L'uso dell'immunoglobulina e della plasmaferesi in paziente con necrolisi epidermica tossica

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IRCCS BONINO PULEJO PIEMONTE

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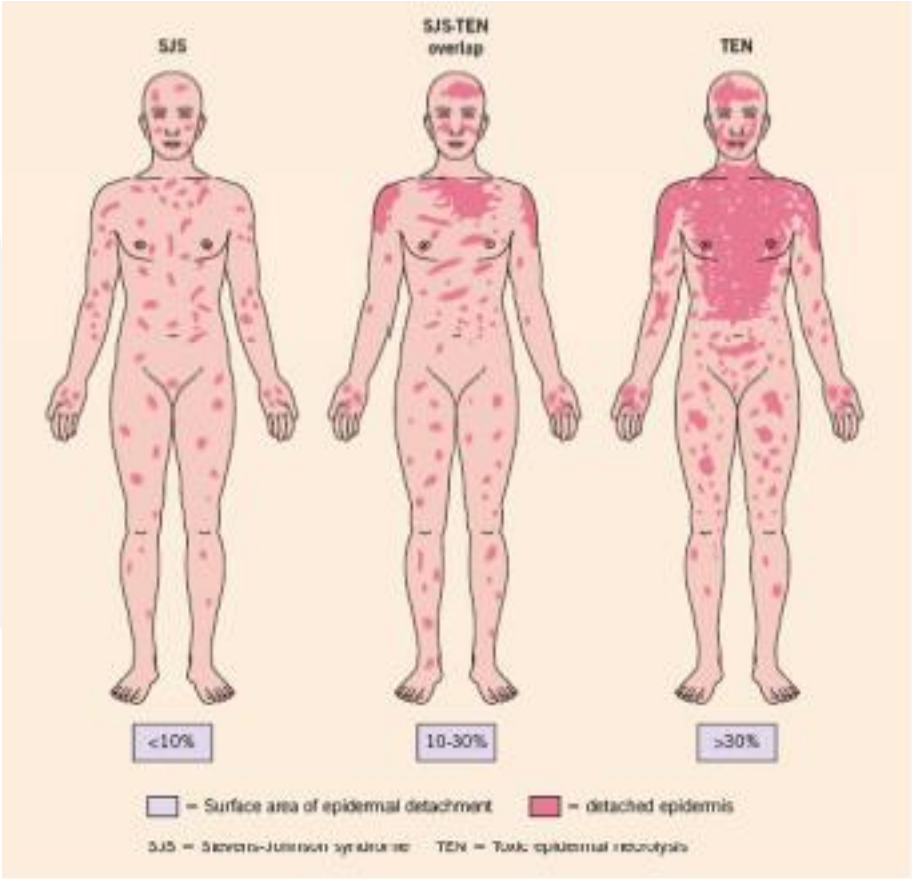
Introduction

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are erythematous skin lesions with blister formation accompanied by mucosal involvement. These conditions are considered to be life- threatening illnesses.

- Patients with SJS have desquamation of the skin affecting <10% of their body surface area whereas patients with TEN have >30% body surface area involvement.

- Patients with skin lesions affecting between 10 and 30% of their body surface area are considered to have SJS/TEN overlap



EPIDEMIOLOGY

The estimated incidence of TEN and overlap of SJS/TEN (based on European epidemiological studies) range from an annual risk between 0.93 per million and 1.89 per million per year.

Based on a large European registry study, SJS is more common than TEN, and both SJS and TEN are more common in women than in men.

The incidence of SJS/TEN is also considerably higher in the HIV-positive population, and has been estimated at 1–2 per 1000 individuals in the population

MORTALITY RATE: Ranging from 6.2% to 32%
the most recent reported mortality rate for TEN was 14.3% (2000-2013)
decreased compared to the mortality rate of 21.6% (1981-1997)

Allergology International 66 (2017) 36e41

ETIOLOGY

Drugs are the leading reported cause of TEN, with the risk of a hypersensitivity reaction mainly in the first few weeks of the drug ingestion

