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GUIDELINE

S3 guideline: Diagnosis and treatment of epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis) – Part 1: Diagnosis, initial management, and immunomodulating systemic therapy

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Participating societies:

DDG – German Dermatological Society

BVDD – Professional Association of German Dermatologists

DGPRÄC – German Association of Plastic, Reconstructive and Aesthetic Surgeons

DGAKI – German Society for Allergology and Clinical Immunology

Summary

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are rare, predominantly drug-induced, acute, life-threatening diseases of skin and mucosae. SJS and TEN are nowadays considered variants of one disease entity with varying degrees of severity called epidermal necrolysis (EN). EN is associated with high morbidity and mortality and constitutes a major disease burden for affected patients. The guideline "Diagnosis and treatment of epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis)" was developed under systematic consideration of existing scientific literature and in a formal consensus process according to regulations issued by the Association of Scientific Medical Societies in Germany (AWMF) to establish an evidence-based framework to support clinical decision-making. The interdisciplinary guideline commission consisted of representatives from various specialist societies and patient representatives. The guideline is aimed at specialists in the fields of dermatology, ophthalmology, plastic surgery, intensive care, and pediatrics in hospitals and offices, as well as other medical speciallved in the diagnosis and treatment of EN. The guideline is also aimed at patients, their relatives, insurance funds, and policy-

Ruben Heuer and Maren Paulmann contributed equally to the publication.

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DGAI – German Society of Anesthesiology and Intensive Care Medicine
DGGG – German Society for Gynecology and Obstetrics
DGI – German Society for Infectious Diseases
DGKJ – German Society of Pediatrics and Adolescent Medicine
DGKCH – German Society for Pediatric Surgery
DGMP – German Society for Medical Psychology
DGP – German Society of Nursing Science
DGU – German Society for Urology
DGV – German Society for Burn Treatment
DOG – German Society of Ophthalmology
German Pain Society
DeGPT – German-speaking Society for Psychotraumatology

makers. This first part focuses on the diagnostic aspects, the initial management as well as the immunomodulating systemic therapy.

KEYWORDS
Drug reaction, epidermal necrolysis, Lyell syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

The present guideline consists of two separately published short versions of the complete guideline which is freely available at www.awmf.org. Selected tables and figures are freely available as Online Supplement in German and English language. In both published versions, the recommendations are complete and unabridged while the content on medical background and available studies is presented in shortened form. A complete list of references and evidence tables, as well as conflicts of interest of the participating authors are provided in the AWMF long version and in the guideline report.

METHODS

In the course of a kick-off event, the key questions to be addressed were defined by the guideline group. Subsequently, these were processed as a systematic review, recommendations and statements were drafted, followed by voting by those guideline members entitled to vote in a formal consensus procedure. The terminology and symbols listed in Table 1 were used for the standardized presentation of the recommendations.

Process of consensus formation

During digital consensus meetings on July 26, 2023, September 06, 2023, and October 17, 2023, a consensus concerning the proposals for recommendations was reached by means of a nominal group process. Experts with moderate or high conflicts of interests did not vote in the respective relevant chapters.

External review

An extensive external review was performed after preparation of the guideline. This included, among others, the participating societies, patient representatives, and physicians with experience in treatment of patients with EN. The guideline was piloted in the hospitals and outpatient departments of the participating experts. The final approval was given after evaluation by the 2 + 2 committee of the German Dermatological Society/the German Dermatologists Association, and evaluation by all participating societies.

CLINICAL INTRODUCTION

Classification

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are rare, predominantly drug-induced, acute life-threatening diseases of skin and mucous membranes.[2,3]

An immunological reaction results in epidermal and epithelial necrosis associated by severe systemic symptoms. The clinical picture is characterized by extensive

TABLE 1 Strengths of recommendation – word choice, symbols, and interpretation (modified from Kaminski-Hartenthaler et al., 2014[1]).

Recommendation strength	Word choice	Symbol
Strong recommendation for a procedure	"… shall …"	**A**
Weak recommendation for a procedure	"… should …"	**B**
Recommendation **open** / no recommendation	"…may be considered …"	**0**
Weak recommendation **against** a procedure	"… should not …"	**B**
Strong recommendation **against** a procedure	"… shall not …"	**A**

exanthema consisting of macules and/or target-like individual lesions without trizonal structure (atypical target lesions), blisters, and erosions of epidermis and epithelia of mucous membranes.[4–7]

Stevens-Johnson syndrome and TEN are nowadays considered variants of one disease entity with varying degrees of severity called epidermal necrolysis (EN). Stevens-Johnson syndrome is defined as skin detachment of less than 10% with respect to the body surface area (BSA); TEN is diagnosed in case of epidermal detachment of more than 30% BSA. Skin detachment between 10% and 30% BSA is referred to as SJS/TEN overlap.[4]

Pathophysiology

Background text without recommendation; see AWMF long version

Prevention (HLA diagnosis)

Background text without recommendation; see AWMF long version

DIAGNOSTIC WORKUP AND INITIAL MANAGEMENT

Basic diagnostic workup if EN is suspected

History

For additional material, see AWMF long version and Appendix

History and clinical findings with assessment of the temporal dynamics of skin lesions and other symptoms are crucial to establish the diagnosis. Moreover, a complete drug history including not only drugs prescribed daily but also compounds taken sporadically is required. The period of the last four weeks is paramount. In individual cases, drugs (for example, with long half-life) started up to 3 months earlier may be considered.[8]

Often, unspecific general symptoms such as fever, headache, and a general feeling of malaise are present even before manifestation of exanthema, enanthema, or erosive mucosal involvement.[8,9]

Clinical presentation

Background text shortened; see AWMF long version

The evolving exanthema shows rapid dynamics and may develop from first localized skin redness to generalized manifestation with epidermolysis within one day or several days. Parallel to this, in almost all cases detachment of mucous membranes usually develops at the same time in several areas (oral and genital mucosa, conjunctiva, nasal mucosa, less often tracheal or bronchial mucosa).[4] These erosive mucosal lesions are often very painful and typically hemorrhagic. Depending on the affected localization, they result in reduced food intake through to complete refusal to eat, dysuria, or photophobia. The subsequently developing fibrinous coatings result in adhesions that will further increase pain and impair respective functions. Given that mucosal detachments are present in SJS, SJS/TEN overlap, and TEN, the various severity grades of EN cannot be distinguished based on their mucosal involvement. Occasionally (in less than 10% of all cases), there is no hemorrhagic-erosive mucosal involvement.[4]

An important clinical sign in EN is that application of tangential pressure on erythematous and non-erythematous areas results in skin detachment (positive Nikolsky's sign I), but also that the blisters can be moved by applying pressure (positive Nikolsky's sign II).[10–12] Another potentially useful differentiating characteristic is the inspection of the blister base, which presents wet in EN due to the subepidermal detachment (wet Nikolsky's sign). This contrasts with the "dry" Nikolsky's sign, where the surface of the blister may be wet while the blister base is dry (for example, in staphylococcal scalded skin syndrome or acute generalized exanthematous pustulosis).[10,13,14]

No 1	Consensus-based recommendation
EC Strong consensus	If EN is suspected, a conventional histology **shall** be performed as a basic diagnostic procedure.
	In cases with atypical presentation/atypical disease course, direct immunofluorescence **shall** always be performed in addition to conventional histology.
	Bacterial swabs for pathogens and resistances, as well as routine laboratory testing (differential blood count, liver and kidney function tests, electrolytes, and CRP), **shall** be performed initially.
	During the phase of rapid progression of skin changes, patients **shall** be clinically evaluated several times a day. The disease activity and dynamics of skin/mucous membrane changes **should** be recorded and photo-documented once a day during the acute phase (or according to the frequency of dressing changes).

The disease process consists of three phases: the prodromal phase, the phase of epidermolysis, and the phase of re-epithelialization. Usually, the dynamics of spread of skin detachment is greatest at the beginning of the epidermolytic phase and then remains stagnant.

Laboratory tests

Background text shortened; see AWMF long version

No specific laboratory parameters are available as diagnostic markers of EN.

