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The Current Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis CME

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Abstract and Introduction

Abstract

Stevens–Johnson syndrome has long been considered to resemble erythema multiforme with mucosal involvement, but is now thought to form a single disease entity with toxic epidermal necrolysis. Although

Stevens–Johnson syndrome is less severe, etiology, genetic susceptibility and pathomechanism are the same for Stevens–Johnson syndrome/toxic epidermal necrolysis. The condition is mainly caused by drugs, but also by infections and probably other risk factors not yet identified. Identification of the cause is important for the individual patient and in cases of drug-induced disease withdrawal of the inducing drug(s) has an impact on the patient's prognosis. If an infectious cause is suspected, adequate anti-infective treatment is needed. Besides this, supportive management is crucial to improve the patient's state, probably more than specific immunomodulating treatments. Despite all of the therapeutic efforts, mortality is high and increases with disease severity, patients' age and underlying medical conditions. Survivors may suffer from long-term sequelae such as strictures of mucous membranes including severe eye problems.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are diseases within the spectrum of severe cutaneous adverse reactions (SCAR) affecting skin and mucous membranes. Although different in clinical pattern, prognosis and etiology, erythema multiforme with mucosal involvement, also called erythema exsudativum multiforme majus (original term still used in Europe), erythema multiforme majus (EMM) or bullous erythema multiforme is part of this spectrum. Unfortunately, the terminology of these severe and sometimes life-threatening mucocutaneous reactions has been inconsistent for decades until a consensus definition published in 1993 suggested the differentiation of EMM from SJS, TEN and their overlap. This consensus classification has been successfully used in several large epidemiological studies performed during the last 20 years. For the first time these studies provided reliable information on demographic data and on the incidence of SJS and TEN. In case reports and case series a variety of drugs have been reported to be associated with SJS and TEN, but risk estimates for certain drugs and drug groups to induce SJS/TEN were not available before the epidemiological studies. A genetic predisposition of patients developing SCAR had long been suspected, but HLA alleles related to SJS/TEN and specific for certain drugs in defined populations were only found in recent years. Furthermore, biological specimens of patients with SCAR were systematically collected and investigated, providing the basis for pathogenetic considerations and new therapeutic approaches.

Clinical Pattern & Diagnostic Procedures

Stevens–Johnson syndrome and TEN are characterized by cutaneous erythema with blister formation of various extent and hemorrhagic erosions of mucous membranes, such as stomatitis, balanitis, colpitis, severe conjunctivitis and blepharitis. Frequently, fever and malaise are the first symptoms of the disease, which may persist or even increase once the muco-cutaneous lesions appeared.

Consensus Definition

The classification published by Bastuji-Garin *et al*. in 1993 is based on the type of single lesions and on the extend of blisters and erosions related to the body surface area (BSA).[1]

The lesions found in these severe skin reactions are typical targets with a regular round shape and a well-defined border with at least three different concentric zones: a purpuric central disk with or without a blister, a raised edematous intermediate ring and an erythematous outer ring. By contrast, atypical raised targets present with only two zones and a poorly defined border, while atypical flat targets are characterized by vesiculous or bullous lesions in the center, which may be confluent.[1]

Typical or atypical raised targets are characteristic for EMM. They appear mainly on the limbs, but sometimes also on the face and trunk, especially in children (Figure 1). By contrast, widespread, often confluent purpuric macules (spots) or atypical flat targets predominantly on the trunk are the cutaneous pattern in SJS (Figure 2). Various mucosal sites are severely affected in both conditions and do not allow the differentiation. Since only small blisters appear on the target lesions in most cases of EMM, skin detachment is usually limited, often to 1 or 2% of the BSA, whereas it is higher but below 10% in SJS. By definition a diagnosis of TEN requires skin detachment of more than 30% of the BSA, which reflects the entire trunk without buttocks. Widespread macules and atypical targets, as seen in SJS, precede the epidermal sloughing in most cases (TEN with maculae),

although few cases of TEN develop on large erythema without signs of confluent macules and little more than 10% of detachment (TEN without spots, also called TEN on large erythema).

Figure 1. Typical Targets with Three Concentric Zones in Erythema Multiforme Majus.