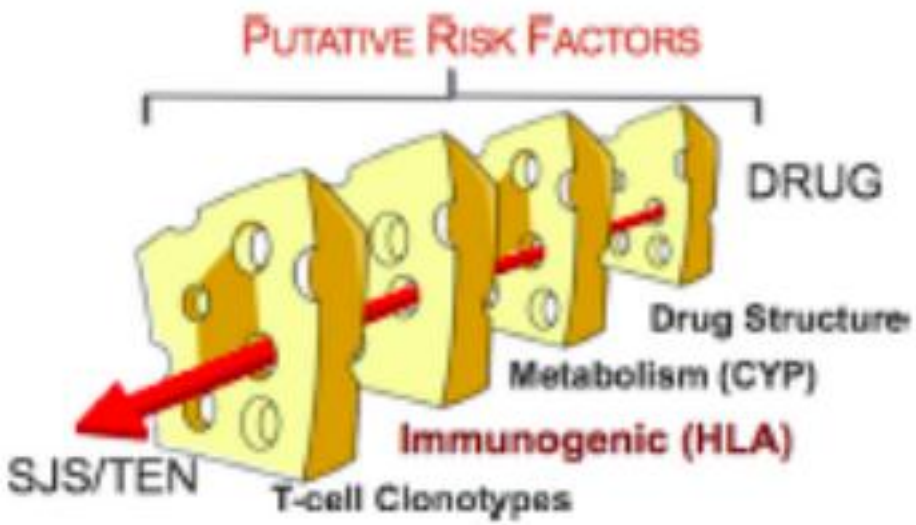


Fig. 1 "Swiss cheese" risk model of Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). *CYP* cytochrome P450, *HLA* human leukocyte antigen

Allergology International 66 (2017) 36e41

Genetic susceptibility

Table 1 Genetic associations of Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) in various populations

Drug classification	Culprit drug	SJS and/or TEN	*HLA* allele and CYP	Ethnicity and references
Antibiotics	Sulfonamide	TEN	*A**29, *B**12, *DR**7	European [4]
	Sulfamethoxazole	SJS/TEN	*B**38	European [21]
Anticonvulsants	Carbamazepine	SJS/TEN	*B**15:02	Han Chinese [5, 150], Thai [19], Indian [22], Malaysian [23]
		SJS/TEN	*B**15:11	Japanese [6], Korean [7], Han Chinese [8, 9]
		SJS/TEN	*B**59:01	Japanese [14]
		SJS/TEN	*A**31:01	Japanese, northern European [15, 16]
	Lamotrigine	SJS/TEN	*B**15:02	Han Chinese [17]
	Oxcarbazepine	SJS/TEN	*B**15:02	Han Chinese [18]
	Phenytoin	SJS/TEN	*B**15:02	Han Chinese [17, 18], Thai [19]
		SJS/TEN	*CYP2C9**3	Han Chinese, Japanese, Malaysian [30]
Antiglaucoma drugs	Methazolamide	SJS/TEN	*B**59:01, *CW**01:02	Korean and Japanese [20]
Antiretrovirals	Nevirapine	SJS/TEN	*CYP2B6*	African in Mozambique [33]
			*C**04:01	African in Malawi [151]
NSAIDs	Oxicam	SJS/TEN	*A**2, *B**12	European [4, 21]
		TEN	*B**73	
Xanthine oxidase inhibitors	Allopurinol	SJS/TEN	*B**58:01	Han Chinese [13], Thai [12], Japanese [10], Korean [11], European [21]

CYP cytochrome P450, *HLA* human leukocyte antigen, *NSAID* nonsteroidal anti-inflammatory drug

Drugs associated with Stevens-johnson

Strongly associated*	Associated•
Allopurinol Carbamazepine Lamotrigine Meloxicam Nevirapine Phenobarbital, primidone Phenytoin, fosphenytoin Piroxicam, tenoxicam Sulfadiazine, sulfadoxine, sulfamethoxazole, sulfasalazine	Amifostine Amoxicillin, ampicillin Azithromycin, clarithromycine, erythromycin Cefadroxil, cefixim, ceftriaxone, cefuroxim Ciprofloxacin, levofloxacin, pefloxacin Diclofenac Doxycyclin Etoricoxib Metamizole Oxcarbazepine Pipemidic acid Rifampicine

25% of cases cannot be clearly attributed to a drug

Pathogenesis

SJS/TEN, from an immunologic standpoint, appears to behave most like a delayed-type hypersensitivity reaction (DTH):

Drug or drug-peptide complexes are recognized by T-cell receptors. This results in downstream CD8+ cytotoxic T-cell and NK-cell-mediated cytotoxicity and cytokine expression such as (TNF)-alpha and (IFN)-gamma

