Toxic epidermal necrolysis and Stevens-Johnson syndrome: A review*

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Objectives: **The aims of this review are to summarize the definitions, causes, and clinical course as well as the current understanding of the genetic background, mechanism of disease, and therapy of toxic epidermal necrolysis and Stevens-Johnson syndrome.**

Data Sources: **PubMed was searched using the terms toxic epidermal necrolysis, Stevens-Johnson syndrome, drug toxicity, drug interaction, and skin diseases.**

Data Synthesis: **Toxic epidermal necrolysis and Stevens-Johnson syndrome are acute inflammatory skin reactions. The onset is usually triggered by infections of the upper respiratory tract or by preceding medication, among which nonsteroidal anti-inflammatory agents, antibiotics, and anticonvulsants are the most common triggers. Initially the diseases present with unspecific symptoms, followed by more or less extensive blistering and shedding of the skin. Complete death of the epidermis leads to sloughing similar to that seen in large burns. Toxic epidermal necrolysis is the most severe form of drug-induced skin reaction and includes denudation of >30% of total body surface area. Stevens-Johnson syndrome affects <10%, whereas involvement of 10%–30% of body surface area is called Stevens-Johnson syndrome/toxic epidermal necrolysis overlap. Besides the skin, mucous membranes such as oral, genital, anal, nasal, and conjunctival mucosa are frequently involved in toxic epidermal necrolysis and Stevens-Johnson syndrome. Toxic epidermal necrolysis is associated with a significant mortality of 30%–50% and long-term sequelae. Treatment includes early admission to a burn unit, where treatment with precise fluid, electrolyte, protein, and energy supplementation, moderate mechanical ventilation, and expert wound care can be provided. Specific treatment with immunosuppressive drugs or immunoglobulins did not show an improved outcome in most studies and remains controversial. The mechanism of disease is not completely understood, but immunologic mechanisms, cytotoxic reactions, and delayed hypersensitivity seem to be involved.**

Conclusion: **Profound knowledge of exfoliative skin diseases is needed to improve therapy and outcome of these life-threatening illnesses. (Crit Care Med 2011; 39:1521–1532)**

KEY WORDS: toxic epidermal necrolysis; Stevens-Johnson syndrome; child; drug interactions; drug toxicity; skin diseases; hypersensitivity

Several different manifestations of drug-induced skin reactions have been described. Mild conditions like maculopapular exanthema, urticaria, photoallergic reactions, and fixed eruptions due to drugs occur frequently. More severe manifestations like acute bullous exanthema are rare.

The aims of this review are to summarize definitions, causes, and clinical courses of and therapy for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A systematic literature search was performed over the last 5 yrs using the following terms: "toxic epidermal necrolysis," "Stevens-Johnson syndrome," 'child," and "drug toxicity." This review was exempt from approval by the Research Ethics Committee, University Hospital of Berne, Berne, Switzerland.

In 1956, Lyell (1) reported four cases of skin eruptions following either drug ingestion or staphylococcal infection or of undetermined etiology. Over time, it became clear that he had described three different diseases, including a case of TEN. TEN is the most severe form of drug-induced skin reaction and is defined as epidermal detachment of >30% of body surface area. Similar diseases include SJS, named after the 1922 description by Stevens and Johnson (2) and erythema multiforme. SJS presents with epidermal detachment of <10% of body surface area, whereas involvement of 10%–30% of body surface is defined as SJS/TEN overlap. Differences between TEN, SJS, and erythema multiforme are summarized in Table 1. There is growing evidence that SJS and TEN are a single disease with common causes and mechanisms (3). Most authors give credit for the first description of SJS to Hebra (4) in 1860, but Rosenberg (5) mentions an 1822 publication by Alibert and Bazin that probably refers to the same disease.

The incidence of severe exfoliative skin reactions are estimated at 1 to 7 cases per million person-years for SJS and 0.4 to 1.5 cases per million person-years for TEN (6–10). In children, TEN occurs equally frequently in males and females, whereas in adults women are more frequently affected by a ratio of 3:2 to 2:1. Persons over 60 yrs seem to be more likely to develop TEN (8, 11).

Causes of TEN and SJS

In 74%–94% of cases, TEN is triggered either by preceding medication or by an infection of the upper respiratory tract (13–16).

The first large study to assess the risk of developing SJS or TEN included 245 TEN-patients and 1,147 controls (17). This study distinguished between drugs usually used for short-term periods and

*See also p. 1600.