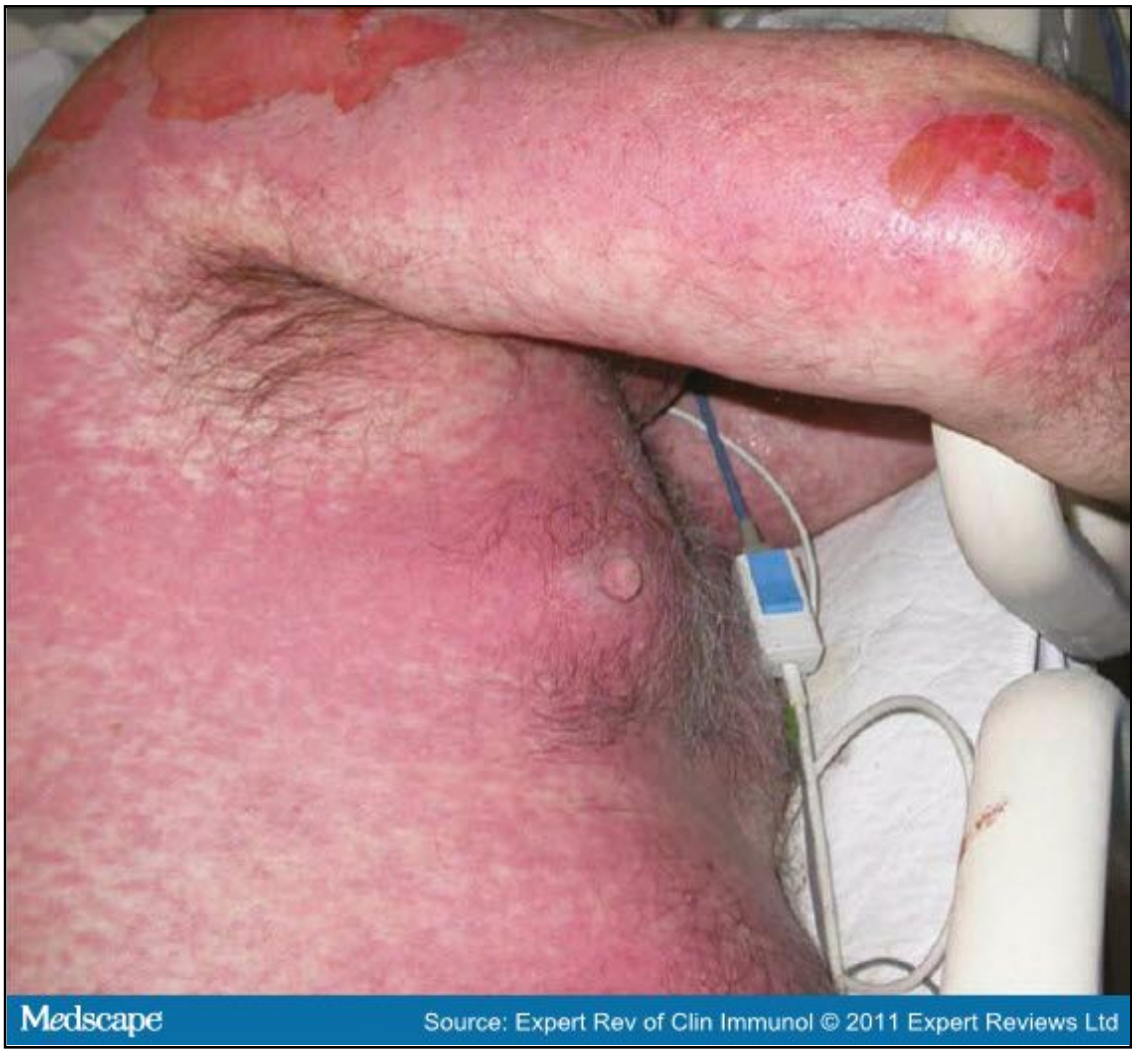

Figure 2. Confluent Purpuric Macules and Limited Areas of Skin Detachment in Stevens–Johnson Syndrome.

Since SJS and TEN can sometimes hardly be separated from one another and limited skin detachment, as in SJS, may evolve to extensive skin necrosis as in TEN, an overlap group of SJS/TEN has been defined with blisters and erosions between 10 and 30% of the BSA called SJS/TEN-overlap (Figure 3). Nikolsky sign is positive in SJS, TEN and their overlap when lesional skin can be pushed slightly aside by pressure of fingers. Direct (epidermis can be 'pushed aside') and indirect Nikolsky sign (an existing blister can be 'pushed away') are distinguished. However, more recently a 'wet' and 'dry' Nikolsky sign were discussed, which refer to the base of the blister, and thus to the level of epidermal separation.[2] Hemorrhagic erosions of at least one site of mucous membranes are present in EMM, SJS and SJS/TEN-overlap, but may be absent in some cases of TEN (Figures 4 & 5).

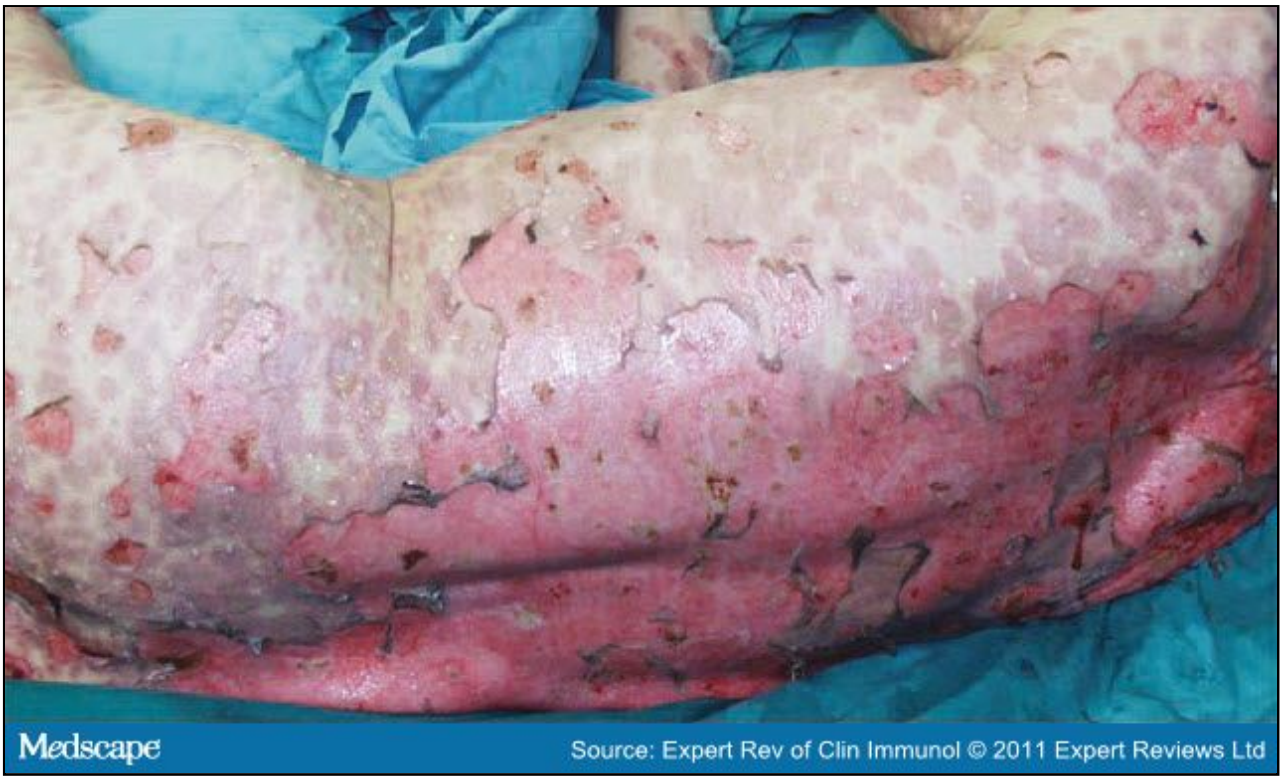

Figure 3. Detachment of Large Epidermal Sheets in Stevens–Johnson Syndrome/toxic Epidermal Necrolysis Overlap; Atypical Target Lesions are Still Present.