OVER EXPRESSION:

Fas Ligand :

Perforin and Granzyme B:

Granulysin

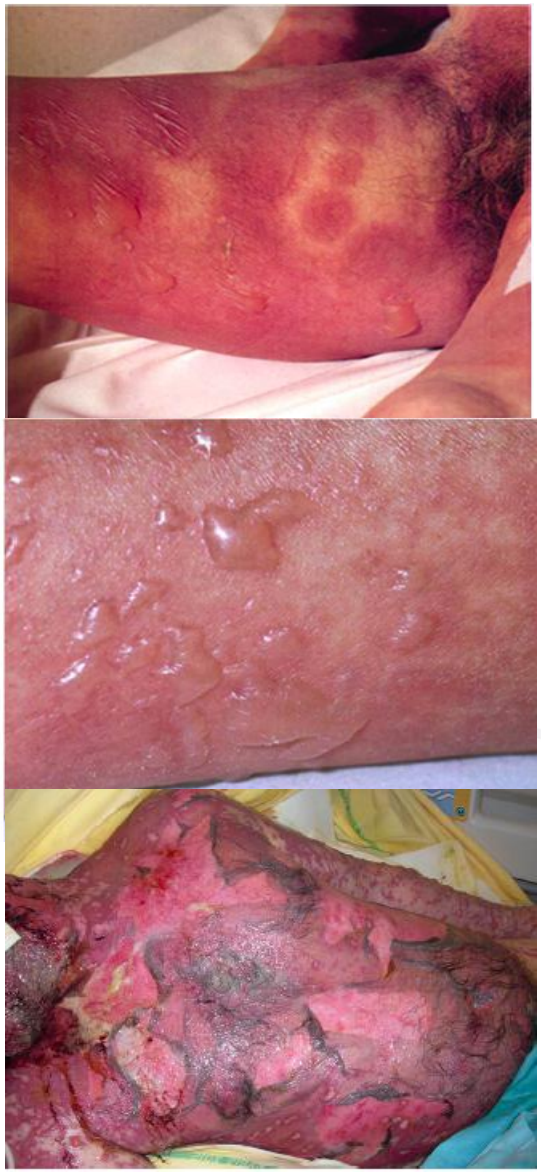
keratinocyte apoptosis

Clinical Presentation

- **Acute phase** (unspecific):
  - Begin in the 3 weeks following introduction of a medication or immunization
  - Fever
  - Photophobia and conjonctival itching
  - Pain on swallowing
  - Malaise and myalgia
  - During one to three days before cutaneous lesions

Clinical Presentation

- **Cutaneous lesions:**
  - Confluent erythematous macules with purpuric centers
  - Skin pain out of proportion to the cutaneous findings
  - Atypical target lesions with darker centers may be present
  - As the disease progresses:
    - Vesicules and bullae form
    - Areas of epidermal detachment develop

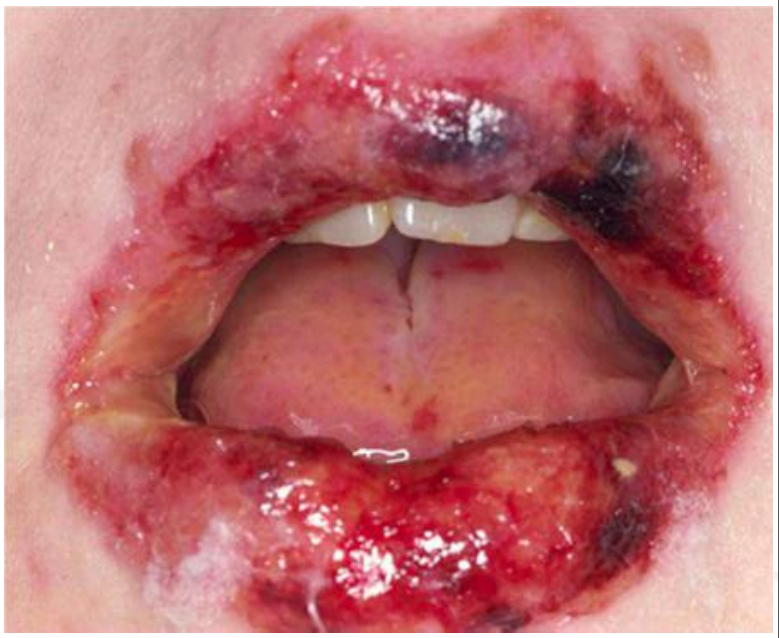


Detachable skin is demonstrated, and gentle pressure causes detachment of epidermis from dermis **(known as a positive Nikolsky sign)**