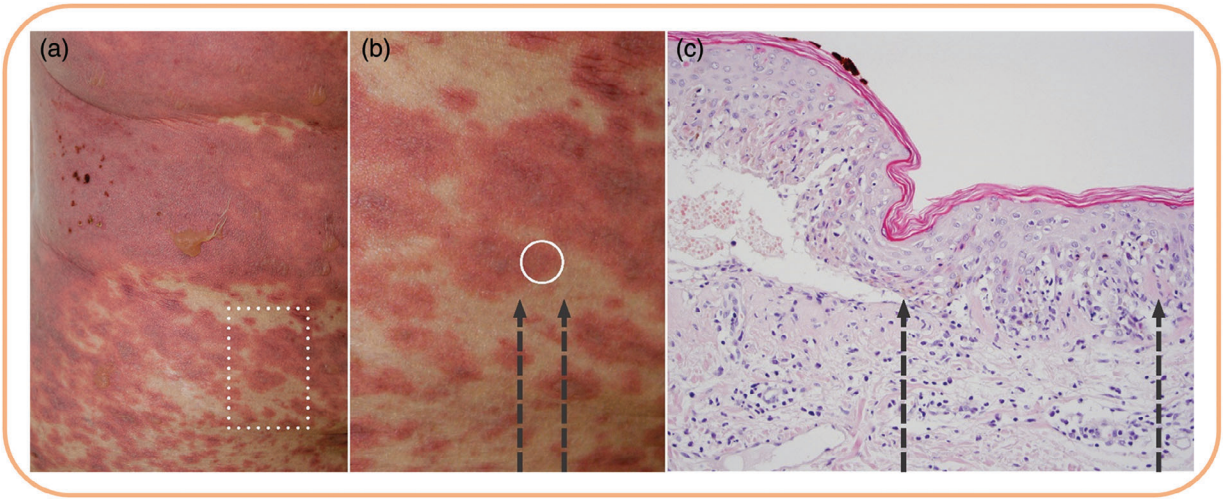

FIGURE 1 Scheme for performing the biopsy and correlation with the histological findings. (a) Confluent macular exanthema with blister formation. (b) The white circle marks the appropriate area for sample collection, corresponding to the erythematous, non-epidermolytic skin at the boundary of the transition from unaffected to affected skin. Areas with epidermal detachment should not be biopsied. (c) Correlation of the biopsy sample with the histological image. Histologically, in the correctly biopsied area (outlined by the two arrows) in the case of epidermal necrolysis, numerous necrotic keratinocytes are found in all epidermal layers. These lead to subepidermal detachment (further to the left in the image), an area not suitable for biopsy as the blister roof usually detaches and is not present in the findings, thereby limiting the assessment.

Further diagnostic workup

No 2	Consensus-based recommendation
EC **Strong consensus**	To detect parainfectious events, an infection-focused investigation consisting of urine status and chest X-ray (or, if necessary, chest computed tomography) **shall** be performed in the presence of clinical signs of infection and elevated CRP.

Histology

Background text shortened; see AWMF long version

If possible, a biopsy for conventional histological work-up should be taken initially in all cases of severe skin reactions (Figure 1). If sufficiently large, the skin sample may be divided with one part being examined by rapid frozen section diagnosis, which may allow for quick differentiation between subepidermal and intraepidermal cleavage.[12,14] If no biopsy can be taken, at least a blister roof should be obtained and examined by microscopy, given that the level of cleavage can be recognized after careful collection.

For sample shipment logistics and processing, consideration must be given to labeling of the skin biopsy as an urgent, so-called express or Cito case and to swift transfer/transport to the corresponding histopathology laboratory. There are no recommendations concerning additional histochemical or immunohistochemical staining. Possibly, these will arise from differential diagnostic considerations. In inflammatory dermatoses, PAS staining may be useful.

In EN, histology reveals necrotic keratinocytes present in the basal layer but also distributed throughout the epidermis, sometimes in larger clusters, resulting in subepidermal detachment. Due to the speed of development, the stratum corneum remains unaltered orthokeratotic and basket-woven (in non-volar skin). Especially in the peripheral areas of epidermolysis, the still intact epidermis presents with vacuolization of the basement membrane zone and often already with individual necrotic keratinocytes. In the upper dermis, an often only scarce perivascular, lymphocytic infiltrate is found that may include individual eosinophils. The intensity of the infiltrate is, however, no decisive criterion, given that the inflammatory infiltrate depends also on the time of biopsy collection and secondary changes that may already have occurred, while EN is also not ruled out by a more pronounced lymphocytic inflammation. The histologic findings are not specific for EN but may also be indicative for generalized bullous fixed drug eruption (GBFDE), EEM (if the sample is collected from the central blister of a target lesion), or toxic exanthema after chemotherapy. They may also be present in the context of stem cell or bone marrow transplants or in connection with graft-versus-host disease. In GBFDE, however, accumulations of melanophages may be found additionally in the upper dermis, while the infiltrate is more frequently characterized by interstitial distribution of eosinophils and neutrophils.[15]

If autoimmune blistering dermatoses, such as pemphigus vulgaris, bullous pemphigoid, or linear IgA dermatosis are considered in differential diagnosis, native tissue from an erythematous area without epidermolysis shall be collected for direct immunofluorescence analysis.[15]

Differential diagnosis

For an overview of differential diagnoses in tabular form, see AWMF long version and Appendix

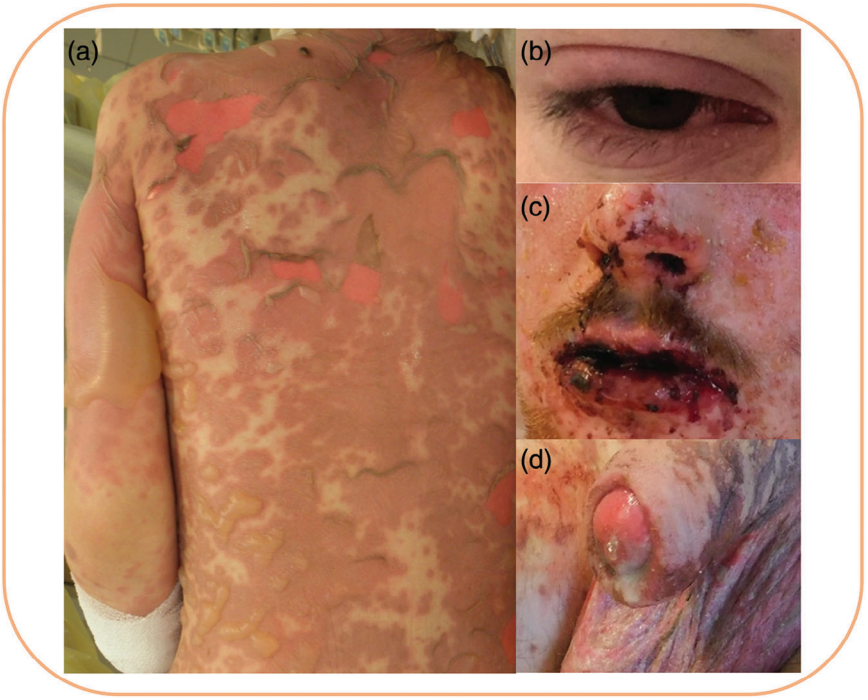

FIGURE 2 Epidermal necrolysis. (a) Erythematous exanthema with individual and confluent atypical flat target lesions and macules, as well as epidermal detachment with individual and confluent blisters; positive Nikolsky signs I and II. (c) Conjunctival injection and blepharitis. (c) Hemorrhagic-erosive mucosal involvement of the nose and lips, (d) genitalia.

Potential differential diagnoses depend on various factors, such as age of the patients, dynamics of development and duration of lesion persistence, as well as extent of the reaction (individual blisters, focal epidermolysis versus extensive detachment).

In children and adolescents, viral exanthema or Kawasaki disease must be considered as differential diagnosis at the onset of the reaction.

In patients presenting clinically with mucosal manifestation without skin involvement, especially the following differential diagnoses should be considered:

- Erythema exsudativum multiforme (EEM) of mucous membranes (previously also called Fuchs syndrome)
- Mucous membrane pemphigoid
- Fixed drug eruption of mucous membranes
- Severe herpangina, acute herpetic gingivostomatitis, or severe aphthous stomatitis

Clinical images (Figure 2), (Figure 3), (Figure 4).

For clinical images of other differential diagnoses, see AWMF long version and Appendix

Identification/narrowing of the causative drug

Background text shortened, see AWMF long version and Appendix

While EN is caused by a drug in 65%–85% of all cases, this applies only to approximately one third of the cases in children.[5,16–19] In the literature, more than 100 drugs have been associated with EN. However, large epidemiological studies have revealed that approximately half of the cases can be explained by drugs with high risk (so-called "highly suspected" drugs) and approximately two third of the cases by drugs with high to moderate risk (so-called "highly suspected" and "suspected" drugs).[5,20–25]

In cases with only one newly taken drug in the relevant time window, it seems straightforward to determine the likely causative agent. The period of the last four weeks is paramount. In individual cases, drugs (for example with a long half-life of > 48 hours), the use of which began within the last 12 weeks may be considered potential causative agents; this should be taken into account especially for highly suspected or suspected drugs. It must be borne in mind, however, that many causative medications mentioned in the literature might have been used for the treatment of prodromal symptoms of EN. Accordingly, the creation of a timeline diagram is recommended, also for what at first may appear to be straightforward cases.

Sometimes, difficulties in identifying the inducing agent arise from the fact that in infections treated by medication, both the infection itself and the drugs (especially antibiotics) used against the infection may be causative. The Appendix (see Appendix, Figure 6) includes atemplate for the creation of a timeline. If no causative drug can be identified, other potential etiological factors need to be considered, especially respiratory infections.[7,16,17,26,27] But other infectious diseases or a combination of infections and drugs may also be potential triggers.[7,16,27–30]

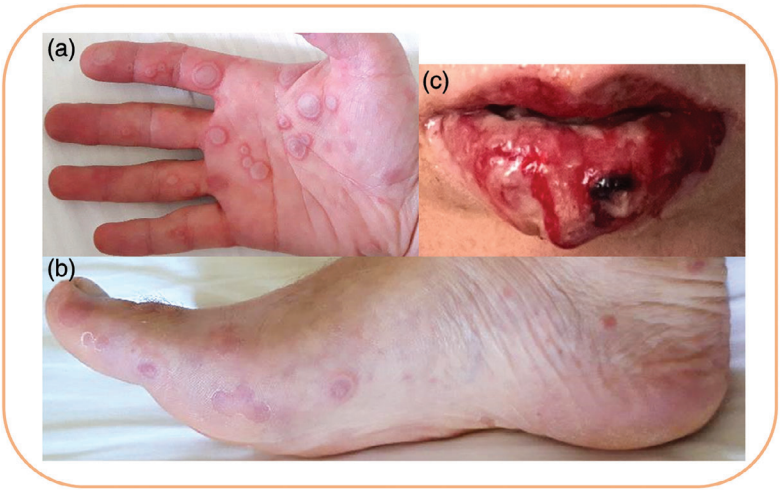

FIGURE 3 Erythema exsudativum ultiforme majus (EEMM). (a, b) Typical targets with a trizonal structure (also called target lesions) and central blister. (c) Hemorrhagic-erosive mucosal involvement as seen in epidermal necrolysis.