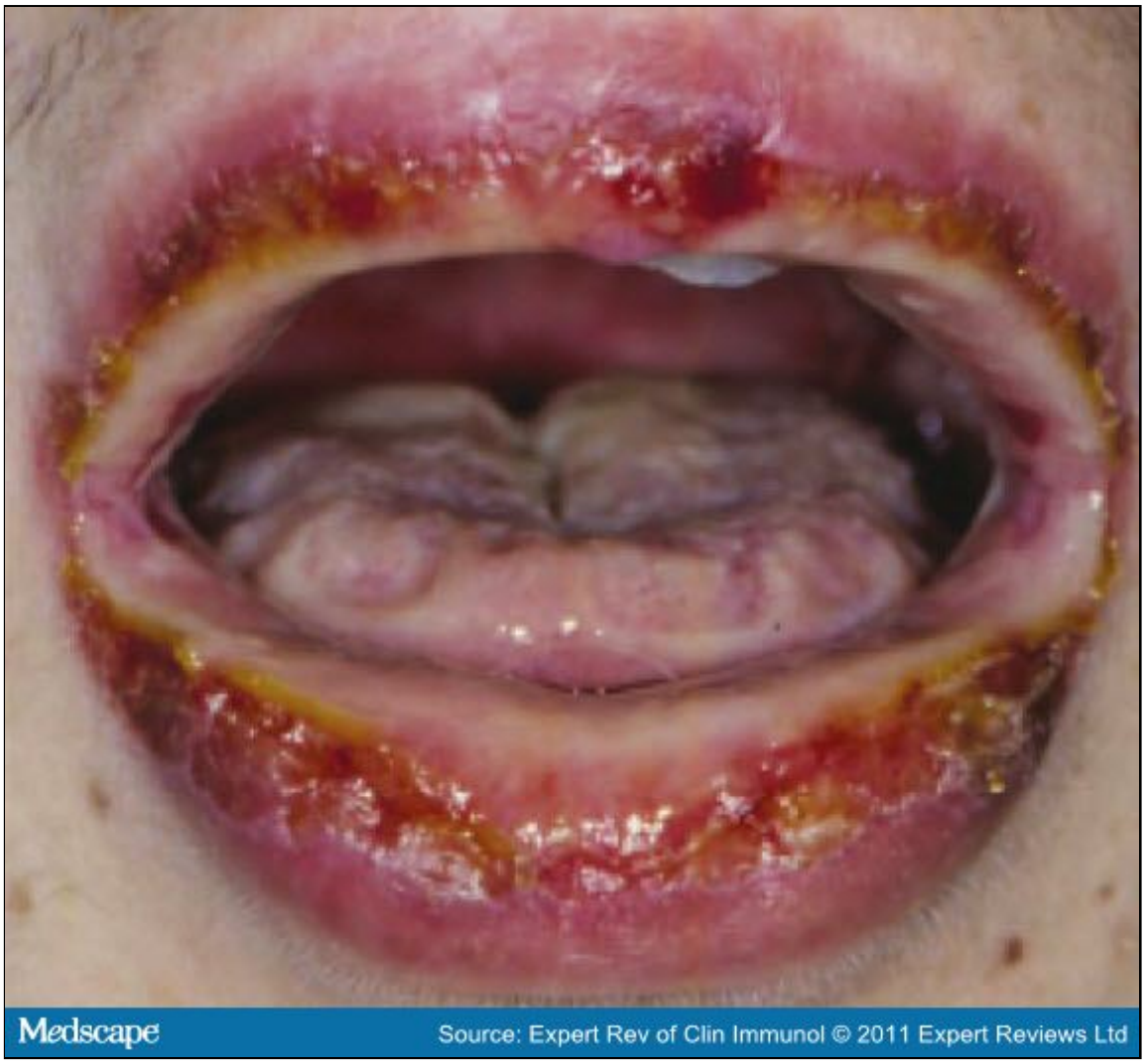

Figure 4. Hemorrhagic Erosions of Lips and Oral Cavity in Erythema Multiforme Majus, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis.

