affected patients, whereas treatment with IVIG did not. Although there are pitfalls of such a retrospective analysis, it supports two major conclusions: evidence does not currently support IVIG as the treatment of SJS/TEN, and a controlled trial using corticosteroids for treatment may be considered.12

Complications in the acute phase, prognosis and long-term sequelae
Transdermal fluid loss may lead to hypovolemia, changes in electrolyte levels and finally to increased catabolic metabolism in the blistering conditions. Septicemia, mainly introduced through central venous lines, is the most frequent cause of death in patients with TEN. The combination of hypovolemia and septicemia increases the risk for shock and multi-organ failure.23,33

Involvement of tracheal and bronchial epithelium, which may develop in up to 20% of the patients with TEN, is one of the most severe complications. Hypoxemia, hypocapnia and metabolic alkalosis are indications for mechanical ventilation and result in an increased risk of death.34 The prognosis of individual patients can be evaluated by applying the severity of illness score, SCORTEN. Seven independent factors including age, skin detachment of 10% or more related to the BSA, underlying malignant diseases, tachycardia and certain lab values are considered. For each positive item, a score value (weight) of one is given, leading to a total between 0 and 7 with the higher score values being indicative of a poorer prognosis (Table 3). SCORTEN is a reliable instrument concerning the prognosis quoad vitam, but was not designed to predict any long-term sequelae.27
The skin usually regenerates without atrophic or hypertrophic scars, unless the upper dermis is affected by trauma or infection. Hyper- and/or hypopigmentation frequently occurs, but may resolve over time. Further long-term cutaneous problems may occur. Reversible hair loss may occur. Involvement of nail matrix may result in onycholysis, partial or complete nail loss and later onychodystrophy, sometimes persisting for years. Depending on the mucosal involvement in the acute stage of the disease, various long-term sequelae may develop. They include depapillation of the tongue, oral synechia and impaired taste. Strictures of the esophagus, the urethra and the anus have also been reported. Vaginal adhesions, mucosal dryness, pruritus and bleeding of the genital mucosa may occur in women after SJS/TEN with genital involvement.3,7,35

Ocular sequelae are usually the most severe for the patient. They result in functional changes of the conjunctival epithelium with dryness and pathological consistency of tears, especially if a sicca syndrome evolves due to damage of the lacrimal duct. Ophthalmologic sequelae include chronic inflammation, entropion, fibrosis, trichiasis and symblepharon. Chronic irritations and insufficiency of limbal stem cells may lead to metaplasia of the corneal epithelium with ulceration and vision loss, resulting in substantial visual impairment and sometimes even blindness.36,37

References

TABLE 3 SCORTEN27

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Weight/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥40 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy Yes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Body surface area detached</td>
<td>≥10%</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia ≥120/min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood urea nitrogen ≥10 mmol/L (≥27 mg/dL)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum glucose ≥14 mmol/L (≥250 mg/dL)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum bicarbonate &lt;20 mmol/L (&lt;20 mEq/L)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Possible score 0-7

Mortality rates predicted by SCORTEN score: 3.2% (score of 0 or 1), 12.1% (score of 2), 35.3% (score of 3), 58.3% (score of 4), >90% (score of 5 or higher)