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There are no sources of external funding.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e31821201ed

Table 1. Classification of exfoliative skin reactions (12)

Reaction	Bullous Erythema Multiforme	Stevens-Johnson Syndrome	Overlap Stevens-Johnson Syndrome- TEN	TEN With Spots	TEN Without Spots
Detachment	<10%	<10%	10%–30%	>30%	>10%
Typical targets	Yes	No	No	No	No
Atypical targets	Raised	Flat	Flat	Flat	
Spots	No	Yes	Yes	Yes	No

TEN, toxic epidermal necrolysis.

drugs used for months or years. The highest risk in the first group was documented for trimethoprim-sulfomethoxazole and other sulfonamide antibiotics (crude relative risk [RR] 172), followed by chlormezanone (crude RR 62), cephalosporins (multivariate RR 14), quinolones (multivariate RR 10), and aminopenicillins (multivariate RR 6.7). For acetaminophen, the RR was calculated to be 0.6 in France but up to 9.3 in other countries. In the long-term-use group, the increased risk was confined largely to the first 2 months of treatment. Crude RRs of other drugs were 90 for carbamazepine followed by oxicam-nonsteroidal anti-inflammatory drugs (RR 72), corticosteroids (RR 54), phenytoin (RR 53), allopurinol (RR 52), phenobarbital (RR 45), and valproic acid (RR 25).

The large EuroSCAR study (18) analyzed RRs for several drugs. Among the newer drugs, strong associations were documented for nevirapine (RR >22), tramadol (RR = 20), pantoprazole (RR = 18), lamotrigine (RR >14), and sertraline (RR = 11). Analysis of older drugs largely confirmed the results from Roujeau et al (17) and showed the following univariate RRs: cotrimoxazole, 102; sulfonamides, 53; carbamazepine, 33; phenytoin, 26; phenobarbital, 17; allopurinol, 11; and oxicam-nonsteroidal anti-inflammatory drugs, 6.4.

Both of these studies included children and adults, with <10% of cases occurring in children. A pooled analysis was performed for children of <15 yrs (19). The univariate analysis showed that anti-infective sulfonamides, phenobarbital, lamotrigine, and carbamazepine were strongly associated with SJS/TEN in children. Valproic acid, acetaminophen, and nonsteroidal anti-inflammatory drugs as a group also increased the risk of SJS/TEN.

Cross-reactivity of drugs might lead to fatal recurrent TEN (20). Potential cross-reactivity among β-lactam antibiotics and cephalosporins exists. Similarly cross-reactivity and recurrence of disease might occur after administration of antiepileptic drugs with the arene-oxide moiety (e.g., phenytoin, phenobarbital, carbamazepine, etc.) and application of other antiepileptics (e.g., valproic acid, levetiracetam, etc.) should be considered.

Other factors associated with SJS/TEN are infectious diseases such as those caused by human immunodeficiency virus (21), herpesvirus, *Mycoplasma pneumoniae* (22–25), and hepatitis A virus (26) and noninfectious conditions including radiotherapy (27, 28), lupus erythematosus (29, 30), and collagen vascular disease (31).

Genetics

Several genetic factors influence the risk of developing TEN/SJS. A statistically significant increase in human leukocyte antigen (HLA)-B12 phenotype among 44 patients surviving TEN was documented (32).

In Han Chinese, two other gene loci have been shown to increase risk for TEN: HLA-B*5801 was present in all patients with severe cutaneous reactions to allopurinol and in only 15% of 135 tolerant patients (33).

HLA-B*1502 was present in all Chinese patients experiencing carbamazepine-induced SJS, while HLA-B*1502 was detected in only 3% of carbamazepine-tolerant patients (34). The risk of carbamazepine-induced SJS/TEN was significantly higher in Thai patients with HLA-B*1502 (35) and in Indian patients (36).

Carbamazapine-induced SJS/TEN was strongly associated with HLA-B*1502 in Chinese patients but patients with carbamazepine-induced maculopapular eruptions had an odds ratio similar to tolerant controls (37). In a European study of 12 patients with carbamazepine-induced SJS/TEN, only four had the HLA-B*1502 allele (38). Remarkably, these four patients had an Asian ancestry, whereas the others did not. This shows that HLA-B*1502 seems to be a useful predictive marker in the Asian population but not in European patients. An HLA-B*1502 screening before treatment with carbamazepine in Asian patients was proposed (39).

Immunopathogenesis

The etiology of TEN is not completely understood. Several theories including immunologic mechanisms, reactive drug metabolites, or interactions between these two have been published in a review (40).

In summary, specific drug hypersensitivity leads to major histocompatibility class I-restricted drug presentation and is followed by an expansion of cytotoxic T-lymphocytes, leading to an infiltration of skin lesions with cytotoxic T-lymphocytes and natural killer cells.

Evidence is supportive of a role for the death receptor Fas and its Fas ligand (CD95) in the pathogenesis of keratinocyte apoptosis during TEN (41). Other findings suggest activation of the perforin/granzyme pathway as a cytotoxic mechanism in SJS/TEN (42).