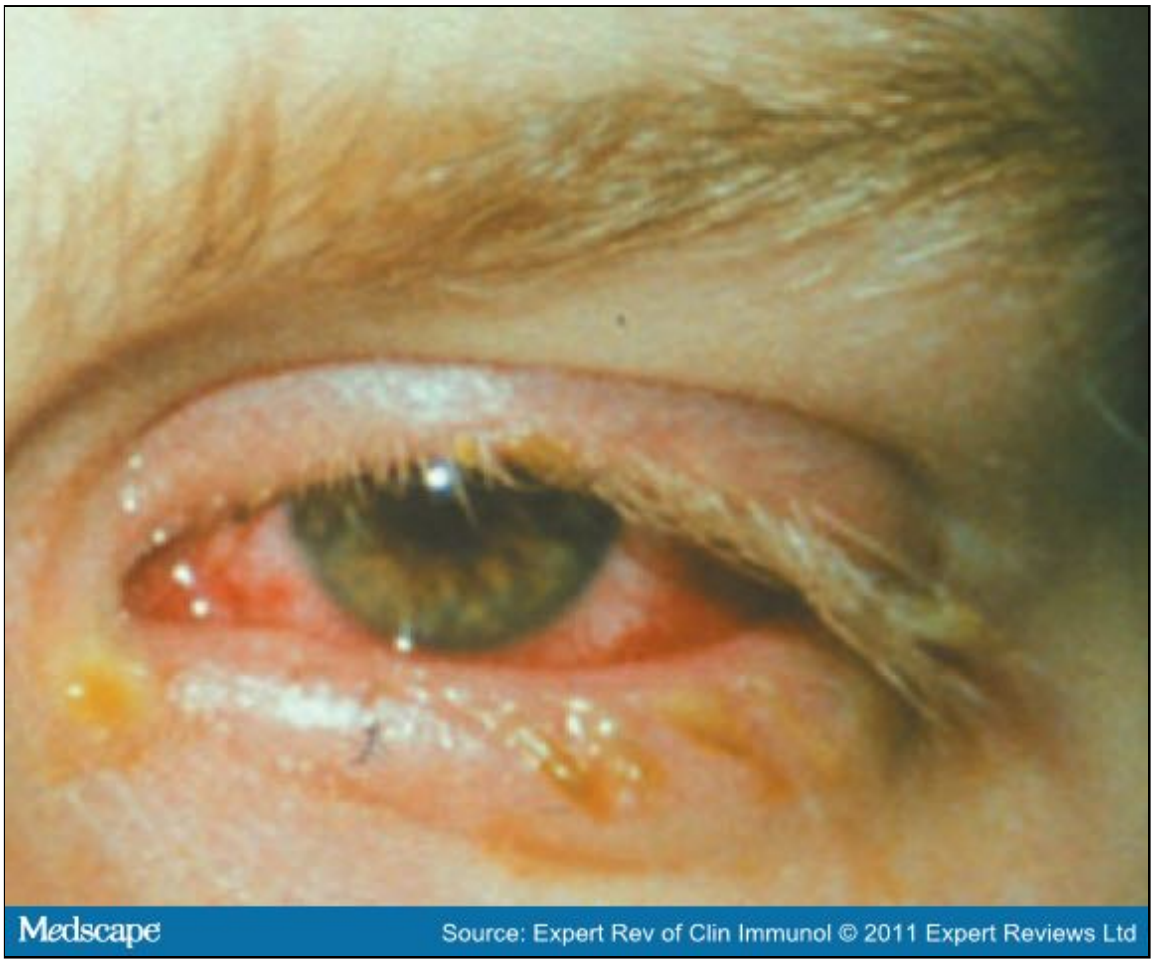

Figure 5. Severe Eye-involvement in Erythema Multiforme Majus, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis.

Whereas SJS, SJS/TEN-overlap and TEN with maculae are considered as a single disease of different severity, EMM is different not only in terms of the clinical pattern, but also in terms of etiology.[1,3]

Histopathology

The fact that SJS as well as TEN were (and often still are) considered as part of the spectrum of erythema multiforme is based on the histopathology. The characteristic pattern presents with necrotic keratinocytes in either wide dissemination or full-thickness necrosis of the epidermis. Vacuolization leading to subepidermal blistering is found in the basal membrane zone. A superficial, often perivascular, lymphohistiocytic infiltrate can be seen in the upper dermis. While various amounts of eosinophils were observed in the infiltrate of tissue biopsies of patients with EMM, SJS or TEN, other investigations reported less epidermal necrosis, more dermal inflammation and more exocytosis in erythema multiforme majus compared with SJS.[4] It is of great importance at what time the biopsy is taken in relation to the onset of the disease and from which part of the lesion. A biopsy taken from the central blister of a typical target lesion in erythema multiforme (EM)/EMM may reveal full-thickness necrosis, whereas a biopsy from the erythematous margin of blisters in SJS/TEN may show only partial necrosis. Therefore, histopathological findings can distinguish SJS/TEN from other diseases, but do not allow the clear differentiation between SJS/TEN and EMM, since both show the histological pattern of what was earlier called the ‘epidermal type of EM’. By contrast, the ‘dermal type of EM’ can be seen in a multiforme-like or target-like skin eruption described as an entity different from EMM and SJS/TEN.[5]

Differential Diagnoses

The differential diagnoses of SJS may vary with the clinical presentation and the extent of the skin detachment.

In an early stage of the disease, maculopapular eruptions, induced by drugs or viruses, have to be considered. They may also present with oral lesions and conjunctivitis; however, not as hemorrhagic and erosive as in SJS. The important differentiation from EMM marked by typical targets has been described earlier. However, in children atypical forms of EMM may occur with target lesions in wide dissemination but well demarcated and not confluent, making the correct diagnosis more difficult.[6] In elderly patients a multiforme-like or target-like skin eruption caused by drugs has to be considered as a differential diagnosis of SJS.[5]

In a later stage of the disease, when blisters and skin detachment are already present, it is of major importance to rapidly perform a Tzanck-test or cryostat histology for information on the layer of epidermal separation in order to exclude the possible diagnosis of staphylococcal scalded-skin syndrome. Although purpuric macules and target lesions are not seen in staphylococcal scalded-skin syndrome and mucosal involvement rarely occurs, the clinical diagnosis should always be supported by histology including conventional histopathological examination.[7] In contrast to the skin lesions seen in SJS/TEN, generalized bullous fixed drug eruption (GBFDE) is characterized by well-defined, round or oval plaques of a dusky violaceous or brownish color. Frequently, blisters occur on these plaques, although rarely exceeding 10% of the BSA. Compared to SJS/TEN, fever, malaise and mucosal involvement are less intense and the prognosis is far better in GBFDE. The history of patients with GBFDE often reveals previous fixed drug eruptions.[8] The differentiation between SJS/TEN and GBFDE has to be carried out on a clinical basis, because the histopathology will also show a subepidermal blister with necrosis of the blister roof. Furthermore, autoimmune blistering diseases, such as pemphigus vulgaris and bullous pemphigoid, as well as bullous phototoxic reactions, have to be considered as possible differential diagnoses.

Desquamation of large sheets of skin in erythroderma or exfoliative dermatitis is sometimes clinically confused with epidermal detachment in SJS/TEN. This is also the case for acute generalized exanthematous pustulosis, in the course of which, after confluence of dozens of nonfollicular pustules, a Nikolsky-like phenomenon may imitate detachment in SJS/TEN, although this is much more superficial.[8,9]

Epidemiology & Risk Factors

Incidence & Demographic Data

For decades mainly case reports and case series of severe skin reactions have been published. After the first large-scale retrospective studies were performed in France and Germany in the 1980s, a population-based registry on SJS, TEN and EMM was started in Germany in 1990. It has been operating since then and, based on a high coverage rate of 80–90%, was able to provide robust incidence rates for SJS, TEN and their overlap of 1–2 cases per 1 million population per year.[10]

For SJS and TEN the distribution of gender is almost equal (slightly more females) and a female preponderance of approximately 65% could be observed in SJS/TEN-overlap, whereas more men or boys develop EMM (almost 70%).

The mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TEN-overlap and almost 50% for patients with TEN. For SJS, SJS/TEN-overlap and TEN together the mortality rate is almost 25%.[11] In order to evaluate the mortality due to SJS/TEN, time of death in relation to the onset of the reaction, age of the patient, underlying diseases and the amount of skin detachment have to be considered. By contrast, virtually no patient with EMM dies as a consequence of this condition.