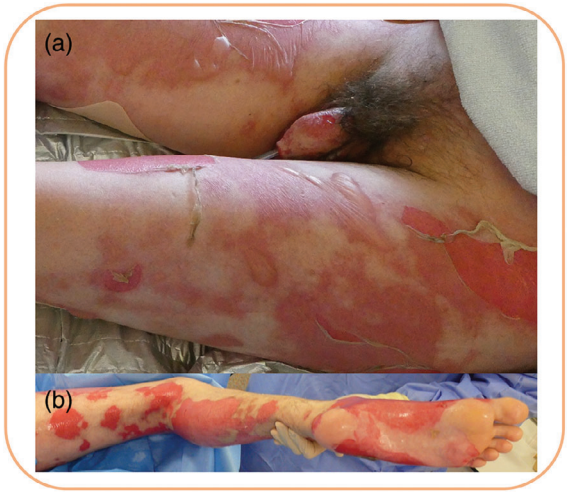

FIGURE 4 Generalized Bullous Fixed Drug Eruption (GBFDE). (a, b) Erythematous plaques sharply demarcated from healthy skin with flaccid blister formation and epidermal detachment that does not extend beyond the erythema. No or mild mucosal involvement of the mouth and genitalia.

No 3	Consensus-based recommendation
EC **Strong consensus**	Potential causative drugs (for identification of causative drugs see box "Notes on identification/narrowing of possible causative drugs" of the AWMF long version) **shall** be discontinued.
	Medications taken for less than 4 days, or more than 28 days **may** generally be continued. Drugs from the group of "suspected" or "highly suspected" drugs **shall** be considered as possible triggers and discontinued, even if their use began within the last 12 weeks.
	If the causative drug remains unclear, all non-essential medications (see background text) **shall** be discontinued.
	Other active substances from the same substance group as the likely causative drug **may** be administered (for exceptions, see background text).

Given that EN is a substance-specific reaction, the causative active substance must be avoided in future. Other active substances from the same substance group as the likely causative drug may be administered. In individual cases, however, the avoidance of chemically closely related substances is advisable, for example, the avoidance of oxcarbazepine in case of carbamazepine as causative drug. In case of sulfamethoxazole (component of cotrimoxazole) as causative drug, other antibacterial sulfonamides like sulfadiazine and sulfadoxine, as well as sulfasalazine should be avoided, but not sulfone-containing diuretics and antidiabetic drugs. If penicillins are identified as causative agent, cephalosporins of the 1st generation (and vice versa) should be avoided. If the inducing agent remains unclear, it is recommended to discontinue all non-essential medications that have been newly administered in the relevant time window.

Integration of the various disciplines

Background text shortened; see AWMF long version

Patients with EN suffer initially from erythematous, later often extensive bullous skin changes and erosive mucosal lesions. The resulting deficiency of the skin barrier causes malfunction of the water and electrolyte balance, an increased risk of infection, immunological dysfunction, and dysregulation of the body temperature.

No 4	Consensus-based recommendation
EC Strong consensus	A dermatological examination **shall** be performed within 24 hours if EN is suspected.
	In cases of a clinically probable diagnosis of EN, an ophthalmological examination **shall** be performed within 24 hours.
	If possible, within 48 hours, but no later than within the first week, a gynecological and/or urological evaluation **should** also be performed for all patients.
	Depending on the clinical presentation, (repeated) consultative evaluations by the following specialities **should** be performed during the course of the acute treatment phase: nutritional medicine, gastroenterology, otolaryngology, infectious diseases, nephrology, and pulmonology.
	Psychotherapeutic support **shall** be offered to clinically stable and responsive patients.
	Patients **shall** receive physiotherapy if needed.
	Patients with pain, regardless of the pain level, **may** be offered a consultation with a pain specialist.
	For a pain level ≥ 4/10 on the numerical rating scale (NRS) despite provision of standard analgesic measures, a pain specialist **shall** be consulted.

In more than 60% of the patients, mucosal erosions involve the ocular mucosa with potential consequences like symblepharon formation and even blindness. Therefore, dermatological and ophthalmological examinations must be performed at an early stage in all patients with EN. During the entire acute treatment phase, regular (every 1–2 days) re-evaluations of the clinical findings by dermatologists and ophthalmologists are recommended.[17]

During integration, the underlying disease of the patients must also be considered. Oncological diseases, for example, will often require continued treatment during the acute phase of EN. Especially for patients with pre-existing psychiatric disease, whose disease was caused by respective medication, early psychiatric evaluation is essential (Figure 5).

Disease severity and prognosis

Epidermal necrolysis manifests with different extent of affected surface area, sequelae, or complications, that is, with different disease severity. This chapter aims at providing orientation on the evaluation of disease severity beyond the specific dermatological evaluation and treatment. The aim is to illustrate the relevance of intensive medical care and "burn surgical" therapy, while also providing support in decision-making with respect to the need and timing of transfer to the intensive care unit of a (specialized) burn center (for available centers, see: https://verbrennungsmedizin.de/brandverletztenzentren).

Assessment of affected body surface area

Background text without recommendation; see AWMF long version

Assessment of prognosis

Background text shortened; see AWMF long version

The prognosis of patients with extensive skin detachment depends, apart from the affected body surface area, mainly on their age and pre-existing diseases. While the mortality is very high with 13% in SJS, 43% in SJS/TEN overlap forms, and 49% in TEN, it is considerably lower in children than in adults (5.5% at 0–18 years and 29.8% at > 18 years, aggregated for all severity levels).[31] All the more important is the avoidance of sequelae in children.

The assessment of mortality in EN is a process complicated by many influencing factors. Various clinical and laboratory parameters, patient age, and pre-existing underlying diseases, as well as status and severity of the underlying disease in combination with the affected body surface area need to be considered.

No 5	Consensus-based recommendation
EC Consensus	A prognostic assessment using SCORTEN (*severity-of-illness score for toxic epidermal necrolysis*) **shall** be performed within the first 24 hours after admission, as well as on day 3 and, if necessary, on day 5.

At admission of the patients, the *severity-of-illness score for toxic epidermal necrolysis* (SCORTEN; see Appendix) introduced by Bastuji-Garin et al. has proven its worth for the assessment of mortality.[32] The score should be performed within the first 24 hours after admission and on day 3. Some studies recommend re-evaluation on day 5.[33,34]

Causes of death are usually catheter infections with subsequent sepsis, urosepsis, pneumonias, respiratory and multiple organ failure, and quite often complications of comorbidities.[35]

Criteria for transfer to a burn center/intensive care unit

Background text shortened; see AWMF long version

Extensive skin detachments are associated with immunological barrier impairment, dysfunction of thermoregulation, and large fluid losses through hemodynamic instability. In children, standardized and hygiene-compliant dressing management in combination with the possibility of intensive care surveillance and treatment is indicated from an affected body surface area of 10%. From 15% skin detachment, this should be considered also for adults. Such

FIGURE 5 Checklist of initial interventions (after diagnosis). Chapters mentioned refer to AWMF long version.

Checklist of initial interventions (after diagnosis)

The following list represents a selection of the interventions of the S3 guideline EN.
For further details and the full extent of all recommendations, we refer to the respective chapters.
Additional consulting opportunity by the Center for the Documentation of Severe Skin Reactions (dZh) at the University Medical Center Freiburg possible (e-mail: dzh@uniklinikfreiburg. de; phone: 0761 270 67230).