Recent publications show that granulysin probably is the key mediator for disseminated keratinocyte death in SJS/TEN. Granulysin levels in the sera of patients with SJS/TEN are much higher than in patients with ordinary drug-induced skin reactions or healthy controls (43). Furthermore granulysin levels correlate with clinical severity (44).

Since the mechanism is not IgE mediated, a desensitization of the triggering drug is not an option.

Clinical Course

Drug-induced TEN typically presents with fever and influenza-like symptoms 1 to 3 wks after the application of the suspected drug (45). One to 3 days later, signs begin in the mucous membranes, including eyes, mouth, nose, and genitalia in up to 90% of cases. Skin lesions manifest as generalized macules with purpuric centers. The macules progress to large confluating blisters with subsequent epidermal detachment, yet never show involvement of the hair (Fig. 1). In the following 3 to 5 days, separation of the epidermis progresses and leads to large denuded areas (Fig. 2). The large wound area leads to extreme pain, massive loss of fluid and protein, bleeding, evaporative heat loss with subsequent hypothermia, and infection (46).

Histopathology shows separation of the epidermis at the dermal-epidermal

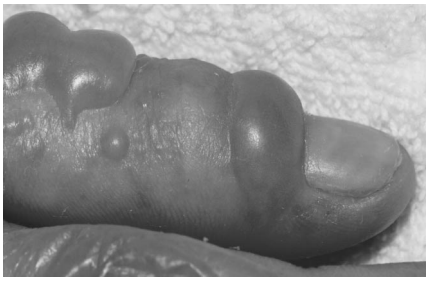

Figure 1. Confluating blisters 3 days after onset of skin reaction in a patient with toxic epidermal necrolysis.

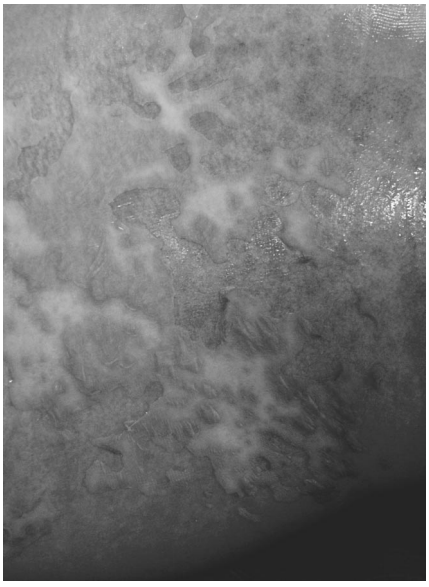

Figure 2. Large denuded areas following epidermal detachment 5 days after onset of skin symptoms.

junction of the skin, extracutaneous epithelium, and mucous membranes. Clinically, this can be detected by a positive Nikolsky sign, which describes detachment of the full-thickness epidermis when light lateral pressure is applied with the examining finger.

Unlike the situation in full-thickness burns, the epidermal appendages remain largely intact, which allows re-epithelialization without scarring. Re-epithelialization of the epidermis begins about 1 wk after onset of skin reactions and takes up to 3 wks (47).

Gastrointestinal involvement frequently occurs in the mouth and esophagus but also in the small bowl and colon (48–50). Patients with TEN usually do not develop a paralytic ileus, which allows early enteral nutrition (51). Involvement of the gastrointestinal tract may lead to stenosis or strictures and consecutive long-term complications with dysphagia and ileus-like symptoms. Vulvovaginal involvement may also lead to vaginal stenosis or strictures (52, 53).

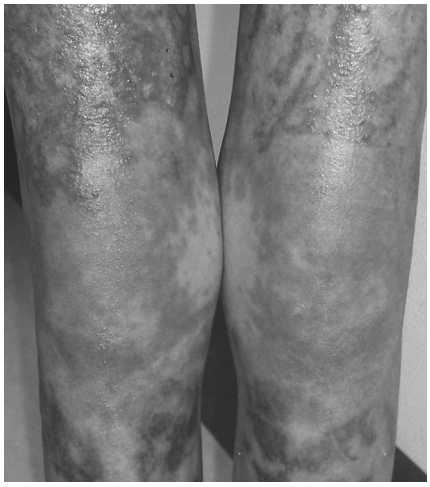

Figure 3. De- and hyperpigmentation of the skin 6 months after toxic epidermal necrolysis.

Hyper- and hypopigmentation occur in virtually all children and tend to fade with time but usually do not resolve completely (Fig. 3). Hypertrophic changes and scarring of the skin occur infrequently (54). Long-term sequelae also involve fingernails and toenails, usually after inflammation of the nail beds and loss of the nails during the acute phase of TEN. Nails can develop deformities that are usually not painful and not associated with significant functional disability.