In Europe, approximately 5% of the patients with SJS/TEN were HIV-infected, but the number seems to have decreased in the past decade. As expected, the distribution of age and gender differs between HIV-infected and non-HIV-infected patients with SJS/TEN, while mortality rate and outcome are comparable.[12]

Etiology & Risk Estimation

Stevens–Johnson syndrome and TEN very rarely occur without any drug use. However, sometimes the drug history only reveals long-term medication, which cannot be considered to be the cause of the adverse reaction.

Viral infections and mycoplasma pneumonia infection were also reported as potential causes.[13] It is often difficult to decide whether symptoms such as oronasal soreness, conjunctival injection or fever are signs of an acute infection or the beginning of SJS/TEN. Various medications are taken frequently to treat such symptoms, including analgesics and antipyretics. To date, neither a possible interaction of infection and medication nor the interaction of different drugs could be clarified, and a reliable *in vitro* or *in vivo* test to determine the link between a specific drug and SJS/TEN in an individual case is not yet available. Oral provocation tests with the suspected drug cannot be recommended for safety reasons, although the reaction may not occur again, as studies performed in Finland in the 1970s could show.[11] Patch tests have frequently provided negative or false-negative results and are not of any help during the time of acute illness. Thus, the detection of the culprit drug mainly relies on the time interval between introduction of the drug and onset of the skin reaction. Recently, an algorithm for assessment of drug causality in SJS and toxic epidermal necrolysis (ALDEN) has been published, which provides structured help to identify the responsible drug.[14] It includes the findings of epidemiologic studies that were able to provide risk estimates for drugs inducing SJS/TEN and is based on the following criteria: time latency between beginning of drug use and index-day (i.e., onset of the adverse reaction), drug present in the body before index-day (taking into account the drug's half-life, as well as the patient's liver and kidney function), information on prechallenge/rechallenge and dechallenge (if available), type of drug/notoriety (based on drug lists that require a regular update) and alternative causes. Numerical score values lead to a causality assessment for each individual drug a patient is exposed to, reaching from 'very unlikely', 'unlikely', 'possible', 'probable' to 'very probable'.[14]

However, drugs could be identified as causes of SJS/TEN in no more than 75% of the cases in these studies, while in at least 25% of the cases no drug cause could be determined. Some part of the latter might be caused by infection, some part remains unknown so far.

In addition to causality assessment in an individual case, the risk of a certain medication has to be estimated in larger populations. In order to get an idea of how frequently SJS/TEN may be caused by a specific drug, it is not sufficient to rely on the absolute number of cases exposed to that drug prior to the onset of the reaction. Furthermore, the comparison of the absolute number of cases and all people who have taken that drug in a certain time period (e.g., 1 year) is required. Because the number of people who take a certain drug is not known, prescription data in defined daily doses are helpful as a reference for drug use. Owing to the fact that SJS and TEN usually occur during the first course of drug intake (without prior sensitization), further assumptions need to be made for risk estimation. This was carried out for risk evaluation of antiepileptic drugs. More than 90% of SJS/TEN cases occurred in the first 63 days of drug use. Across a range of assumptions about the frequency of incident use, the risk estimates vary between 1 and 10 per 10,000 new users for a number of antiepileptic drugs (carbamazepine, lamotrigine, phenobarbital and phenytoin) except valproic acid, for which much lower risk estimates were calculated.[15]

Another option for risk evaluation of drugs is the case–control study design. Two large case–control studies were performed in Europe in the last 20 years: first, the international case–control study on SCAR (also called the SCAR study) was undertaken in several European countries between 1989 and 1995. In terms of drugs usually taken for a short time, the risk was increased for cotrimoxazole and other anti-infective sulfonamides, aminopenicillins, quinolones, cephalosporines and chlormezanone. For drugs with long-term use, such as carbamazepine, phenobarbital, phenytoin, oxicam-NSAIDs and allopurinol, the crude relative risk was increased. For these drugs, the risk appears to be higher during the first 2 months of intake.[16] Second, the European ongoing case–control surveillance of SCAR (EuroSCAR-study) recruited cases and controls in partly the same and some additional European countries between 1997 and 2001, comprising more recent data on drug risks for SJS/TEN. A total of 379 'community' cases of SJS and TEN (i.e., patients who developed the adverse reaction outside the hospital and who were admitted because of symptoms of SCAR) were compared with 1505 controls in terms of drugs use. Among medications with prior alerts, two were strongly associated with SJS/TEN: nevirapine and lamotrigine. Both shared the overall pattern of 'highly suspected' drugs (recent onset of use and infrequent comedication with another highly suspected drug).[17] Although the indication of these agents is completely different – lamotrigine is an antiepileptic, nevirapine an anti-HIV drug – the manufacturers had proposed that adverse reactions could be avoided to both by slow titration of the doses (lead-in periods), but

obviously this did not work for severe skin reactions such as SJS/TEN.[12,17]

A high risk could be confirmed for all previously suspected drugs, such as allopurinol, anti-infective sulfonamides (especially cotrimoxazole), carbamazepine, phenytoin, phenobarbital and oxicam-NSAIDs. Risk estimates for allopurinol were actually increasing, turning it into the leading cause of SJS/TEN in Europe and Israel.[17,18]

The median latency time between the beginning of use and onset of SJS/TEN (also called index-day) was less than 4 weeks for most drugs (15 days for carbamazepine, 24 days for phenytoin, 17 days for phenobarbital and 20 days for allopurinol), whereas it was much longer for drugs with no associated risk (above 30 weeks for valproic acid). In general, no significant risk persisted after 8 weeks of use. Penicillins, which have often been accused to cause SJS/TEN, did not show an increased risk, whereas the relative risk of other antibiotic groups such as cephalosporines, macrolides, quinolones and tetracyclines was moderate. The same magnitude of risk was calculated for acetic acid NSAIDs such as diclofenac. Many commonly used medications, such as β-blockers, ACE inhibitors, calcium channel blockers, sulfonamide-related diuretics and sulfonylurea antidiabetics, insulin and propionic acid NSAIDs such as ibuprofen were not associated with a detectable risk to induce SJS/TEN (Box 1).[17]

Box 1. Practical Recommendations.