General interventions

- ☐ Daily inspection of skin and mucous membranes
- ☐ Marking the boundaries of the affected area (erythema versus healthy skin)
- ☐ Determination of detached body surface area (Chapter 3.5.1)
- ☐ Photographic documentation
- ☐ Assessment of SCORTEN on day 1, 3, (5) (Table 12.4)
- ☐ Check the indication for transfer to intensive care unit/burn center (Chapter 3.5.3)

Local interventions of the skin (Chapter 4.2.1)

- ☐ Wound cleansing with preheated antiseptic solutions or gels
- ☐ Positioning on aluminum-vapor-coated nonwoven fabric
- ☐ In cases of small areas of epidermal detachment: leave epidermis in situ, relieve blisters by puncture
- ☐ In cases of extensive epidermal detachment: careful removal, if necessary
- ☐ Non-adherent, active substance-free silicone wound contact layers or fatty gauze
- ☐ Diagnostic swabs from various localizations (Chapter 4.2.9)

Local interventions of mucous membranes

Eyes (Chapter 4.2.3)

- ☐ Consultation within 24 h
- ☐ Initial interventions: Preservative-free lubricants and eye ointment at night
- ☐ Prevent corneal exposure (sedated or unconscious patients)

Lips (Chapter 4.2.2)

- ☐ Several times daily white petrolatum or dexpanthenol-containing ointment

Mouth (Chapter 4.2.2)

- ☐ Antiseptic mouth rinse (without alcohol), local anesthetics as needed
- ☐ If necessary, ENT consultation to assess pharyngeal and laryngeal involvement

Genitalia (Chapter 4.2.4)

- ☐ If possible, gynecological/urological consultation within 48 h
- ☐ Insertion of urinary catheter in case of erosive involvement of the genital mucosa/urinary problems
- ☐ Cleansing of urogenital area with sterile water/physiological saline and, if necessary, antiseptic solution; protective basic care (for example, white paraffin ointment); covering of eroded areas with non-adherent dressing

Systemic immunomodulatory therapy (Chapter 4.1)

- ☐ Case-by-case decision after individual risk-benefit assessment

Analgesia (Chapter 4.2.8)

- ☐ Upon request of the patient, consultation with pain specialist regardless of the pain level and at pain level ≥ 4/10 on the numeric rating scale (NRS) despite provision of standard analgesic measures within 48 h, if possible

Antipyresis (Chapter 4.2.8)

- ☐ Use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, metamizole, or acetaminophen as needed, provided they do not represent potential causative drugs

Nutrition (Chapter 4.2.10)

- ☐ Oral/enteral (via nasogastric/nasoduodenal tube) is preferred over parenteral

Additional actions

- ☐ Report to
  - ☐ National registry Center for the Documentation of Severe Skin Reactions (dZh) (reports are integrated into the international RegiSCAR study with centralized specimen collection, established since 1990 with existing ethics committee approval)
  - ☐ IRTEN, international registry and specimen collection since 2020 (ethics committee approval must be obtained by reporting centers)
- ☐ Re-evaluation of the causative drug and assurance of discontinuation

a treatment is performed in regional burn centers (compare "Center indications" for patients with severe burn injuries in AWMF guidelines to burn injuries).[36,37]

If the transfer is performed because of the extensive wound care, the underlying disease of the patients and their immune status towards the required wound care in a burn center must always be assessed and discussed in advance. In such cases, transfers to burn centers with connection to respective specialized clinics or, if possible, directly to such a clinic are preferred (for example, immunosuppressed patients).

Given the prevalence of severe eye involvement in EN, care should be taken to ensure acute ophthalmological treatment after transfer.[38,39]

No 6	Consensus-based recommendation/statement	
EC Consensus	Affected body surface area (epidermal detachment)	Recommendation for transfer in **pediatric** patients with EN
	< 10%	Transfer to a pediatric intensive care unit or a burn center **may** be considered.
	≥ 10%	Transfer to a pediatric intensive care unit or a burn center **shall** be performed.
	> 30%	Transfer to a burn center **shall** be performed.
	Irrespective of skin involvement, EN-related organ dysfunctions are considered admission criteria if they require intensive medical treatment.	
	Early contact with the intensive care unit or burn center **should** be made to jointly determine the indication and timing for transfer.	

No 7	Consensus-based recommendation/statement	
EC Strong consensus	Affected body surface area (epidermal detachment)	Recommendation for transfer in **adult** patients with EN
	< 15%	Transfer to an intensive care unit or a burn center **shall not** be performed.
	≥ 15%	Transfer to an intensive care unit or a burn center **may** be considered.
	> 30%	Transfer to a burn center **shall** be performed.
	Irrespective of skin involvement, EN-related organ dysfunctions are considered admission criteria if they require intensive medical treatment.	
	Early contact with the intensive care unit or burn center **should** be made to jointly determine the indication and timing for transfer.	

In cases with extensive skin involvement, burn centers usually have better facilities for skin treatment. A corresponding transfer from an intensive care unit to a burn center should be evaluated with respect to the overall condition of the patient (ability of transfer) and the jointly agreed therapeutic goal. Transports over longer distances are often experienced as very agonizing by patients. Especially for large distances, the indication for transfer by air transport should be made generously.

In case of very long stays in hospital, the closeness of relatives plays also an important role for the mental situation of the patients.

Advanced diagnosis/follow-up diagnosis

Background text without recommendation; see AWMF long version

Communication with the patient

Background text shortened; see AWMF long version

In addition to the medical care in the strict sense, a good communication practice is a crucial factor for the success of acute medical care of EN. This will strengthen the therapeutic alliance between patient and attending physicians and is essential for the management of therapy. A considerate, empathetic, and honest communication will, for example, facilitate the consideration of nonverbal/paraverbal signals and contextual factors in the interpretation of subjective expressions, such as information on pain intensity. Subsequent to sedation, patients will also benefit from interpersonal communication concerning spatial and temporal reorientation and promotion of social continuity. Accordingly, communication plays an important role in prevention of delirious and posttraumatic stress states and is, therefore, of major importance for disease experience and management beyond the acute phase of the disease.[40]

During the preparation of the guideline, 14 interviews were conducted with EN patients and/or their relatives with the aim to identify unknown needs in medical care. These were evaluated by qualitative analysis methods and form the basis for the practical tips below.

Practical tips for patient communication

The following needs may be more significant in EN and should be considered in the communication between affected patients and attending physicians:

Information needs

- Need for clear, honest, and comprehensible information about …
  - cause and severity of the disease
  - expected disease course/duration of hospitalization
  - therapy planning (for example, coordination of interdisciplinary cooperation)
- Consideration of the clouded consciousness (for example, after sedation or mental trauma)

Affective needs

- (Re-)establishment of the trust in medical care by …
  - explicit acceptance of responsibility by the attending physicians with respect to acute treatment
  - joint therapy planning
  - considerate and confident conversational behavior
  - maintenance of contact with the outside world, especially to close contact persons including initiation of contact to (recovered) affected patients
- Observance of privacy and personal stress limits

Social needs

- Establishment of fixed contact persons
- Extended visiting rights for relatives
- Initiation of continuous medical care after discharge from hospital

SYSTEMIC THERAPY – IMMUNOMODULATORY/IMMUNOSUPPRESSIVE

Background text shortened; see AWMF long version

Various immunosuppressive or immunomodulatory therapeutic options are used for the treatment of EN, although their administration is controversially discussed in the identified literature. During the conducted systematic literature search and meta-analysis, a significant methodical heterogeneity in both primary studies and reviews about EN was observed.

For reasons of better readability, only a shortened presentation of the systematic evidence evaluation is included in the present guideline. A detailed presentation of methods and results including the evidence and GRADE *Summary of Findings* tables is available in the guideline report/evidence report published separately.

Indications for systemic immunomodulatory therapy

At admission of patients with EN, the reaction is often still in its early stages. At that time, the maximum degree of skin detachment is not yet predictable. Therefore, the decision for systemic therapy should be based on the assumption that all patients may develop TEN.

For certain patient groups, administration of a specific systemic immunomodulatory therapy is contraindicated. In the respective chapters on the systemic therapies, these patient groups are described in the background text.

No 8	Consensus-based statement
EC – Statement **Strong consensus**	SJS, SJS/TEN overlap, and TEN **do not differ** with respect to systemic therapy.

No 9	Consensus-based recommendation
EC **Strong consensus**	A differential approach in the choice of systemic therapy for EN based on the patient's sex **cannot be recommended**. *A systematic literature search was conducted. No studies could be identified or included on these questions.*

The median latency of skin detachment from onset of the reaction to its maximum is 8 days (range 0–35 days).[35] In one third of the patients, the onset of the reaction is characterized by the occurrence of mucosal lesions, in one third by the occurrence of exanthema, and in the last third by the presence of unspecific prodromal symptoms. These may resemble a flu-like infection with fever, exhaustion, headache, and/or sore throat and precede skin and mucosal lesions by one to three days.[3,8]

No 10	Consensus-based recommendation
EC **Strong consensus**	Therapy **should** be initiated immediately after diagnosis. Any comorbidities (see background text) **shall** be considered when selecting the therapy.

No 11	Consensus-based recommendation
EC **Strong consensus**	If EN has already persisted for several days and no progression of the skin (see Statement 12) or mucous membranes has been observed for over 24 hours, the expected benefit of initiating a new systemic therapy **should** be critically evaluated.

No 12	Consensus-based statement
EC – Statement **Strong consensus**	Progression is defined as further spreading of redness, possibly with blister formation/skin detachment. New blister formation on/detachment of already reddened skin is not considered progression. To determine the extent of erythema, marking the boundaries of redness with a skin marker is helpful; regular photographic documentation over time is required.

Considering only the exanthema, this will usually progress for 4 to 5 days. Only in very few cases is progression beyond this time anticipated. Blister formation develops with some delay on the already existing exanthema and may subsequently, usually within 5 to 7 days, spread over the entire reddened areas.[3,8,41] Therefore, systemic therapy should only be administered, if progression of the exanthema/erythema has occurred in the last 24 hours. If there is only progression of blister formation, the therapeutic benefit of systemic therapy is doubtful.