In TEN, pulmonary edema and progressive respiratory failure develop within the first days and large ulcerations and epithelial necrosis of the bronchial epithelium occur, which has to be suspected when dyspnea, bronchial hypersecretion, normal chest radiograph, and hypoxemia are present during the early stages of the disease (55).

Intubation and mechanical ventilation may be required and is associated with higher mortality (56). Permissive hypercapnia with moderate respiratory acidosis (pH $>$7.20) can help to prevent barotrauma and ventilator-induced lung injury (57). Treatment with inhaled nitric oxide might be helpful. $Pa_{O_2}/F_{I_{O_2}}$ ratio improved an average of 162% after administration of low-dose inhaled nitric oxide (average 6.7 ppm), but nonsurvivors had a significantly less favorable initial response (58).

SJS/TEN survivors may have persistent respiratory sequelae and a reduction in carbon monoxide diffusing capacity of up to 35%–40% below normal even if they did not require mechanical ventilation (59).

Ophthalmic complications are seen in about 30% of the surviving children, up to 74% in adults (60), and are severe in 25% of cases (61).

The acute stage of ophthalmic involvement persists 2 to 6 wks and shows swollen and erythematous eyelids, bacterial conjunctivitis, suppurative keratitis, or endophthalmitis. If there is significant inflammation, topical steroids can reduce the circle of cicatrization and eyelid deformities (62). Extensive scarring due to overgrowth with conjunctival epithelium, membranous or pseudomembranous conjunctivitis, ankyloblepharon, or symblepharon with additional complications like entropion or lagophthalmos leads to a severe dry eye syndrome or loss of vision.

Persistent inflammation and ulceration may lead to the destruction of limbal stem cells and stem cell deficiency (63, 64). Even after limbal stem cell transplantation, the prognosis is poor (65). Chronic ophthalmic complications occur more frequently in patients with initial ocular involvement (60), but loss of vision due to chronic corneal inflammation also occurs in patients without initial affection of the eye and is considered to be the most severe long-term complication in TEN/SJS survivors (61).

Long-term treatment with steroids and vigorous lubrication helps to prevent late complications such as impaired tear production, aberrant lashes, and metaplasia. Photophobia occurs frequently and may resolve gradually over months (61, 66–68).

Amniotic membrane transplantation has been increasingly performed in recent years and may prevent chronic complications. A recent review shows good results in six children (69).

Other organ manifestations occur rarely. Involvement of the kidneys with glomerulonephritis, tubulonecrosis, and pancreatitis (70), as well as involvement of the liver including hepatocellular necrosis or cholestasis, has been reported (71–75).

The mortality of SJS is estimated to be 1%–3% (13). In contrast, mortality rates for TEN are between 30% and 50% (76, 77), with death usually resulting from sepsis or multiorgan failure (13, 45, 78). The mortality rate of children appears to be lower than that of adults.

A severity-of-illness score for TEN (SCORTEN) was published (79). This score combined seven independent risk factors for mortality (age ≥40 yrs, heart

rate ≥120/min, history of cancer or hematologic malignancies, involved body surface area >10%, serum urea level >10 mmol/L, serum bicarbonate level <20 mmol/L, serum glucose level >14 mmol/L). Scoring one point for each item, the predicted mortality was 3.2%, 12.1%, 5.3%, 58.3%, and 90.0% for 0–1, 2, 3, 4, and ≥5 points respectively. The predicted mortality was shown to be accurate by other publications (80, 81) but may underestimate mortality in patients with respiratory involvement (82). Others published a lower mortality rate with a standardized treatment protocol (83) or analyzed that body surface involvement and age probably need more weight in calculations (84).

Treatment

Immediate discontinuation of the triggering drug reduces mortality and improves prognosis (85, 86). Readministration of the suspected drug can cause a relapse of TEN (87).

The management of TEN is similar to the treatment of extensive burns, and several studies have demonstrated that early transfer to a burn unit reduces morbidity and mortality significantly: TEN survivors had been transferred to a burn unit 7.5 days earlier than nonsurvivors with a mortality of 4% vs. 83%. Bacteremia, septicemia, and length of hospitalization were also reduced with early transfer (88). The largest trial showed a mortality of 29.8% after transfer to a burn center within 7 days vs. 51.4% ($p < .05$) after 7 days (89). Other studies largely support early transfer to a burn unit (85, 90–93).

However, several differences between TEN and burns need to be respected. In TEN, which in contrast to burns affects only the superficial dermal layers, fluid, electrolyte, and energy requirements are usually lower than in burns of the same extent (90). Initial provision of 2 mL/kg/% affected body surface area results in adequate urine output and significant correction of blood pressure in adults (94).