Drugs with a high risk to induce SJS/TEN

- Their use should be carefully weighed and they should be suspected promptly
  - Allopurinol
  - Carbamazepine
  - Cotrimoxazole (and other anti-infective sulfonamides and sulfasalazine)
  - Lamotrigine
  - Nevirapine
  - NSAIDs (oxicam type; e.g., meloxicam)
  - Phenobarbital
  - Phenytoin
- An interval of 4–28 days between the 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 high expected benefits, the timing of administration is important to determine which one(s) must be stopped and if some may be continued or reintroduced
- 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 antiepileptics
- Diuretics and oral antidiabetics with sulfonamide structure do not appear to be risk factors for SJS/TEN

Drugs with a moderate (significant but substantially lower) risk for SJS/TEN

- Cephalosporines
- Macrolides
- Quinolones
- Tetracyclines
- NSAIDs (acetic acid type; e.g., diclofenac)

Drugs without increased risk for SJS/TEN

- β-blockers
- ACE inhibitors
- Calcium channel blockers
- Thiazide diuretics (with sulfonamide structure)
- Sulfonylurea antidiabetics (with sulfonamide structure)
- Insulin
- NSAIDs (propionic acid type; e.g., ibuprofen)

ACE: Angiotensin-converting enzyme; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis. Adapted from [17].

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Pathophysiology & Genetics

As explained previously, drugs are the etiologic factor in the majority of SJS/TEN cases. However, it is still unknown, how a certain drug may actually induce epidermal necrosis. T cells, especially $CD8^+$ lymphocytes, have been identified to play an important role in the process that is most likely mediated by cytokines. $CD8^+$ T cells from the blister fluid of patients with TEN induced by co-trimoxazole were tested for their cytotoxic function and reacted without restimulation against the parent drug (cotrimoxazole and sulfamethoxazole), but not against the metabolite. This finding challenged the hypothesis that metabolites may be directly involved in the process of

epidermal cell death. In addition, these cytotoxic T-cells killed autologous lymphocytes and keratinocytes in a drug-specific, perforin/granzyme-mediated pathway restricted to MHC class I.[19] Later, the cytolytic protein granulysin, which is produced by drug-specific $CD8^+$ T cells and natural killer (NK) cells, was identified as the most important factor for the epidermal destruction. Its concentrations in the blister fluid of SJS/TEN patients were two to four orders of magnitude higher than those of other cytotoxic proteins such as perforin, granzyme B or soluble Fas ligand, and depleting granulysin reduced the cytotoxicity. Furthermore, the concentration of granulysin in the blister fluid was positively correlated with the clinical severity of the disease (i.e. was higher in TEN as compared with SJS).[20]

Recently, functionally active $CD94/NKG2C^+$ cells were detected in the blister fluid but also in the peripheral blood of patients with SJS/TEN. This activating receptor might be involved in triggering cytotoxic T cells in the acute stage of the disease.[21]

T-cell activation by drug antigens requires the interaction of the T-cell receptor (TCR) with the MHC on antigen-presenting cells. Thus, the drug may bind to the MHC molecule, which is recognized by the TCR leading to specific TCR activation, or the drug may bind first to a specific TCR that then interacts with the MHC. Both ways are possible, but drugs with a strong association to specific HLA alleles are more suggestive to interact primarily with the HLA molecule.[22]

A genetic predisposition for SJS/TEN has long been discussed. After preliminary data from Europe had suggested an association with certain HLA types more than 20 years ago, a research group from Taiwan was the first to demonstrate that 100% of Han-Chinese patients with SJS/TEN due to the use of carbamazepine were positive for the allele HLA-B*1502.[23] This finding could not be confirmed in Europe showing that ethnicity matters more than previously thought in this context.[24] For allopurinol-induced cases of SJS/TEN a 100% association with HLA-B*5801 could be demonstrated in a Han-Chinese population, whereas in the European population the association was present in no more than 55%.[25,26] Strong associations such as those in Han-Chinese suggest that these alleles must be involved in the presentation of a specific drug antigen in a better way than other HLA alleles.[22] Thus, the risk of SJS/TEN is not only related to the exposure with high-risk drugs, but also to a genetic predisposition. In more homogeneous ethnic groups with a high prevalence of reaction to a given medication strong genetic associations may be easier to detect.[27]

Therapeutic Considerations

Until the pathogenesis of SJS/TEN is completely solved, treatment is based on nonspecific and symptomatic means. The latter are most important for patients with large amount of skin detachment requiring intensive care in specialized units. Furthermore, sequelae such as strictures of mucous membranes and symblepharon, which may lead to long-lasting impairment, should be prevented.

Topical Treatment

Although the blisters are fragile, they should be left in place or only be punctured. Erosions can be treated with chlorhexidine, octenisept or polyhexanide solutions and impregnated nonadhesive mesh gauze. The latter is important if environmental factors, such as high room temperature or alternating pressure mattress, lead to skin dryness. Silver sulfadiazine should be avoided, at least if the causative drug was cotrimoxazole or another anti-infective sulfonamide. Some burn care specialists debride the skin under general anesthesia and apply allografts or other types of coverage. However, this rather aggressive procedure is not tolerated well by many elderly patients with underlying diseases.[28] Furthermore, hypertrophic scars may occur if debridement is carried out extensively and if allografts are fixed with staples directly into the skin.

For affected mucosal surfaces, specialized care is critical. The severity of the mucosal involvement is often not in line with the amount of skin detachment and overlooked mucosal lesions can lead to life-long problems. A multidisciplinary approach is needed and in case of urethral involvement urologists should be involved. Appropriately placed wet dressings or sitz baths may help to avoid adhesions or strictures of genital erosions in girls and women. Disinfectant mouth wash should be used to treat oral erosions and mild ointment, such as

dexpanthenol, should be applied on erosions and bloody crusts of the lips.

In the case of eye-involvement, regular ophthalmologic consultation is crucial. Specialized lid care is needed on a daily basis and anti-inflammatory eye drops should be given several times per day. Severe blepharitis may lead to entropion with trichiasis (ingrowing eye lashes) causing further corneal damage. Various specialized approaches to ocular involvement have been suggested, such as stem cell generation of replacement cells, amniotic membrane transplantation and scleral lenses, but are not yet widely accepted.[29,30] Nevertheless, experienced ophthalmologists should be involved in the care of all patients with SJS/TEN, even those that do not present with eye-involvement right away, since it may occur with some delay.