The presence of multimorbidity with frequently associated polypharmacy results not only in poorer disease prognosis, but will also complicate the decision as to whether, and which, systemic interventions can be used. With increasing susceptibility for destabilization of various body systems, potential drug interactions, or adverse drug effects, the indication for a systemic therapy decreases with unclear therapeutic benefit. Instructions on the treatment of multimorbid patients can be found in the S3 guideline "Multimorbidity".[42]

Monotherapy with corticosteroids

Background text shortened; see AWMF long version

No 13	Evidence-based recommendation
Grade of recommendation **0** **Strong consensus**	In addition to supportive and organ-oriented therapy for EN, a systemic monotherapy with corticosteroids **may** be considered.
GRADE Very low (⊕◯◯◯) to moderate (⊕⊕⊕◯)	Comparison of corticosteroids (CS) versus other therapies (supportive, cyclosporine A [CsA], intravenous immunoglobulins [IVIG], or etanercept); evidence from prospective or retrospective comparative observational studies and one RCT; for detailed study characteristics and results see *evidence report*.
	Mortality:
Very low (⊕◯◯◯)	CS versus supportive: statistically significant advantage for CS (RR 0.5, 95% confidence interval (CI): 0.26–0.96; 8 observational studies, n = 202)
Low (⊕⊕◯◯)	CsA versus CS: no statistically significant difference (RR 0.45, 95% CI: 0.11–1.82; 2 observational studies, n = 62)
Very low (⊕◯◯◯)	IVIG versus CS: no statistically significant difference (RR 0.4, 95% CI: 0.08–1.94; 2 observational studies, n = 48)
Moderate (⊕⊕⊕◯)	Etanercept versus CS: no statistically significant difference (RR 0.51, 95% CI: 0.16–1.63; 1 RCT, n = 91)
	Serious complication – occurrence of sepsis:
Very low (⊕◯◯◯)	CS versus supportive: no statistically significant difference (RR 0.18, 95% CI: 0.02–1.44; 2 observational studies, n = 32)
Low (⊕⊕◯◯)	CsA versus CS: no statistically significant difference (RR 0.62, 95% CI: 0.21–1.81; 3 observational studies, n = 110)
Moderate (⊕⊕⊕◯)	Etanercept versus CS: no statistically significant difference (RR 0.45, 95% CI: 0.09–2.32; 1 observational study, n = 91)
	Serious complication – occurrence of organ failure:
Very low (⊕◯◯◯)	CS versus supportive: statistically significant advantage for CS (RR 0.31, 95% CI: 0.1–0.97; 4 observational studies, n = 57)
	Occurrence of sequelae of the eyes (Group 1):
Low (⊕⊕◯◯)	CsA versus supportive: no statistically significant difference (RR 1.75, 95% CI: 0.08–37.39; 1 observational study, n = 17)
	Occurrence of sequelae of the eyes (Group 2):
Very low (⊕◯◯◯)	CS versus supportive: no statistically significant difference (RR 2.14, 95% CI: 0.31–14.56; 2 observational studies, n = 35)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae in other organ systems (Group 1)
Further results:	No statistically significant difference regarding the occurrence of sequelae in other organ systems (Group 2) (CS versus supportive: 1 observational study, n = 15 [GRADE: very low]), length of hospital stay (CS versus supportive: 4 observational studies, n = 69 [GRADE: very low]; CsA versus CS: 3 observational studies, n = 110 [GRADE: low]), and time to re-epithelialization (CsA versus CS: 3 observational studies, n = 110 [GRADE: low]; Etanercept versus CS: 1 RCT, n = 91 [GRADE: moderate]).
Bibliography	[36,43–53]

Apart from supportive therapy, administration of CS is the most common systemic therapy in EN. In the literature, numerous case reports, case series, and mostly retrospective observational studies exist that are heterogeneous with respect to the used methods and reported effects of the intervention. In an earlier systematic review, a benefit of CS compared to supportive therapy was identified with respect to mortality. This was, however, not statistically significant (Zimmermann et al.: *odds ratio* [OR]: 0.54, 95% CI: 0.29–1.01 [study level]); OR: 0.78, 95% CI: 0.45–1.35 [patient level]).[54] On the other hand, there is the result of a *Cochrane Review* with meta-analysis including only two prospective observational studies (RR: 2.5, 95% CI: 0.72–9.03).[55]

Recommended dose and duration of therapy, see Chapter 0.

In the following selected clinical treatment situations, systemic corticosteroids shall not be used or only be used in well-justified cases, and a purely supportive therapy or other systemic therapies shall be preferred:

- sepsis (if appropriate, hydrocortisone for therapy of septic shock after intensive medical care decision),
- insufficient control of existing diabetes mellitus,
- poorly controlled arterial hypertension.

Summary of evidence: There is no evidence of high quality that may serve as basis for a recommendation for or against monotherapy with CS in patients with EN. Apart from the available data, the recommendation is based on the clinical experience of the guideline group.

Monotherapy with intravenous immunoglobulins (IVIG)

Background text shortened; see AWMF long version

No 14	Evidence-based recommendation
Grade of recommendation **0** **Consensus**	A systemic monotherapy with intravenous immunoglobulins (off-label) for the treatment of EN **cannot be conclusively evaluated**.
GRADE Very low (⊕◯◯◯) to moderate (⊕⊕⊕◯)	Comparison of IVIG versus other therapies (supportive, CS, CsA, etanercept); evidence from prospective or retrospective comparative observational studies; for detailed study characteristics and results see *evidence report*.
	Mortality:
Very low (⊕◯◯◯)	IVIG versus supportive: no statistically significant difference (RR 1.25, 95% CI: 0.93–1.69; 10 observational studies, n = 462)
Very low (⊕◯◯◯)	IVIG versus CS: no statistically significant difference (RR 0.4, 95% CI: 0.08–1.94; 2 observational studies, n = 48)
Moderate (⊕⊕⊕◯)	CsA versus IVIG: statistically significant advantage for CsA (RR 0.18, 95% CI: 0.05–0.58; 2 observational studies, n = 91)
Low (⊕⊕◯◯)	Etanercept versus IVIG: no statistically significant difference (RR 0.12, 95% CI: 0.01–2.1; 1 observational study, n = 14)
	Serious complication – occurrence of sepsis:
Low (⊕⊕◯◯)	IVIG versus supportive: no statistically significant difference (RR 1.15, 95% CI: 0.81–1.63; 2 observational studies, n = 63)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae of the eyes (Group 1 + 2), occurrence of sequelae in other organ systems (Group 1)
Further results:	No statistically significant difference in need for mechanical ventilation (IVIG versus supportive: 1 observational study, n = 31 [GRADE: low]) and length of hospital stay (IVIG versus supportive: 3 observational studies, n = 109 [GRADE: low]; CsA versus IVIG: 1 observational study, n = 54 [GRADE: low]). Statistically significant prolongation of time to re-epithelialization (IVIG versus supportive: 1 observational study, n = 45 [GRADE: low]).
Bibliography	46,53,56–67

Considering the entirety of comparative study designs, the efficacy of monotherapy with IVIG is heterogeneous with respect to the used methods and the reported effects of the intervention. Concerning the comparison of IVIG with other therapies (supportive, corticosteroids), one part of the studies provided evidence for an advantage while one part of the studies provided evidence for a disadvantage with respect to mortality.[53,56,63,65–67] In the meta-analysis, however, the respective evidence remained without statistical significance.

Recommended dose and duration of therapy, see Chapter 0.

In the following selected clinical treatment situations, IVIG shall not be used or only be used in well-justified cases, and a purely supportive therapy or other systemic therapies shall be preferred:

- administration only after exclusion of IgA deficiency and no administration in case of known IgA deficiency.
- chronic kidney disease of grade 3–4 and acute renal failure; given that this is a relative contraindication, IVIG may be administered after risk-benefit assessment, for example, with reduced infusion rate or avoidance of sucrose-stabilizing formulations.[68]

Summary of evidence: There is no evidence of high quality that may serve as the basis for a recommendation for or against monotherapy with IVIG in patients with EN. With the lack of statistically significant effects, indications for a benefit of IVIG monotherapy, evidence for the superiority of CsA and supportive therapy versus IVIG (mortality, time to epithelialization), and a significant benefit of IVIG in combination with CS compared to IVIG alone (very low confidence in effect estimate, see Chapter 0), there is no systematically validated basis for a recommendation of IVIG as monotherapy.

Although no evidence for a benefit of IVIG monotherapy was found, which might possibly suggest a recommendation against IVIG monotherapy, the guideline commission decided against such a recommendation. This decision is based both on the experience of commission members with respect to the relevance of dose and formulation of the preparations that were considered in the included studies and on the studies excluded during evaluating the evidence.