Clinical Presentation

- **Mucosal lesions:**

- Painful crust and erosions may occur on any mucosal surface
- Occurs in 90 % of cases



- **Ocular**

- Pain and photophobia
- Severe conjonctivitis with purulent discharge and bullae
- Corneal ulceration is frequent

- **Urogenital:**

- Urethritis and genital erosions
- In women: erosive and ulcerative vaginitis

- **Pharyngeal** mucosa is affected in nearly all patients.

Complications:

Acute

- Massive loss of fluids and electrolytes through denude skin
- Electrolytes imbalance
- Hypovolemic shock with renal failure
- Bacteremia
- Insulin resistance
- Hypercatabolic state
- Hepatic involvment and pancreatitis
- Leukopenia, thrombocytopenia and anemia
- pneumonia
- Multiple organ failure

Long term sequelae

- Dermatologic: scarring
- Ophtalmologic: corneal scarring
- Oral and genital: synechiae and stenosis

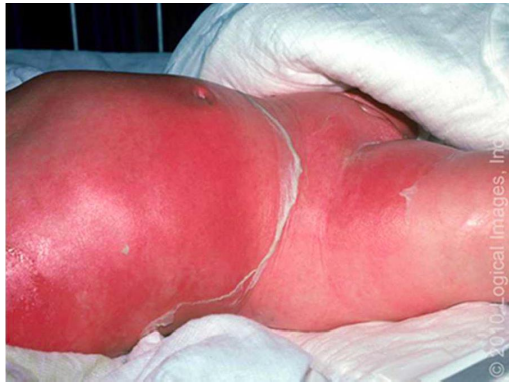
DISEASE SEVERITY SCORE

Table 2 SCORTEN severity-of-illness score

SCORTEN Parameter	Individual score	SCORTEN (sum of individual scores)	Predicted mortality (%)
Age > 40 years	Yes = 1, No = 0	0-1	3.2
Malignancy	Yes = 1, No = 0	2	12.1
Tachycardia (>120/min)	Yes = 1, No = 0	3	35.8
Initial surface of epidermal detachment >10%	Yes = 1, No = 0	4	58.3
Serum urea >10 mmol/l	Yes = 1, No = 0	>5	90
Serum glucose >14 mmol/l	Yes = 1, No = 0		
Bicarbonate >20 mmol/l	Yes = 1, No = 0		

Table 1 Differential diagnosis of Stevens–Johnson syndrome/toxic epidermal necrolysis

Erythema multiforme major
Pemphigus vulgaris
Mucous membrane pemphigoid
Bullous pemphigoid
Paraneoplastic pemphigus
Bullous lupus erythematosus
Linear IgA bullous dermatosis
Generalized bullous fixed drug eruption
Bullous acute graft-versus-host disease
Staphylococcal scalded skin syndrome
Acute generalized exanthematous pustulosis



British Journal of Dermatology (2016) **174**, pp1194–1227

management:

- **Immediate withdrawal** of any potential causative agents
- **Supportive care**
- **wound care**:
  - sterile handling of the wound, use antiseptic solutions and nonadherent gauze dressings
- **Ocular care:**
  - daily cleaning and lubrication with drops or ointment
- **Fluid and electrolytes** management
- **Nutritional** support
- **Pain control**
- **Treatment of superinfection**:
  - no prophylactic antibiotics
  - Check for signs of superinfection
  - Antibiotic choice should be based upon specifific culture data whenever possible.
  - Infections with gram-negative rods (Pseudomonas) are problematic

STEROIDS

Two small case series have reported decreased anticipated mortality rates with high dose corticosteroids dexamethasone (100 mg IV for 3 days) and methylprednisone (1000 mg IV for 3 days).