Older studies suggest that nutritional requirements are similar to those in burn injury (95–97), but newer studies show that pediatric SJS/TEN patients require approximately 600 calories or 22% less per day than patients with burns (98). A statistically generated equation estimating the energy requirement in the pediatric SJS/TEN population was developed: caloric needs = (preinjury weight [kg] × 24.6) + (wound size [%] × 4.1) + 940 calories.

Other authors suggested that energy intake of 120% of the predicted basal metabolic rate and intake of 3 grams per kilogram protein result in adequate wound healing, whereas higher energy provisions enhance weight status (99).

Negative prognostic factors are hypernatremia (100), increased blood urea nitrogen, neutropenia, thrombocytopenia, visceral involvement, and delayed presentation (14, 90, 101).

Besides providing adequate analgesia, it is also essential to prevent dehydration and superinfection. Treatment of the skin lesions with antimicrobial materials like copper sulfate (102), silver nitrate (103), or sulfadiazine cream (which contains sulfonamide and might lead to cross-reactivity with sulfonamide antibiotics) and covering with biological or synthetic materials have been proposed. In less developed countries, banana leaf dressings and boiled potato peel bandage may cover wounds satisfactorily (104). Porcine xenograft skin and human allograft cadaveric skin have been used, but there is a trend to nonadherent (semi-)synthetic materials. For example, Biobrane has been used with good results and showed reduced pain and improved mobilization in elderly patients (105–107). Other materials like Acticoat, Aquacel Ag, or Suprathel are synthetic materials containing nanocrystalline silver, which serves as an antimicrobial agent and is released for up to 7–14 days. The need of painful dressing changes can be reduced. Several case reports, including one case of a young infant, show good results (108–113).

Additionally, it can be helpful to prevent shear forces and other mechanical disruptions to prevent further areas of skin desquamation (114).

Considering the immunologic background of TEN, treatment with immunosuppressive drugs was expected to be beneficial.

Corticosteroids inhibit a wide range of intracellular processes in turn modifying the inflammatory and immune response and have been used in the management of SJS and TEN for >30 yrs.

Several reports have been published showing benefits of corticosteroid treatment. In a randomized prospective trial, pediatric patients treated with methylprednisolone showed a significantly shorter duration of fever than did others with supportive care only (115).

However, other analyses suggest increased mortality and morbidity. Pediatric patients with SJS treated with high doses of corticosteroids did not recover sooner than those treated with supportive care alone. Patients in the steroid group had a higher incidence of medical complications (53% vs. 0%), most commonly infection (24%) and gastrointestinal bleeding (21%) (116).

Mortality was significantly higher in a steroid treated group with 66% vs. 33% in the nonsteroid group (103). Administration of corticosteroids for >48 hrs was associated with a higher rate of infection, longer hospitalization, and increased mortality rate. A multivariate analysis documented that treatment with corticosteroids is an independent risk factor for increased mortality (88).

However, a recently published large retrospective study included 281 patients and evaluated the treatment of corticosteroids and intravenous immunoglobulins (IVIGs) either alone or in combination compared to supportive care only. Neither intravenous immunoglobulins nor corticosteroids showed any significant effect on mortality in comparison with supportive care (117).

Publications evaluating the treatment of TEN or SJS with corticosteroids are summarized in Table 2.

In vitro studies showed that intravenous immunoglobulin was able to block the Fas receptor (41), which was the rationale for the therapeutic use of immunoglobulins geared toward the inhibition of apoptosis.

Cessation of cutaneous blistering was observed in all patients within an average of 2 days after IVIG was initiated. No correlation between the timing or dosing and time to objective response was identified in pediatric patients with SJS or TEN (118).

A retrospective trial compared treatment with IVIGs to standard supportive care (119). The survival was 88%, and the authors recommended a dose of 1 g/kg/day for 3 days. Other studies with combined 32 patients reported a survival of 100% (120–122). IVIG-treated patients showed a shorter duration of fever and shorter hospitalization (123).

These optimistic results have not been confirmed by several other studies: a retrospective chart review found a higher mortality and a longer hospitalization in patients treated with IVIGs (124). Other studies showed no significant difference in mortality, multiorgan failure, duration

Table 2. Corticosteroid treatment of Stevens-Johnson syndrome or toxic epidermal necrolysis