Supportive Care

The room temperature should be increased (30–32°C), especially if large amounts of the BSA are denuded, and bedding on an alternating pressure mattress is recommended. Patients with skin detachment of more than 30% have an increased risk for different systemic complications. Highly specialized dermatology units are the preferable treatment units for patients with SJS/TEN, but if not available, transfer to a burn unit or intensive care ward with daily dermatologic consultation seems to be the best option. SJS/TEN patients need fluid replacement with electrolyte (0.7 ml/kg/% affected area) and albumin solution (5% human albumin, 1 ml/kg/% skin detachment). This requires exact calculation of the amount of denuded skin, which is sometimes difficult, frequently leading to overestimation. Furthermore, one has to keep in mind that SJS/TEN patients only need two-thirds to three-quarters of the fluids of burn patients. If patients are not able to eat, they require feeding through a gastric tube (1500 calories in 1500 ml over the first 24 h, increasing by 500 calories to 3500–4000 calories per day). Monitoring for infection is needed and, if clinically suspected, empirical anti-infective treatment with the local standard regimens should be started until culture and sensitivity results are available. Depending on the severity of mucosal involvement and the extent of skin detachment, sedation and analgesic therapy have to be ensured.[31]

Immunomodulating Treatment

In addition to supportive care, various immunomodulating therapies are discussed for SJS/TEN, including glucocorticosteroids and intravenous immunoglobulins (IVIg). Since most publications on steroid treatment are case reports and case series in different settings, their results can hardly be compared. An increased rate of infections, the risk of masking septicemia, a delay of re-epithelialization, a prolonged duration of hospitalization and a higher mortality have been the arguments against the systemic treatment with glucocorticosteroids.[8,11,31] However, in recent years steroid pulse therapy (e.g., with dexamethasone) has been proposed in the acute stage of SJS/TEN, but few case series include more than ten cases. Mortality was not higher and time of re-epithelialization was not longer than expected, although small numbers did not bear any statistical significance.[32] A small series of five patients from Japan suggested that early steroid pulse therapy may help to prevent ocular complications.[33] Nevertheless, data are not sufficient to draw any final conclusion on the benefits of steroid pulse therapy in the treatment of SJS/TEN.

Case series reporting on the positive effects of TEN treatment with plasmapheresis, hyperbaric oxygen and cyclophosphamide have been published, but they are only of limited value, as the observations were not controlled. Thalidomide, an effective TNF-α inhibitor *in vitro* successfully used in graft-versus-host disease, revealed a higher death rate in the only randomized controlled trial ever performed concerning the treatment of TEN.[11,31] IVIg, which had 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*, is still discussed controversially. A number of case compilations on SJS/TEN patients treated successfully with IVIg have been published. However, it has to be taken into account that numerous cases appear at least twice in these articles and, therefore, the numbers of successfully treated patients should be cautiously interpreted. In addition, there are also studies showing that IVIg do not have an overall positive effect.[34] 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.[35] For the evaluation of the prognosis of individual patients with SJS/TEN the severity of illness score of toxic epidermal necrolysis (SCORTEN) was used.[36,37] The results

of this study revealed a higher mortality than predicted by SCORTEN and renal failure in most patients who died. Two further studies undertaken in North American burn units suggest that IVIg do not improve the outcome of TEN patients.[38,39] In principle, an effective treatment should also work in severely affected patients, reducing the mortality in patients with a high risk to die. Low mortality in patients with low risk of dying, such as young patients with limited skin detachment, is not the appropriate criterion for evaluation of the efficacy of treatment.

'Real life' data on treatment, meaning therapeutic modalities outside of a certain study protocol, have been analyzed in patients included in the EuroSCAR-study, the primary aim of which was risk estimation of drugs inducing SJS/TEN. In 281 patients with SJS/TEN from France and Germany, mortality was chosen as the end point and linked to the treatment with corticosteroids, IVIg, the combination of both, and supportive care only. Odds ratios were calculated suggesting a benefit for the treatment with corticosteroids, but not for the treatment with IVIg. Although such a retrospective analysis has some pitfalls, two major conclusions could be drawn: first, IVIg is not the best treatment of SJS/TEN and cannot generally be recommended; second, a controlled therapeutic trial using corticosteroids should be undertaken.[40]

Recently, a controlled trial using cyclosporin as systemic immunomodulating therapy in SJS/TEN was published revealing a lower death rate than expected based on SCORTEN calculations.[41] One may speculate that this beneficial result may be related to a potential effect of cyclosporin on granulysin, but further immunologic investigations are needed to prove this hypothesis. Nevertheless, the results of this trial are striking and the use of cyclosporin according to a clear protocol in a different setting than that of the specialized dermatologic unit in France should be encouraged.

In spite of the controversial discussion around the world, most experts agree that all drugs potentially triggering SJS/TEN in a specific patient must be withdrawn. Substances with long half-lives or persistent reactive metabolites have been shown to cause problems long after they have been discontinued.[42] The medications that have been introduced in the month preceding the onset of the adverse reaction are the most probable trigger factors. However, the time latency between beginning of drug use and onset of the SJS/TEN varies. Whereas antiepileptic drugs and allopurinol are frequently tolerated for several weeks, antibiotics and anti-infective sulfonamides usually show a much faster reaction onset.[17]

To differentiate more or less severe reactions as early as possible in the evolution of the disease, is a real clinical challenge, followed by the thorough but rapid consideration of therapeutic options for the individual patient. An interdisciplinary approach proved favorable and is, therefore, highly recommended.