Intravenous Immunoglobulin (IVIg)

IVIg was proposed as a potential therapeutic agent for TEN based on its ability to significantly block keratinocyte apoptosis by inhibiting the Fas receptor

17 studies: 11 retrospective, 6 prospective
In total 374 pz were included
1 metanalysis

Treatment of Toxic Epidermal Necrolysis With High-Dose Intravenous ImmunoglobulinsMulticenter Retrospective Analysis of 48 Consecutive Cases

Arch Dermatol. 2003;139(1):26-32. doi:10.1001/archderm.139.1.26

Table 3. Characteristics of the IVIG Treatment and Clinical Response*

Time from onset of TEN to IVIG treatment, d	7.3 ± 6 (2-30)
Total dose of IVIG, g/kg	2.7 ± 1 (0.65-5.8)
Daily dose of IVIG, g/kg	0.7 ± 0.4 (0.375-2.9)
Time to objective response, d	2.3 ± 1.2 (1-6)
Duration of IVIG treatment, d	4 ± 0.9 (1-5)
Objective response rate, %	90 (43/48 patients)
Survival rate, %	88 (42/48 patients)
Time to complete skin healing, d	15 ± 9.5 (4-40)

Infusion of IVIG (mean total dose, 2.7 g/kg [range, 0.65-5.8 g/kg]; mean consecutive days, 4 [range, 1-5 days]) was associated with a rapid cessation (mean, 2.3 days [range, 1-6 days]) of skin and mucosal detachment in 43 patients (90%) and survival in 42 (88%).

Patients who responded to IVIG had received treatment earlier in the course of disease and, on average, higher doses of IVIG.
Early infusion of high-dose IVIG is safe, well tolerated, and likely to be effective in improving the survival of patients with TEN.

We recommend early treatment with IVIG at a total dose of 3 g/kg over 3 consecutive days (1 g/kg per day for 3 days).

Table 4. Comparison of Therapeutic and Clinical Parameters in Treated Patients Who Survived and Died*

Parameter	Survived (n = 42)	Died (n = 6)
Age, y	39.6 ± 23.2 (4-95)	66.2 ± 12.8 (48-77)
Skin detachment, % of TBSA	42 ± 20 (10-95)	65 ± 30.7 (30-95)
Time to IVIG treatment, d	6.8 ± 6.1 (2-30)	10.2 ± 4.3 (3-15)
Total dose of IVIG, g/kg	2.8 ± 1 (0.65-5.8)	2.0 ± 0.59 (1.5-3)
Underlying disease, No. (%) of cases	22 (52)	6 (100)
Renal and/or cardiovascular insufficiency	2 (5)	3 (50)
Ischemic and/or hypertensive disease	5 (12)	4 (67)
Cancer	4 (10)	2 (33)
Infectious disease	5 (12)	2 (33)
Prior use of systemic corticosteroids for TEN, % of cases	11 (26)	1 (17)

Abbreviations: IVIG, intravenous immunoglobin; TBSA, total body surface area; TEN, toxic epidermal necrolysis.
*Data are given as mean ± SD (range) unless otherwise specified.

International Journal of Dermatology

Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens–Johnson syndrome: a retrospective comparative study in China

65 consecutive patients with either TEN or SJS, admitted over a 14-year period from January 1993 to October 2007,

For patients admitted after January 2001, additional therapy with a dose of 0.4 g/kg/day of IVIG for 5 days was applied.

In the 45 patients with TEN treated without IVIG, 10 deaths were observed.

In the further study of combination therapy, 12 patients with TEN and eight patients with SJS were admitted.

There were two deaths in the TEN group and one death in the SJS group

Conclusion Combination therapy with corticosteroid and IVIG exhibited a tendency to reduce the mortality rate in comparison with the solo administration of corticosteroid.

The decrease in the mortality rate, however, was not statistically significant.

Combination therapy also arrested progression earlier and decreased the hospitalization time, meaning that the total dose of corticosteroid may be reduced. Combination therapy, however, did not lead to earlier tapering of corticosteroid. No severe adverse effects of IVIG were found during treatment.

Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.12925
Journal of Dermatology 2015; 42: 768–777

ORIGINAL ARTICLE

Efficacy of additional i.v. immunoglobulin to steroid therapy in Stevens–Johnson syndrome and toxic epidermal necrolysis

IVIG (400 mg/kg per day) administrated for 5 days consecutively was performed as an additional therapy to systemic steroids in adult patients with SJS or TEN.

steroids were administrated at maximum doses of 20 mg/day (case 2), 30–60 mg/day (cases 1, 4, 6 and 8) of prednisolone or prednisolone equivalent, or as steroid pulse therapy, 1000 mg/day of methylprednisolone for 3 days

All of the patients survived and the efficacy on day 7 of the IVIG was 87.5% (7/8 patients).