Author(s) and Year	Study Type	Diagnosis	No. of Patients With/Without Corticosteroids	Treatment	Time to Arrest in Days (Range) With/Without Corticosteroids	Time to Complete Skin Healing in Days (Range)	Mortality With/Without Corticosteroids	Other
Rasmussen 1976 (116)	Retrospective	SJS	17/15	Prednisone 40–80 mg/m^2/day	NR	NR	NR	All nine complications in patients with steroids; hospitalization with steroids 21 days without 13 days
Rasmussen 1980 (164)	Retrospective	TEN[a]	24/51	Prednisone 60 mg/m^2/day	1–3	7–12	NR	
Halebian et al 1986 (103)	Retrospective comparative trial	TEN	15/15	240–1000 mg hydrocortisone daily over maximum 7 days	NR	NR	66%/33%	
Kelemen et al 1995 (88)	Retrospective	TEN/SJS	14/37	NR	NR	NR	50%/3%	Infection, hospitalization, and mortality reduced in patients with less than 48 hrs of steroids
Pasricha et al 1996 (165)	Retrospective	TEN	5/0	Dexamethasone 12–20 mg/day decreasing dose 7–10 days	NR	NR	0%	
Kakourou et al 1997 (115)	Retrospective	TEN/SJS	10/6	Methylprednisolone 4 mg/kg/day	7.0 ± 3.3/9.8 ± 3.0	NR	0%/0%	Shorter period of fever with steroids
Léauté-Labrèze et al 2000 (166)	Retrospective	SJS	6/11	1 mg/kg/day decreasing over 1 wk	NR	18/19	0%/0%	No benefit concerning duration of disease
Forman et al 2002 (167)	Retrospective	TEN/SJS	11/28	NR	NR	NR	Overall 3.6%	21% complications
Lam et al 2004 (168)	Retrospective	TEN/SJS	9/2	Prednisolone 2 mg/kg/day for 3–5 days	NR	NR	0%/0%	Hospitalization 10 days
Kardaun and Jonkman 2007 (169)	Retrospective	TEN/SJS	12/0	Dexamethasone 100 mg or 1.5 mg/kg for 3 days	2.3	16.8	8.3%	
Yamane et al 2007 (170)	Retrospective	TEN/SJS	111/6	Prednisolone 10–600 mg/day	NR	NR	3.6%/16.6%	
Schneck et al 2008 (117)	Retrospective multicenter	TEN/SJS	159/122	NR	NR	NR	17.6%/27.8%	No significant benefit from any treatment
Hanken et al 2009 (171)	Retrospective	TEN	8/0	30–250 mg prednisone, duration NR	12 days	NR	0%	
Yang et al 2009 (172)	Retrospective	TEN SJS	47 18	Methylprednisolone 1–1.5 mg/kg/day	6.3 5.7	NR	27% 16.7%	16% more likely to die with steroids
Koh and Tay 2010 (173)	Retrospective	TEN/SJS	5/5	Prednisolone 0.5–1.5 mg/kg/day up to 1 month Hydrocortisone 10–15 mg/kg/day average 4 days (range 2–6)	1.5/4.2 days	NR	0%/0%	

NR: not reported; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]Unclear if all patients had TEN/SJS by today's definition.

of mechanical ventilation, severity of systemic inflammation, incidence of sepsis, time to recovery or length of stay in hospital (125), or in progression of detachment or speed of re-epidermalization (126). The largest trial included 281 patients and did not show decreased mortality with IVIGs (117).

Table 3 summarizes studies with treatment of TEN or SJS with IVIGs. In summary, the specific treatment of SJS/TEN with immunoglobulins remains controversial, and large randomized controlled trials are needed.

The only double-blind, randomized, placebo-controlled trial concerning treatment of TEN was performed for thalidomide (127). Thalidomide inhibits the production of tumor necrosis factor alpha and interleukin-6 secreted by monocytes and lymphocytes. The progression of skin reaction was similar in both groups, but mortality was increased in the thalidomide group (83%) vs. placebo (30%), which led to the discontinuation of the study. Thus, thalidomide cannot be considered a safe or effective treatment of TEN.

Cyclosporine inhibits CD8 activation and also has antiapoptotic activity. Theoretically, this inhibits epidermal apoptosis and leads to improved outcome. To date, large trials have not been performed, but several case reports with up to 29 patients have been published using cyclosporine 3–10 mg/kg daily (128–137). Patients treated with cyclosporine had a significantly shorter time until stop of progression and complete re-epithelialization. Failure of ≥4 organs and severe leukopenia and mortality were also significantly less frequent in the cyclosporine group (138).