Acute Complications, Prognosis & Long-lasting Sequelae

Transdermal fluid loss leads to hypovolemia, changes in electrolyte levels and finally to a katabolic metabolism in TEN patients. Most dangerous, however, is the occurrence of infections. Septicemia, mainly induced through central-venous lines, is the most frequent cause of death. The combination of septicemia and hypovolemia increases the risk for the development of shock and multiorgan failure.[28,31]

One of the most severe complications is the involvement of tracheal and bronchial epithelium, which may develop in up to 20% of the patients with TEN. Hypoxemia, hypocapnia and metabolic alkalosis point to the need of mechanical ventilation, which increases the risk of death.[28] The prognosis of individual patients can be evaluated by applying SCORTEN. Seven independent factors including age, skin detachment of 10% or more related to the BSA, underlying malignant diseases, tachycardia and certain laboratory values are considered. For each positive item a score value (weight) of one is given, leading to a total between zero and seven, with the prognosis being poor for high overall score values (Table 1).[36,37] Thus, SCORTEN is a reliable instrument concerning the prognosis *quoad vitam*, but was not designed to predict any sequelae, neither ocular, cutaneous or those of other mucosal areas.

Table 1. Severity of Illness Score for Toxic Epidermal Necrosis.

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Factor	Score	Weight/score value†
Age	≥40 years	1
Malignancy	Yes	1
Body surface area detached (day 1)	≥10%	1
Tachycardia	≥120/min	1
Serum urea	≥10 mmol/l	1
Serum glucose	≥14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1
	Possible score	0–7

†The higher the total score value, the poorer is the prognosis of the patient. Adapted from [36].

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As long as the upper dermis is not affected by trauma or infection, the skin regenerates without atrophic or hypertrophic scars. Frequently, hyper- and/or hypo-pigmentations appear, which are patient specific and decrease over time. Further cutaneous sequelae are pruritus, hyperhidrosis and xerodermia (dry skin). Furthermore, reversible hair loss can be observed. The involvement of nail matrix may lead to onycholysis, partial or complete nail loss and later onychodystrophy, which may persist for months and even years.[8]

Depending on the mucosal involvement in the acute stage of the disease, various long-lasting sequelae and complications may develop. Those are depapillation of the tongue, synechia and impairment of taste in the mouth. In some cases, strictures of the esophagus, the urethra and the anus were reported. Vaginal adhesions, mucosal dryness, pruritus and bleeding of the genital mucosa may develop in women suffering from SJS/TEN.[11]

Sequelae that are considered most severe for the patient frequently affect the eyes. They result in functional changes of the conjunctival epithelium with dryness and pathological consistence of tears, especially if a sicca syndrome evolves due to lacrimal duct damage. Ophthalmologic sequelae may result in chronic inflammation, entropium, fibrosis, trichiasis and symblepharon. Chronic irritations and insufficiency of limbal stem cells may lead to metaplasia of the corneal epithelium with ulceration and visus loss, sometimes resulting in blindness.[29,30]

Expert Commentary

In terms of clinical classification of SJS and TEN, especially its relationship to EMM, the consensus definition should be applied. It is widely accepted and has been successfully used in several epidemiological studies. Using it adequately allows for comparison of studies including therapeutic trials. Large-scale randomized controlled trials would be the ideal, but they do not seem to be feasible owing to the rarity of SJS/TEN. To demonstrate a measurable therapeutic effect would need at least thousand patients to be enrolled in such an interventional study, which would take many years to be completed, even when performed on a multinational level. However, smaller treatment studies following a clear and well-defined protocol should be undertaken prospectively, as has been carried out by the team of the French reference center for bullous skin diseases. In addition, the data obtained by that group need confirmation from application in a different setting. So far, supportive therapy must be considered the gold standard. In terms of causality, in the majority of SJS/TEN cases not one single drug can be identified as the culprit. Sometimes there is a multitude of drugs taken before the

onset of the adverse reaction, sometimes no drug at all can be determined, and potential other causes, especially mycoplasma pneumonia and viral infections, have to be considered. Epidemiological studies that allowed for risk estimation in SJS/TEN are also useful for causality assessment in the individual case and their results have been implemented into an algorithm for assessment of drug causality in SJS/TEN (ALDEN). Although this algorithm does not seem easy to handle, it contains a lot of important information concerning the most likely drugs and exposure periods to be causally related.

Five-year View

Based on the most recent immunologic findings, such as the major role of the cytolytic protein granulysin, the pathogenesis of SJS/TEN will be further elucidated. Substances able to block granulysin could enhance the role of immunomodulating treatment. Immunogenetic investigations will attempt to find the link between genetic predispositions marked by certain HLA alleles and immunologic pathways. Drugs have been identified as etiologic factors in approximately 75% of SJS/TEN cases, but the causes of the remaining 25% of cases are not clear. In the next 5 years the role of infections as cofactors or causes needs to be better understood. Furthermore, follow-up examinations of SJS/TEN-survivors are needed and interdisciplinary care of long-lasting sequelae shall be implemented.

Key Issues

- Stevens–Johnson syndrome (SJS) and erythema multiforme majus (also known as erythema multiforme with mucosal involvement) are different conditions that are distinguished in clinical and etiologic terms.
- SJS and toxic epidermal necrolysis (TEN) are considered as one disease entity of different severity. Although SJS is less severe, etiology, genetic susceptibility and pathomechanisms are the same for SJS/TEN.
- SJS/TEN is mainly caused by drugs (up to 75% of cases), but also by infections and probably other risk factors not yet identified.
- A high risk was confirmed for the following drugs: allopurinol, anti-infective sulfonamides (especially cotrimoxazole), carbamazepine, phenytoin, phenobarbital and oxicam-NSAIDs, with increasing risk estimates for allopurinol, making it the leading cause of SJS/TEN in Europe and Israel. Lamotrigine and nevirapine had the highest risk among more recently marketed drugs.
- The pathogenesis of SJS/TEN has not been completely solved, but specific genetic predispositions, which vary among ethnic groups and differ between certain causing drugs, were identified. Certain HLA alleles play an important role in this respect.
- The cytolytic protein granulysin was identified in high concentrations in the blister fluid of SJS/TEN patients and seems to be a marker for the severity of the disease based on skin detachment.
- Since to date no treatment has been identified to be capable of halting the progression of skin detachment, supportive management is crucial to improve the patient's state, probably more than specific immunomodulating treatments. Despite all therapeutic efforts, mortality is high and increases with disease severity, patients' age and underlying medical conditions.
- Survivors may suffer from long-term sequelae such as strictures of mucous membranes including severe eye problems. Therefore, interdisciplinary care and follow-up of patients with SJS/TEN is important.

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