Prompt amelioration was observed in skin lesions and enanthema in the patients in whom IVIG therapy was effective.

Table 4. Diagnosis and symptoms of patients

No.	Age (years)	Sex	Type of disease	Suspected drug	Severity-of-illness score (points)†	Extent of epidermal detachment (%)†	Extent of erythema (%)†	Lip/oral lesions†	Ophthalmic lesions†	Fever (°C)†	SCORTEN†
Case 1	51	Male	SJS	Anticonvulsants	14	0	45	Yes	Yes	35.4	1
Case 2	41	Male	SJS	None‡	17	9	60	Yes	No	35.8	1
Case 3	53	Male	TEN	Cold medicine	22	30	75	Yes	Yes	37.0	3
Case 4	78	Male	SJS	Supplements	15	0	75	Yes	Yes	36.4	1
Case 5	65	Female	TEN	Allopurinol	31	50	90	Yes	Yes	36.8	3
Case 6	52	Male	TEN	Fenofibrate, allopurinol	23	18	30	Yes	Yes	36.6	2
Case 7	67	Female	SJS	Antibiotics, cold medicine	14	0.1	50	Yes	Yes	36.0	1
Case 8	57	Male	SJS	Carbamazepine	15	9	25	Yes	Yes	37.2	1

BJD
British Journal of Dermatology

The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre

H.Y. Lee,[1] Y.L. Lim,[2] T. Thirumoorthy[1] and S.M. Pang[1]

There were 28 cases of SJS/TEN overlap and 36 cases of TEN, with a mean SCORTEN value of 2.6.

The mean dose of IVIg given was 2. 4 g kg and the
mean delay from the onset of epidermal detachment to administration of IVIg was 3 2 days.

There were 20 deaths (31%) in our cohort
Subgroup analysis comparing survivors and nonsurvivors showed a higher SCORTEN in nonsurvivors
There were no differences with regard to the dosage, delay and duration of IVIg administration
There was no mortality difference between patients who receive high-dose (≥ 3 g kg) vs. low-dose (< 3 g kg) IVIg.

This study shows that the use of IVIg does not yield survival benefits in SJS/TEN overlap and TEN, even when corrected for IVIg dosages.

32 patients had no prior exposure to corticosteroids and there was no difference between this subgroup of patients and the entire cohort in terms of disease classification, SCORTEN, daily and cumulative dose of IVIg, delay and duration of IVIg, and mortality

Parameters, mean ± SD unless otherwise stated	Patients treated with IVIg (n = 64)
Sex male, n (%)	26 (41)
Age (years)	57 ± 19
Ethnicity, n (%)	
Chinese	42 (66)
Malay	18 (28)
Indian	4 (6)
SCORTEN overall	2·6 ± 1·2
Disease classification and SCORTEN (n)	
SJS/TEN, n (%)	28 (44)
0–1	7
2	8
3	7
4	6
≥ 5	0
TEN, n (%)	36 (56)
0–1	2
2	16
3	9
4	7
≥ 5	2
Maximum BSA involved (%)	33 ± 19
Cumulative dosage of IVIg (g kg^{-1})[a]	2·4 ± 0·8
Daily dosage (g kg^{-1} per day)[a]	0·6 ± 0·2
Duration of administration (days)[a]	4·0 ± 1·3
Delay to administration (days)[b]	3·2 ± 2·8
Mortality, n (%)	20 (31)