Table 3. Intravenous immunoglobulin treatment of Stevens-Johnson syndrome or toxic epidermal necrolysis

Author(s) and Year	Study Type	Diagnosis	No. of Patients With/ Without IVIG	Average Total IVIG Dose (g/kg)	Time to Arrest in Days (Range) With/ Without IVIG	Time to Complete Skin Healing in Days (Range) With/Without IVIG	Mortality With/ Without IVIG	Other
Viard et al 1998 (41)	Retrospective	TEN/SJS	10/0	2.5	1.5 (1–2)	6.9 (4–12)	0%	
Morici et al 2000 (123)	Retrospective	SJS	7/3	1.9	NR	NR	0%/0%	Duration of fever 8 (3–14) days with IVIG vs. 14 (6–20) days, hospitalization 12 (4–22) days with IVIG vs. 15 (6–25) days
Stella et al 2001 (174)	Retrospective	TEN	9/0	2.8	4.8 (3–10)	12.125 (7–17)	11%	
Tristani-Firouzi et al 2002 (122)	Retrospective	TEN	8/0	2.4	2.1 (1–4)	8.1 (3–14)	0%	Hospitalization 13.6 (4–23) days
Bachot et al 2003 (126)	Prospective open trial	TEN/SJS	34/0	1.0 (3 patients) 2.0 (31 patients)	NR	18 (3–75)	32%	
Campione et al 2003 (175)	Retrospective	TEN/SJS	10/0	2.0	NR	(25–40)	10%	
Metry et al 2003 (118)	Retrospective	SJS	7/0	2.0	2.0 (1–3)	NR	0%	Early treatment correlated with longer time to response than middle or late treatment
Prins et al 2003 (119)	Retrospective multicenter	TEN/SJS	48/0	2.7	2.3 (1–6)	15 (4–40)	12%	
Prins et al 2003 (120)	Retrospective multicenter	SJS	12/0	2.4	2.0 (1–3)	9.0 (4–18)	0%	
Trent and Kerdel 2003 (176)	Retrospective	TEN	16/0	3.9	3.75 (1–17)	8.5 (4–23)	6.25%	Hospitalization 20.3 days
Al-Mutairi et al 2004 (121)	Prospective	TEN	12/0	3.4	2.83 (1–5)	7.33 (5–13)	0%	Hospitalization 12.5 (7–21) days
Brown et al 2004 (124)	Retrospective	TEN	24/21	1.6	NR	17.8 ± 10.3/12.4 ± 5.9	41.7%/28.6%	Hospitalization with IVIG 15.6 ± 12.6 vs. 13.8 ± 6.9 days
Lam et al 2004 (168)	Retrospective	TEN/SJS	3/8	1.0	NR	NR	0%	Hospitalization 10 days
Shortt et al 2004 (125)	Retrospective	TEN	16/16	3.0	NR	11.2 ± 3.6	25%/38%	Hospitalization with IVIG 28.3 vs. 34.9 days, progression with IVIG 13% vs. 27%
Mangla et al 2005 (177)	Open uncontrolled	TEN	10	IVIG 0.05–0.1 g/kg/day for 5 consecutive days 2–4 days after onset	2.1 (1.8–2.5)	8.3 (5.4–10.7)	0%	No systemic complications
Tan et al 2005 (178)	Retrospective	TEN/SJS	12/0	1.75	3.6 (2–8)	NR	8.4%	Hospitalization 20.4 ± 8.0 (10–37) days
Yeung et al 2005 (179)	Prospective/ retrospective controls	TEN/SJS	6/10	3.0	2.8/5.3	9.2/11.2	16.6%/10%	Shorter time to cessation of progression and re-epithelialization with early IVIG treatment
Gravante et al 2007 (92)	Retrospective	TEN/SJS	15/17	2.0	NR	Overall 27 ± 12	41%/27%	Hospitalization 17 ± 9 days
Stella et al 2007 (180)	Retrospective	TEN/SJS	23/8	2.8	5/NR	12.3/NR	26%/75%	Hospitalization of surviving patients with IVIG 16.3 vs. 17 days
Yamane et al 2007 (170)	Retrospective	TEN/SJS	22/95	Max. 1.2	NR	NR	9%/3%	
Schneck et al 2008 (117)	Retrospective multicenter	TEN/SJS	75/206	1.9 (interquart. 1.3–2.1) over 1–7 days	NR	NR	25.3%/20.8%	No significant benefit from any treatment
Teo et al 2009 (181)	Retrospective	TEN	6/0	3.0	NR	NR	16.6%	
Yang et al 2009 (172)	Retrospective	TEN SJS	12/35 8/10	2.0	4.3/7.3 4.3/7.0	NR NR	16.7%/22.8% 12.5%/20.0%	Nonsignificant reduction of mortality, time of progression, and hospitalization
Koh and Tay 2010 (173)	Retrospective	TEN/SJS	4/6	2.0	2.7	NR	25%/0%	

NR, not reported; IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 4. Studies of Stevens-Johnson syndrome or toxic epidermal necrolysis in pediatric patients