Monotherapy with cyclosporine A

Background text shortened; see AWMF long version

No 15	Evidence-based recommendation
Grade of recommendation **0** **Strong consensus**	In addition to supportive and organ-oriented therapy for EN, a systemic monotherapy with cyclosporine A (*off-label*) **may** be considered.
GRADE Very low (⊕◯◯◯) to moderate (⊕⊕⊕◯)	Comparison of CsA versus other therapies (supportive, CS, IVIG); evidence from prospective or retrospective comparative observational studies; for detailed study characteristics and results see *evidence report*.
	Mortality:
Low (⊕⊕◯◯)	CsA versus supportive: no statistically significant difference (RR 1.5, 95% CI: 0.27–8.46; 1 observational study, n = 74)
Low (⊕⊕◯◯)	CsA versus CS: no statistically significant difference (RR 0.45, 95% CI: 0.11–1.82; 2 observational studies, n = 62)
Moderate (⊕⊕⊕◯)	CsA versus IVIG: statistically significant advantage for CsA (RR 0.18, 95% CI: 0.05–0.56; 2 observational studies, n = 91)
	Serious complication – occurrence of sepsis:
Low (⊕⊕◯◯)	CsA versus supportive: no statistically significant difference (RR 1.37, 95% CI: 0.62–3.03; 1 observational study, n = 74)
Low (⊕⊕◯◯)	CsA versus CS: no statistically significant difference (RR 0.62, 95% CI: 0.21–1.81; 3 observational studies, n = 110)
	Serious complication – occurrence of organ failure:
Low (⊕⊕◯◯)	CsA versus supportive: no statistically significant difference (RR 9, 95% CI: 0.5–161.44; 1 observational study, n = 74)
	Occurrence of sequelae of the eyes (Group 1):
Low (⊕⊕◯◯)	CsA versus supportive: no statistically significant difference (RR 1.75, 95% CI: 0.08–37.39; 1 observational study, n = 17)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae of the eyes (Group 2), occurrence of sequelae in other organ systems (Group 1)
Further results:	No statistically significant difference in the length of hospital stay (CsA versus CS: 3 observational studies, n = 110 [GRADE: very low]) and the time to re-epithelialization (CsA versus CS: 3 observational studies, n = 110 [GRADE: very low]).
Bibliography	[49–51,59,62,69]

In the identified literature, comparative observational studies using CsA as monotherapy were found. These reported evidence both for and against a therapeutic benefit compared to other therapies, partly with statistically significant advantages[59] and partly with non-significant differences.[50,51,62] In a propensity score analysis, a retrospective single-center observational study did not find any significant difference concerning the mortality between CsA and supportive therapy (hazard ratio [HR] 1.54, 95% CI: 0.26–9.28); while the time to re-epithelialization was shortened with CsA in the pooled effect estimate, this was not statistically significant (HR 0.75, 95% CI: 0.48–1.18). In addition, re-epithelialization of the mucous membrane was completed faster (day 10 after onset of the reaction: HR 0.48, 95% CI: 0.23–1.02),[69] again without statistical significance. Within the meta-analysis, there was an additional significant disadvantage of CsA compared to supportive therapy for the outcome serious complications: occurrence of sepsis. Given that the pooled effect estimate exceeds the threshold of minimal clinical importance (RR = 1.1), and while there is a high potential for measurement errors for this outcome, it is unclear whether there is a relevant effect.

Recommended dose and duration of therapy, see Chapter 0.

In the following selected clinical treatment situations, systemic CsA shall not be used or only be used in well-justified cases, and a purely supportive therapy or other systemic therapies shall be preferred:

- sepsis,
- acute renal failure,
- chronic kidney disease of grade 3–4,
- poorly controlled arterial hypertension.

Summary of evidence: There is no evidence of high quality that may serve as basis for a recommendation for or against monotherapy with CsA in patients with EN. Apart from the available data, the recommendation is based on the clinical experience of the guideline group.

Monotherapy with etanercept

Background text shortened; see AWMF long version

No 16	Evidence-based recommendation
Grade of recommendation **0** **Consensus**	In addition to supportive and organ-oriented therapy for EN, a systemic monotherapy with etanercept (*off-label*) **may** be considered.
GRADE Very low (⊕◯◯◯) to moderate (⊕⊕⊕◯)	Comparison of etanercept versus other therapies (supportive, CS, IVIG); evidence from retrospective comparative observational studies and one RCT; for detailed study characteristics and results see *evidence report*.
	Mortality:
Very low (⊕◯◯◯)	Etanercept versus supportive: statistically significant advantage (RR 0.32, 95% CI: 0.11–0.93; 1 observational study, n = 86)
Moderate (⊕⊕⊕◯)	Etanercept versus CS: no statistically significant difference (RR 0.51, 95% CI: 0.16–1.63; 1 RCT, n = 91)
Low (⊕⊕◯◯)	Etanercept versus IVIG: no statistically significant difference (RR 0.12, 95% CI: 0.01–2.1; 1 observational study, n = 14)
	Serious complication – occurrence of sepsis:
Moderate (⊕⊕⊕◯)	Etanercept versus CS: no statistically significant difference (RR 0.45, 95% CI: 0.09–2.32; 1 RCT, n = 91)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae of the eyes (Group 1 + 2), occurrence of sequelae in other organ systems (Group 1)
Further results:	No statistically significant difference in time to re-epithelialization (Etanercept versus CS: 1 RCT, n = 91 [GRADE: moderate]).
Bibliography	52,58

In the direct comparison of etanercept and CS, the RCT showed no statistically significant superiority for etanercept with respect to the outcome mortality. When compared to the calculated SCORTEN scores, however, the reduced mortality on etanercept reached statistical significance while no such superiority was confirmed within the control group treated with CS. When interpreting the results, however, it must be considered that the control group was treated for a disproportionally long time with CS, which may have resulted in delayed wound healing. With respect to mortality, both patient groups were also compared with a historic control group treated only with supportive therapy. Here, a significant benefit was shown for the patients treated with etanercept.[52]

Recommended dose and duration of therapy, see Chapter 0.

In the following selected clinical treatment situations, etanercept shall not be used or only be used in well-justified cases, and a purely supportive therapy or other systemic therapies shall be preferred:

- sepsis,
- active tuberculosis.

Summary of evidence: There is no evidence of high quality that may serve as basis for a recommendation for or against monotherapy with etanercept in patients with EN. Apart from the available data, the recommendation is based on the clinical experience of the guideline group.

Therapy with thalidomide

Background text see AWMF long version

No 17	Evidence-based recommendation
Grade of recommendation **A** **Strong consensus**	A therapy with thalidomide **shall not** be performed.
GRADE High (⊕⊕⊕⊕)	Comparison of thalidomide versus placebo; evidence from a single-center RCT; for detailed study characteristics and results see *evidence report*.
High (⊕⊕⊕⊕)	Mortality: Statistically significant disadvantage of thalidomide versus placebo (RR 2.78, 95% CI: 1.04–7.4)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae of the eyes (Group 1 + 2), occurrence of sequelae in other organ systems (Group 1)
Bibliography	70

Summary of evidence: Based on one available RCT, a recommendation against therapy with thalidomide in patients with EN can be provided.

Combination therapies

Combination therapies with three different systemic therapies in at least one treatment arm were excluded from the analysis.

Corticosteroid plus IVIG

Background text shortened; see AWMF long version

No 18	Evidence-based recommendation
Grade of recommendation **0** **Strong consensus**	A combination therapy of corticosteroids **in parallel** with IVIG (*off-label*) for the treatment of EN **cannot be conclusively evaluated**.
GRADE Very low (⊕◯◯◯) to low (⊕⊕◯◯)	Comparison of combination therapy CS plus IVIG versus other therapies (supportive, CS, IVIG, etanercept + CS); evidence from prospective or retrospective comparative observational studies; for detailed study characteristics and results see *evidence report*
	Mortality:
Very low (⊕◯◯◯)	CS + IVIG versus supportive: no statistically significant difference (RR 0.62, 95% CI: 0.3–1.24; 3 observational studies, n = 165)
Very low (⊕◯◯◯)	CS + IVIG versus CS: no statistically significant difference (RR 0.73, 95% CI: 0.46–1.18; 9 observational studies, n = 548)
Very low (⊕◯◯◯)	CS + IVIG versus IVIG: statistically significant difference (RR 0.46, 95% CI: 0.22–0.96; 3 observational studies, n = 136)
Very low (⊕◯◯◯)	Etanercept + CS versus CS + IVIG: no statistically significant difference (RR 0.28, 95% CI: 0.0–6.58; 1 observational study, n = 46)
	Serious complication – occurrence of sepsis:
Very low (⊕◯◯◯)	CS + IVIG versus supportive: no statistically significant difference (RR 0.9, 95% CI: 0.38–2.11; 1 observational study, n = 19)
Very low (⊕◯◯◯)	CS + IVIG versus CS: no statistically significant difference (RR 0.77, 95% CI: 0.31–1.93; 3 observational studies, n = 140)
Low (⊕⊕◯◯)	CS + IVIG versus IVIG: no statistically significant difference (RR 0.85, 95% CI: 0.42–1.72; 1 observational study, n = 32)
	Serious complication – occurrence of organ failure:
Very low (⊕◯◯◯)	CS + IVIG versus CS: no statistically significant difference (RR 0.69, 95% CI: 0.29–1.66; 2 observational studies, n = 75)
	Occurrence of sequelae of the eyes (Group 1+ 2):
Low (⊕⊕◯◯)	CS + IVIG versus IVIG: no statistically significant difference (RR 0.55, 95% CI: 0.2–1.53; 1 observational study, n = 32)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae in other organ systems (Group1)
Further results:	No statistically significant difference in the need for mechanical ventilation (CS + IVIG versus supportive: 1 observational study, n = 19 [GRADE: very low]; CS + IVIG versus IVIG: 1 observational study, n = 32 [GRADE: low]). Statistically significant shorter length of hospital stay (CS + IVIG versus CS: 4 observational studies, n = 261 [GRADE: low]). Statistically significant shorter time to re-epithelialization (CS + IVIG versus CS: 1 observational study, n = 36 [GRADE: low]).
Bibliography	57,65,67,71–79

Comparative observational studies have been found in the identified literature showing a positive, albeit not significant effect with respect to mortality for the use of combination therapy of CS plus IVIG, especially when compared to CS monotherapy.[72,75,79]

In the included observational studies, IVIG was used at a dose of 0.3–0.5 g/kg body weight (BW) per day for 3 to 5 days and methylprednisolone at 1–1.5 mg/kg BW per day as pulse therapy for 3 to 5 days or tapered for a maximum of two weeks.[72–75]

Recommended dose and duration of therapy, see Chapter 0.