JAMA Dermatology | Original Investigation

Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

A Systematic Review and Meta-analysis

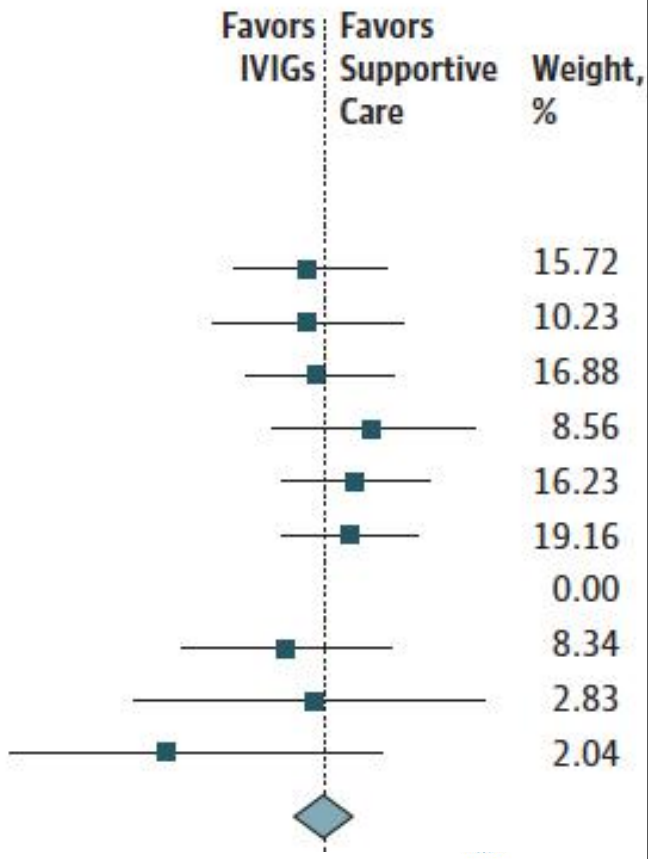
JAMA Dermatol. 2017;153(6 :514-522

Stefanie Zimmermann, PhD; Peggy Sekula, PhD; Moritz Venhoff, DDS; Edith Motschall; Jochen Knaus, MA; Martin Schumacher, PhD; Maja Mockenhaupt, MD, PhD

Figure 4. Comparison of Intravenous Immunoglobulins (IVIGs) and Supportive Care

A Forest plot

Study	No. of Patients (Mortality, %) IVIG	Supportive Care	OR (95% CI)
Meta-analysis at the study level Random-effects model			
Cartotto et al,[29] 2008	30 (27)	31 (32)	0.76 (0.25-2.31)
Dorafshar et al,[18] 2008	17 (24)	11 (36)	0.75 (0.19-2.95)
Firoz et al,[30] 2012	NR	NR	0.88 (0.30-2.56)
Gravante et al,[31] 2007	17 (41)	15 (27)	1.92 (0.43-8.60)
Schneck et al,[19] 2008 (DE)	35 (20)	18 (33)	1.50 (0.51-4.45)
Schneck et al,[19] 2008 (FR)	40 (30)	69 (23)	1.40 (0.51-3.81)
Atzori et al,[32] 2012	15 (0)	6 (0)	NA
Shortt et al,[33] 2004	16 (25)	16 (38)	0.56 (0.12-2.53)
Yip et al,[27] 2005	7 (14)	11 (18)	0.83 (0.06-11.24)
Paquet et al,[34] 2006	6 (17)	5 (60)	0.10 (0.00-2.15)
Heterogeneity $I^2 = 0\%$ (95% CI, 0%-42.7%), $\tau^2 = 0$, $P = .77$			0.99 (0.64-1.54)



Plasmapheresis in Severe Drug-Induced Toxic Epidermal Necrolysis

Arch Dermatol. 1985;121(12):1548-1549.

Five patients with severe drug-induced toxic epidermal necrolysis improved rapidly after one to two plasma exchanges.

The improvement of all five patients treated with plasmapheresis contrasts with the disease's mortality rate of up to 50%, as reported in the literature and as observed among our previously treated patients.

Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis.
J Am Acad Dermatol. 1999;40(3):458.

Sixteen patients were included in this study.

Ten were treated with conventional support measures alone.

Six were treated with plasmapheresis. The average age was 42.4 years;

The average extent of involvement on admission in all patients was 51.5% total body surface area.

The average length of stay in all patients was 14.8 days.

Eight patients (50%) were discharged home, 4 (25%) were discharged to a rehabilitation facility, and 4 (25%) died (2 of sepsis, 2 of cardiopulmonary arrest).

None of the plasmapheresis-treated patients died

Therapeutic Apheresis and Dialysis

Ther Apher. 2002;6(3):225.

Plasma Exchange in Patients with Toxic Epidermal Necrolysis

Gerasimos Bamichas, Taisir Natse, Fotini Christidou, Maria Stangou, Anna Karagianni, Sotiris Koukourikos, Georgios Chaidemenos, Fotis Chrysomallis, Kostas Sombolos

13 pts with drug induced TEN, including 4 pts with malingnant disorders

Skin lesions covered 17% to 100% of total body surface area and 1 to 4 mucous membranes were involved.