Author(s) and Year	Type	Diagnosis	No. of Patients	Treatment	Time to Arrest in Days (Range)	Time to Complete Skin Healing in Days (Range)	Mortality with/without Specific Treatment	Other
Rasmussen 1976 (116)	Retrospective	SJS	32	17 prednisone 40–80 mg/m^2/day 15 supportive care	NR	NR	NR	All nine complications in patients with steroids; hospitalization with steroids 21 days without 13 days
Rasmussen 1980 (164)	Retrospective	TEN[a]	75	Antibiotics; 24 patients: 60 mg prednisone/m^2	1–3	7–12	NR	
Ruiz-Maldonado 1985 (102)	Retrospective	TEN	60	Supportive	NR	14.7	15%	
Kakourou et al 1997 (115)	Retrospective	TEN/SJS	16	10 methylprednisolone 4 mg/kg/day 6 supportive care	7.0 ± 3.3/9.8 ± 3.0	NR	0%/0%	Shorter period of fever with steroids
Morici et al 2000 (123)	Retrospective	SJS	12	7 IVIGs 1.5–2 g/kg single infusion on hospital day 3 (1–8) 2 corticosteroids 3 supportive care	NR	NR	0%/0%/0%	Duration of fever 8 (3–14) days with IVIG vs. 14 (6–20) days Hospitalization 12 (4–22) days with IVIG vs. 15 (6–25) days
Spies et al 2001 (15)	Retrospective	TEN	15	Supportive care			0%	Hospitalization 26 ± 3 days
Forman et al 2002 (167)	Retrospective	SJS or TEN	28	11 patients treated with corticosteroids	NR	NR	3.6% overall	21% complications
Tristani-Firouzi et al 2002 (122)	Retrospective	TEN	8	IVIG 0.5–0.75 g/day for 4 days on hospital day 3.2 (2–5)	2.1 (1–4)	8.1 (3–14)	0%	Hospitalization 13.6 (4–23) days
Metry et al 2003 (118)	Retrospective	SJS Previous reports SJS or TEN	7 28 previous reports	IVIG 2.0 (1.2–4.0) g/kg distributed evenly over 4 days 3.75 (1–10) days after onset of blistering 5 patients corticosteroids	2 (1–3)	NR	NR	Early treatment correlated with longer time to response than middle or late treatment
Lam et al 2004 (168)	Retrospective	SJS or TEN	10	Corticosteroids equivalent dose to prednisolone 1–2 mg/kg/day 3–5 days, if poor response IVIG 1 g/kg/day	4		0%	Hospitalization 10 days
Mangla et al 2005 (177)	Open uncontrolled	TEN	10	IVIG 0.05–0.1 g/kg/day for 5 consecutive days 2–4 days after onset	2.1 (1.8–2.5)	8.3 (5.4–10.7)	0%	No systemic complications
Koh and Tay 2010 (173)	Retrospective	SJS or TEN	15	4 patients: IVIG 2 mg/kg over 2–4 days 5 patients: corticosteroids equivalent to 0.5–1.5 mg/kg/day prednisolone decreasing dose over 2–4 wks 6 patients: supportive care only	NR	NR	25%/0%	Hospitalization 22.7 days with IVIG vs. 7.7 days without IVIG

NR, not reported; IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]Unclear if all patients had TEN/SJS by today's definition.

Overall, cyclosporine treatment seems promising, but larger trials are needed to confirm the preliminary results.

Abnormal inherited metabolic pathways are presumed in some cases, which could lead to a diminished detoxifying capacity. Administration of *N*-acetylcysteine enhances the oxidant buffering capacity of glutathione and inhibits nuclear factor kappa B, a transcription factor induced by tumor necrosis factor alpha and interleukin-6 (139). Treatment with *N*-acetylcysteine has been published with good results (140, 141), but numbers are small and controlled trials have not been performed.

Plasmapheresis has been used in several case reports and small studies, mostly in adult patients but also in children as young as 1 yr. The procedure can be considered safe. One to eight plasma exchange sessions have been used, predominantly with good results (142–148).

Infliximab (149–154), azathioprine (155), methotrexate (156), cyclophosphamide (157–160), and recombinant granulocyte colony-stimulating factor (161–163) were also used for the treatment of TEN, but the data are limited and need further evaluation.

Since most studies have been performed in adult patients and treatment of TEN and SJS in pediatric patients has not been studied extensively, we provide an overview of all larger studies performed in pediatric patients in Table 4.

CONCLUSION

TEN is a life-threatening exfoliative skin disease that shows blistering and extensive shedding of the skin, and finally presents with large denuded areas. Other organs are frequently affected, and an interdisciplinary team is needed to provide optimal therapy. Although the incidence is relatively low, it is important to identify patients at risk to avoid delaying therapy. Treatment modalities vary widely between supportive care alone, specific treatment with immunosuppressive drugs, IVIGs, and plasmapheresis. To date, no treatment has been shown to be superior, but in almost all cases no prospective randomized controlled trials have been performed.

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