The limitations for certain patient groups concerning the therapy with CS and IVIG are provided in the respective chapters on the monotherapy (Chapters 0 und 0).

Summary of evidence: There is no evidence of high quality that may serve as basis for a recommendation for or against combination therapy with CS plus IVIG in patients with EN. Apart from the available data, the recommendation is based on the clinical experience of the guideline group.

Corticosteroid plus etanercept

Background text shortened; see AWMF long version

No 19	Evidence-based recommendation
Grade of recommendation **0** **Strong consensus**	A combination therapy of corticosteroids **in parallel** with etanercept (*off-label*) for the treatment of EN **cannot be conclusively evaluated**.
GRADE Very low (⊕◯◯◯) to low (⊕⊕◯◯)	Comparison of combination therapy CS plus etanercept versus other therapies (CS, CS + IVIG); evidence from retrospective comparative observational studies; for detailed study characteristics and results see *evidence report*.
	Mortality:
Low (⊕⊕◯◯)	CS + Etanercept versus CS: no statistically significant difference (RR 0.69, 95% CI: 0.01–32.12; 1 observational study, n = 25)
Very low (⊕◯◯◯)	CS + Etanercept versus CS + IVIG: no statistically significant difference (RR 0.28, 95% CI: 0.01–6.58; 1 observational study, n = 46)
	Serious complication – occurrence of organ failure:
Low (⊕⊕◯◯)	CS + Etanercept versus CS: no statistically significant difference (RR 0.67, 95% CI: 0.17–2.67; 1 observational study, n = 25)
"Critical outcomes" for which no data were available:	Quality of life/psychosocial well-being, occurrence of sequelae of the eyes (Group 1 + 2), occurrence of sequelae in other organ systems (Group 1)
Further results:	No statistically significant difference in the length of hospital stay (CS + Etanercept versus CS: 1 observational study, n = 25 [GRADE: low]) and the time to re-epithelialization (CS + Etanercept versus CS: 1 observational study, n = 25 [GRADE: low]).
Bibliography	[78,80]

Compared to the monotherapy with CS, Ao et al. observed a shortened time to re-epithelialization and duration of hospitalization, as well as reduced concentrations of IL-6, IL-15, and IL-18 in the serum of patients on combination therapy.[80] With respect to mortality, Zhang et al. observed no significant difference for the administration of CS and etanercept compared to the combination of CS and IVIG.[78]

Recommended dose and duration of therapy, see Chapter 0.

The limitations for certain patient groups concerning the therapy with CS and etanercept are provided in the respective chapters on the monotherapy (Chapters 0 und 0).

Summary of evidence: There is no evidence of high quality that may serve as basis for a recommendation for or against combination therapy with CS + etanercept in patients with EN. The recommendation is predominantly based on the clinical experience of the guideline group.

Corticosteroid plus cyclosporine A

No 20	Consensus-based recommendation
EC **Strong consensus**	A combination therapy of corticosteroids **in parallel** with cyclosporine A (*off-label*) for the treatment of EN **cannot be conclusively evaluated**.

Currently, a few case reports, but no comparative observational studies are available for a combination therapy with CS plus CsA.[81]

Recommended dose and duration of therapy, see Chapter 0.

The limitations for certain patient groups concerning the therapy with CS and CsA are provided in the respective chapters on the monotherapy (Chapters 0 und 0).

Systemic therapy in patients < 18 years of age

Concerning the systemic therapy of EN in patients < 18 years of age, subgroup-specific results were only reported on CS and IVIG (in each case as monotherapy) within the systemic monotherapies and combination therapies mentioned above.[47,67] The limitations for certain patient groups mentioned in the chapters of the respective therapies remain valid.

Recommended dose and duration of therapy, see Chapter 0.

No 21	Consensus-based recommendation
EC **Strong consensus**	Children and adolescents **shall** be treated in accordance with the aforementioned recommendations.
	A systematic literature search was conducted. No studies could be identified or included on these questions.

Systemic therapy during pregnancy and breast-feeding

No 22	Consensus-based recommendations
EC **Strong consensus**	The indication for administering immunomodulatory systemic therapy during pregnancy **shall be made cautiously** and in consideration of the previous recommendations.
	During breastfeeding, the aforementioned recommendations **may** be applied analogously, taking into account any contraindications for breastfeeding.
	A systematic literature search was conducted. No studies could be identified or included on these questions.

For evaluation of a potential harmful effect of medical therapies on pregnancy, we refer to the respective summaries of product characteristics and databases (for example, embryotox).

Dosage and duration of systemic immunomodulatory therapies

Background text without recommendation; see AWMF long version.

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CONFLICT OF INTEREST STATEMENT

A list of the conflicts of interest of the participating authors is provided in the AWMF long version.

REFERENCES

1. Kaminski-Hartenthaler A, Meerpohl JJ, Gartlehner G, et al. [GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations]. *Z Evid Fortbild Qual Gesundhwes*. 2014;108:413-420.
2. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. *Br J Dermatol*. 1979;100:69-86.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331:1272-1285.
4. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1993;129:92-96.
5. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol*. 2002;138:1019-1024.
6. Grünwald P, Mockenhaupt M, Panzer R, Emmert S. Erythema exsudativum multiforme, Stevens-Johnson-Syndrom/toxische epidermale Nekrolyse – Diagnostik und Therapie. *J Dtsch Dermatol Ges*. 2020;18:547-553.
7. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol*. 2013;69:173. e1-13;quiz185-186.
8. Mockenhaupt M, Roujeau J-C. Epidermal Necrolysis (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis). In: Kang S, Amagai M, Bruckner AL, et al. (eds.) *Fitzpatrick's Dermatology, 9e*. McGraw-Hill Education; 2019.
9. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol*. 1994;102:28S-30S.