The patients underwent from 2 to 5 PE sessions exchanging 6.6 to 17.6 L of plasma.

Three patients died (23%) while the remaining 10 (77%) had a full recovery.

Plasmapheresis may be an effective treatment in patients with drug- induced TEN hospitalized outside a burn unit.

Intensive Care Med (1999) 25: 1307–1310

BRIEF REPORT

A. Furubacke
G. Berlin
C. Anderson
F. Sjöberg

Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis?

PE was started on the day of arrival in five patients or 1±3 days after arrival in three patients.

Eight patients with a median age of 45 years and with a median skin involvement total body surface area of 38 % were treated.

The time from onset of the cutaneous signs until complete re-epithelialisation was 24 days (13±55) for the seven survivors.

Five patients fulfilled the diagnostic criteria of sepsis.

One patient with extensive ischaemic cardiac disease developed septic shock and died

Two patients developed side effects from PE.

Table 2 Comparisons between our study and two recently published ones [7, 8]

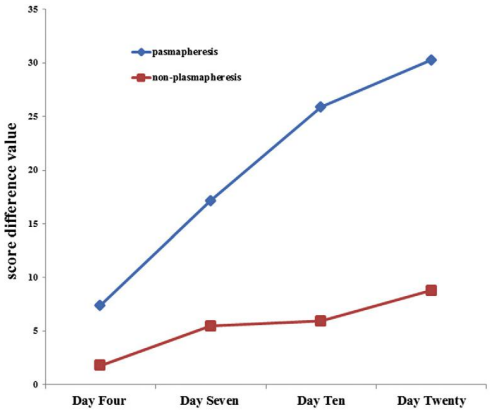
	No. of patients	Mean (range) age (years)	Mean (range) TBSA (%)	Plasma exchange	Mean (range) time from onset to complete re-epi-thelialisation (days)	Mortality [No. (%)]
Our study	8	47 (5–89)	45 (12–100)	Yes	27 (13–38)	1/8 (12.5)
Koo and Foo [7]	22	44 (7–60)	57 (30–90)	No	20 (7–53)	2/22 (9)
Yarbrough [8]	14	47 (16–77)	78 (45–100)	No	16 (Not stated)	2/14 (14)

Contents lists available at ScienceDirect
Journal of Critical Care
journal homepage: www.jccjournal.org

Successful treatment of toxic epidermal necrolysis using plasmapheresis: A prospective observational study

28 patients with TEN or SJS/TEN:
randomly divided into plasmapheresis group (n = 13) and non-plasmapheresis (n = 15)

The plasmapheresis group was further divided into two subgroups: the pure plasmapheresis group (n = 6), and the co-plasmapheresis group,
whose members were treated with plasmapheresis in combination with glucocorticoids and/or IVIg (n = 7).



The comparison between the plasmapheresis and non-plasmapheresis therapy

The rate of recovery in the plasmapheresis group was higher than in the non-plasmapheresis group (2.49 ± 1.02 vs 0.88 ± 0.99, P b 0.001)

Plasmapheresis as a first line therapeutic strategy might present significant advantages in comparison to glucocorticoids and/or IVIg in reducing the mortality of TEN patients as well as in shortening the duration of stays in the intensive care unit. Furthermore, plasmapheresis combined with the IVIg or/and glucocorticoids might not be advantageous compared to the effect of plasmapheresis alone

TNF-a Antagonists (Infliximab, Entanercept)

Two cases have been reported that showed rapid resolution of skin lesions in TEN after systemic anti-TNF- therapy with infliximab (5 mg/kg as single-shot therapy)

Entanercept is another TNF- inhibitor that had promising results in a series of 10 patients with SJS/TEN who were given single 50 mg subcutaneous dose with rapid re epithelialisation and no deaths despite a SCORTEN-predicted mortality of 50%

International Journal of *Molecular Sciences*

Review

Review of Toxic Epidermal Necrolysis

Victoria Harris [1,*], Christopher Jackson [2] and Alan Cooper [3]

CONCLUSION

Immunoglobulin could be effective in patients with SJS/TEN in the early fase of the diseases

Plasmapheresis could be a valuable in patients with SJS/TEN

Randomized controlled trials are needed to evaluate the tailored therapy for patients, according to disease severity

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GRAZIE