10. Salopek TG. Nikolsky's sign: is it 'dry' or is it 'wet'? *Br J Dermatol*. 1997;136:762-767.
11. Paulmann M, Mockenhaupt M. Schwere arzneimittelinduzierte Hautreaktionen: Klinik, Diagnostik, Ätiologie und Therapie. *J Dtsch Dermatol Ges*. 2015;13:625-645.
12. Mockenhaupt M. Severe cutaneous adverse drug reactions. In: Burgdorf WHC PG, Wolff HH, Landthaler M (eds.). *Braun-Falco's Dermatology*. Heidelberg: Springer; 2009.
13. Sidoroff A, Halevy S, Bavinck JN, et al. Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. *J Cutan Pathol*. 2001;28:113-119.
14. Mockenhaupt M, Idzko M, Grosber M, et al. Epidemiology of staphylococcal scalded skin syndrome in Germany. *J Invest Dermatol*. 2005;124:700-703.
15. Ziemer M, Mockenhaupt M. Severe Drug-Induced Skin Reactions: Clinical Pattern, Diagnostics and Therapy. In: Uday K, ed. *Skin Biopsy*. IntechOpen; 2011:Ch. 6.
16. Maverakis E, Wang EA, Shinkai K, et al. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Standard Reporting and Evaluation Guidelines: Results of a National Institutes of Health Working Group. *JAMA Dermatol*. 2017;153:587-592.
17. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol*. 2016;174:1194-1227.
18. Levi N, Bastuji-Garin S, Mockenhaupt M, et al. Medications as risk factors of stevens-johnson syndrome and toxic epidermal necrolysis in children: A pooled analysis. *Pediatrics*. 2009;123(2):e297-e304.
19. Krüger D, Paulmann M, Mockenhaupt M. Stevens-Johnson-Syndrom/Toxisch epidermale Nekrolyse im Kindes- und Jugendalter: Häufigkeit, Ausprägung und Auslöser. *J Dtsch Dermatol Ges*. 2019;17:69-70.
20. Guillaume JC, Roujeau JC, Revuz J, et al. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol*. 1987;123:1166-1170.
21. Correia O, Chosidow O, Saiag P, et al. Evolving Pattern of Drug-Induced Toxic Epidermal Necrolysis. *Dermatology (Basel, Switzerland)*. 1993;186:32-37.
22. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981–1985. *Arch Dermatol*. 1990;126:37-42.
23. Schöpf E, Stühmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. *Arch Dermatol*. 1991;127:839-842.
24. Kubo H, Irie A, Inagaki F, Hoshi M. Melibiosylceramide as the sole ceramide dihexoside from the eggs of the sea urchin, Anthocidaris crassispina. *J Biochem*. 1988;104:755-760.
25. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol*. 2008;128:35-44.
26. Yetiv JZ, Bianchine JR, Owen JA, Jr. Etiologic factors of the Stevens-Johnson syndrome. *South Med J*. 1980;73:599-602.
27. Seminario-Vidal L, Kroshinsky D, Malachowski SJ, et al. Society of Dermatology Hospitalists supportive care guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. *J Am Acad Dermatol*. 2020;82:1553-1567.
28. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther*. 2010;88:60-68.
29. Millar BC, Bell JB, Montes A, et al. Colony stimulating activity in the serum of patients with multiple myeloma is enhanced by interleukin 3: a possible role for interleukin 3 after high dose melphalan and autologous bone marrow transplantation for multiple myeloma. *Br J Haematol*. 1990;75:366-372.
30. Liew YCC, Choo KJL, Oh CC, et al. Mycoplasma-induced Stevens-Johnson syndrome/toxic epidermal necrolysis: Case-control analysis of a cohort managed in a specialized center. *J Am Acad Dermatol*. 2022;86:811-817.
31. Naegele D, Sekula P, Paulmann M, Mockenhaupt M. Incidence of Epidermal Necrolysis: Results of the German Registry. *J Invest Dermatol*. 2020;140:2525-2527.
32. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis. *J Invest Dermatol*. 2000;115:149-153.
33. Bansal S, Garg VK, Sardana K, Sarkar R. A clinicotherapeutic analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis with an emphasis on the predictive value and accuracy of SCORe of Toxic Epidermal Necrolysis. *Int J Dermatol*. 2015;54:e18-e26.
34. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, et al. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol*. 2006;126:272-276.
35. Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol*. 2013;133:1197-1204.
36. Torres-Navarro I, Briz-Redon A, Botella-Casas G, et al. Accuracy of SCORTEN and ABCD-10 to predict mortality and the influence of renal function in Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Dermatol*. 2020;47:1182-1186.
37. von Wild T, Stollwerck PL, Namdar T, et al. Are Multimorbidities Underestimated in Scoring Systems of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Like in SCORTEN? *Eplasty*. 2012;12:e35-NA.
38. Chronopoulos A, Mockenhaupt M, Pleyer U. Okuläre Beteiligung bei Stevens-Johnson-Syndrom und toxisch epidermaler Nekrolyse. *Der Ophthalmologe*. 2021;118:519-532.
39. Chang YS, Huang FC, Tseng SH, et al. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. *Cornea*. 2007;26:123-129.
40. Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI). S3-Leitlinie Analgesie, Sedierung und Delirmanagement in der Intensivmedizin (DAS-Leitlinie), Version 5.0. 2021;AWMF-Registernummer: 001/012.
41. Bachot N, Roujeau JC. Physiopathology and treatment of severe drug eruptions. *Curr Opin Allergy Clin Immunol*. 2001;1:293-298.
42. Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e.V. (DEGAM). S3-Leitlinie Multimorbidität – Living guideline, Version 2.1. 2023;AWMF-Register-Nr. 053-047LG.
43. Brand R, Rohr JB. Toxic epidermal necrolysis in Western Australia. *Australas J Dermatol*. 2000;41:31-33.
44. Chatproedprai S, Wutticharoenwong V, Tempark T, Wananukul S. Clinical Features and Treatment Outcomes among Children with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A 20-Year Study in a Tertiary Referral Hospital. *Dermatol Res Pract*. 2018;2018:3061084.
45. Dicle Ö, Yılmaz E, Alpsoy E. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Retrospective Evaluation. [Turkish]. *Turkderm-Turk Arch Dermatol Venereol*. 2009;43:15-20.
46. Kim KJ, Lee DP, Suh HS, et al. Toxic epidermal necrolysis: analysis of clinical course and SCORTEN-based comparison of mortality rate and treatment modalities in Korean patients. *Acta Derm Venereol*. 2005;85:497-502.
47. Koh MJ, Tay YK. Stevens-Johnson syndrome and toxic epidermal necrolysis in Asian children. *J Am Acad Dermatol*. 2010;62:54-60.
48. Léauté-Labrèze C, Lamireau T, Chawki D, et al. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child*. 2000;83:347-352.
49. Shah R, Chen ST, Kroshinsky D. Use of cyclosporine for the treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Am Acad Dermatol*. 2021;85:512-513.
50. Singh GK, Chatterjee M, Verma R. Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid. *Indian J Dermatol Venereol Leprol*. 2013;79:686-692.

51. Thakur V, Vinay K, Kumar S, et al. Factors Predicting the Outcome of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A 5-Year Retrospective Study. *Indian Dermatol Online J*. 2021;12:258-265.
52. Wang CW, Yang LY, Chen CB, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest*. 2018;128:985-996.
53. Yip LW, Thong BY, Tan AW, et al. High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits. *Eye*. 2005;19:846-853.
54. Zimmermann S, Sekula P, Venhoff M, et al. Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2017;153:514-522.
55. Jacobsen A, Olabi B, Langley A, et al. Systemic interventions for treatment of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome. *Cochrane Database Syst Rev*. 2022;3:Cd013130.
56. Brown KM, Silver GM, Halerz M, et al. Toxic epidermal necrolysis: does immunoglobulin make a difference? *J Burn Care Rehabil*. 2004;25:81-88.
57. Chan L, Cook DK. A 10-year retrospective cohort study of the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in a New South Wales state referral hospital from 2006 to 2016. *Int J Dermatol*. 2019;58:1141-1147.
58. Dreyer SD, Torres J, Stoddard M, et al. Efficacy of Etanercept in the Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Cutis*. 2021;107:E22-E28.
59. González-Herrada C, Rodríguez-Martín S, Cachafeiro L, et al. Cyclosporine Use in Epidermal Necrolysis Is Associated with an Important Mortality Reduction: Evidence from Three Different Approaches. *J Invest Dermatol*. 2017;137:2092-2100.
60. Gravante G, Delogu D, Marianetti M, et al. Toxic epidermal necrolysis and Steven Johnson syndrome: 11-years experience and outcome. *Eur Rev Med Pharmacol Sci*. 2007;11:119-127.
61. Imahara SD, Holmes 4th JH, Heimbach DM, et al. SCORTEN overestimates mortality in the setting of a standardized treatment protocol. *J Burn Care Res*. 2006;27:270-275.
62. Kirchhof MG, Miliszewski MA, Sikora S, et al. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. *J Am Acad Dermatol*. 2014;71:941-947.
63. Marchitto MC, Sung S, Doong J, Chien AL. Toxic epidermal necrolysis: a review of 20 years of data. *J Eur Acad Dermatol Venereol*. 2018;32:e263-e264.
64. Paquet P, Kaveri S, Jacob E, et al. Skin immunoglobulin deposition following intravenous immunoglobulin therapy in toxic epidermal necrolysis. *Exp Dermatol*. 2006;15:381-386.
65. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol*. 2008;58:33-40.
66. Shortt R, Gomez M, Mittman N, Cartotto R. Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis. *J Burn Care Rehabil*. 2004;25:246-255.
67. Williams V, Reddy M, Bansal A, et al. Intensive care needs and long-term outcome of pediatric toxic epidermal necrolysis - A 10-year experience. *Int J Dermatol*. 2021;60:44-52.
68. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol*. 2003;139:33-36.
69. Poizeau F, Gaudin O, Le Cleach L, et al. Cyclosporine for Epidermal Necrolysis: Absence of Beneficial Effect in a Retrospective Cohort of 174 Patients-Exposed/Unexposed and Propensity Score-Matched Analyses. *J Invest Dermatol*. 2018;138:1293-1300.
70. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet*. 1998;352:1586-1589.
71. Hsieh MH, Watanabe T, Aihara M. Recent Dermatological Treatments for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan. *Front Med (Lausanne)*. 2021;8:636924.
72. Jagadeesan S, Sobhanakumari K, Sadanandan S, et al. Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: A prospective comparative open-labelled study of 36 cases. *Indian J Dermatol Venereol Leprol*. 2013;79:506-511.
73. Xiao Y, Gang W. Clinical analysis of severe drug eruption treated with hemoperfusion and continuous renal replacement therapy combined. *Journal of the Dermatology Nurses' Association Conference: 24th World Congress of Dermatology Milan Italy*. 2019;12.
74. Yang Y, Xu J, Li F, Zhu X. Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China. *Int J Dermatol*. 2009;48:1122-1128.
75. Yang L, Shou YH, Li F, et al. Intravenous Immunoglobulin Combined With Corticosteroids for the Treatment of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Propensity-Matched Retrospective Study in China. *Front Pharmacol*. 2022;12:750173.
76. Yeong EK, Lee CH, Hu FC, M ZW. Serum bicarbonate as a marker to predict mortality in toxic epidermal necrolysis. *J Intensive Care Med*. 2011;26:250-254.
77. Yun SJ, Choi MS, Piao MS, et al. Serum lactate dehydrogenase is a novel marker for the evaluation of disease severity in the early stage of toxic epidermal necrolysis. *Dermatology*. 2008;217:254-259.
78. Zhang J, Lu CW, Chen CB, et al. Evaluation of Combination Therapy With Etanercept and Systemic Corticosteroids for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Multicenter Observational Study. *J Allergy Clin Immunol Pract*. 2022;10:1295-1304. e6.
79. Zhu QY, Ma L, Luo XQ, Huang HY. Toxic epidermal necrolysis: performance of SCORTEN and the score-based comparison of the efficacy of corticosteroid therapy and intravenous immunoglobulin combined therapy in China. *J Burn Care Res*. 2012;33:e295-308.
80. Ao S, Gao X, Zhan J, et al. Inhibition of tumor necrosis factor improves conventional steroid therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis in a cohort of patients. *J Am Acad Dermatol*. 2022;86:1236-1245.
81. Sullivan JR, Watson A. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous cyclosporin: a discussion of pathogenesis and immunosuppressive management. *Australas J Dermatol*. 1996;37:208-212.

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